Primary Therapy of Patients with Early Breast Cancer: Evidence, Controversies, Consensus

Opinions of German Specialists to the 14th St. Gallen International Breast Cancer Conference 2015 (Vienna 2015)

Primärtherapie bei Patientinnen mit Mammakarzinom: Evidenz, Kontroversen, Konsens

Meinungsbild deutscher Experten zur 14. Internationalen St.-Gallen-Konsensuskonferenz (Wien 2015)

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Key words
- breast cancer
- St. Gallen consensus
- adjuvant therapy
- neoadjuvant therapy
- multigene signatures

Schlüsselwörter
- Mammakarzinom
- St.-Gallen-Konsensus
- adjuvante Therapie
- neoadjuvante Therapie
- Multigensignaturen

Deutschsprachige Zusatzinformationen online abrufbar unter: www.thieme-connect.de/ejournals/toc/gebfra

received 2.5.2015
revised 17.5.2015
accepted 17.5.2015

Bibliography
DOI http://dx.doi.org/10.1055/s-0035-1546120
Published online 17.06.2015
Geburtsh Frauenheilk 2015; 75: 556–565 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0016-5751

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Abstract

For the first time, this year's St. Gallen International Consensus Conference on the treatment of patients with primary breast cancer, which takes place every two years, was held not in St. Gallen (Switzerland) but – for logistical reasons – in Vienna (Austria) under its usual name. The 2015 St. Gallen International Consensus Conference was the 14th of its kind. As the international panel of the St. Gallen conference consists of experts from different countries, the consensus mirrors an international cross-section of opinions. From a German perspective, it was considered useful to translate the results of the votes of the St. Gallen conference into practical suggestions, particularly in light of the recently updated treatment guideline of the Gynecologic Oncology Group (AGO-Mamma 2015) in Germany. A German group consisting of 14 breast cancer experts, three of whom are members of the international St. Gallen panel, has therefore provided comments on the results of this year's votes at the 2015 St. Gallen Consensus Conference and their impact on clinical care in Germany. The 14th St. Gallen conference once again focused on surgery of the breast and the axilla, radio-oncologic and systemic treatment options for primary breast cancer depending on tumor biology, and the clinical use of multigene assays. The conference also considered targeted therapies for older and for younger patients, including the diagnosis/treatment of breast cancer during and after pregnancy and the preservation of fertility.

Zusammenfassung

Die alle 2 Jahre stattfindende internationale Konsensuskonferenz in St. Gallen zur Behandlung von Patientinnen mit primärem Mammakarzinom wurde dieses Jahr zum 14. Mal veranstaltet und fand aus logistischen Gründen erstmals nicht in St. Gallen (Schweiz), sondern unter gleichem Namen in Wien (Österreich) statt. Da sich das internationale Panel in St. Gallen aus Experten unterschiedlicher Länder zusammensetzt, spiegelt der Konsensus ein internationales Meinungsbild wider. Aus deutscher Sicht erscheint es daher sinnvoll, die Abstimmungsergebnisse vor dem Hintergrund der aktualisierten Therapieempfehlungen der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-Mamma 2015) für den Therapiealltag in Deutschland zu konkretisieren. Eine deutsche Arbeitsgruppe aus 14 Brustkrebsexperten, von denen 3 Mitglieder des internationalen St.-Gallen-Panels sind, hat daher die Abstimmungsergebnisse der St.-Gallen-Konsensuskonferenz 2015 für den Klinikalltag in Deutschland zeitnah kommentiert. Inhaltliche Schwerpunkte der 14. St.-Gallen-Konferenz waren erneut operative Fragestellungen der Brust und der Axilla, radioonkologische und systemische Therapieoptionen des primären Mammakarzinoms unter Berücksichtigung der Tumorbiologie sowie der klinische Einsatz von Multigen-Assays. Ein Fokus lag zudem auf der Behandlung älterer und jüngerer Patientinnen, inkl. spezieller Situationen wie die Diagnostik/Behandlung eines Mammakarzinoms in und nach einer Schwangerschaft sowie dem Erhalt der Fertilität.

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Introduction

The St. Gallen Consensus Conference on the treatment of patients with primary breast cancer continues to be of global importance. The panel of this year's 14th St. Gallen Consensus conference consisted of 49 experts from 19 different countries, among them three representatives from Germany. The recommendations were based on the majority votes of the panelists. The panelists consisted of experts from different specialties and continents, most with very different healthcare systems and resources. Under these conditions, the consensus achieved largely mirrors the opinions of the experts, with individual opinions and – in the final instance – the overall opinions based on published evidence-based data. The main publication of this year's St. Gallen Consensus Conference is available since May 12th in Annals of Oncology [1]. Nevertheless, it was considered useful to translate the results of the St. Gallen conference into practical suggestions, particularly in view of the updated treatment guidelines of the Breast Commission of the Gynecologic Oncology Group (AGO) published in 2015 [1].

Basis of the St. Gallen Consensus

In addition to topics like (neo)adjuvant systemic therapy, the St. Gallen Consensus also focused on developments in loco-regional surgery and radiation therapy. Another increasingly important topic were differences in the biology of breast cancer disease and the impact on prognosis and treatment. The aim of the conference was to summarise proposals, supported by the majority of panelists, and to achieve a consensus for clinical practice. If this was not possible, the aim was to develop a pragmatic solution which took specific national differences into account and to define areas which should be clarified in future controlled clinical trials.

The panelists answered the questions by voting "yes" (agreement), "no" (rejection) or "abstain" (insufficient data, no opinion possible). Other questions required the panelists to choose between several options.

Surgical Therapy

The main issues in the surgical treatment for primary breast cancer at this year's St. Gallen conference were resection margins and surgery of the axilla, both in primary treatment and after neoadjuvant chemotherapy.

