

Initial Treatment of Patients with Primary Breast Cancer: Evidence, Controversies, Consensus

Spectrum of Opinion of German Specialists at the 15th International St. Gallen Breast Cancer Conference (Vienna 2017)

Erstbehandlung von Patientinnen mit primärem Mammakarzinom: Evidenz, Kontroversen, Konsens

Meinungsbild deutscher Experten zur 15. Internationalen St. Gallen-Konsensuskonferenz (Wien 2017)

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ABSTRACT

The St. Gallen International Consensus Conference on the treatment of patients with primary breast cancer has been held regularly (every second year in the last six years) for more than 30 years. This year, the findings of the International St. Gallen Consensus Panel and their implications for clinical practice were again discussed by a German working group of leading breast cancer specialists. Five of the breast cancer specialists from Germany were also members of this year's St. Gallen panel. A comparison between the St. Gallen recommendations and the annually updated treatment guidelines of the Gynecologic Oncology Group (AGO 2017) and the S3-guideline agreed upon in 2017 is useful. The recommendations of the St. Gallen panel represent an international cross-section of opinions of experts from different countries and different disciplines, while the S3-guideline and AGO guidelines are evidence-based. The motto of this year's 15th

St. Gallen Conference was "Escalating and De-Escalating". The rationale behind this concept was to promote more individualized treatment and thereby reduce overtreatment as well as undertreatment.

ZUSAMMENFASSUNG

Seit über 30 Jahren findet regelmäßig (in den letzten 6 Jahren alle 2 Jahre) die internationale St. Gallen-Konsensuskonferenz zur Behandlung von Patientinnen mit primärem Mammakarzinom statt. Die Ergebnisse des internationalen St. Gallen-Konsensus-Panels wurden auch dieses Jahr wieder von einer deutschen Arbeitsgruppe führender Brustkrebsexperten für den Klinikalltag in Deutschland diskutiert. Fünf der Brustkrebsexperten aus Deutschland sind zugleich Mitglieder des diesjährigen St. Gallen-Panels. Der Vergleich der St. Gallen-Empfehlungen mit den jährlich aktualisierten Therapieempfehlungen der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-Mamma 2017) und der aktuell im Jahre 2017 abgestimmten S3-Leitlinie ist sinnvoll. Die Empfehlungen des St. Gallen-Panels stellen ein Meinungsbild von Experten unterschiedlicher Länder und Fachdisziplinen dar, wohingegen S3-Leitlinie und AGO-Empfehlungen evidenzbasiert sind. Die diesjährige 15. St. Gallen-Konsensuskonferenz stand unter dem Motto „Escalating and De-Escalating“, das sich durch alle Therapiebereiche zog, die zur Abstimmung standen. Ziel war es, Patientinnen individuellere Therapieoptionen anzubieten und das Risiko einer Über- bzw. Untertherapie zu vermeiden.

Introduction

The panel of this year's 15th St. Gallen Consensus Conference on the initial treatment of primary breast cancer consisted of 72 specialists on breast cancer from 24 countries, making the panel significantly larger than in previous years. Five members of the panel are from Germany. Since 30 years the recommendations of the St. Gallen Consensus Conference have attracted much interest worldwide. This is still the case, even though evidence-based guidelines are becoming increasingly important.

The St. Gallen recommendations are based on majority votes by the panelists. The panelists vote on questions which are put to the vote; they have the option of voting "yes" (agreement), "no" (rejection) or "abstain" (insufficient data, no opinion possible). Other questions may require panelists to choose between several different options. The questions and topics which were put to the vote were chosen by the St. Gallen Committee. The aim is to obtain the opinion of the majority of the panel members based on their own practical experience and, ideally, to use this to create an international consensus for clinical practice.

As the St. Gallen panelists work in different disciplines and come from different countries with different healthcare systems and resources, the consensus essentially reflects the opinions of these specialists. Voting by the panel aims to take account of the currently available evidence. With that in mind, for several years a German working group has regularly commented on the voting

results of the St. Gallen panelists and the implications for clinical practice in Germany. The comments given by the German working group also take the current treatment guidelines of the Breast Commission of the Gynecologic Oncology Group (AGO) [1] into account; this year, the update of the S3-guideline which is due to be completed shortly was also included in the comparison.

Basis of the St. Gallen consensus

The motto of the 15th St. Gallen Consensus Conference was "Escalating and De-Escalating". Given the fact that our understanding of tumor biology is becoming ever more detailed and that therapy is now based on this more detailed information, the focus was on developing strategies which could be used to select the appropriate treatment for individual patients from a range of available options; the aim is to avoid the risk of overtreatment or undertreatment. The choice of treatment is guided by analyzing which patients require more intensive treatment and which patients can have reduced treatment without leading to a worsening of their prognosis.

Surgical Issues

The focus of the surgical questions in primary breast cancer was on adequate margin of resection and on the right surgical approach in the axilla.

Resection margins for DCIS

If a patient with histologically confirmed ductal carcinoma in situ (DCIS) undergoes breast-conserving surgery (no invasive carcinoma present) and adjuvant radiation of the breast is planned, a second resection is not required if there was no ink on tumor (R0) and the histologically confirmed tumor-free margin is of at least 2 mm. This should not be understood to indicate that a second resection is necessary for smaller tumor-free margins; the decision whether second resection is required depends on the individual case and on the assessment by an interdisciplinary team.

The German group of experts agree with the majority vote of the St. Gallen panelists. The German specialists refer to the AGO 2017 guidelines [1]: the guidelines propose that if the tumor-free resection margin is less than 2 mm a second resection is discussed with the patient. According to the AGO guidelines, the majority of patients with DCIS should undergo adjuvant radiation of the breast after breast-conserving surgery (BCS). However, it is important to note in each individual case that radiotherapy reduces the risk of local recurrence but probably does not affect the probability of overall survival [1] except in higher-risk cases.

