Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23–01 investigators

Summary

Background For patients with breast cancer and metastases in the sentinel nodes, axillary dissection has been standard treatment. However, for patients with limited sentinel-node involvement, axillary dissection might be overtreatment. We designed IBCSG trial 23–01 to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤2 mm) sentinel nodes and tumour of maximum 5 cm.

Methods In this multicentre, randomised, non-inferiority, phase 3 trial, patients were eligible if they had clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after sentinel-node biopsy, had one or more micrometastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension. Patients were randomly assigned (in a 1:1 ratio) to either undergo axillary dissection or not to undergo axillary dissection. Randomisation was stratified by centre and menopausal status. Treatment assignment was not masked. The primary endpoint was disease-free survival. Non-inferiority was defined as a hazard ratio (HR) of less than 1·25 for no axillary dissection versus axillary dissection. The analysis was by intention to treat. Per protocol, disease and survival information continues to be collected yearly. This trial is registered with ClinicalTrials.gov, NCT00072293.

Findings Between April 1, 2001, and Feb 28, 2010, 465 patients were randomly assigned to axillary dissection and 469 to no axillary dissection. After the exclusion of three patients, 464 patients were in the axillary dissection group and 467 patients were in the no axillary dissection group. After a median follow-up of 5·0 (IQR 3·6–7·3) years, we recorded 69 disease-free survival events in the axillary dissection group and 55 events in the no axillary dissection group. Breast-cancer-related events were recorded in 48 patients in the axillary dissection group and 47 in the no axillary dissection group (ten local recurrences in the axillary dissection group and eight in the no axillary dissection group; three and nine contralateral breast cancers; one and five regional recurrences; and 34 and 25 distant relapses). Other non-breast cancer events were recorded in 21 patients in the axillary dissection group and eight in the no axillary dissection group (20 and six second non-breast malignancies; and one and two deaths not due to a cancer event). 5-year disease-free survival was 87·8% (95% CI 84·4–91·2) in the group without axillary dissection and 84·4% (80·7–88·1) in the group with axillary dissection (log-rank p=0·16; HR for no axillary dissection *vs* axillary dissection was 0·78, 95% CI 0·55–1·11, non-inferiority p=0·0042). Patients with reported long-term surgical events (grade 3–4) included one sensory neuropathy (grade 3), three lymphoedema (two grade 3 and one grade 4), and three motor neuropathy (grade 3), all in the group that underwent axillary dissection, and one grade 3 motor neuropathy in the group without axillary dissection. One serious adverse event was reported, a postoperative infection in the axilla in the group with axillary dissection.

Interpretation Axillary dissection could be avoided in patients with early breast cancer and limited sentinel-node involvement, thus eliminating complications of axillary surgery with no adverse effect on survival.

Funding None.

Introduction

The first randomised trial to validate sentinel-node biopsy in breast cancer was published in 2003.[1] That trial and others confirmed that sentinel-node biopsy accurately staged the axilla, so that if the sentinel node is not involved, the other axillary nodes are most probably disease-free and the patient can be spared axillary dissection.[2–4] If the sentinel node was involved, standard practice was axillary dissection (Berg levels I and II in the USA,[5,6] and all three Berg levels in many European countries[4]). Axillary dissection removes any disease within the axilla, after which disease recurrence in the axilla is rare.[7–10] It might also have a favourable effect on survival, although this effect has never been proven since its main use was as a disease staging procedure.[4,11,12] However, short-term and long-term side-effects of axillary dissection have always been a concern. These side-effects include lymphoedema, pain, and reduced arm movement.[13,14]

Sentinel-node biopsy very quickly became an integral part of the conservative treatment of breast cancer because

Lancet Oncol 2013; 14: 297–305

Published Online March 11, 2013 http://dx.doi.org/10.1016/S1470-2045(13)70035-4

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on May 28, 2013

See **Comment** page 266

Molecular Senology Unit, Senology Division (V Galimberti MD), **Breast Diagnosis and Surgery Unit, Senology Division** (S Zurrida MD), **Senology Division** (A Luini MD, P Baratella MD, C Chifu MD, M Sargenti MD, M Intra MD, O Gentilini MD), **Integrated Breast Surgery Unit, Senology Division** (P Veronesi MD), **IBCSG Central Pathology Office, Division of Pathology and Laboratory Medicine** (G Viale MD, MG Mastropasqua MD, G Mazzarol MD), **Research Unit in Medical Senology, Department of Medicine** (M Colleoni MD), **and Department of Medicine** (A Goldhirsch MD), **European Institute of Oncology, Milan, Italy** (U Veronesi MD); **Department of Mathematics and Statistics, College of Engineering and Mathematical Sciences, University of Vermont, Burlington, VT, USA** (BF Cole PhD); **IBCSG Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA** (B F Cole, KN Price BS, M Regan SD, RD Gelber PhD); **University of Milan, Milan, Italy** (G Viale, P Veronesi); **Breast Surgery Division, Centro di Riferimento Oncologico, Aviano, Italy** (S Massarut MD); **Department of Surgery, Institut Gustave**

Roussy, Villejuif, France (J-R Garbay MD)**; Department of Surgical Oncology, Institute of Oncology, Ljubljana, Slovenia** (J Zgajnar MD)**; Department of Breastsurgery, Herlev Hospital, Herlev, Denmark** (H Galatius MD)**; Department of Surgery, Ospedale Alessandro Manzoni, Lecco, Italy** (A Recalcati MD)**; Riverina Cancer Care Centre, Wagga Wagga, NSW, Australia** (D Littlejohn FRACS)**; Breast Center, Kantonsspital, Switzerland** (M Bamert MD)**; Frontier Science and Technology Research Foundation, Boston, MA, USA** (KN Price, R D Gelber)**; Harvard Medical School, Boston, MA, USA** (MM Regan, RD Gelber)**; International Breast Cancer Study Group and University of Sydney, Centennial Park, NSW, Australia** (AS Coates MD)**; and Harvard School of Public Health, Boston, MA, USA** (RD Gelber)