Resection margin after breast-conserving surgery (BCS)

If a patient with invasive breast cancer undergoes breast-conserving surgery followed by adjuvant radiation and systemic treatment, the resection margin after excision must be tumor-free (R0) (i.e., no invasive tumor cells on the inked margin). The German specialists agreed with the majority vote of the St. Gallen panelists that no additional safety margin is necessary. According to the majority vote in St. Gallen, breast-conserving surgery is possible to treat both multifocal (yes votes: 71%) and multicentric (unilateral; yes votes: 80%) invasive breast cancer – provided that the resection margin is tumor-free and surgery is followed by adjuvant radiation therapy. However, the German experts specified their agreement by referring to the recommendations for multicentric (unilateral) breast cancer in the current 2015 AGO guidelines [2]. The guidelines state that the decision for breast-conserving surgery in patients with primary breast cancer must be taken on an individual basis and depends on the proximity of individual lesions. Discussions with the patient should consider both oncological safety and satisfactory cosmetic outcome after surgery. Mastectomy (skin-sparing or subcutaneous) with immediate reconstruction (e.g. using an implant) (with or without mesh) is also possible in individual cases.

The German group agreed with the majority vote of the St. Gallen panelists that the extent of the resection margin does not depend on tumor biology and that no additional (larger) safety margin is necessary in younger patients (< 40 years) or patients with lobular breast cancer. This also applies to surgery after neoadjuvant chemotherapy (NACT) and cancer with extensive intraductal component. However, when treating patients with ductal carcinoma in situ (DCIS) the German group recommends a resection margin of at least 2 mm [2]. The German group does not agree with the majority vote of the St. Gallen panelists. To ensure adequate clinical and pathological evaluation of findings, the German group recommends discussing the preoperative and postoperative situation in an interdisciplinary tumor board using the most recent mammography and breast and axillary sonography.

Surgical procedure after NACT

The St. Gallen panel offered no recommendations for the treatment of the axilla before or after neoadjuvant therapy in patients with non-palpable axillary nodes which appear normal on ultrasound. The German group again refers to the current 2015 AGO recommendations for therapy [2] which offer two choices in this context (i.e., cN0 prior to NACT): sentinel lymph node biopsy (SNB: sentinel node biopsy) performed either prior to (during port placement) or after neoadjuvant therapy. The preferred approach is to perform SNB prior to NACT (AGO LoE 2b GR B + vs. LoE 2a GR B ± after NACT). If there is no involvement of the sentinel lymph nodes, axillary lymph node dissection (ALND) after NACT is not required.

The issue whether SNB is sufficient in a patient with palpable and/or sonographically suspicious lymph nodes (cN+) at primary diagnosis, which are then found to be clinically/sonographically normal (ycN0) after NACT (down-staging), and whether or when complete ALND is necessary was discussed at length. The majority of St. Gallen panelists stated that SNB is an adequate approach after NACT in these patients. If involvement of one or more sentinel lymph nodes is confirmed, the St. Gallen panel recommends ALND.

The German group agrees with this recommendation, based on data of the ACOSOG Z1071 study [3]. It was additionally noted that clinically suspicious lymph nodes should be evaluated **prior** to NACT using cytology (fine needle aspiration) or preferably histology (core needle biopsy) and marked with a clip if possible. After performing NACT (ycN0), the German group recommends deciding on an individual basis whether SNB is sufficient or whether ALND is indicated [2]. In the opinion of the German group, the reliability of SNB after NACT (cN+ prior to NACT) depends on the number of resected lymph nodes. In the two studies carried out to investigate this question, the false negative rate for 1–2 investigated lymph nodes (no tumor involvement) was between 18 and 21% and only dropped below 10% after three or more lymph nodes were resected and investigated

The German group pointed out that the false negative rate (FNR: negative SN but positive axilla) will only be the same as the FNR for primary surgery if three resected lymph nodes are tumor-free. This corresponds to the internationally accepted false negative rate for primary surgery. ALND can therefore be replaced by

Table 1 Recommendations of the AGO Guideline Commission 2015 on the surgical treatment of the axilla before and after NACT [2] (SLNB: sentinel lymph node biopsy, NACT: neoadjuvant chemotherapy, LoE: level of evidence, GR: grade of recommendation, BCS: breast-conserving surgery, ALND: axillary lymph node dissection, CNB: core needle biopsy, FNA: fine needle aspiration, ACOSOG: American College of Surgeons Oncology Group, SNB: sentinel node biopsy).

				Oxford/AGO LoE/GR		
SLNB prior to or after NACT in cN0 patients						
SLNB before NACT				2b	B	+
SLNB after NACT*				**2b**	B	±
Additional surgery depending on SLNB						
cN status (before NACT)	pN status (before NACT)	cN status (after NACT)	Surgical approach			
cN0	pN0(sn)	–	Nil	1a	A	+
cN0	pN+(sn) corresponding to ACOSOG Z11**	ycN0	ALND	3	B	±
cN0	pN+(sn) not corresponding to ACOSOG**	ycN0	ALND	2b	B	+
cN+	cN+ (CNB/FNA)	ycN0	SNB*	**2b**	B	±
			ALND	2b	B	+
		ycN+ (CNB/FNA)	ALND	2b	B	++

* **technetium + patent blue**; ** T1/T2, BCS, 1–2 SLN pos., tangential field whole-breast radiation

SNB alone. However, in patients with histologically proven lymph node involvement detected prior to NACT and 1–2 involved (sentinel) lymph nodes after NACT (ypN+ SN) the German panel recommends carrying out ALND based on the most recent study data [3–5] (**Table 1**). The consensus is also that the primary tumor should be resected within the new tumor margins after NACT.

The German group agrees with the St. Gallen panelists that ALND is not necessary at primary surgery in patients with 1–2 lymph nodes with proven macro-metastatic disease if the patient meets the ACOSOG Z0011 criteria [6]: tumor less than 5 cm (pT1–2), no extracapsular lymph node involvement, breast-conserving surgery, adequate adjuvant systemic therapy, tangential field radiation. If mastectomy is performed, ALND is indicated if the sentinel lymph nodes are involved with macro-metastatic disease. Alternatively, ALND is not required in patients with mastectomy for whom radiation therapy is planned after surgery. The options should be discussed with the patient and weighed up by an interdisciplinary tumor board with the decision taken on an individual basis. The German group bases its assessment on the current 2015 AGO guidelines [2].