Multifocal or multicentric breast cancer

It is generally agreed that patients with invasive early breast cancer and multifocal (more than two lesions in a single quadrant) or multicentric (lesions in more than one quadrant) disease can have breast-conserving surgery if the margins of the resected tumors are clear (tumor-free resection margins) and they subsequently undergo adjuvant radiation of the breast. According to the AGO 2017 guidelines [1], the decision to carry out BCS in patients with multicentric breast cancer must be taken on a case-by-case basis and should depend on the number of lesions present.

The German specialists also agree with the St. Gallen vote that the required width of the tumor-free resection margin was not affected by the underlying tumor biology.

Postoperative resection margins after neoadjuvant chemotherapy (NACT)

Patients with early breast cancer who have complete tumor regression (ycT0) after NACT can subsequently undergo breast-conserving surgery. Control imaging and preoperative marking should be done prior to surgery, which is then carried out within the “new margins”. It is not necessary to remove the entire tumor bed of the initial primary tumor. The prerequisite for this approach is that patients undergo adjuvant radiotherapy of the operated breast.

According to the majority vote of the St. Gallen panelists, resection is not required in these patients if the margins are completely clear (no tumor cells in the resection margin is sufficient). According to the majority vote, this also applies to patients with multifocal residual tumor in the resected surgical specimen. The German experts add that this minimum requirement must be complied within all cases, and that in individual cases, even if the margin is tumor-free on microscopic examination, second resection should still be considered if there is any suspicion of residual tumor, although this decision should be taken by an interdisciplinary (clinical pathology) tumor board. This also applies if only partial radiation of the tumor bed was done but pathological exami-

nation found no residual tumor. An interdisciplinary tumor board should decide whether this corresponds to complete remission or whether second resection of the tumor bed is necessary to ensure that there is no residual tumor.

Nipple areola-sparing mastectomy can be carried out after the patient has completed neoadjuvant systemic therapy. Here the German experts agree with the majority vote of the St. Gallen panel.

No Axillary Dissection – for Which Patients?

With the introduction of sentinel node biopsy (SNB), axillary lymph node dissection (ALND) has become less important. Since then, the discussion has focused on when ALND is not required. Because of the significant side effects of this invasive procedure (pain, hematoma, restricted mobility, chronic lymphedema) the potential benefit needs to be clearly defined.

The German experts agree with the majority of St. Gallen panelists that ALND is not recommended for patients with 1–2 positive sentinel lymph nodes (i.e. with macrometastasis) if the patient is scheduled to undergo tangential field radiotherapy post-operatively following BCS or post-mastectomy radiotherapy of the thoracic wall with tangential coverage of part of the axillary lymph nodes. Treatment of these patients must additionally include adequate systemic therapy.

The St. Gallen panelists did not differentiate between axillary radiotherapy of the lymph nodes with standard radiotherapy or with high tangent radiation to treat patients who had BCS. In both cases, ALND is not necessary according to the St. Gallen consensus. The German experts agree with this consensus [2]. They add that reducing the extent of surgery should not lead to increased radiation therapy. The German experts refer in this context to the careful differentiations made in the AGO 2017 guidelines (► Fig. 1) [1]. Patients with 1–2 affected sentinel lymph nodes (SLN) who do not undergo ALND should receive conventional breast radiotherapy. As hypofractionated radiotherapy is increasingly used in Germany, these patients should be included in the INSEMA trial.

The St. Gallen panelists and the German experts agree that tumor biology (lymph node infiltration, hormone receptor status, grading) of patients with 1–2 positive SLN does not affect the decision to perform ALND.

ALND after NACT

The German experts agree with the majority vote of the St. Gallen panel that for patients who have clinically unsuspecting axillary lymph nodes (on palpation and/or sonography) at primary diagnosis (cN0), SNB after neoadjuvant therapy is recommended and ALND is not indicated. The German experts recommend that in addition to palpation, sonography should be an indispensable part of the pre-treatment assessment of the axilla. The German experts also agree with the St. Gallen panel that for patients with clinically negative axillary lymph nodes scheduled for NACT, SNB should be carried out *after* NACT rather than before.

This would mean that many patients (about 30% have a positive SLN *before* NACT) would be spared ALND who would otherwise – given the finding of a positive SLN prior to NACT – have

Axillary lymph node dissection ALND I

	Oxford/AGO LoE/GR		
▶ Axillary lymph node dissection			
▶ Endpoint: survival (with adequate multimodal therapy)	3	D	–
▶ Endpoint: staging	3	A	–
▶ Endpoint: locoregional tumor control	2a	A	+/-
▶ Axillary lymph node dissection for			
▶ DCIS	2b	B	--
▶ If SLN excision is possible	1a	A	--
▶ SN positive (cT1/2 cN0*, <3 SN+, BCT + tangential radiation, adequate systemic therapy)	1b	B	+/-
▶ SN+ (microscopic)	1b	A	–
▶ SN (i+)	2b	B	--
▶ SN + mastectomy (no radiation of the thoracic wall)	1b	B	+
▶ SN + mastectomy (radiation of the thoracic wall)			
▶ Only if T1, T2 and 1–2 positive SLN	5	D	+/-
▶ Axilla dissection indicated but not possible			
▶ Radiation analogous to AMAROS trial	1b	B	+

* Study participation recommended

▶ **Fig. 1** AGO 2017 guidelines on axillary lymph node dissection (ALND) in primary invasive breast cancer [1]. With the kind permission of AGO Breast.

had ALND. Both the AGO guidelines [1] and the St. Gallen consensus recommend ALND [3] for patients who have positive SLN *after* NACT. The indication for adjuvant radiotherapy does not just depend on tumor size but increasingly also on biological factors. This recommendation should definitely be discussed with the radiation therapist. German breast centers repeatedly claim that evaluating SLN *prior to* NACT is important to determine whether postoperative irradiation of the thoracic wall and the regional lymph nodes is indicated when examination shows SLN involvement. The procedure should not be recommended because it would cause an overtreatment in 30% of patients.