Correspondence to:
Dr Viviana Galimberti, Department of Surgery, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
viviana.galimberti@ieo.it

it allowed avoidance of axillary dissection in a large proportion of patients with early breast cancer, while still providing information to guide adjuvant treatment. However, with the development of sentinel-node biopsy came new and more exhaustive methods of assessing the sentinel node to ensure that no disease in that location was missed. Before the era of sentinel-node biopsy, about three sections per axillary lymph node were typically examined; subsequently, the entire sentinel node was serial sectioned and all sections examined.[15] This assessment resulted in the frequent identification of micrometastatic foci (≤2 mm in diameter) and isolated tumour cells, whose prognostic significance was unknown.

We designed the International Breast Cancer Study Group (IBCSG) 23–01 multicentre randomised controlled trial to identify whether axillary dissection might be overtreatment in patients who have micrometastases only in the sentinel node. Specifically, we designed the trial to compare outcomes in patients with sentinel-node micrometastases treated with axillary dissection with outcomes in those receiving no further treatment to the axilla.

Methods

Study design and patients

IBCSG 23–01 was a two-group, multicentre, randomised, non-inferiority, phase 3 trial comparing no axillary dissection with axillary dissection in patients with breast cancer and micrometastases in the sentinel node. Patients were recruited from 27 institutions between April 1, 2001, and Feb 8, 2010.

We registered eligible patients for the trial before surgery after they had given written informed consent. Women eligible for registration could be any age with clinical, mammographic, ultrasonographic, or pathological diagnosis of breast cancer, provided they had no previous or concomitant malignancy, pure ductal carcinoma in situ, previous systemic therapy for breast cancer, cancer chemoprevention treatment in the preceding year, distant metastases, palpable axillary nodes, or Paget's disease without invasive cancer. Pregnant or lactating women were also ineligible. On the basis of the 2005 American Society of Clinical Oncology (ASCO) guidelines[5] and to increase accrual, the criteria for eligibility were broadened in June, 2006, to include patients with one or more positive sentinel nodes (formerly only one); multicentric or multifocal tumours (formerly only unicentric); and largest lesion size of 5 cm or smaller (formerly ≤3 cm).

Patients could be scheduled for mastectomy or conservative breast surgery. They were included in the trial and randomly assigned to treatment if, during or after surgical treatment for breast cancer, they were found to have a tumour of a maximum diameter of 5 cm or less by pathological measurement of the surgical specimen, and one or more micrometastatic foci (≤2 mm) in the sentinel nodes, but no macrometastatic disease. We included isolated tumour cells[16,17] within the definition of micrometastatic.

The independent data and safety monitoring committee reviewed accrual, safety, and number of events every 6 months. The protocol was approved by the institutional review boards of all participating centres, and all participants provided written informed consent. Data were obtained at the participating centres and transmitted to the IBCSG data management centre in Amherst, New York, USA, via the DataFax or iDataFax system.

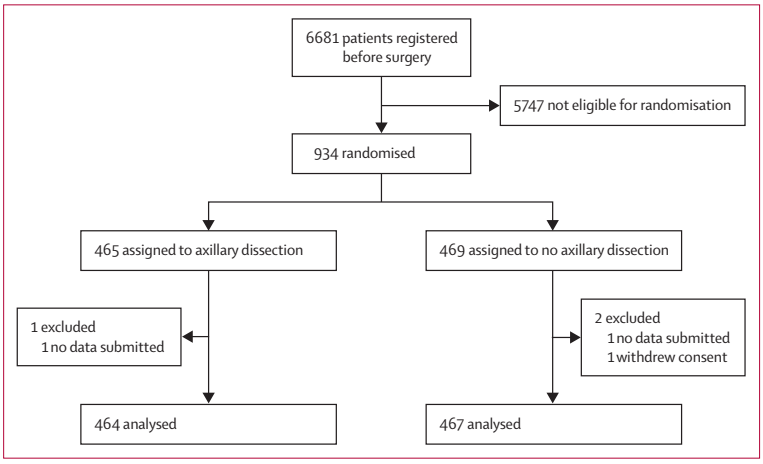

Figure 1: **Trial profile**

Randomisation and masking

Patients were randomly allocated (in a 1:1 ratio) to either axillary dissection or no axillary dissection. Randomisation was done with permuted blocks generated by a congruence algorithm. Randomisation was stratified by participating centre and menopausal status. After confirming eligibility, participating centre staff accessed the central randomisation system via the internet and entered required information including stratification factors. The randomisation system assigned a patient identification number, treatment group, and date of randomisation via the computer screen with a follow-up email. The IBCSG data management centre developed and maintains the randomisation system. Masking was not done in this surgical trial. The patient, participating centre staff, trial management staff, and others were aware of the assigned treatment.

Procedures

The sentinel node could be examined in one of three ways: (1) preoperatively under local anaesthesia—if the patient had a micrometastatic node and was randomly assigned to the axillary dissection group, she underwent axillary dissection during the operation to remove the primary; (2) intra-operatively, with intra-operative sentinel-node examination, and axillary dissection done during the operation to remove the primary; (3) intra-operatively with later histological examination, and later

second surgery under general anaesthesia if randomly assigned to undergo axillary dissection. All sentinel nodes were entirely sectioned at 50–200 µm intervals and all sections (frozen or permanent) were examined with haematoxylin and eosin staining by pathologists at each participating centre. Cytokeratin immunostaining was used only when the presence of micrometastases was suspected, but not certain, or not determined, on haematoxylin and eosin-stained sections. The treating physician assessed and reported long-term surgical events (sensory neuropathy, lymphoedema, and motor neuropathy) at every follow-up visit (every 4 months from the date of randomisation for the first year, and every 6 months for years 2–5) on the basis of the National Cancer Institute Common Toxicity Criteria version 2. Serious adverse events were recorded as they occurred.