Adjuvant Radiation Therapy

Partial breast irradiation after breast-conserving surgery

The majority of St. Gallen panelists consider partial breast radiation to be the definitive radiotherapy (without whole-breast radiation) for patients who are suitable according to the criteria of ASTRO (American Society of Radiation-Oncology) and ESTRO (European Society for Radiotherapy & Oncology) [7–10]. Patients considered by ASTRO as "suitable" must meet the following criteria: ≥ 60 years, no BRCA 1/2 mutation, HR+, tumor ≤ 2 cm (T1), tumor-free resection margin ≥ 2 mm, N0, no lymph node invasion, unicentric/unifocal disease, invasive-ductal or other favorable histology (mucinous, tubular, colloid), no extensive intraductal component. Partial breast irradiation alone is not indicated in patients with DCIS or patients who have previously undergone neoadjuvant chemotherapy. However, some studies have reported a positive effect of IORT (intraoperative radiotherapy) as a prior boost after NACT. The criteria proposed by ESTRO differ only slightly from those of ASTRO, with ESTRO recommending a different age limit (≥ 50 years) and T stage (pT1–2). Otherwise the ASTRO criteria apply [7–10].

The St. Gallen panel recommends that patients classified by ESTRO as "intermediate" and by ASTRO as "cautionary" should not receive partial breast irradiation, as the results of different studies are not yet available. The St. Gallen vote, which points out that partial breast irradiation could be an option not limited to patients with favorable tumor biology, is imprecise as the patient selection criteria were not adequately defined. Further clinical studies are recommended.

The German group refers to the current 2015 AGO guidelines [2]. Partial breast irradation alone is not a standard in Germany. It is used in individual cases to treat patients with favorable tumor biology and low risk of recurrence (pT1 pN0 R0 G1–2, HR+, HER2–, non-lobular tumor, > 50 years, no extensive DCIS) as interstitial brachytherapy or intraoperative irradiation using 50 kV source or electrons (LOE 1b B ±). It can also be administered intraoperatively as boost prior to whole-breast irradiation (LOE 2b B +) to reduce the number of radiotherapy fractions.

Hypofractionated radiation after BCS

In the opinion of the German specialists, low risk patients aged > 65 years should receive hypofractionated radiation (without boost; 2.67 Gy delivered in 15–16 fractions) after BCS rather than standard fractionated radiation (2 Gy in 25 fractions). In higher-risk patients and patients aged between 40 and 65 years, conventional radiation therapy (with integrated or sequential boost) or hypofractionated radiation with sequential boost are both valid therapy options. The AGO states that hypofractionated radiation is not indicated for women below the age of 40 years treated with radiotherapy of the supra-/infraclavicular lymphatic region; the AGO recommends to treat these patients using conventional radiotherapy (**Table 2**) [2].

The majority vote in St. Gallen goes far beyond the German therapy recommendations to this point, favouring hypofractionated irradiation; the majority of St. Gallen panelists recommend hypofractionated irradiation irrespective of age. According to the St. Gallen vote, hypofractionated irradiation therapy is also indicated for patients, irrespective of age, who had prior adjuvant chemotherapy and for patients with axillary lymph node involvement in whom radiation of lymphatic drainage areas is indicated.

Radiation of regional lymph nodes after BCS

All of the St. Gallen panelists and the German group agree that patients without lymph node involvement (pN0) do not require

Table 2 Recommendations of the AGO Guideline Commission 2015 for radiation therapy after breast-conserving surgery [2] (LoE: level of evidence, RT: radiation therapy, BCS: breast-conserving surgery).

	Radiation therapy (RT) after breast-conserving surgery (BCS; invasive cancer): radiation of the breast	
	LoE 1b B	**AGO ++**
< 40 years	Conventional RT (25–28 fractions) with integrated or sequential boost	
40–65 years	Conventional RT with integrated or sequential boost, or hypofractionated RT with sequential boost	
> 65 years	Low risk:	Hypofractionated RT without boost (15–16 fractions)
	High risk:	RT similar to women aged 40–65 years
Elderly patients	Individual counseling which may include omission of RT according to individual risk after geriatric assessment	
Any age (regional lymph nodes)	If additional radiation of the regional lymph nodes, conventional fractionated RT (25–28 fractions).	

Participation in clinical trials recommended

adjuvant radiotherapy of the regional lymph nodes after BCS. Radiation of the breast alone is not sufficient in patients with lymph node involvement. The German group agrees with the majority of St. Gallen panelists that radiation of the regional lymph nodes is additionally indicated in these patients, but without radiation of the internal mammary lymph nodes; however, the German group again refers to the current AGO guidelines of 2015. According to these guidelines, it is important to differentiate between patients with involvement of 1–3 lymph nodes and patients where ≥ 4 nodes are involved. Additional irradiation of the regional lymph nodes is indicated when four or more lymph nodes are affected. The data on 1–3 involved lymph nodes has been interpreted differently by the German Society of Radiooncology (DEGRO) and the AGO. The DEGRO considers radiotherapy of the chest wall indicated if 1–3 lymph nodes are affected, while the AGO only considers radiotherapy to be indicated in these cases if the patients have additional risk factors such as young age and aggressive tumor biology.

Radiotherapy after mastectomy

It is important to differentiate between the indication for radiotherapy of the thorax and radiotherapy of the lymphatic drainage area. For radiation of the regional lymph nodes, the same rules apply as for BCS. According to the AGO recommendation [2] the standard therapy for patients after mastectomy consists of adjuvant radiation of the chest wall in patients with T3/T4 tumors (with the exception of "low risk" patients), patients with lymph node involvement (the DEGRO recommendation is radiotherapy for all patients, irrespective of risk, while the AGO differentiates between high and low risk patients) and patients in whom R0 resection was not possible.

The majority of St. Gallen panelists also confirmed that adjuvant radiotherapy of the chest wall is indicated after mastectomy in patients with tumors larger than 5 cm. The panelists saw no general indication for adjuvant radiotherapy for patients with 1–3 involved lymph nodes but recommended radiation therapy for patients with unfavorable tumor biology. Half of the panelists also considered that radiotherapy was indicated for younger women (< 40 years) with 1–3 involved lymph nodes. The German group agrees in principle with the results of this vote and points out that the indication for risk-adapted radiotherapy is in accordance with AGO guidelines [2], particularly when treating patients with 1–3 involved axillary lymph nodes. The AGO defines risk as follows: it is assumed that there is a low risk of local recurrence if at least three of the following four favorable criteria are present: pT1, stage 1 cancer, HR-positive, HER2-negative. Younger age (< 45 years), medial tumor location and negative ER status are assumed to be correlated with an increased risk of local recurrence. The St. Gallen panelists additionally consider that adjuvant radiotherapy after mastectomy is indicated for patients with positive SNB who did not have ALND. However, the panelists state that radiotherapy is not indicated in patients with tumor-free lymph nodes (pN0) after ALND if no SNB was performed and fewer than eight lymph nodes were resected and examined histologically. The German group again refers to the AGO guidelines in 2015 [2], to adapt the indication for adjuvant radiotherapy after mastectomy in pT3 pN0 patients to the patient's individual risk. If the patient has no additional risk factors, radiotherapy is not mandatory; adjuvant radiation therapy is strongly recommended (LoE 1a A++) for younger higher-risk women (e.g. with an unfavorable tumor biology).