The question whether SNB is sufficient in patients with suspicious lymph nodes (i/cN+) on palpation and/or sonography at primary diagnosis but which are clinically/sonographically unremarkable (ycN0) after NACT (“down-staging”: axillary conversion after NACT) and whether (or even when) complete ALND should be carried out has been discussed intensively. Histological confirmation of these suspicious lymph nodes should be attempted with punch biopsy. The German experts agree with 54% of the St. Gallen panelists that SNB is not sufficient for patients who have 1–2 involved axillary lymph nodes after NACT. ALND should be performed if macrometastasis are present in one or more SLN after NACT.

Both groups agree that in certain situations SNB alone can be considered in patients (i/cN+) with axillary conversion to yicN0 after NACT. Certain methods such as clip marking of the involved lymph nodes prior to carrying out NACT can lower the false-negative rate. The “plus/minus” option in the AGO 2017 guidelines [1] can be used in selected cases to avoid ALND. The German experts emphasize that these methods require further study under controlled conditions, e.g. in the context of the upcoming prospective multicenter SenTa register study of AGO and the German Breast Group (GBG).

Adjuvant Radiation

Hypofractionated breast radiation following BCS now standard

At the St. Gallen conference, the questions on adjuvant radiation therapy focused on whether it is possible to reduce the extent of radiation while offering the same efficacy and in which clinical situations this would be feasible. According to the majority vote of the St. Gallen panelists, the standard option after BCS is hypofractionated whole breast radiation. According to the vote, this particularly applies to patients older than 50 years. The German experts agree with the respective vote and refer to the current AGO 2017 guidelines [1].

AGO has recommended hypofractionated radiation on a high level (LoE: 1a A, GR: ++ [1]. A total dose of 40 Gy should be delivered in 15–16 fractions over 3–4 weeks. Conventional radiation therapy delivers a total dose of 50 Gy given in 25–28 fractions over 5–6 weeks. In the AGO 2017 guidelines, conventional radiation therapy has a lower grade of recommendation [1]. From 2017 on, patients should be informed about the significantly shorter duration of radiation, and breast centers should implement the new recommendations.

Is partial-breast radiation after BCS an option?

According to the majority of St. Gallen panelists, partial-breast radiation after BCS (without whole breast radiation) should only be the definitive radiation treatment if patients can be classified as “suitable” based on the criteria of the ASTRO (American Society of Radiation-Oncology) or ESTRO (European Society for Radiotherapy & Oncology) [4,5]. The German experts do not entirely agree with this vote and refer to the AGO guidelines on patients older than 70 years of age [1]. In the opinion of the German panel of experts, the indication for patients between the ages of 50 and 70 years is clear. The decision to opt for partial-breast radiation must be taken on a case-by-case basis and must be discussed with the patient (▶ **Fig. 2**) [1].

The ASTRO classifies the following patients as suitable: age ≥ 60 years, no BRCA 1/2 mutation, ER+, tumor size ≤ 2 cm (T1), tumor-free resection margin ≥ 2 mm, N0, no lymph node invasion, unicentric/unifocal, invasive-ductal or other favorable histology (mucinous, tubular, colloid), no extensive intraductal component. The criteria of the ESTRO differ only minimally with regard to age (≥ 50 years) and T-stage (pT1–2) [4–7].

A narrow majority of the St. Gallen panelists do not recommend partial-breast irradiation as the sole radiotherapy modality

Boost and partial-breast radiation after BCS for invasive cancer

	Oxford/AGO LoE/GR		
▶ Boost radiation of the tumor bed (improved local control, no survival benefit)			
▶ premenopausal	1b	B	++
▶ post-menopausal, if >T1, G3, HER2-positive, triple-negative, extensive intraductal component (EIC) (at least one factor present)	2b	B	+
▶ Intraoperative radiotherapy (IORT) (intraoperative accelerated partial breast irradiation [APBI])			
▶ As boost radiation prior to whole-breast irradiation	2a	B	+
▶ As sole radiotherapy modality (IORT 50 kV, intraoperative extended radiotherapy [IOERT])**			
▶ > 50 years**	1a	A	+/-*
▶ > 70 years**	1a	A	+
▶ Postoperative part-breast irradiation as the sole radiotherapy modality in selected patients (APBI)			
▶ Interstitial brachytherapy	1b	B	+/-*
▶ > 70 years**	1b	B	+
▶ Intracavitary balloon technique	2b	B	-*
▶ Intensity modulated radiotherapy (IMRT)***	2b	B	-*
* Study participation recommended			
** Only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS, IORT during first surgery			
*** No long-term data available			

▶ **Fig. 2** AGO 2017 guidelines on partial-breast radiation after breast-conserving surgery (BCS) for primary invasive breast cancer [1]. With the kind permission of AGO Breast.

after BCS was not indicated for patients whom the ESTRO classifies as “intermediate” and the ASTRO as “cautionary” [4,5]. The German experts agree with the St. Gallen recommendation.

The German experts point out that partial-breast irradiation as the sole radiotherapy treatment is currently not standard in Germany. It may be administered as sole radiotherapy modality only in selected cases for patients with a favorable tumor biology and a low risk of recurrence (pT1 pN0 R0 G1-2, HR+, non-lobular, age > 50 years, no extensive DCIS) as interstitial brachytherapy or intraoperatively [1].

Boost irradiation of the tumor bed after resection of the primary tumor is not necessary if the patient is older than 60 years of age and has no increased risk (low grade, favorable biology, low multigene score). The German experts agree with the vote of the St. Gallen panelists.

Radiotherapy (RT) of locoregional lymph nodes (SCG/ICG)

	Oxford/AGO LoE/GR		
RT to supraclavicular/infraclavicular lymphatic regions			
▶ ≥ pN2a or level III involvement	1a	A	++
▶ pN1a high risk*	2a	B	+
* Central or medial tumor location, and G2-3 or ER/PR-negative premenopausal, lateral location, and G2-3 or ER/PR-negative			
▶ pN0 premenopausal, high risk**	2a	B	+/-
** Central or medial tumor location, and G2-3, and ER/PR-negative			
▶ After NACT/NAT (indications as for post-mastectomy RT [PMRT])	AGO ¹	2b	B
▶ After NACT/NAT if cN+ (core needle/fine needle biopsy [CNB/FNA]) (indications as for PMRT)	DEGRO ¹	2b	A
¹ Different interpretation of published data by AGO and DEGRO			

▶ **Fig. 3** AGO 2017 guidelines on adjuvant radiotherapy of the regional lymph nodes in primary invasive breast cancer [1]. With the kind permission of AGO Breast.