	Axillary dissection (n=464)	No axillary dissection (n=467)
General characteristics		
Age (years)		
Median (range)	53 (28–81)	54 (26–81)
Preoperative sentinel-node biopsy		
No	287 (62%)	286 (61%)
Yes	177 (38%)	181 (39%)
Menopausal status		
Pre	204 (44%)	207 (44%)
Post	260 (56%)	260 (56%)
Pathological tumour size		
<2 cm	316 (68%)	322 (69%)
2–2·9 cm	106 (23%)	112 (24%)
≥3 cm	35 (8%)	28 (6%)
Unknown	7 (2%)	5 (1%)
Oestrogen receptor status		
Negative	51 (11%)	40 (9%)
Positive	409 (88%)	425 (91%)
Unknown	4 (<1%)	2 (<1%)
Progesterone receptor status		
Negative	108 (23%)	115 (25%)
Positive	352 (76%)	350 (75%)
Unknown	4 (<1%)	2 (<1%)
Sentinel-node tumour size		
≤1 mm	323 (70%)	320 (69%)
1·1–2 mm	131 (28%)	135 (29%)
>2 mm	10 (2%)	11 (2%)
Unknown	0	1 (<1%)
Tumour grade		
Grade I	118 (25%)	90 (19%)
Grade II	214 (46%)	241 (52%)
Grade III	129 (28%)	135 (29%)
Unknown	3 (<1%)	1 (<1%)
Lymphoscintigraphy		
No	17 (4%)	15 (3%)
Yes	447 (96%)	452 (97%)
Excisional biopsy		
No	404 (87%)	410 (88%)
Yes	60 (13%)	57 (12%)
Sentinel-node biopsy		
Axillary only	456 (98%)	448 (96%)
Internal mammary only	1 (<1%)	0
Both	7 (2%)	19 (4%)

(Continues in next column)

(Continued from previous column)

Characteristic or therapy	Axillary dissection (n=464)	No axillary dissection (n=467)
Axillary dissection performed		
No	17 (4%)	453 (97%)
Yes	447 (96%)	14 (3%)
Number of sentinel-nodes removed		
1	226 (49%)	254 (54%)
2	153 (33%)	134 (29%)
3	52 (11%)	50 (11%)
4	15 (3%)	21 (4%)
5	11 (2%)	5 (1%)
≥6	7 (2%)	3 (<1%)
Median (range)	2 (1–9)	1 (1–8)
Number of metastatic sentinel-nodes		
1	440 (95%)	450 (96%)
2	23 (5%)	17 (4%)
3	1 (<1%)	0
Number of axillary nodes removed		
Median (range)	21 (1–44)	2 (1–29)
Additional involved nodes		
No	405 (87%)	455 (97%)
Yes	59 (13%)	12 (3%)
Internal mammary nodes removed		
No	450 (97%)	448 (96%)
Yes	14 (3%)	19 (4%)
Local treatment*		
Mastectomy	44 (9%)	42 (9%)
Breast-conserving surgery	420 (91%)	425 (91%)
Without radiotherapy	10/420 (2%)	12/425 (3%)
With radiotherapy	410/420 (98%)	413/425 (97%)
Intraoperative radiotherapy only	79/420 (19%)	80/425 (19%)
Postoperative radiotherapy only	293/420 (70%)	297/425 (70%)
Combination radiotherapy	36/420 (9%)	35/425 (8%)
Unspecified radiotherapy	2/420 (<1%)	1/425 (<1%)
Systemic therapy		
Any systemic therapy	441 (95%)	451 (97%)
Hormonal therapy only	292 (63%)	315 (67%)
Chemotherapy only	42 (9%)	33 (7%)
Combination therapy	107 (23%)	103 (22%)

Data are number of patients (%) unless otherwise indicated. *Percentages for type of surgery are based on entire population, those for radiotherapy (no or yes) and for type of radiotherapy are based on only the breast-conserving surgery subpopulation.

Table 1: **Patient characteristics and adjuvant therapies**

	Axillary dissection (n=447)	No axillary dissection (n=453)	p value†
Sensory neuropathy	82 (18%)	55 (12%)	0·012
Grade 1	60 (13%)	40 (9%)	
Grade 2	15 (3%)	6 (1%)	
Grade 3	1 (<1%)	0	
Grade 4	0	0	
Unknown grade	6 (1%)	9 (2%)	
Lymphoedema	59 (13%)	15 (3%)	<0·0001
Grade 1	33 (7%)	10 (2%)	
Grade 2	20 (4%)	3 (<1%)	
Grade 3	2 (<1%)	0	
Grade 4	1 (<1%)	0	
Unknown grade	3 (<1%)	2 (<1%)	
Motor neuropathy	37 (8%)	13 (3%)	0·0004
Grade 1	25 (6%)	11 (2%)	
Grade 2	9 (2%)	1 (<1%)	
Grade 3	3 (<1%)	1 (<1%)	
Grade 4	0	0	
Unknown grade	0	0	

*Excludes 31 patients (17 in the axillary dissection group and 14 in the no-axillary-dissection group) who did not receive the randomly assigned treatment. †Based on Fisher's exact test comparison of the occurrence of any grade event across treatment groups.