If adjuvant radiotherapy is indicated after mastectomy, the majority of St. Gallen panelists voted to include radiation of the regional lymph nodes in addition to the chest wall but without radiation of the internal mammary nodes. However, one third of the panelists abstained from voting.

According to the AGO guidelines, adjuvant irradiation of the internal mammary lymph node chain can be considered for stage pN1–2 hormone-positive lesions, based on the data of the EORTC trial reported by Poortmans et al. [11], if the patient has an overall higher risk and underwent prior adjuvant chemotherapy (LoE 1 b^{abstract} B +). For higher-risk pN0 patients with centrally or medially located cancers, the decision should be individually (AGO 2015 guidelines: LoE 1b B ±). According to the AGO guidelines, adjuvant irradiation of the internal mammary lymph node chain should not be carried out in patients with cardiac risk factors or receiving trastuzumab treatment [2].

The St. Gallen panel recommends irradiation of the chest wall and the regional lymph nodes (excluding the internal mammary lymph nodes postoperatively) in women who undergo reconstructive surgery. The German group recommends that adjuvant radiotherapy should be discussed with the patient and the reconstructive surgeon prior to surgery. Moreover, the tumor biology must also be taken into account. The decision must be weighed carefully in node-negative patients or patients with 1–3 involved lymph nodes and discussed with the patient. On the one hand, irradiation of the implant increases the risk of capsular contracture; on the other hand, prior irradiation of the chest wall is associated with significantly higher late complications after reconstruction.

Otherwise, the German group agrees with the majority vote of the St. Gallen panelists whereby the indication for postoperative radiotherapy after neoadjuvant chemotherapy (NACT) must be based on the initial tumor stage, i.e. prior to NACT, and must take into account lymph node involvement (verified histologically by core needle biopsy) or positive sentinel lymph nodes. The German experts strongly support studies with reduced irradiation of the chest wall and the regional lymph nodes. This applies particularly to patients who responded well to NACT with complete pathological remission of the lymph nodes (down-staging). This situation is very common in clinical practice (before NACT: pN+; after NACT: ypN0).

Table 3 Opinions of the St. Gallen panelists on the suitability of multigene expression testing to provide prognostic and predictive information for luminal breast cancer ([1], modified by H. H. Kreipe, Hanover) (PAM 50 ROR: PAM 50 risk of recurrence). Figures indicate the percentage of "yes"-votes of the St. Gallen panelists..

Gene expression testing in luminal breast cancer: St. Gallen consensus 2015			
Test name/% approval	**Prognosis for < 5 years**	**Prognosis for > 5 years**	**Indication for chemotherapy**
Prediction Analysis of Microarrays 50 (PAM 50) – Risk of Recurrence (ROR) (Prosigna®)	92 %[1]	63 %[1]	38 %[3]
Recurrence Score (Oncotype Dx®)	83 %[1]	44 %[3]	80 %[1,2]
Endopredict®	70 %[1]	38 %[3]	38 %
Mammaprint®	81 %[1]	33 %[3]	30 %[3]

Approved with the following restrictions: [1] Should only be used in selected patients if all other criteria are insufficient for clinical decision-making. [2] Validated clinical data only available for this assay. [3] The opinion expressed here differs significantly from the published evidence (see AGO).

Pathology

In clinical practice, the subtypes luminal A and luminal B (HER2-negative) are usually based on the estrogen receptor (ER) and progesterone receptor (PR) status as well as levels of the proliferation marker Ki-67. Determination of hormone receptor (HR) and Ki-67 status must be done in a quality-assured laboratory. If Ki-67 determination is done by the hospital's pathology lab, the laboratory must be familiar with the reference standards. If Ki-67 is used for differentiation, then one group of St. Gallen panelists (36.4%) proposed a Ki-67 level of at least 20–29% as cut-off for luminal-B cancer. The German group wishes to point out that the Ki-67 level in luminal A subtype breast cancers is likely to be ≤ 10%, even if at present there is no consensus on a cut-off value. There is still some uncertainty on therapeutic consequences of Ki-67 levels between 10 and 30%.

Risk stratification based on multigene expression testing can **currently** not replace immunohistochemical assessment in the determination of the intrinsic subtype but can be used to complement immunohistochemistry in doubtful cases. All panelists agree that when differentiating between luminal A and luminal B (HER2-negative) breast cancer types, multigene expression testing is only useful in doubtful cases (e.g. intermediate Ki-67 levels between 10–35%).

The importance of tumor-infiltrating lymphocytes in triple-negative and HER2-positive breast cancer is **currently** being discussed. According to the majority vote of the St. Gallen panelists, the extent of lymphocyte infiltration cannot serve as either a prognostic or a predicative marker. The German group agrees. However, recent research appears to show that in the near future tumor-infiltrating lymphocytes could become important for prediction and possibly therapy [12].

Importance of multigene expression signatures

When treating patients with hormone-sensitive primary breast cancer, the question whether the patient requires chemotherapy prior to endocrine treatment is very important. The St. Gallen panel voted individually on the prognostic and predictive value of the following, currently available multigene assays: OncotypeDX® Recurrence Score (RS), MammaPrint 70® (MP), Prosigna® PAM 50 Risk of Recurrence (ROR), EndoPredict® (EP) and Breast Cancer Index (BCI).

With votes ranging from 58.3 to 92.9%, the St. Gallen panelists viewed multigene assays (RS, ROR, EP) as a means of providing patients with ER-positive/HER2-negative breast cancer with prognostically relevant information about the next five years. However, the majority of the panelists stated that the assays did not provide prognostically relevant information over and above the period of five years. The only positive majority vote (63.2%) in this context was for the ROR Score; 40% of panelists voted for the EP test. The German group would like to point out that the available data for EP and ROR are similarly valid with regard to estimating the risk of recurrence in HR-positive postmenopausal patients more than 5 years after primary diagnosis.