Which patients require more extensive radiation volumes?

The German experts agree with the St. Gallen majority vote whereby patients after BCS who have four or more involved lymph nodes should receive adjuvant radiation of the non-axillary lymph nodes with additional radiation of the supraclavicular and infraclavicular lymph nodes. If 1-3 lymph nodes are involved, 54% of the St. Gallen panelists recommended adjuvant radiation of the non-axillary regional lymph nodes if the patient had a higher risk, e.g., unfavorable tumor biology. The German experts agree with this opinion and refer to the current AGO guidelines (▶ **Fig. 3**) [1].

Adjuvant post-mastectomy radiotherapy

Adjuvant post-mastectomy radiotherapy includes radiation of the thoracic wall and the regional lymph nodes. The German experts do *not* generally agree with the two narrow majority votes of the St. Gallen panelists who stated that adjuvant radiation must be standard treatment

1. after mastectomy in patients with no lymph node involvement (pN0) and a tumor size of 5 cm or above, and
2. in *all* patients who have involvement of 1-3 lymph nodes

The German experts refer to the AGO guidelines [1] which state that this should only apply to patients who have additional risk factors or an increased risk of recurrence (▶ **Fig. 4**).

The German experts point out that adjuvant radiation (of the thoracic wall and regional lymph nodes) after mastectomy is only standard for patients with 1-3 involved lymph nodes and additional risk factors (unfavorable tumor biology, or younger age [<40 years]) and for patients with positive SNB who had not had ALND. In the latter case, the German experts again refer to the

Indication for thoracic wall radiotherapy (PMRT) for patients with 1–3 axillary lymph node metastases

No PMRT necessary LoE 3b B AGO +	PMRT should be discussed LoE 3b B AGO +/-	PMRT recommended LoE 3b B AGO +
<p>ER-positive, G1, HER2-negative, pT1 (if at least 3 of the 4 criteria apply)</p> <p><i>Kyndi M et al. 2013</i></p>	<p>Patients to whom the listed risk criteria (high-risk/low-risk) do not apply</p>	<p>≥ 45 years and > 25% positive axillary lymph nodes at axillary dissection or < 45 years and (ER-negative or > 25% positive axillary lymph nodes at axillary dissection or medial tumor location)</p> <p><i>Truong PT et al. 2005</i></p> <p>< 40 years or HER2-positive or lymphovascular invasion</p> <p><i>Shen H et al. 2015</i></p> <p>G3 oder lymphovascular invasion or triple-negative</p> <p><i>Various publications</i></p>
<p>Note: "If irradiation of the lymphatic drainage pathways is indicated, then the thoracic wall should also be irradiated."</p>		

► **Fig. 4** AGO 2017 guidelines on the indications for radiation of the thoracic wall in patients with primary invasive breast cancer and 1–3 involved metastases in the axillary lymph nodes [1]. With the kind permission of AGO Breast.

current AGO guidelines [1] which state that ALND is the preferred option for these patients – despite the higher risk of comorbidities. A re-assessment of the AMAROS trial [8] will offer additional information whether radiotherapy on the regional lymph nodes after mastectomy in patients with involved SLN is as safe as ALND without radiation therapy.

Radiotherapy after neoadjuvant systemic therapy

According to the St. Gallen consensus, the indication for adjuvant radiation after neoadjuvant systemic therapy is based on the stage of disease before and after neoadjuvant therapy (78%). The German experts agree with this opinion but qualified their agreement by pointing out that prospective randomized data on this are lacking. In the majority of cases in Germany, only the clinical stage prior to starting neoadjuvant therapy is taken into account when deciding whether postoperative radiation therapy is indicated. From a German perspective, this point requires additional clinical study. The results of the randomized NSABP B-51 study will offer further insights but will only be available in a few years.

Pathology

Is traditional pathology enough?

In unclear cases multigene expression analysis should help to make the treatment more individual. The question in this context is whether traditional pathological parameters such as hormone receptor (HR) status, HER2-status, grading, or proliferation index (Ki-67) as well as immunohistochemistry in general are still sufficient as exclusive basis for therapeutic decisions concerning breast cancer subtypes.

For the differentiation between luminal A-like and luminal B-like (HER2-negative) breast cancer patients based on immunohistochemistry, the St. Gallen panelists voted unanimously that this is important for tumor biology evaluation. According to the majority vote, the differentiation provides clinically relevant information for the appropriate therapy. The German experts agree with both statements but pointed to the methodological problems involved in subtyping using only immunohistochemistry [1]. Referring to the AGO guidelines, the German experts point out that currently there is no generally accepted pathohistological marker of the intrinsic subtypes defined by gene expression. Nevertheless, immunohistochemical subtyping can offer some guidance in clinical practice when deciding on the appropriate treatment [1].

Classification into luminal A-like or luminal B-like cancer can – according to the majority vote of the St. Gallen panelists – be done immunohistochemically based on estrogen and progesterone receptor status (ER and PR) as well as the degree of differentiation (grading). The majority of the St. Gallen panelists voted for additional determination of the Ki-67 proliferation index in addition to HR status as criterion for classifying tumors as luminal A-like or luminal B-like. The German experts agree with this but point to the methodological problems involved in Ki-67 determination [1]. The St. Gallen panelists did not vote on a cut-off for Ki-67 in 2017. Some of the St. Gallen panelists pointed out that differentiating between luminal A-like and luminal B-like cancers could also be done with multigene expression analysis. The German specialists supported this suggestion.