Table 2: **Long-term surgical events***

	Axillary dissection (n=464)	No axillary dissection (n=467)
Disease-free survival events*		
Total	69 (15%)	55 (12%)
Breast cancer events		
Local	10 (2%)	8 (2%)
Regional	1 (<1%)	5 (1%)
Distant	34 (7%)	25 (5%)
Contralateral breast	3 (<1%)	9 (2%)
Non-breast cancer events		
Second (non-breast) primary†	20 (4%)	6 (1%)
Death without cancer event	1 (<1%)	2 (<1%)
Deaths		
Total	19 (4%)	17 (4%)

*Includes all breast cancer events, all non-breast cancer events, and deaths with cause unknown. †Types (number) of second primaries in the group with axillary dissection were gastrointestinal (four), genitourinary (two), gynaecological (six), haematological (two), laryngeal (two), lung (one), and sarcoma (three). Types (number) in the group without axillary dissection were gastrointestinal (two), gynaecological (three), and melanoma (one).

Table 3: **Disease-free survival events and deaths at 5·0 years median follow-up of intention-to-treat population**

Statistical analysis

The primary endpoint was disease-free survival, determined as the number of years from randomisation until first evidence of invasive relapse at any site, second primary tumour (contralateral or non-breast), or death. Secondary endpoints were overall survival, site of recurrence (we were particularly interested in axillary recurrences), and surgical complications of axillary dissection. We calculated overall survival as the number of years from randomisation to death from any cause.

As originally designed, target accrual was 1960 patients with analysis planned after 558 events. These targets were based on having 90% power to detect non-inferiority of no axillary dissection with a one-sided statistical significance level of 10% (ie, $\alpha=0\cdot10$) under the assumption that 5-year disease-free survival with axillary dissection was 70% and defining non-inferiority as a hazard ratio (HR) of less than 1·25 (no axillary dissection relative to axillary dissection).

Accrual started on April 1, 2001, and closed on Feb 28, 2010, after 934 patients had been randomised. The primary reasons for early closure were that the projected time to complete accrual was too long and the event rate was lower than expected. Following the recommendation of the independent data and safety monitoring committee, we decided to continue follow-up of patients and do the primary analysis after a median follow-up of 60 months, when at least 100 events were expected to have occurred. We made this decision without any knowledge of endpoint treatment comparisons. We did no interim analyses, thus the full statistical significance level of 10% was expended in the present analysis, which represents the final analysis in terms of type I error-spending.

We compared the numbers of long-term surgical effects across the treatment groups using Fisher's exact test after excluding patients who did not receive the treatment allocated by randomisation.

We assessed disease-free survival and overall survival using the Kaplan-Meier product-limit method. We used the log-rank test, stratified by menopausal status, to compare the treatment groups. We converted the log-rank test statistic (O−E, observed minus expected numbers of events) and its variance (V) into an HR comparing no axillary dissection versus axillary dissection using the formula $HR=\exp([O-E]/V)$.[18] We estimated CIs and p values for HRs on the basis of a normal distribution following natural logarithm transformation. We did the one-sided test of non-inferiority of no axillary dissection comparing the observed HR with 1·25 (ie, null hypothesis HR ≥1·25). We assessed and compared the cumulative incidence of breast cancer events, defined as invasive relapse at any site or contralateral breast cancer, using the Gray method,[19] treating second primaries and other-cause deaths as competing risks.

We did the predefined primary analysis on the intention-to-treat population, defined as all eligible, randomised patients, regardless of what treatment they actually received. A secondary, per-protocol analysis excluded patients who did not receive the treatment allocated by randomisation.

We did multivariable analyses on disease-free survival in the intention-to-treat population using the proportional hazards regression model, stratified by menopausal status. We first evaluated each predictor in a univariate analysis. We then entered significant (two-sided p<0·05) predictors, together with treatment group, in the multivariable regression model. We subsequently re-assessed the remaining variables for inclusion in the multivariable model. We assessed the interaction between treatment group and each predictor by including the appropriate product term in the multivariable regression model.

All HRs, except the analysis of overall survival, were assessed with 95% CIs, or 99% CIs for subgroup analyses. For the analysis of overall survival, we used a 90% CI for comparison with the ACOSOG Z0011[13] trial. The statistical analysis was done with SAS Version 9.2 and R Version 2.15.1. This study is registered with ClinicalTrials.gov, NCT00072293.

Role of the funding source

The International Breast Cancer Study Group (IBCSG) sponsored the trial. There was no pharmaceutical support or specific funding source related to the trial. The IBCSG was solely responsible for the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

6681 patients were registered for the trial before surgery between April 1, 2001, and Feb 28, 2010 (figure 1). Of these, 934 (14%) patients from 27 clinical centres in Europe, South America, and Australia were included in the randomisation, of which 583 (62%) were from the European Institute of Oncology, Milan, Italy.

Three randomised patients were excluded from the analysis (two had no data submitted because no tumour was found in a sentinel node, and one withdrew consent for treatment and follow-up shortly after randomisation). After exclusion of these three patients, 931 patients (464 in the group with axillary dissection and 467 in the group without axillary dissection) were available for analysis as the intention-to-treat population (figure 1). Follow-up compliance was good and similar in the two treatment groups; of 807 patients remaining disease-free, only nine (2·3%) of 395 in the axillary dissection group and seven (1·7%) of 412 in the no axillary dissection group had most recent follow-up before 2010. In the group allocated to axillary dissection, 17 patients did not receive axillary dissection, and in the group allocated to not receive axillary dissection, 14 patients received axillary dissection. The per-protocol population excluded these 31 patients.