The only test acknowledged by the majority (80.5%) of St. Gallen panelists as providing reliable prognostic information on the benefits of additional adjuvant chemotherapy was the Oncotype DX. From the perspective of the German group there are currently no findings from prospective studies which prove the predictive significance of any multigene assay; the data for the Oncotype DX test based only on retrospective studies [2]. In principle, the St. Gallen panelists recommend that patients with node-negative (HR-positive, HER2-negative) cancer should either undergo determination of Ki-67 levels or multigene testing if it is unclear whether chemotherapy is indicated.

From a German perspective, multigene testing is only justified if the histopathological findings do not clearly show whether chemotherapy is indicated or not. The opinion of the St. Gallen panelists on the clinical use of the above-listed multigene assays is summarized in **Table 3**. The German group wishes to point out that the published evidence evaluated by the AGO differs significantly from that of the St. Gallen panel [2].

Endocrine Treatment

The questions on endocrine therapy focused on the additional use of ovarian function suppression (OFS) in premenopausal patients and the duration of endocrine therapy.

Additional OFS for premenopausal patients?

Based on recent data from the SOFT study [13], the St. Gallen panelists and the German group agreed that additional OFS (GnRHa, bilateral salpingoophorectomy, bilateral ovarian irradiation) can be an option for young (≤ 35 years) premenopausal patients who have premenopausal estrogen serum levels after (neo)adjuvant chemotherapy. However, the German group would like to point out that the SOFT study defined "premenopausal" as menstruation or evidence of premenopausal estradiol serum levels within eight months of completing (neo)adjuvant chemotherapy. Endocrine therapy must be chosen based on individual risk and after taking possible side-effects into account. The potential range of side-effects must be discussed with the patient. Combining aromatase inhibitors or tamoxifen with OFS is associated with

significantly higher side-effects than tamoxifen alone; side-effects can include loss of libido, joint pain, osteoporosis, mood swings, depression, cognitive impairment, etc. It is important that the patient is given full and detailed information on these points.

The majority of St. Gallen panelists also considered additional OFS to be indicated if four or more lymph nodes are involved (89.7%), if the patient has G3 cancer (55.9%), and if multigene testing indicates that the patient has higher risk (60%). The German group does not agree with these statements. In the opinion of the German experts, grading, lymph node involvement and multigene test results are not sufficient to justify additional OFS as no prospective data are currently available. The German group considers for patients with these criteria adjuvant chemotherapy.

If additional OFS is indicated, the panelists discussed whether it should be administered in addition to tamoxifen therapy or with an aromatase inhibitor. The majority of St. Gallen panelists voted for a combination therapy with an aromatase inhibitor if the patient is very young (≤ 35 years: 59.4%), if the patient has four or more involved lymph nodes (92.5%), if multigene testing shows that the patient has a higher risk (65.8%), and – with a small majority (57.1%) – if the patient has G3 cancer. A narrow majority of panelists (51.2%) voted *against* a combination therapy with aromatase inhibitors when treating patients who are still premenopausal after adjuvant chemotherapy.

The German group does not agree with either of these votes and wishes to point out that the questions voted upon were based on a retrospective evaluation of the SOFT study [13], which is not described in detail in the full publication. The SOFT study does not currently provide any data on overall survival. Although the patient populations are not completely identical and this limits their use for comparisons, (adjuvant chemotherapy 10 vs. ca. 50%), the data from the SOFT/TEXT study findings are in contradiction to the ABCSG12 study [14]. According to the latter study, survival of patients who received anastrozole and GnRH over three years was poorer (HR 1.63; 95% CI: 1.05–1.45; p = 0,030) after a median follow-up time of 9.4 years compared to tamoxifen and GnRH analogs. The German group states that the decision whether OFS should be recommended in combination with tamoxifen or an aromatase inhibitor should be individually decided after a detailed discussion with the patient and careful weighing up of the benefits, risks and side-effects.

The St. Gallen panelists voted with a narrow majority (56.7%) for OFS over five years. The German group recommends an initial period of 2–3 years and a maximum period of OFS administration of five years, depending on the side-effects and risks. If treatment includes an aromatase inhibitor, e.g. in patients for whom tamoxifen is absolutely contraindicated, therapy should always be combined with OFS in premenopausal patients.

Postmenopausal patients

The St. Gallen panelists and the German group agree that treatment with tamoxifen is still an adequate option for postmenopausal patients with hormone-sensitive breast cancer. However, aromatase inhibitors are the preferred option in higher risk patients, e.g. patients with four or more involved lymph nodes, or with G3 cancer and higher Ki-67 levels, or with evidence of HER2 overexpression. The age of the patient plays no role in the decision whether to administer tamoxifen or an aromatase inhibitor.

If an aromatase inhibitor is indicated, it should be given upfront in higher risk patients. A switch to tamoxifen after two years is an option for patients who do not tolerate the aromatase inhibitor well. The St. Gallen panelists did not consider the question whether aromatase inhibitors should be the preferred option when treating patients with lobular cancer (compared to ductal carcinoma). After considering the data from the ATAC and BIG 1–98 trials, the German group clearly recommends aromatase inhibitor therapy for patients with lobular carcinoma [15, 16].

Therapy over a period of ten years?

Extended endocrine therapy over a period of ten years is an important option in high-risk pre- and postmenopausal patients with hormone-sensitive breast cancer. The St. Gallen panelists proposed continuing tamoxifen therapy for a further five years after an initial five years of adjuvant tamoxifen treatment in premenopausal patients, irrespective of the patient's current menopausal status, if the patient has lymph node involvement or G3 cancer and higher Ki-67 levels. In postmenopausal patients the options are either to continue with tamoxifen or with an aromatase inhibitor for a further 5 years.

The German group agrees with the vote of St. Gallen panelists on patients with lymph node involvement and recommends tamoxifen therapy for premenopausal patients and tamoxifen or an aromatase inhibitor for postmenopausal patients. Other factors such as tumor grade and Ki-67 levels have not had similar validation with regard to an increased risk of recurrence after 5 years' endocrine therapy. In the opinion of the German experts, continued endocrine therapy in patients with these factors is an individual decision. This applies irrespective of the patient's menopausal status.