Significance of tumor-infiltrating lymphocytes (TILs)

The importance of tumor-infiltrating lymphocytes (TILs) for triple-negative or HER2-positive early breast cancer has been discussed

for years. As the extent of lymphocyte infiltration has no clinical consequences, the detection of TILs does not currently have to be included in the pathologist's report. The German experts agree with the majority vote of the St. Gallen panelists but point to the potential importance of TILs as markers for the immunogenicity of certain breast cancer subtypes.

Importance of multigene expression signature for prognosis

In patients with hormone-sensitive primary breast cancer, the question whether patients with a high risk of recurrence ("at risk" situation) require chemotherapy in addition to endocrine treatment comes up regularly in clinical practice. With their vote the St. Gallen panelists confirmed that multigene expression analysis is not indicated in patients with ER-positive, HER2-negative, well-differentiated pT1a/b cancer without lymph node involvement and with a low Ki-67 proliferation index. The German experts added that multigene expression testing is only justified if – based on classic histopathological findings – it is not possible to decide whether chemotherapy is indicated.

Other votes at the St. Gallen Consensus Conference dealt with the currently available multigene expression analyses Onco-typeDX® Recurrence Score (RS), MammaPrint 70® (MP), Prosigna® PAM 50 Risk of Recurrence Score (ROR), EndoPredict® (EP) and the Breast Cancer Index (BCI), which is currently not available in Germany. Almost all questions went to a separate vote for each specific assay but results were similar overall.

The overwhelming majority of St. Gallen panelists viewed the above-listed and currently available multigene expression tests (RS, MP, ROR, EP, BCI) as an opportunity to obtain information which will be prognostically relevant for patients with ER-positive/HER2-negative early breast cancer, irrespective of whether patients had lymph node involvement or not. The German experts agree with the St. Gallen panelists but add the caveat that BCI is not relevant for Germany as it is currently not available there.

Multigene expression signatures and the indication for chemotherapy

For patients with node-negative cancer or 1–3 involved lymph nodes (pN0/1a), the currently available multigene expression tests can contribute to a more realistic assessment of prognosis, according to the majority vote of the St. Gallen panelists, an opinion with which the German experts concur. Whether it is indeed possible to base the decision for or against chemotherapy on the results of multigene expression testing was confirmed by 59% of the St. Gallen panelists for the RS test, 43% for the MammaPrint, 47% for the PAM 50 test, and 16% for the EPclin test. Differences in the assessment of the respective tests cannot be clearly deduced from the current data [9, 10]. It also does not correspond to the AGO guidelines on the clinical usefulness of the tests as an aid to decision-making for or against adjuvant chemotherapy, as the guidelines do not differentiate between the yes/no of individual tests but only assess the level of evidence [1].

Half of the St. Gallen panelists would use multigene expression analysis in patients with no lymph node involvement when considering whether extended endocrine therapy (more than five years) is indicated. The other half of the panelists was of the opinion that

multigene expression signatures do not offer a useful option when considering whether or not to prescribe extended endocrine therapy to these patients. The German experts agree with this and pointed out that multigene expression analysis primarily aims to make a prognostic statement rather than serve as the basis for treatment decisions. The current data do not allow any conclusions to be drawn on whether extended endocrine therapy offers benefits in cases with an increased risk of late recurrence (after 5–10 years and more).

Adjuvant Endocrine Therapy

Importance of ovarian function suppression

On the basis of the current data [11, 12], the St. Gallen panelists and the German experts agree that ovarian function suppression (OFS: GnRHa, bilateral ovariectomy) in addition to tamoxifen or an AI can be an option for premenopausal patients who have premenopausal estrogen levels in blood and/or have started to menstruate within eight months after (neo)adjuvant chemotherapy. The St. Gallen panelists had the opinion that additional adjuvant OFS was principally indicated in very young patients (< 35 years). The German experts criticize this exclusive focus on age as the data was obtained from retrospective, explorative analyses.

The German experts emphasize that the essential reason for prescribing OFS was persistent ovarian function after (neo)adjuvant chemotherapy and an increased risk of recurrence (e.g. four or more affected lymph nodes). They had the opinion that additional OFS should only be discussed with premenopausal patients who have an increased risk of recurrence.

If additional OFS is indicated, the question arises whether this should be administered in addition to tamoxifen or an aromatase inhibitor. The St. Gallen panelists and the German panel of experts agree that the combination of OFS plus an aromatase inhibitor could be an option for some patients. The St. Gallen vote therefore corresponds to the current AGO guidelines [1]. The German experts recommend that decision on additional OFS and on whether OFS should be combined with tamoxifen or with an aromatase inhibitor should be taken on a case-by-case basis after detailed discussions with the patient about benefits and risks. It should be noted that aromatase inhibitors must always be combined with OFS when treating premenopausal patients.

Endocrine treatment of postmenopausal patients

With regard to the treatment of postmenopausal patients, the German panel of experts agree with the St. Gallen panelists on all questions concerning adjuvant endocrine treatment. Thus, treatment with tamoxifen alone is still an adequate therapy option. However, especially for patients with increased risk, aromatase inhibitor-based therapy is the preferred option in the first five years. The German experts refer to the current AGO guidelines [1].

An increased risk which would support the upfront administration of an aromatase inhibitor would be, for example, a patient with lymph node involvement (pN+), G3 carcinoma or elevated Ki-67 expression. An aromatase inhibitor should be used upfront in patients with invasive lobular histology [13, 14]. After complet-

ing adjuvant chemotherapy, aromatase inhibitors should be considered if the patient is postmenopausal.

Extended adjuvant endocrine therapy

Extended adjuvant endocrine treatment for longer than five years is an important option for patients with increased risk of recurrence, irrespective of their menopausal status. For premenopausal patients who remain premenopausal during therapy, this means that they can be treated with tamoxifen for a total of ten years if they have an increased risk of recurrence at primary diagnosis. The German panel of experts agree with the majority vote of the St. Gallen panelists.