Patient and tumour characteristics were well balanced between the treatment groups (table 1). Median patient age was 54 years (range 26–81). 520 (56%) of the 931 evaluable patients were postmenopausal. 638 (69%) patients had tumours <2 cm, 63 (7%) had tumours ≥3 cm, and 264 (28%) had grade III disease. Tumours were

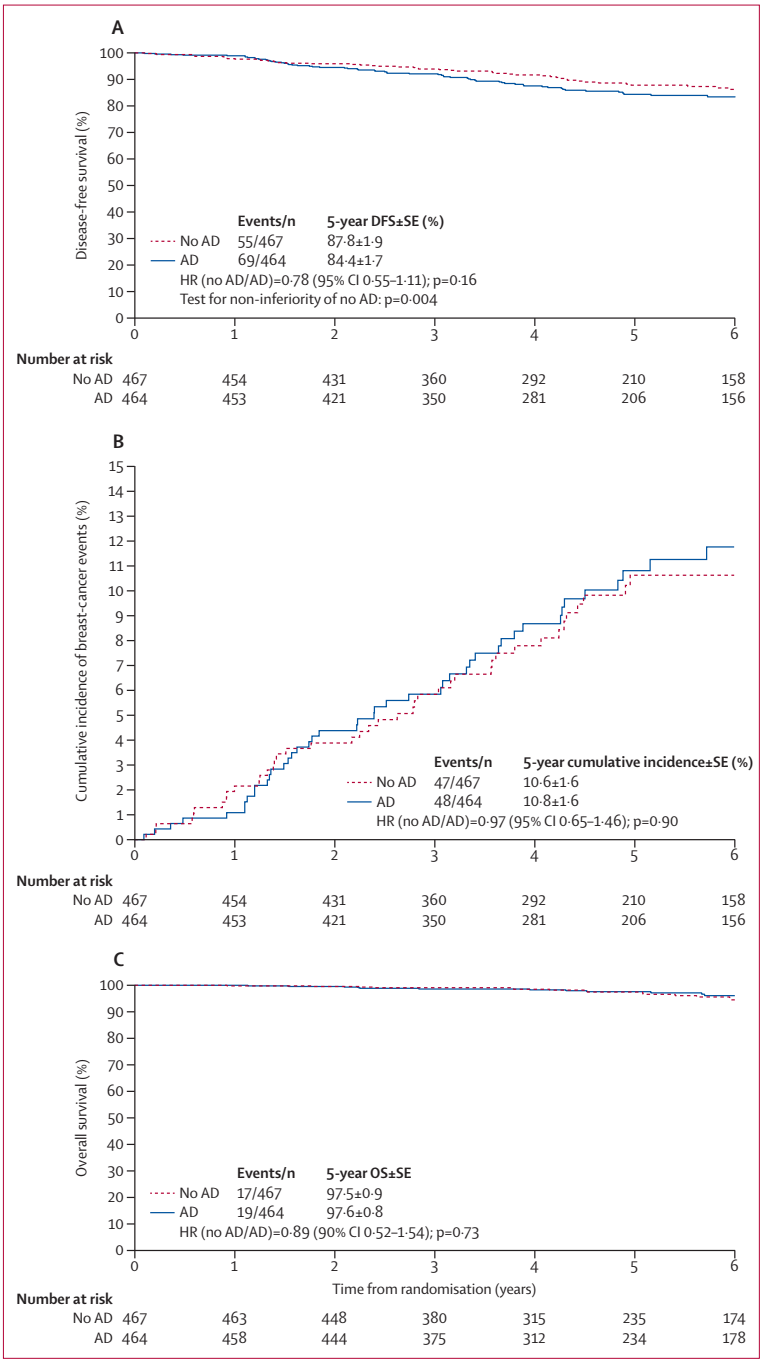

Figure 2: **Analysis of disease-free survival, cumulative incidence, and overall survival by intention to treat (n=931 patients)**

AD=axillary dissection. DFS=disease-free survival. OS=overall survival. (A) Disease-free survival. (B) Cumulative incidence of breast-cancer events. (C) Overall survival in the intention-to-treat population of 931 patients.

oestrogen-receptor positive in 834 (90%) patients, and progesterone-receptor positive in 702 (75%) patients. 643 (69%) patients had sentinel-node micrometastasis ≤1·0 mm, 266 (29%) had micrometastasis 1·1–2·0 mm, and 21 (2%) had metastasis >2·0 mm. 899 (97%) patients underwent lymphoscintigraphy, and one or two sentinel nodes were found in 767 (82%) of patients. Excision biopsy was performed in 117 (13%) patients. The median number of axillary nodes removed in the axillary dissection group was 21·0. Additional involved axillary nodes were found in 13% of patients in the axillary dissection group. Among the 447 patients in the axillary dissection group who received axillary dissection, 59 (13%) had at least one additional axillary node involved; 37 (8%) had one, 13 (3%) had two, and nine (2%) had three or more involved. Breast-conserving surgery was definitive treatment in 91% of patients in both treatment groups (420 in the axillary dissection group and 425 in the no axillary dissection group). The remaining patients underwent mastectomy. 823 (97%) of the 845 patients who received breast-conserving surgery were given adjuvant radiotherapy. Patients either received conventional postoperative radiotherapy alone, in combination with intra-operative treatment or intra-operative treatment alone. Adjuvant radiotherapy consisted of one-shot intra-operative treatment with electrons (ELIOT,[20] alone or in combination with postoperative radiotherapy) in 230 (27%) of patients who received breast-conserving surgery. Hormonal therapy alone was given to 607 (65%) patients, chemotherapy alone was given to 75 (8%) patients, and combinations of hormonal therapy and chemotherapy were given to 210 (23%) patients (table 1).

