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IBCSG 23-01 randomised controlled trial comparing axillary dissection versus no axillary dissection in patients with sentinel node micrometastases

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CONFLICTS OF INTEREST

None of the authors have any conflicts of interest.

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Abstract

Background—For breast cancer patients with a metastatic sentinel node (SN), axillary dissection (AD) has been standard treatment. However, for patients with minimal SN involvement, AD may be overtreatment. IBCSG Trial 23-01 was designed to determine whether no AD is non-inferior to AD in patients with one or more micrometastatic (≤2 mm) SNs and tumour ≤5 cm.

Methods—In this multicentre trial patients were randomised to AD or no AD. Eligibility was limited to patients with clinically-palpable axillary lymph node(s) and a primary tumour ≤ 5 cm who, after sentinel node biopsy, had one or more micrometastatic (≤ 2 mm) sentinel lymphs nodes with no extracapsular extension. The primary endpoint was disease-free survival (DFS). Non-inferiority was defined as a hazard ratio of <1·25 for no AD vs. AD. The analysis was intention to treat. Patients were randomly allocated in a 1:1 ratio to AD or no AD with stratification by centre and menopausal status. There was no attempt to blind the treatment assignment. The trial is registered with ClinicalTrials.gov, NCT00072293. Per protocol, disease and survival information continues to be collected yearly.

Findings—From 2001 to 2010, 934 patients were randomised; 931 were evaluable (464 in the AD group and 467 in the no AD group). After a median follow-up of 5·0 (IQR 3.6–7.3) years, there were 124 DFS events, including breast-cancer-related events in 95 patients (local, 18; contralateral breast, 12; regional, 6; and distant, 59), and other events in 29 (second malignancy, 26; death without prior cancer event, 3). Five-year DFS was 87·8% (95% CI 84·4%–91·2%) in the no AD group and 84·4% (95% CI 80·7%–88·1%) in the AD group (log-rank p=0·16) (HR no AD vs. AD=0·78, 95% CI 0·55–1·11, non-inferiority p=0·0042). Patients with reported long-term surgical events (grade 3–4) included 1 sensory neuropathy (grade 3), 3 lymphedema (2 grade 3 and 1 grade 4), and 3 motor neuropathy (grade 3), all in the AD group, and 1 grade 3 motor neuropathy in the no AD group. One serious adverse event was reported, a post-operative infection in the axilla in the AD group.

Interpretation—AD in patients with early breast cancer represented in this study (most had tumours < 3 cm (92%; 856/931), received breast conserving surgery (91%; 845/931) and adjuvant systemic therapy (96%; 892/931)) should be avoided when the SN is minimally involved, thus eliminating complications of axillary surgery with no adverse effect on survival.

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Keywords

breast cancer; sentinel node; axillary node; micrometastasis; sentinel node biopsy; axillary dissection; lymph node

INTRODUCTION

The first randomised trial to validate sentinel node biopsy (SNB) in breast cancer was published in 2003.[1] This trial and others confirmed that SNB accurately stages the axilla, so that if the sentinel node (SN) is uninvolved the other axillary nodes are disease-free with high probability and the patient can be spared axillary dissection (AD).[2–4] If the SN is involved by metastasis, standard practice at the time was to perform AD (levels I and II in the United States,[5,6] and all three Berg levels in many European countries[4]).

AD removes any disease within the axilla – after which disease recurrence in the axilla is almost unknown[7–10] – and may also have a favourable effect on survival, although this has never been proven;[4,11] its main use was as a disease staging procedure. [4,12] However short and long-term side effects of AD have always been a concern. These include lymphedema, pain, and reduced arm movement.[13,14]

SNB very quickly became an integral part of the conservative treatment of breast cancer because it permitted avoidance of AD in a large proportion of patients, with early breast cancer, while still providing information to guide adjuvant treatment.

However, with the development of SNB came new and more exhaustive methods of evaluating the SN in order to ensure that any disease there was not missed. Whereas around three sections per axillary lymph node were typically examined in the pre-SNB era, the entire SN was serial sectioned and all sections examined.[15] This evaluation resulted in the frequent identification of micrometastatic foci (≤2 mm in diameter) and isolated tumour cells (ITCs), whose prognostic significance was uncertain.