Treatment of postmenopausal patients who received tamoxifen over the first five years followed by an aromatase inhibitor should preferably consist of an aromatase inhibitor for a further 2–5 years if the patients have a moderate to high risk of recurrence. After they switch from tamoxifen to an aromatase inhibitor they will receive an aromatase inhibitor for at least five years and up to a maximum of eight years. The majority of St. Gallen panelists were opposed to further treatment with tamoxifen for patients with an increased risk of recurrence. The German panel of experts agree on most points. They once more refer to the current AGO guidelines [1] but consider that further treatment with tamoxifen could be an option for patients with poor tolerance of the aromatase inhibitor.

Patients who receive an aromatase inhibitor right from the start of treatment for a period of over five years as part of adjuvant endocrine therapy should continue to receive an aromatase inhibitor for a further three to five years if they have an increased risk of recurrence. The duration of extended endocrine therapy with an aromatase inhibitor should depend on the patient's tolerance of the aromatase inhibitor, the patient's individual risk profile, and the expected absolute benefit.

Even in this situation, the majority of the St. Gallen panelists opposed a switch to tamoxifen in the context of extended adjuvant endocrine therapy. As the upfront administration of an aromatase inhibitor is primarily an option for patients with an increased risk of recurrence, the St. Gallen panel also recommended not to stop endocrine adjuvant therapy after five years. The German panel of experts agree but again emphasize that continued treatment with tamoxifen can be an option when aromatase inhibitors are poorly tolerated [1]. As a general rule, there should be an early switch if there are significant side effects during endocrine therapy: If endocrine therapy is clearly indicated after the benefits and risks have been carefully weighed up, then any form of endocrine therapy is better than discontinuing treatment.

Adjuvant Chemotherapy

The St. Gallen vote on adjuvant chemotherapy focused on patients who might have a prognostic benefit from postoperative chemotherapy and should therefore receive chemotherapy postoperatively.

When considering patients without lymph node involvement (pN0), their prognosis as well as the decision for or against adjuvant chemotherapy should be based on immunohistochemical assessment of the tumor biology, which can be supplemented by

multigene expression testing in cases of uncertainty. *Relative* indications for adjuvant chemotherapy are poorly differentiated G3 tumors, lymph node involvement (pN+), high Ki-67 proliferation index, very young patient age (<35 years) and low hormone receptor (HR) expression (<10%). The German experts agree with the St. Gallen panelists and add that, based on these criteria, it is important to consider the risk-benefit-ratio.

The majority of St. Gallen panelists also considered extensive lymphovascular tumor invasion a relative indication for adjuvant chemotherapy. The German experts refer to the current AGO guidelines and state that lymphovascular tumor invasion is not an indication for chemotherapy [1]. From the German point of view chemotherapy is not necessarily indicated, if there are no additional risk factors.

Luminal B-like breast cancer *without* HER2 overexpression

For patients with luminal B-like breast cancer, a common question in clinical practice is whether adjuvant chemotherapy is indicated in addition to endocrine therapy. Adjuvant chemotherapy is indicated if there is an increased risk of recurrence [1]. The German experts agree with the majority of St. Gallen panelists that adjuvant chemotherapy should be recommended to patients with early luminal B-like breast cancer and prognostically unfavorable tumor biology confirmed by immunohistochemistry, irrespective of lymph node status. The German experts point out that in patients with no lymph node involvement tumor size should also be taken into account for treatment decision. If the primary tumor is very small (pT1a pN0) and there are no additional negative criteria, adjuvant chemotherapy is not indicated from the German point of view.

The St. Gallen panelists and the German experts confirm again that multigene expression analysis can be an effective method in patients with luminal-B-like breast cancer to determine whether the patient has an increased 10-year risk of metastasis and chemotherapy is therefore indicated. The majority of St. Gallen panelists voted that adjuvant chemotherapy is not necessary if RS is low as long as there is no lymph node involvement or if less than three nodes are involved. The German experts agree with this opinion and refer to the prospective data collected in the TAILORx trial which had a follow-up of five years [15]. The findings of this study have been confirmed by recent data from the West German Study Group (WSG) Phase III Plan B trial, which also had a follow-up of just under five years [16, 17].

The findings referred specifically to low-risk patients with an RS of less than 11 and no lymph node involvement or fewer than three involved lymph nodes and a follow-up of five years. If the RS score is intermediate, the St. Gallen panelists and the German specialists agree that avoiding adjuvant chemotherapy should only be considered in individual cases. For the final assessment (adjuvant chemotherapy indicated yes/no) it is necessary to wait until data on patients with intermediate scores are available from the TAILORx trial [15].

Initial prospective data on patients with 1–3 involved lymph nodes with a follow-up of just under five years are now also available for the MP score [18]. Based on preliminary data, adjuvant chemotherapy is not required for patients with 1–3 involved

lymph nodes if the risk profile is low according to MP score. No prospective data are available yet for ROR and EP. However, according to retrospective data from prospective studies with EP, the cumulative risk of metastasis for low risk, node-positive patients (just under 20% of patients) who receive only endocrine therapy is about 5%. This means that chemotherapy is not necessary in this patient population [9, 10]. The German specialists additionally point out that results of the votes of the St. Gallen panelists were not always consistent with previous votes on multi-gene expression signatures.

The St. Gallen panelists and the German experts agree that adjuvant chemotherapy should be anthracycline-based and taxane-based for patients with luminal B-like (HER2-negative) breast cancer.

Triple-negative breast cancer

For patients with early invasive ductal triple-negative breast cancer (TNBC: ER-, PR-, HER2-), the established anthracycline/taxane-based regimens are the adjuvant therapy of choice. This applies irrespective of the underlying breast cancer phenotype and tumor stage (I–III) and, in the opinion of the German specialists, also applies to patients with or without germline mutations (*BRCA1/2* mutation).

A narrow majority of the St. Gallen panelists had the opinion that TNBC is also an indication for platinum-based adjuvant chemotherapy. The German specialists do *not* agree with this vote as currently there is no data available which would justify the adjuvant administration of a platinum-based regimen. The German specialists therefore reject the use of *BRCA1/2* testing to determine whether carboplatin is indicated in an adjuvant setting. In the opinion of the German specialists, the decision whether adjuvant carboplatin is indicated must be taken on a case-by-case basis.