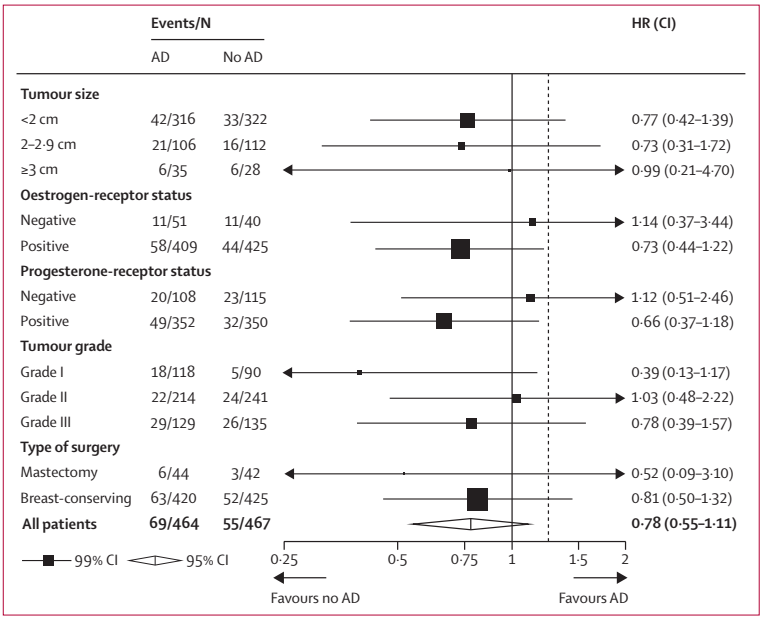

Figure 3: **Analysis of subgroups defined by tumour size, oestrogen-receptor status, progesterone-receptor status, tumour grade, and type of surgery, by intention to treat (n=931)**
HRs compare no axillary dissection versus axillary dissection among subgroups of the intention-to-treat population. Each subgroup HR is shown as a black square with the size of the square being inversely proportional to the variance of the corresponding log-HR estimate (ie, larger squares indicate lower variability in the estimate). The HR for all patients is shown as a diamond. The horizontal axis is displayed on a logarithmic scale.

Long-term sequelae of the surgical intervention to the axilla included sensory neuropathy, lymphoedema, and motor neuropathy. As expected, these events were more frequent and more severe in the group with axillary dissection than in the group without axillary dissection (table 2). Serious adverse events were also recorded in the trial, and one patient had a postoperative infection in the axilla attributed to protocol-assigned treatment (axillary dissection).

At a median follow-up of 5·0 (IQR 3·6–7·3) years, we noted 95 breast cancer events (48 in the group with axillary dissection and 47 in the group without axillary dissection; table 3). Second-primary (non-breast) cancer events occurred in 26 additional patients (20 in the group with axillary dissection, six in the group without axillary dissection). An additional two patients in the group that did not undergo axillary dissection died with no evidence of a cancer event, and one death in the group that underwent axillary dissection did not have additional information. Thus, a total of 124 events were available for the analysis of disease-free survival (69 events in the group with axillary dissection, 55 in the group without axillary dissection). We recorded 19 deaths in the group with axillary dissection and 17 deaths in the group without axillary dissection, with or without a previous cancer event.

Distant metastasis was the first event in 59 patients (34 in the group with axillary dissection, and 25 in the group without axillary dissection). Locoregional recurrence was the first event in 24 patients (11 in the group with axillary dissection, 13 in the group without axillary dissection). Regional recurrences occurred in one patient in the group with axillary dissection and in five patients in the group without axillary dissection; the recurrence in the group with axillary dissection involved the axilla and four recurrences involved the axilla in the group without axillary dissection. All six patients with a regional recurrence received breast-conserving surgery. Four of these patients received radiotherapy (the patient in the axillary dissection group received postoperative radiotherapy only, two in the group without axillary dissection group received intra-operative radiotherapy only, and one in the group without axillary dissection received both intra-operative and postoperative radiotherapy).

5-year disease-free survival was 84·4% (95% CI 80·7–88·1) in the group with axillary dissection and 87·8% (84·4–91·2) in the group without axillary dissection (log-rank p=0·16; figure 2A). Disease-free survival in the group without axillary dissection was non-inferior to the axillary dissection group (HR 0·78, 95% CI 0·55–1·11; non-inferiority p=0·0042). Results for the per-protocol population were similar (disease-free survival HR 0·80, 0·56–1·14; non-inferiority p=0·0073).

The 5-year cumulative incidence of breast cancer events was 10·8% (95% CI 7·6–14·0) in the group with axillary dissection and 10·6% (7·5–13·8) in the group without axillary dissection group (HR 0·97, 95% CI 0·65–1·46, p=0·90; figure 2B). 5-year overall survival was 97·6% (95% CI 96·0–99·2) in the group with axillary dissection and 97·5% (95·8–99·1) in the group without axillary dissection (HR 0·89, 90% CI 0·52–1·54; log-rank p=0·73; figure 2C).

We did a subgroup analysis on subgroups defined by tumour size, oestrogen-receptor status, progesterone-receptor status, tumour grade, and type of surgery (figure 3). In all subgroups the observed HR was lower than 1·25, and the group without axillary dissection was significantly (ie, p<0·10) non-inferior to the group without axillary dissection in the following subgroups: tumour size smaller than 2 cm (non-inferiority p=0·017), tumour size of 2·0–2·9 cm (p=0·053), oestrogen-receptor positive (p=0·0034), progesterone-receptor positive (p=0·0023), grade I tumour (p=0·0031), grade III tumour (p=0·042), and breast-conserving surgery (p=0·012).