We hypothesised that in patients with micrometastases only in the SN, AD might be overtreatment; we designed the IBCSG 23-01 multi-centre randomised controlled trial to determine whether this was the case.

Specifically the trial was designed to compare outcomes in patients with SN micrometastases treated with AD, with outcomes in those receiving no further treatment to the axilla. The primary study endpoint was disease-free survival (DFS) but we were also interested in axillary recurrence rates and axillary surgery complication rates in the two arms.

PATIENTS AND METHODS

Study design and patients

IBCSG 23-01 was a two-arm, multicentre, randomised, non-inferiority, phase 3 trial comparing no AD with AD in breast cancer patients with sentinel node micrometastases. Patients were recruited from 27 institutions between April, 2001, and February, 2010. The protocol was approved by the institutional review boards of all participating centres, and all participants provided written informed consent. Data were collected at the participating centres and transmitted to the IBCSG data management centre in Amherst, New York, via the DataFax or iDataFax system.

Eligible patients were registered for the trial prior to surgery after giving written informed consent (figure 1, flow chart). 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. Eligibility was amended

in June, 2006 to broaden eligibility by allowing patients with one or more positive SNs (formerly only one); multicentric/multifocal tumours (formerly only unicentric), and largest lesion size ≤ 5 cm (formerly ≤ 3 cm).

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

The independent Data and Safety Monitoring Committee reviewed accrual, safety, and number of events every 6 months.

Randomization and masking

Patients were randomly allocated in a 1:1 ratio to AD or no AD using permuted blocks generated by a congruence algorithm. The randomization was stratified by participating centre and menopausal status. After confirming eligibility, participating centre staff accessed the central randomization system via the internet and entered required information including stratification factors. The randomization system assigned a patient ID, treatment group, and date of randomization via the computer screen with a follow-up email. The IBCSG data management centre developed and maintains the randomization 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.

Sentinel node examination

The SN could be examined in either of three ways: (a) Preoperatively under local anaesthesia; if the patient had a micrometastatic node and was randomised to AD, she received AD during the operation to remove the primary. (b) Intra-operatively, with intra-operative SN examination, and AD performed during the operation to remove the primary. (c) Intra-operatively with later histological examination, and later second surgery under general anaesthesia if randomised to AD. All SNs were entirely sectioned at 50–200 μm intervals and each section (frozen or permanent) was examined by haematoxylin and eosin staining. Cytokeratin immunostaining was used only when the presence of micrometastasis was suspected but not certain, or not determined, on haematoxylin and eosin-stained sections.

End points

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

Accrual and statistical analyses

As originally designed, target accrual was 1,960 patients with analysis planned after 558 events. These targets were based on having 90% power to detect non-inferiority of no AD with a one-sided statistical significance level of 10% (i.e., α=0.10) under the assumption that five-year DFS with AD was 70% and defining non-inferiority as a hazard ratio of less than 1·25 (no AD relative to AD).

Accrual started on 1 April 2001 and closed on 28 February 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, it was decided to continue patient follow-up and perform the primary analysis after a median follow-up of 60 months, when at least 100 events were expected to have occurred. This decision was made without any knowledge of endpoint treatment comparisons. No interim analyses were 10 performed, 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.

Long term surgical events (sensory neuropathy, lymphedema, and motor neuropathy) were assessed at each follow-up visit (every four months from the date of randomization for the first year, and every six months years 2 to 5) and reported by the treating physician based on the National Cancer Institute Common Toxicity Criteria version 2. Serious adverse events were collected as they occurred. The numbers of long-term surgical effects were compared across the treatment groups using Fisher's exact test after excluding patients who did not receive the treatment allocated by randomisation.

DFS and OS were evaluated using the Kaplan-Meier product-limit method. The log-rank test, stratified by menopausal status, was used to compare the treatment groups. The log-rank test statistic (O–E, which denotes "observed minus expected" numbers of events) and its variance (V) were converted into a hazard ratio (HR) comparing no AD versus AD using the formula $\mathrm{HR}=\exp([\mathrm{O}-\mathrm{E}]/\mathrm{V})$.[18] Confidence intervals (CI) and p values for HRs were estimated based on a normal distribution following natural logarithm transformation. The one-sided test of non-inferiority of no AD was performed comparing the observed HR with 1·25 (i.e., null hypothesis HR ≥1·25). The cumulative incidence of breast cancer events, defined as invasive relapse at any site or contralateral breast cancer, was evaluated and compared using the method of Gray, [19] treating second primaries and other-cause death as competing risks. The pre-defined primary analysis was carried out 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.