Patients with TNBC and no lymph node involvement who have a very small primary tumor (pT1a pN0) do not require adjuvant chemotherapy. The German panel of experts agree with the majority vote of the St. Gallen panelists on this point. They refer to data from recent trials [19–21] which showed a 10-year survival rate of more than 90% for TNBC patients with pT1a pN0 carcinoma. The German specialists additionally refer to the NCCN guidelines which also do not recommend chemotherapy for patients with pT1a carcinoma [22].

Dose-dense therapy (with G-CSF support) can be prescribed for patients with early TNBC, but the majority of the panelists voted that this is not the best option. The German panel of experts recommend that in general the treatment of patients with early TNBC should not primarily be adjuvant. If adjuvant chemotherapy is indicated, the AGO guidelines state that this treatment should be neoadjuvant [1]. The GeparSixto trial clearly showed that adding platinum in the neoadjuvant setting offered significant benefits for the pathologic complete response rate and for survival, irrespective of *BRCA* status [23].

HER2-positive breast cancer

Patients with early HER2-positive breast cancer as defined in the ASCO/CAP guidelines [24] and *with* lymph node involvement (N+) require chemotherapy in addition to anti-HER2 targeted treat-

ment. According to the majority vote of the St. Gallen panelists, the therapy should be anthracycline- and taxane-based. The German specialists agree but also point to the benefits associated with the anthracycline-free TCH regimen (docetaxel, cyclophosphamide, trastuzumab). The TCH regimen is an effective treatment option which is associated with better cardiac tolerability compared to anthracycline/taxane-based regimens. This has been shown by the recently published 10-year data of the BCIRG 006 study [25]. AGO Breast therefore recommends the TCH regime as a valid therapy option [1]. The German specialists and the St. Gallen panelists agree that adjuvant chemotherapy should include a taxane.

According to the majority vote of the St. Gallen panelists, adjuvant anti-HER2 targeted therapy is generally indicated from tumor stage pT1b in patients with HER2-positive breast cancer *without* lymph node involvement (N0). The majority of patients with pT1a carcinoma do not require anti-HER2 targeted therapy. The German specialists agree with the St. Gallen panelists and refer to the current AGO guidelines [1].

The majority vote of the St. Gallen panelists and the German specialists agree, that when adjuvant chemotherapy is indicated for pN0 carcinoma with HER2 overexpression, then weekly paclitaxel (twelve cycles) plus trastuzumab is a valid option. This applies to tumors with diameters of up to 2 cm. Due to limited available data, the results of the vote were less clear-cut for tumors with diameters of 2–3 cm. A majority of St. Gallen panelists considered the combination of docetaxel/cyclophosphamide plus trastuzumab a useful treatment option. The German specialists did *not* agree with this vote because the data for this regimen is still insufficient and the regimen is not recommended by AGO.

Adjuvant anti-HER2 targeted therapy

After receiving neoadjuvant chemotherapy in combination with trastuzumab/pertuzumab (dual antibody blockade), patients with HER2-positive breast cancer should receive further adjuvant treatment with trastuzumab. The duration of anti-HER2 targeted therapy should be one year including neoadjuvant therapy. At present, the adjuvant use of dual antibody blockade with trastuzumab/pertuzumab is not indicated. The German specialists agree with the respective majority votes of the St. Gallen panelists – but reserve their final opinion until the presentation of promising data from the APHINITY study at ASCO 2017. The data of APHINITY have been just published [26].

For the first time a vote was taken on the potential use of anti-HER2 targeted biosimilar antibodies. The majority of St. Gallen panelists considered biosimilars – once they have been approved for use – as an acceptable option for (neo)adjuvant therapy to treat HER2-positive early breast cancer. The German specialists agree. Positive data have been presented in the meantime at this year annual meeting of the American Society of Clinical Oncology (ASCO) 2017 [27, 28].

Neoadjuvant treatment for HER2-positive or triple-negative breast cancer

The German specialists welcome the majority vote of the St. Gallen panelists on the importance of neoadjuvant systemic therapy. A clear majority of the panelists confirmed that neoadju-

vant therapy should be the preferred therapy concept from stage II for patients with early HER2-positive breast cancer and patients with TNBC, even when breast-conserving surgery is possible. The St. Gallen vote on this issue corresponds to the AGO guidelines [1].

Patients with HER2-positive disease should receive taxane-based neoadjuvant chemotherapy plus anti-HER2 targeted treatment. More than 80% of panelists considered dual antibody blockade with pertuzumab/trastuzumab a recommended neoadjuvant therapy in combination with a taxane. Only around 30% would prescribe trastuzumab alone in addition to chemotherapy.

For patients with TNBC the St. Gallen panelists recommended neoadjuvant chemotherapy with platinum or an alkylating agent or sequential chemotherapy with anthracyclines and taxanes. The majority of St. Gallen panelists also considered albumin-bound nab-paclitaxel followed by epirubicin/cyclophosphamide (EC) to be a possible neoadjuvant regimen for patients with early TNBC. In the GeparSepto trial, this regimen almost doubled the rate of pathologic complete response rate in TNBC patients compared to the control arm where patients received conventional paclitaxel followed by epirubicin/cyclophosphamide [29]. The German experts agree with the respective voting outcomes on the neoadjuvant treatment of HER2-positive and triple-negative breast cancer.

Post-neoadjuvant Therapy

Options for post-neoadjuvant therapy are currently being evaluated to treat those cases where anthracycline-/taxane-based NACT does not result in pathologic complete remission (pCR). For patients with TNBC, 49% of the St. Gallen panelists recommended adjuvant treatment with capecitabine. The German specialists do *not* agree with this voting outcome which is based on data from the CREATE-X study [30].

The study [30] had shown a benefit for patients who received further treatment with capecitabine, but the neoadjuvant portion of the study is not sufficiently transparent. The precise composition of the study population is not clear, i.e., the doses and number of cycles used to treat patients, the number of patients who received reduced or delayed doses, and the number of patients who discontinued neoadjuvant treatment. The German specialists therefore recommend that adjuvant administration of capecitabine in the post-neoadjuvant setting of patients with TNBC should only be done in selected cases and after a detailed discussion of the risks and benefits with these high-risk patients.