Table 4 shows the multivariable proportional hazards regression analysis for disease-free survival. All variables in table 1 were assessed for predictive ability, but only those predictors that were significant in univariate analysis (two-sided p<0·05; data not shown) were included in the multivariable model. The regression estimates shown in table 4 were based on the 913 patients without missing data regarding tumour size, hormone-receptor status, or tumour grade. Tumour size and tumour grade were significant predictors of disease-free survival, whereas axillary dissection versus no axillary dissection had no significant effect on disease-free survival. Oestrogen-receptor status and progesterone-receptor status, although significant in the univariate analysis, were not significant predictors in the multivariable analysis. Removal of these variables from the model had a negligible effect on the treatment-comparison HR (disease-free survival HR 0·75, 95% CI 0·53–1·07, p=0·11). Nodal characteristics, including the number of sentinel nodes removed, were not significant predictors. No significant interactions were noted between treatment group and any of the other predictors (data not shown); thus, we detected no evidence of heterogeneity of HRs across the subgroups defined by the prognostic factors.

	Hazard ratio (95% CI)	p value
Treatment group		
Axillary dissection	1·00	
No axillary dissection	0·76 (0·53–1·08)	0·13
Tumour size		
<2 cm	1·00	
2–2·9 cm	1·57 (1·05–2·35)	0·029
≥3 cm	1·94 (1·04–3·63)	0·038
Overall p value (all three groups)		0·026
Oestrogen-receptor status		
Negative	1·00	
Positive	0·72 (0·39–1·35)	0·31
Progesterone-receptor status		
Negative	1·00	
Positive	0·86 (0·53–1·39)	0·55
Tumour grade		
Grade I	1·00	
Grade II	0·85 (0·51–1·41)	0·52
Grade III	1·70 (1·00–2·88)	0·050
Overall p value (all three groups)		0·0049

*Based on the 913 patients without missing data for any of the variables listed in the table.

Table 4: **Multivariable proportional-hazards regression analysis of disease-free survival***

Discussion

At a median follow-up of 5·0 years, we noted no difference between the axillary dissection and no axillary dissection groups for the primary endpoint of disease-free survival (panel). Accrual was slower than anticipated, mainly because small metastases were rare. 6681 patients were screened for enrolment, but only 934 (14%) met the requirement of micrometastic sentinel nodes. Although accrual was lower than projected, the protocol-specified criterion of non-inferiority of no axillary dissection compared with axillary dissection was fulfilled. In fact, disease-free survival was much better than anticipated overall: 5-year disease-free survival was well above the 70% assumed in the protocol. Most patients (92%) in our study had tumours smaller than 3 cm, received breast-conserving surgery (91%), and had adjuvant systemic therapy (96%), and thus our results are most directly applicable to these patient subpopulations.

Overall survival did not differ between the two groups either. Furthermore, the rate of disease recurrence was reassuringly low in the undissected axilla (<1%), which was not unexpected in view of similar findings in other studies.[1,21] However, non-sentinel axillary nodes were metastatic in 13% of the axillary dissection group. The discrepancy between the low rate of axillary recurrence in the group without axillary dissection and the high rate of axillary involvement in the axillary dissection group might be due to systemic treatment and whole breast irradiation, both of which can eliminate low volume axillary metastasis.[4] In fact, 927 of our patients (>99%) received radiotherapy or systemic treatment, or both. Note, however, that 92 (22%) of the patients in the group without axillary dissection who had breast-conserving surgery received either no radiation therapy (12 patients; 3%) or received ELIOT (partial breast irradiation) alone (80 patients; 19%), which cannot sterilise any residual axillary disease. It is also possible that intact axillary lymph nodes can eliminate low volume disease by immunosurveillance mechanisms.[4]

Our findings are consistent with those of the ACOSOG Z0011 trial,[13,21,22] which recruited 856 patients with limited macrometastatic sentinel-node involvement (not more than two metastatic sentinel nodes) undergoing conservative surgery only, and randomly assigned them to axillary dissection versus no further axillary treatment. After a median follow-up of 6·3 years, the groups did not differ for any endpoint. The authors concluded that for patients with limited sentinel-node involvement, no axillary dissection is justified, provided that patients receive both traditional whole breast radiation and systemic adjuvant treatment. Results from ACOSOG Z0011 and IBCSG 23–01 are shown side by side in the appendix.

See Online for appendix

Unlike ACOSOG Z0011, 9% of the patients in our trial received mastectomy. Although numbers are small, subgroup analysis suggested that no axillary dissection might be acceptable for patients undergoing mastectomy (figure 3) provided the invasive component of the breast lesion is small.

Axillary dissection has traditionally been a guide to adjuvant treatment rather than a treatment itself. However, in our study, the two groups did not differ in terms of proportions receiving any type of adjuvant therapy, indicating that detailed axillary node involvement—identified in the group with axillary dissection—had no influence on adjuvant treatment. Results from the AMAROS study,[23,24] which compared axillary dissection with axillary radiotherapy in patients with early breast cancer and a positive sentinel node also showed that axillary dissection had no influence on the administration of adjuvant treatment in the first 566 patients assessed. Thus the information provided by axillary dissection is no longer useful.

Other reasons exist for wanting to spare women axillary dissection when the sentinel node is positive: generally, about half of such patients have no other axillary involvement (87% of our patients in the axillary dissection group) and axillary dissection is overtreatment for them. Furthermore, biological characteristics of the primary tumour, such as hormone receptor expression,[25,26] HER2 status,[27,28] and tumour proliferation rate (eg, Ki67 labelling index),[27,28] substitute the prognostic information formerly provided by axillary status.

In conclusion, it is possible that our trial and ACOSOG Z0011 will change clinical practice, sparing many patients with early breast-cancer axillary dissection, especially when the sentinel node is minimally involved, thus reducing surgical complications related to axillary dissection with no adverse effect on survival. In fact, the 2011 St Gallen Consensus Conference[29] has already moved in that direction recommending that micrometastases in a single sentinel node should not be an indication for axillary dissection irrespective of the type of breast surgery given.