Multivariable analyses were performed on DFS in the intention-to-treat population using the proportional hazards regression model, stratified by menopausal status. Each predictor was first evaluated in a univariate analysis. Statistically-significant (2-sided $p<0{\cdot}05$) predictors where then entered, together with treatment group, in the multivariable regression model. The remaining variables were subsequently re-evaluated for inclusion in the multivariable model. The interaction between treatment group and each predictor was evaluated by including the appropriate product term in the multivariable regression model.

All hazard ratios, excepting the analysis of OS, were evaluated with 95% confidence intervals or 99% confidence intervals for subgroup analyses. For the analysis of OS, a 90% confidence interval was used in order to facilitate comparison with the ACOSOG Z0011[13] trial. The statistical analysis was performed using SAS Version 9.2 and R Version 2.15.1. This study is registered with ClinicalTrials.gov, NCT00072293.

Role of the funding source

The study was not supported by sources outside the International Breast Cancer Study Group (IBCSG). The IBCSG was solely responsible for the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the paper for publication. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

RESULTS

Baseline characteristics and treatment

A total of 6681 patients were registered for the trial prior to surgery between 4 April 2001 and 1 February 2010. Of these, 934 patients (14% of those screened) from 27 clinical centres were randomised after informed consent and determination of eligibility, especially with respect to micrometastatic involvement of sentinel lymph nodes. Of these, 583 (62%) were from the European Institute of Oncology, Milan.

Three randomised patients were excluded from the analysis for the following reasons: 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 excluding these three patients, 931 were available for analysis as the intention-to-treat population (figure 1). Follow-up compliance was good and similar in the two treatment arms; of patients remaining disease-free, only 2.3% in the AD group and 1.7% in the no AD group had most recent follow up prior to 2010. In the group allocated to AD, 17 did not receive AD, and in the group allocated to no AD, 14 received AD. 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). More postmenopausal (56%) than premenopausal patients (44%) were randomised. Sixty-nine percent of patients had tumours <2 cm, 7% had tumours ≥3 cm, and 28% had grade III disease. Tumours were oestrogenreceptor positive in 90% of patients, and progesterone-receptor positive in 75% of patients. Sixty-nine percent of patients had SN micrometastasis ≤1·0 mm, 29% had micrometastasis 1·1–2·0 mm, and 2% had metastasis >2·0 mm. Most patients (97%) underwent lymphoscintigraphy, and 1 or 2 sentinel nodes were found in 82% of patients. Excision biopsy was performed in 13% of patients. The median number of axillary nodes removed in the AD group was 21·0. Additional involved axillary nodes were found in 13% of patients in the AD group. Among the 447 patients in the AD group who received AD, 59 (13%) had at least one additional axillary node involved; 37 (8%) had one, 13 (3%) had two and 9 (2%) had three or more involved. Breast-conserving surgery was definitive treatment in 91% of patients in both the AD and no AD groups. The remaining patients underwent mastectomy.

Among patients who received breast-conserving surgery, adjuvant radiotherapy was given to 98% in the AD group and 97% in the no AD groups (table 1). 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 28% of patients in the AD group and 27% of patients in the no AD group who received breast-conserving surgery. Hormone treatment alone was given to 63% and 67% of patients in the AD and no AD groups, respectively (table 1). Chemotherapy alone was given to 9% and 7% of patients the AD and no AD groups, respectively. Combinations of hormonal therapy and chemotherapy were given to 23% and 22% of patients in the AD and no AD groups, respectively.

Outcomes

Long term sequelae of the surgical intervention to the axilla comprised sensory neuropathy, lymphedema, and motor neuropathy. As expected, these events were more frequent and more severe in the AD group than in the no AD group (table 2). Serious adverse events were also collected in the trial, and one patient experienced a post-operative infection in the axilla attributed to protocol-assigned treatment (AD).