The German specialists have the opinion that this should not just apply to the administration of capecitabine but also more generally when a patient with TNBC does not achieve pathologic complete remission (pCR) with neoadjuvant therapy. Outside of clinical trials, such patients should only receive post-neoadjuvant chemotherapy on a case-by-case basis. 55% of the St. Gallen panelists voted in favor of post-neoadjuvant chemotherapy.

Because of the more unfavorable prognosis of patients with TNBC who do not respond or show only limited response to neoadjuvant therapy, it was proposed that these patients should – where possible – receive treatment as part of a clinical trial. The

German experts agreed with the vote of the St. Gallen panel on this point.

Preventing alopecia

Alopecia is a common side effect of chemotherapy and much dreaded by patients. Results from recent studies appear to indicate that constant cooling of the scalp using specially designed cooling caps can reduce or even prevent hair loss in some patients [31]. The St. Gallen panelists and the German experts consider this to be an interesting, new, supportive development.

Adjuvant use of bone-modifying therapy

Adjuvant use of a bisphosphonate (zoledronic acid every six months or daily oral clodronate) in addition to adjuvant endocrine therapy in postmenopausal patients can extend the disease-free survival (DFS) period. This applies irrespective of the bone mineral density of the affected woman. However, a meta-analysis [32] of the adjuvant use of bisphosphonates showed that only patients with lymph node involvement benefited from bisphosphonate therapy.

This also applies to premenopausal patients if these patients receive a GnRH-analogue in addition to adjuvant endocrine therapy is new. This new recommendation is based on data from the Austrian ABCSG 12 study [33]. Due to the lack of data from corresponding studies, the adjuvant administration of denosumab (60 mg, every 6 months) is currently not indicated. The German specialists agree with the respective majority votes of the St. Gallen panelists.

Special Situations

Older patients

The German specialists agree with the vote by the St. Gallen panelists whereby the use of standard adjuvant (chemo-) therapy should not depend on patient age per se. The treatment decision must be guided by the patient's comorbidities, remaining life expectancy, stage of disease, and the patient's personal preferences. Similarly, the St. Gallen panelists do not give a maximum age after which adjuvant chemotherapy is no longer indicated.

This also applies to the indication for adjuvant radiotherapy in postmenopausal patients if the patient previously had breast-conserving surgery, adjuvant endocrine therapy is planned, and the patient is low-risk and has estrogen receptor-positive breast cancer without lymph node involvement. The indication for adjuvant radiation should be based on life expectancy (< 10 years yes/no) and on potential comorbidities.

Breast cancer and pregnancy

If the patient wishes to become pregnant after she has completed primary therapy, adjuvant endocrine treatment can be paused after an in-depth discussion of the risks and benefits with the patient. The current data recommend that patients should receive endocrine adjuvant therapy for at least 18 months prior to becoming pregnant. The German specialists point out that the benefit of adjuvant endocrine therapy is correlated with the duration

of therapy. Moreover, there are currently no data on the oncologic safety of pausing adjuvant endocrine therapy. This must explicitly be discussed with the patient. In principle, the patient's individual risk should be referred to in the consultation. If the patient wishes to have children, therapy planning should include encouraging the patient to visit a fertility clinic.

Male breast cancer

Male breast cancer is usually estrogen receptor-positive, and standard therapy consists of adjuvant treatment with tamoxifen. According to the majority vote of the St. Gallen panelists, a vote with which the German experts concur, adjuvant treatment with an aromatase inhibitor in combination with an LHRH-analog is also an option. Treatment with only an aromatase inhibitor is not an option.

Is Genetic Testing for High-risk Mutations Useful?

The question whether genetic testing should be generally recommended or recommended to certain groups has been discussed many times. The general principle is that the indication for genetic testing is only relative as long as it does not have therapeutic/prophylactic consequences. Voting at the St. Gallen conference focused on the genetic testing of high-risk mutations such as *BRCA1/2* testing. The panelists voted almost unanimously in favor of recommending genetic testing to or discussing it with women from high-risk families (clear positive family history).

The majority of St. Gallen panelists voted in favor of genetic testing to patients who are younger than 40 years at primary diagnosis. The German experts point out that this differs from the AGO guidelines [1]. AGO recommends general testing without a positive family history for patients under the age of 36 years [1]. This lower age is based on the at least 10% higher probability of *BRCA1/2* mutations in these women.

The German specialists agree with the St. Gallen panelists that an age cut-off of less than 50 years is unsuitable for recommending genetic testing to patients without a familial history. There is therefore no general indication that patients below the age of 50 years should be tested. The situation is different for patients with TNBC. The St. Gallen panelists and the German specialists recommend that these patients undergo genetic testing if they are younger than 60 years of age at primary diagnosis.

The St. Gallen panelists and the German specialists agree that confirmation of *BRCA1/2* mutation will affect the decision on surgical treatment as well as further prophylactic measures. The majority of St. Gallen panelists also believe that this will affect systemic therapy. The German specialists do *not* agree with the voting result for early breast cancer and refer to the AGO recommendations on neoadjuvant and post-neoadjuvant therapy in patients with TNBC [1]. The group of German specialists add that testing for the high-risk *PALB2* mutation in addition to *BRCA1/2* testing could also be an option if there is a positive familial history and the patient is ≤ 35 years of age.

Targeted Intervention Through Diet and Increased Physical Exercise?

The German experts do *not* agree with the majority vote of the St. Gallen panelists who stated that patients with breast cancer require a special diet and should do more exercise. In general, patients should try not to be significantly overweight, and they should be supported in their endeavor at healthy physical exercise and a balanced diet to improve overall well-being. However, the German specialists have the opinion that lifestyle interventions over and above normal follow-up are not recommended, as there is no evidence of a significant reduction in the risk of recurrence and no positive impact on breast cancer-specific survival rates has been established.

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