Panel: Research in context

Systematic review

To prepare the protocol for this clinical trial, we searched PubMed using the search terms: "breast cancer", "axillary dissection", "sentinel node", "sentinel node involvement", "sentinel node biopsy micrometastases", and "prognosis". We did not put a date limit on the search and only retrieved papers in English. There were data studies at the time on the prognostic significance of micrometastatic sentinel-node involvement. When preparing the paper we did a further PubMed search using the same search terms and conditions. More data were available and, particularly, the ACOSOG Z0011 trial had been published indicating limited macrometastatic involvement of the sentinel node could be left untreated provided early breast-cancer patients received whole breast irradiation and systemic treatment.

Interpretation

In conjunction with the findings of ACOSOG Z0011,[13,21,22] our data indicate that axillary dissection can be avoided in patients with early breast cancer and limited sentinel-node involvement, thus eliminating complications of axillary surgery with no adverse effect on survival.

Contributors

VG, SZ, RDG, KNP, AG, and PV participated in the design and concept of the study. GV, MGM, and GM participated in the pathology review. VG, SZ, AL, PV, PB, CC, MS, MI, OG, GM, J-RG, JZ, HG, AR, DL, MB, and MC participated in the data collection and enrolment of patients. VG did the literature search. BFC, RDG, KNP, and MMR participated in the data analysis. VG, BFC, ASC, and RDG participated in the interpretation of results. All authors have participated in drafting and finalising the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This clinical trial was supported by the medical institutions that enrolled women into the trial and the International Breast Cancer Study Group, which is funded in part by: Swiss Group for Clinical Cancer Research; Swiss Cancer League/Cancer Research Switzerland/Oncosuisse (Grant ID: ICP OCS 01688–03–2005), Frontier Science and Technology Research Foundation; The Cancer Council Australia; Australian New Zealand Breast Cancer Trials Group (National Health Medical Research Council); US National Institutes of Health (grant number CA-75362); Swedish Cancer Society; Foundation for Clinical Cancer Research of Eastern Switzerland (OSKK). There was no pharmaceutical company support for this trial. We thank the patients, physicians, nurses, and data managers who have participated in the International Breast Cancer Study Group Trial 23–01. We thank Sandra Lippert for data management and Don Ward for help with the English.

References

1 Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; **349:** 546–53.

2 Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. *N Engl J Med* 1998; **339:** 941–46.

3 Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol* 2010; **17:** 1854–61.

4 Veronesi U, Viale G, Paganelli G, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. *Ann Surg* 2010; **251:** 595–600.

5 Lyman GH, Giuliano AE, Somerfield MR, et al, and the American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; **23:** 7703–20.

6 Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; **305:** 569–75.

7 Veronesi U, Galimberti V, Paganelli G, et al. Axillary metastases in breast cancer patients with negative sentinel nodes: a follow-up of 3548 cases. *Eur J Cancer* 2009; **45:** 1381–88.

8 Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg* 2004; **240:** 462–68.

9 Smidt ML, Janssen CM, Kuster DM, Bruggink ED, Strobbe LJ. Axillary recurrence after a negative sentinel node biopsy for breast cancer: incidence and clinical significance. *Ann Surg Oncol* 2005; **12:** 29–33.

10 Siponen ET, Vaalavirta LA, Joensuu H, Leidenius MH. Axillary and supraclavicular recurrences are rare after axillary lymph node dissection in breast cancer. *World J Surg* 2012; **36:** 295–302.

11 Van Zee KJ, Manasseh DME, Bevilacqua JLB, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol* 2003; **10:** 1140–51.

12 Mansel RE, Goyal A. European studies on breast lymphatic mapping. *Semin Oncol* 2004; **31:** 304–10.

13 Olson JA Jr, McCall LM, Beitsch P, et al, and the American College of Surgeons Oncology Group Trials Z0010 and Z0011. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011. *J Clin Oncol* 2008; **26:** 3530–35.

14 Lucci A, McCall LM, Beitsch PD, et al, and the American College of Surgeons Oncology Group. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol* 2007; **25:** 3657–63.

15 Viale G, Maiorano E, Mazzarol G, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer* 2001; **92:** 1378–84.

16 Greene FL, Page DL, Fleming ID, et al, eds. American Joint Committee on Cancer: AJCC cancer staging manual, 6th edn. New York: Springer, 2002: 157–64.

17 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual. 7th ed. New York: Springer, 2010: 143–64.

18 EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group. *N Engl J Med* 1988; **319:** 1681–92.

19 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16:** 1141–54.

20 Veronesi U, Orecchia R, Luini A, et al. Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery: experience with 590 cases. *Ann Surg* 2005; **242:** 101–06.

21 Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; **252:** 426–32.

22 Wasif N, Maggard MA, Ko CY, Giuliano AE. Underuse of axillary dissection for the management of sentinel node micrometastases in breast cancer. *Arch Surg* 2010; **145:** 161–66.

23 Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010; **28:** 731–37.

24 The EORTC. 10981-22023 AMAROS trial website: http://research.nki.nl/amaros/.

25 Colleoni M, Rotmensz N, Peruzzotti G, et al. Size of breast cancer metastases in axillary lymph nodes: clinical relevance of minimal lymph node involvement. *J Clin Oncol* 2005; **23:** 1379–89.

26 Goldhirsch A, Glick JH, Gelber RD, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Natl Cancer Inst* 1998; **90:** 1601–08.

27 Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ, and the Panel members. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009; **20:** 1319–29.

28 Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 2003; **21:** 3357–65.

29 Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ, and the Panel members. Panel members. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International expert consensus on the primary therapy of early breast cancer 2011. *Ann Oncol* 2011; **22:** 1736–47.