Irrespective of menopausal status, there is only a relative indication for prolonging endocrine therapy over and above a period of five years in patients without lymph node involvement. However, patients who were premenopausal at the start of therapy and became postmenopausal during therapy should receive endocrine therapy even after 5 years of tamoxifen therapy if they have an increased risk of recurrence.

Extended endocrine therapy

If extended endocrine therapy (> 5 years) is indicated for patients who have received two years' tamoxifen therapy followed by three years' therapy with an aromatase inhibitor, the majority of St. Gallen panelists voted that treatment for these patients should consist either of a further five years of tamoxifen or a further two years of an aromatase inhibitor. The German group agrees. They would like to point out that both a 2-year continued treatment with an aromatase inhibitor or a further five years treatment with tamoxifen can be clinically useful, even if there is no reliable data for either of the strategies and no data which offers a direct comparison of both strategies. There is currently no evidence for the benefit of aromatase inhibitor therapy administered for more than five years [17]. However, a decision to continue treatment can be taken together with the patient based on individual considerations.

If a postmenopausal patient receives adjuvant upfront treatment with an aromatase inhibitor for five years and endocrine treatment is planned for a further five years, the decision must be taken on an individual basis as there are currently no data available from controlled studies. There was no clear-cut vote by the St. Gallen panelists on this point; continued treatment with tamoxifen or an aromatase inhibitor was rejected each time by a narrow majority. A narrow majority of 54.5% voted not to continue further endocrine therapy in these patients.

The German group agrees with all three majority votes but would like to emphasize that all of these cases must be regarded as individual decisions which must be taken based on the risks and benefits, the tolerability of treatment, and the patient's tumor burden. In principle, the panelists and the German group agree that patients who do not tolerate treatment with an aromatase inhibitor and who are switched to tamoxifen (again), can receive tamoxifen for more than five years. Generally, patients who experience severe side-effects with endocrine therapy should be switched as early as possible, as any form of endocrine therapy is better than discontinuing therapy.

Adjuvant Chemotherapy

Luminal A breast cancer

Luminal A breast cancers are defined as breast cancers with high hormone receptor (HR) expression, which are HER2-negative and have a low proliferation rate. Based on this definition, endocrine therapy is the treatment of choice. Experts generally agree that additional adjuvant chemotherapy is usually not indicated and should only be administered to individual high-risk patients after weighing the benefits and side-effects. A relative indication for additional adjuvant chemotherapy in a patient with Luminal A breast cancer could be high tumor load (≥ 4 involved lymph nodes, stage T3).

The German specialists and the international experts do not recommend adjuvant chemotherapy in patients with 1–3 involved lymph nodes with no additional risk factors. In the opinion of the German experts, this also applies to patients with extensive lymphovascular invasion as an isolated risk factor; unlike the majority of St. Gallen panelists (67.6%), the German group sees no indication for adjuvant chemotherapy in these patients unless additional risk factors are also present.

Luminal B breast cancer *without* HER2 overexpression

Endocrine therapy is also an important part of systemic therapy for patients with luminal B breast cancer. The St. Gallen panelists and the German group agree that adjuvant chemotherapy is usually indicated because of the higher risk of recurrence. If chemotherapy is indicated, the preferred treatment should be an anthracycline/taxane-based regimen, e.g. four cycles of anthracycline/cyclophosphamide (AC) followed by twelve weeks of paclitaxel administered once a week or six cycles of docetaxel/doxorubicin/cyclophosphamide every three weeks (TAC). Six cycles of an anthracycline-based regimen (without taxane) is now considered obsolete. One option for patients with a high risk of recurrence (e.g. ≥ 4 involved lymph nodes) is a dose-dense schedule supported by G-CSF.

Adjuvant chemotherapy is not required for patients with up to three involved lymph nodes and low risk in multigene expression tests (RS, MP, PAM50 ROR, EP). The first prospective data of the Plan B study (HR+, HER2−) showed an excellent 3-year survival rate of more than 98% for patients with 0–3 affected lymph nodes and low RS (≤ 11) [18]. Data on intermediate RS are not currently conclusive and offer no basis for decision-making. The German group is awaiting the results of a number of ongoing studies (TailorX, RxPONDER, MINDACT, PlanB, ADAPT).

Triple-negative breast cancer

Established anthracycline/taxane-based regimens are the therapy of choice for patients with ductal triple-negative breast cancer (TNBC: ER−, PR−, HER2−). This also applies to patients with BRCA mutation. In the opinion of some of the panelists (yes: 45%; no: 52.5%), dose-dense regimes (supported by G-CSF) could also be an option for these patients. The German group agrees with the majority vote of the St. Gallen panelists. The majority of St. Gallen panelists (92.9%) and the German group also agree that platinum-based regimens are not generally indicated for TNBC. However, a narrow majority of St. Gallen panelists (57.9%) recommends a platinum-based regimen for patients with TNBC and BRCA mutation. The German group does *not* agree with the use of a platinum-based regimen as an adjuvant treatment for patients with TNBC, as there are currently no data to support this. The German group recommends the use of neoadjuvant therapy for these patients and, if possible, enrolment in clinical studies focusing on this issue.

HER2-positive breast cancer

According to the majority vote of the St. Gallen panelists (81.4%) with which the German group agrees, adjuvant anti-HER2 targeted therapy is indicated for T1b-patients with proven HER2 positivity as defined by the ASCO-CAP guidelines [19]. To treat stage T1c cancer and above, all of the St. Gallen panelists voted for adjuvant chemotherapy combined with an anti-HER2 targeted therapy.

Adjuvant chemotherapy should preferably consist of a sequential anthracycline/taxane-based regimen; anti-HER2 targeted therapy should be administered concurrently to taxane therapy. A combination of 12× weekly paclitaxel plus trastuzumab (for 1 year) (without anthracycline) can be an effective therapeutic option for patients with node-negative stage T1b/c cancer.

The monoclonal antibody trastuzumab is the agent of choice for adjuvant anti-HER2 targeted therapy. A double antibody blockade with trastuzumab/pertuzumab or a dual blockade with trastuzumab/lapatinib are not currently indicated for adjuvant therapy as they have not yet been approved for use in this setting.