At a median follow-up of 5.0 (IQR 3.6–7.3) years, there were 95 breast cancer events (table 3)—48 and 47 in the AD and no AD groups, respectively. Second-primary (non-breast) cancer events occurred in 26 additional patients—20 in the AD group, 6 in the no AD group. An additional two patients in the no AD group died with no evidence of a prior cancer event and one death in the AD group lacks additional information. Thus, a total of 124 events were available for the analysis of DFS—69 in the AD group, and 55 in the no AD group. There were 19 and 17 deaths in the AD and no AD groups, respectively, with or without a prior cancer event.

Distant metastasis was the first event in 59 patients—34 in the AD group, and 25 in the no AD group. Locoregional recurrence was first event in 24 patients—11 in the AD group, and 13 in the no AD group. There were regional recurrences in 1 patient in the AD group and 5 patients in the no AD group; one recurrence involved the axilla in the AD group and four involved the axilla in the no AD group. All 6 patients with a regional recurrence received breast-conserving surgery. Four of these patients received radiotherapy (the patient in the AD group received postoperative radiotherapy only, two in the no AD group received intra-operative radiotherapy only, and one in the no AD group received both intra-operative and postoperative radiotherapy.

Five-year DFS was 84·4% (95% CI 80·7%–88·1%) in the AD group and 87·8% (95% CI 84·4%–91·2%) in the no AD group (log-rank p=0·16; figure 2A). DFS in the no AD group was non-inferior to the AD group (HR for no AD vs. AD 0·78 [95% CI 0·55–1·11], non-inferiority p=0·0042). Results for the per-protocol population were similar (DFS HR 0·80 [95% CI 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 AD group and 10·6% (95% CI 7·5–13·8) in the no AD group (HR 0·97 [95% CI 0·65–1·46] p=0·90; figure 2B). Five-year OS was 97·6% (95% CI 96·0%–99·2%) in the AD group and 97·5% (95% CI 95·8%–99·1%) in the no AD group (HR 0·89 [90% CI 0·52–1·54], log-rank p=0·73; figure 2C).

Subgroup analysis was performed 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 less than 1·25, and no AD was significantly (i.e., p<0·10) non-inferior to AD group in the following subgroups: tumour size <2 cm (non-inferiority p=0·017), tumour size 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).

The multivariable proportional hazards regression analysis for DFS is shown in table 4. All variables in table 1 were evaluated for predictive ability but only those predictors that were significant in univariate analysis (2-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 DFS, while AD vs. no AD had no significant effect on DFS. ER status and PgR status, while significant in 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 hazard ratio (DFS 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. There were no significant interactions between treatment group and any of the other predictors (data not shown); thus, no evidence of heterogeneity of hazard ratios was detected across the subgroups defined by the prognostic factors.

DISCUSSION

At a median follow-up of 5.0 years, we found no difference between the AD and no AD arms for the primary endpoint of DFS. Accrual was slower than anticipated, mainly because small metastases were rare. There were 6,681 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 AD compared to AD was fulfilled. In fact DFS was much better than anticipated overall: five-year DFS rates were well above the 70% assumed in the protocol. Most patients in our study had tumours less than 3 cm (92%), received breast conserving surgery (91%) and adjuvant systemic therapy (96%), and thus our results are most directly applicable to these patient subpopulations.

OS also did not differ between the two arms. Furthermore there was a reassuringly low rate of disease recurrence in the un-dissected 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 AD arm. The discrepancy between the low rate of axillary recurrence in the no AD arm and the high rate of axillary involvement in the AD arm may be due to systemic treatment and whole breast irradiation, both of which can eliminate low volume axillary metastasis.[4] In fact most of our patients (95–97%) received RT or systemic treatment (or both). Note however that 22% of no AD arm patients who had breast-conserving surgery received no radiation therapy (3%) or received ELIOT (partial breast irradiation) alone (19%) which cannot sterilize any residual axillary disease. It is also possible that intact axillary lymph nodes can eliminate low volume disease by immuno-surveillance mechanisms.[4]

Our findings are consistent with those of the recent ACOSOG Z0011[13,21,22] trial which recruited 856 patients with limited macrometastatic SN involvement (not more than two metastatic SNs) undergoing conservative surgery only, and randomised them to AD versus no further axillary treatment. After a median follow-up of 6·3 years, there were no differences between the arms for any endpoint. The authors concluded that for patients with limited SN involvement, no AD is justified provided that patients receive both traditional whole breast radiation and systemic adjuvant treatment. Supplemental table S1 in the webappendix shows results for both Z0011 and IBCSG 23-01.

Unlike Z0011, 9% of the patients in our trial received mastectomy. Although numbers are small, sub-group analysis suggested that no AD may be acceptable for patients undergoing mastectomy (figure 3) provided the invasive component of the breast lesion is small. AD has traditionally been a guide to adjuvant treatment rather than a treatment itself. However in our study there was no difference between the two arms in terms of proportions receiving any type of adjuvant therapy, indicating that detailed axillary node involvement – determined in the AD arm – had no influence on adjuvant treatment. The AMAROS study, which is comparing AD with axillary RT in patients with early breast cancer and a positive SN also found that AD had no influence on the administration of adjuvant treatment in the first 566 patients assessed[23,24]. Thus the information provided by AD is no longer useful. There are other reasons for wanting to spare women AD when the SN is positive: in general about 50% of such patients have no other axillary involvement (87% of our AD arm patients) and for them AD is overtreatment. Furthermore biologic characteristics of the primary tumour, such as hormone receptor expression,[25,26] HER2 status,[27,28] and tumour proliferation rate (e.g., Ki67 labelling index)[27,28] substitute the prognostic information formerly provided by axillary status.

In conclusion, it is likely that our trial and Z0011 will change clinical practice, allowing no AD in many patients with early breast cancer especially when the SN is minimally involved,

thus reducing AD surgical complications 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 SN should not be an indication for AD irrespective of the type of breast surgery given.

PANEL

Systematic Review

In order to prepare this clinical trial protocol, we searched the medical literature for morbidity associated with axillary dissection and sentinel node biopsy, sentinel lymph node procedures, and the significance of occult micrometastatic disease in axillary nodes. As the trial progressed we followed emerging data on the results of sentinel node biopsies and as a result amended the protocol to broaden the eligibility.

Interpretation

These results are likely to change clinical practice. AD in patients with early breast cancer represented in this study should be avoided when the sentinel node is minimally involved, thus eliminating complications of axillary surgery with no adverse effect on survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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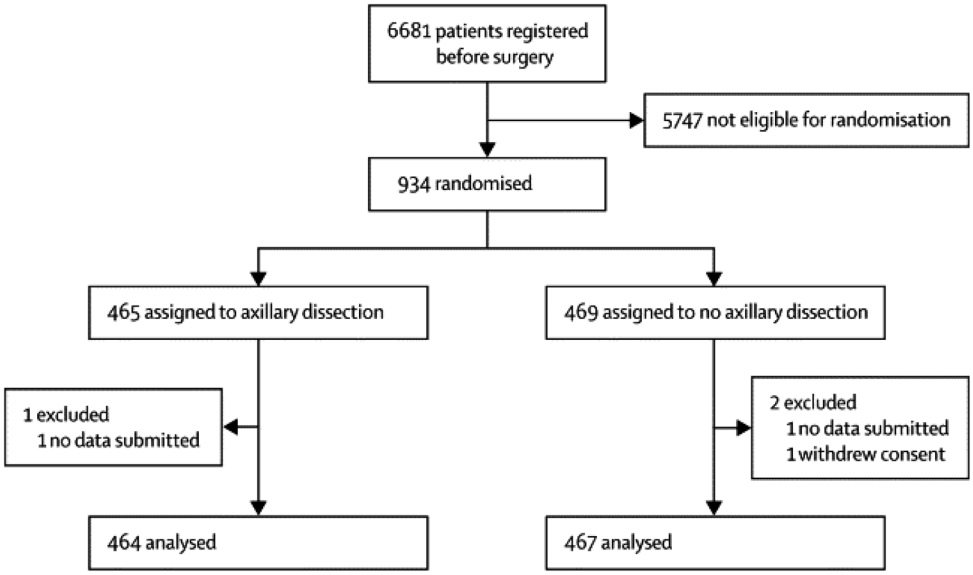

Figure 1.