Neoadjuvant Therapy

HER2-positive breast cancer

The experts agree that a sequential anthracycline/taxane-based chemotherapy regimen plus trastuzumab is also the therapy of choice for the treatment of HER2-positive breast cancer in the neoadjuvant setting. The German group do *not* fully share the opinion of the majority of St. Gallen panelists for pertuzumab combined with trastuzumab and a taxane (73%) as a neoadjuvant option. The St. Gallen majority vote may well be due to the large number of US panelists: in contrast to Europe, in the USA pertuzumab/trastuzumab/taxane has been approved for the neoadjuvant treatment of HER2-positive breast cancer. As long as it has not been approved, dual blockade with pertuzumab and trastuzumab in the neoadjuvant setting is an individual decision in Germany. The German group would like to point out that an anthracycline-free TCH regimen (docetaxel, carboplatin, trastuzumab) can be a neoadjuvant therapeutic option for patients with cardiac risk factors.

Triple-negative breast cancer

Neoadjuvant therapy is an important aspect of therapy for patients with TNBC. Therapy consists of a sequential regimen with an anthracycline combination followed by a taxane. Reversing the sequence achieves comparable response rates. The GeparSep-

Table 4 Selection of positive studies on neoadjuvant therapy with platinum [2] (pCR: pathological complete remission; NPLD: non-pegylated doxorubicin; TNBC: triple-negative breast cancer; Cb: carboplatin; qw: once a week; q3w: every three weeks; FEC: 5-fluorouracil, epirubicin and cyclophosphamide; CALGB: Cancer and Leukemia Group B; AUC: area under the concentration-time curve; Bev: bevacizumab).

Authors	Study	Regimen	pCR rate
Sikov WM, et al. [21]	CALGB 40603 Phase II	Paclitaxel 80 mg/m² qw × 12 + Carboplatin AUC6 q3w × 4 – dd AC q2w × 4	TNBC ± Cb: 54 vs. 41 % (ypT0/is ypN0)
von Minckwitz G et al. [22]	Gepar Sixto Phase II	NPLD 20 mg/m² qw × 18 + Paclitaxel 80 mg/m² qw × 18 ± Carboplatin AUC1.5 qw × 18 + Bev 15 mg/kg q3w × 6	TNBC ± Cb: 53 vs. 37 % (ypT0 ypN0)
Ando M et al. [23]	Phase II	Paclitaxel 80 mg/m² qw × 12 + Carboplatin AUC5 q3w × 4 – FEC q3w × 4	TNBC ± Cb: 61 vs. 26 %

to study [20] showed a significantly higher rate of complete pathological response (pCR) for nab-paclitaxel compared to paclitaxel – followed by four cycles of epirubicin/cyclophosphamide (EC) every three weeks. In TNBC patients receiving nab-paclitaxel the pCR rate almost doubled. The results of further studies (ETNA, ADAPT) will be presented at upcoming international conferences. The St. Gallen panel does not recommend platinum for the neoadjuvant therapy of TNBC patients. The German group has a different opinion. The data from several prospective randomized neoadjuvant studies [21–23] show a clear advantage from the use of platinum, particularly in patients with family history or BRCA mutations (**Table 4**) [2].

Luminal A breast cancer

Neoadjuvant chemotherapy is currently not an option to treat hormone-sensitive luminal A breast cancer. The German group therefore does *not* agree with the majority vote of the St. Gallen panelists, who recommends neoadjuvant chemotherapy for these patients if breast-conserving surgery is *not* possible. The German group would like to point out that neoadjuvant chemotherapy is rarely indicated for patients with luminal A breast cancer; the limited sensitivity of these cancers to chemotherapy means that tumor shrinkage (pCR) which would improve operability and prognosis is unlikely.

However neoadjuvant *endocrine* therapy can be an effective option for postmenopausal patients with highly hormone-sensitive breast cancer. The German group agrees with the majority vote of the St. Gallen panelists on this point but would like to note that because of the limited available data, neoadjuvant endocrine therapy should only be considered for older patients with clinically relevant comorbidities (multimorbid patients) and that the decision must be taken on an individual basis. A further option is to offer patients neoadjuvant endocrine therapy through participation in clinical trials. The German group recommends to individually decide neoadjuvant endocrine treatment based on treatment effects, side effects and comorbidities. The majority of St. Gallen panelists recommended continuing neoadjuvant therapy in these patients either for several (4–8) months or until the maximum response is achieved. According to the German group surgery should be followed whenever possible.

Adjuvant Use of Bone Modifying Agents (BMA: Bisphosphonates, Denosumab)

The use of bisphosponates in an adjuvant setting (zoledronic acid every six months or oral clodronate daily) in addition to adjuvant endocrine therapy can be an option for some postmenopausal patients if the goal is to prolong disease-free survival. The German group concurs with the majority vote of the St. Gallen panelists on this point. Data obtained from a large meta-analysis [24] have shown that the positive effect of adjuvant bisphosphonates (BP) was limited to postmenopausal patients. It should be noted that BP are only approved for the treatment of osteoporosis and bone metastases.

This does not apply to premenopausal patients, irrespective of whether they are given a GnRH analogue in addition to tamoxifen or not. The German group agrees with the majority vote of the St. Gallen panelists. Based on the data of the Austrian ABCSG-12 trial [13] the opinion of the German group is that administration of adjuvant bisphosphonate to premenopausal patients combined with administration of GnRH can be an option in individual cases but cannot be the general standard. Both groups agreed that currently the adjuvant use of denosumab is not indicated – the relevant data on this point are still lacking.

Older and Younger Patients

All the experts agree that the use of adjuvant standard (chemo-)therapy to treat patients without clinically relevant (significant) comorbidities does not depend on the patient's age. This also applies to the question whether adjuvant radiotherapy is required after breast-conserving surgery in postmenopausal patients with estrogen receptor-positive breast cancer if the patient is receiving continuing endocrine therapy. In both cases, age per se only plays a subsidiary role in the decision for therapy, meaning that it is not possible to give an absolute age limit. The indication for adjuvant therapy should be guided by the woman's life expectancy (biological age).

For patients below the age of 40 years with TNBC, the German group agrees with the majority vote of the St. Gallen panelists who proposed that these patients receive genetic counseling and undergo BRCA1/2 testing (73 %). With regard to the question whether this should also apply if the age limit is raised to < 60 years, the vote of the St. Gallen panelists was evenly split (50 %). There was a clear vote in favor of testing patients with TNBC and a positive family history (90.9 %). The German group agrees with this and bases its recommendations on the new 2015 AGO guidelines. The St. Gallen panel rejected testing for further mutations in other genes by a narrow majority (50 %). The German group agrees with this majority vote.