CONSORT diagram showing the 931 patients in the analytic cohort of IBCSG Trial 23- 01 for the intention-to-treat (ITT) analysis. The trial included a registration step prior to surgery with eligibility based on clinical features. Only patients with eligible pathological features determined at primary breast surgery (one or more positive sentinel nodes and largest tumour lesion size ≤ 5 cm) were eligible for randomisation.

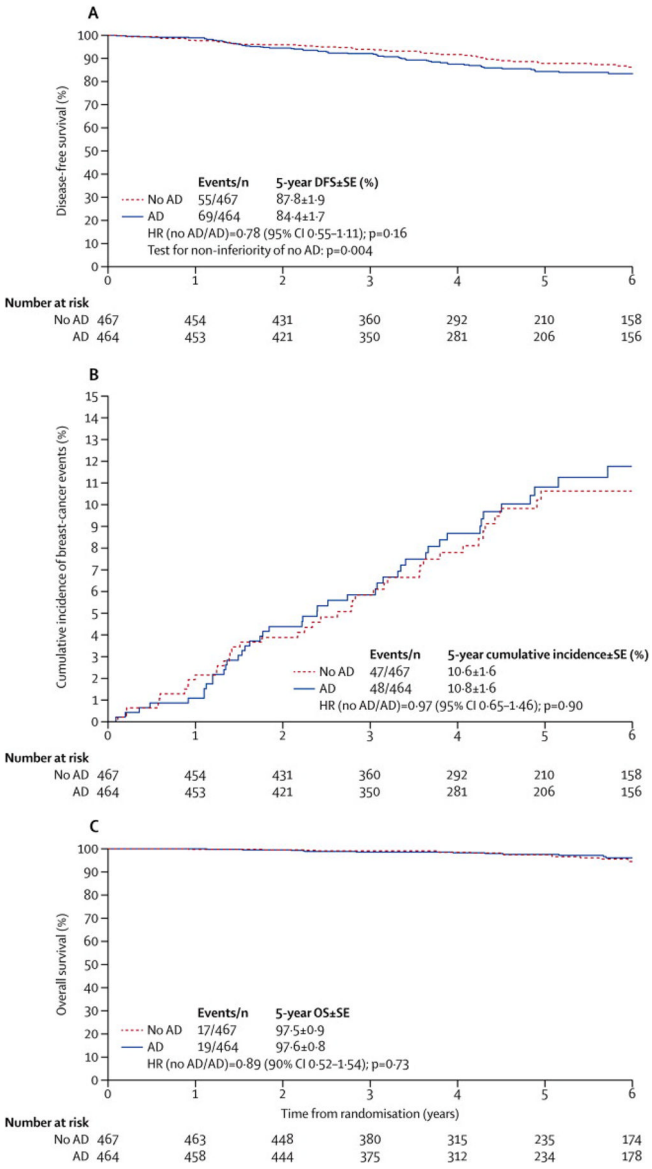

Figure 2.

Comparison of axillary dissection (AD, solid line) to no axillary dissection (No AD, dashed line) for disease-free survival (A), cumulative incidence of breast cancer events (B), and overall survival (C) in the intention-to-treat population of 931 patients.

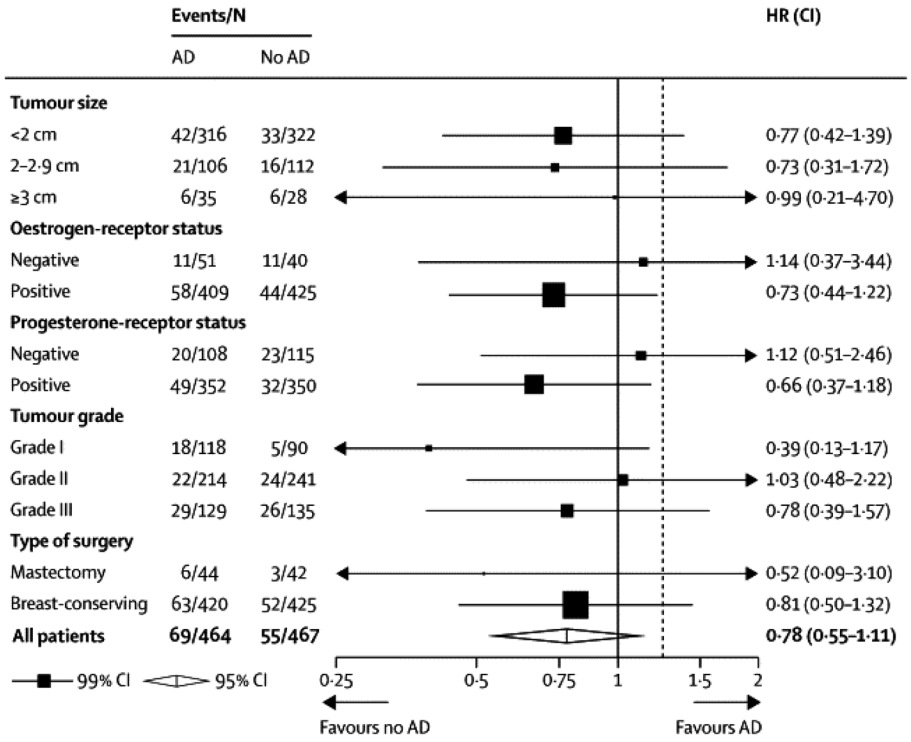

Figure 3.

Hazard ratios and confidence intervals comparing axillary dissection (AD) with no axillary dissection (No AD) among subgroups of the intention-to-treat population of 931 patients. Each subgroup hazard ratio is shown as a black square with the size of the square being inversely proportional to the variance of the corresponding log-hazard-ratio estimate (i.e., larger squares indicate lower variability in the estimate). The hazard ratio for all patients is shown as a diamond. The horizontal axis is displayed on a logarithmic scale.

Table 1

Patient characteristics and adjuvant therapies

Characteristic or therapy	Axillary Dissection (n=464)	No Axillary Dissection (n=467)
Age, years		
Median (range)	53 (28–81)	54 (26–81)
Pre-operative SNB		
No	287 (62%)	286 (61%)
Yes	177 (38%)	181 (39%)
Menopausal status		
Pre	204 (44%)	207 (44%)
Post	260 (56%)	260 (56%)
Pathologic 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%)

Characteristic or therapy	Axillary Dissection (n=464)	No Axillary Dissection (n=467)
Internal mammary only	1 (<1%)	0
Both	7 (2%)	19 (4%)
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 (RT)	10 (2%)	12 (3%)
With RT	410 (98%)	413 (97%)
Intraoperative RT only	79 (19%)	80 (19%)
Postoperative RT only	293 (70%)	297 (70%)
Combination RT	36 (9%)	35 (8%)
Unspecified RT	2 (<1%)	1 (<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%)

*Percentages for type of surgery are based on entire population, those for radiotherapy (no, yes) and for type of radiotherapy are based on only the breast-conserving surgery subpopulation.

Table 2

Long-term surgical events*

Event	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%)	
Lymphedema	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 3

Disease free survival events and deaths at 5.0 years median follow-up

	Axillary Dissection (n = 464)	No Axillary Dissection (n = 467)	Total (n = 931)
Disease free survival events*			
Total	69 (15%)	55 (12%)	124 (13%)
Breast cancer events			
Local	10 (2%)	8 (2%)	18 (2%)
Regional	1 (<1%)	5 (1%)	6 (1%)
Distant	34 (7%)	25 (5%)	59 (6%)
Contralateral breast	3 (<1%)	9 (2%)	12 (1%)
Non-breast cancer events			
Second (non-breast) primary†	20 (4%)	6 (1%)	26 (3%)
Death without prior cancer event	1 (<1%)	2 (<1%)	3 (<1%)
Deaths	19 (4%)	17 (4%)	36 (4%)

*Includes all breast cancer events, all non-breast cancer events, and deaths with cause unknown

†Types (number) of second primaries in the axillary dissection group were gastrointestinal (4), genito-urinary (2), gynaecological (6), hematologic (2), laryngeal (2), lung (1), and sarcoma (3). Types (number) in the no-axillary dissection group were gastrointestinal (2), gynaecological (3), melanoma (1).

Table 4

Multivariable proportional-hazards regression analysis of DFS*

Variable	Hazard ratio (95% CI)	p value
Multivariable analysis		
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		*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		*0·0049*

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