The St. Gallen panelists and the German group agree that it is not useful to test all breast cancer patients for other high-risk mutations (e.g., PALB2), but testing is recommended for patients with a family history of breast cancer and patients ≤ 35 years. According to the majority vote of the St. Gallen panelists, testing of patients < 50 years is not generally indicated; however testing is in-

dicated in patients with ER-negative and HER2-negative breast cancer (70%). The German group agrees with this statement but points out that such testing is only useful if it is therapeutically relevant or if testing could have surgical consequences, for example, a recommendation to undergo prophylactic mastectomy or contralateral prophylactic mastectomy or bilateral salpingoophorectomy in patients with BRCA mutation. In the opinion of the German group, testing should be carried out in all patients with ER and HER2-negative breast cancer, irrespective of patient age, if the findings will affect the decision for therapy. The likelihood of detecting mutations decreases with increasing patient age. The German group mentions that this also applies to patients with basal-like breast cancer. The vote of the St. Gallen panelists was more restricted. Both groups agree that detection of BRCA1/2 mutation only affects neoadjuvant therapy; because of the lack of data, mutation detection does not affect the decision for adjuvant therapy.

Both groups also agree that preservation of fertility is an integral consideration in the treatment of younger patients. One option could be the use of GnRH analogs. The German group agrees that younger women should be offered counseling but points out that the data are still controversial. It is important to consider potential side-effects when making a decision.

The majority of St. Gallen panelists (78.9%) voted to offer ovarian function suppression (OFS) to younger patients (< 40 years) with HR-negative breast cancer in addition to chemotherapy. The German group discussed this point in great depth but did not reach a consensus. Based on the current therapy guidelines of the AGO [1], the German group recommends discussing it with the patient and making the decision on an individual basis.

Breast Cancer and Pregnancy

If breast cancer is diagnosed during pregnancy, delivery should not be induced prematurely. Breast-conserving surgery is possible. Lymphoscintigraphy and SNB can be carried out. If endocrine therapy is indicated, treatment should only be commenced after delivery. On each of these points, the German group agrees with the majority vote of the St. Gallen panelists. The German group does not agree with the narrow majority vote of the St. Gallen panel (52.6%), who recommends immediate breast reconstruction after mastectomy. The German group justifies their position with reference to the longer operation times and the increased risk of complications.

If a patient with breast cancer wishes to become pregnant, ongoing endocrine treatment can be interrupted. The majority of St. Gallen panelists (60.6%) voted that interruption of endocrine therapy should only occur after 18–30 months if the patient wishes to become pregnant, and the majority of panelists (61.1%) recommended that this should only be considered if there is no increased risk of recurrence.

The German group would like to emphasize that the patient should have received tamoxifen for at least 18 months, as the benefit of adjuvant therapy decreases after 18 months according to the analysis of the EBCTCG. The German group also points out that the benefit of adjuvant therapy is correlated to the duration of therapy. This needs to be discussed with the patient. The decision when and whether adjuvant endocrine therapy should be interrupted in order to become pregnant depends on the individual situation and the patient's age.

Breast Cancer in Men

Breast cancers in men are usually hormone-sensitive; treatment should consist of systemic therapy with tamoxifen. Aromatase inhibitors ± LHRH analogs are not an option unless administered in clinical trials.

Nutrition and Physical Activity

Both groups agree that patients with breast cancer do not require a special diet. A balanced diet is generally beneficial for the patient's overall well-being and health. However a positive effect on breast-cancer specific survival rates has not been clearly proven. Regular physical activity and moderate sports activities as well as avoiding obesity significantly prolong the time to recurrence and improve overall survival. Supplements are recommended for patients with Vitamin D deficiency.

Conflict of Interest

The post-St. Gallen meeting was organized by I-MED-Institute GmbH and supported by a non restricted grant from Celgene GmbH.

NH received honoraria from the following companies: Celgene, Genomic Health, NanoString, Novartis, Roche. JH received honoraria from the following companies: Novartis, Celgene, Roche, GSK, Genomic Health and carried out research with the help of funding from GSK. HHK received honoraria from the following companies: Roche, Genomic Health, AstraZeneca, Novartis. CL received honoraria from the following companies: Genomic Health, Roche, Celgene and carried out research with the help of funding from Eisai. VM received honoraria from the following companies: Amgen, Celgene, Roche and carried out research with the help of funding from Amgen. HS received honoraria from the following companies: Makosch media, Amgen, Celgene, NanoString. AS received honoraria from the following companies: Roche, Celgene, Amgen and carried out research with the help of funding from Roche. CT received honoraria from the following companies: Amgen, AstraZeneca, Celgene, Genomic Health, NanoString, Novartis, Pfizer, Roche, Teva. CJ received honoraria from the following companies: Travel Grant Celgene. JUB received honoraria from the following companies: Roche, Novartis, Pfizer, Celgene, Teva, Amgen and carried out research with the help of funding from DIZG. PAF received honoraria from the following companies: Amgen, Novartis, Roche, Pfizer, Teva, Genomic Health, GSK, NanoString and carried out research with the help of funding from Novartis, Amgen. WJ received honoraria from the following companies: Roche, Novartis, Sanofi-Aventis, AstraZeneca, Pfizer, Chugai, Amgen and carried out research with the help of funding from Roche, Novartis, Sanofi-Aventis, AstraZeneca, Pfizer, Chugai, Amgen. HJL received honoraria from the following companies: Roche, Novartis, Eisai, Celgene. AScharl received honoraria from the following companies: Celgene, Roche, Novartis, Teva, Amgen, AstraZeneca, Sanofi, Glaxo, Eisai, Riemser, Janssen-Cilag. SL carried out research with the help of funding from Celgene, Amgen, Roche, Novartis, Pfizer, Abbott. All other authors declare no conflict of interest.

Comment

The authors take full responsibility for preparation of the manuscript. The authors would like to thank Professor Diethelm Wallwiener, Director of the University Gynecological Clinic in Tübingen for his critical review of the manuscript. The authors would like to thank Ms. Birgit-Kristin Pohlmann, Nordkirchen, for her editorial support during the preparation of the manuscript.

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