Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

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Summary

Background If treatment of the axilla is indicated in patients with breast cancer who have a positive sentinel node, axillary lymph node dissection is the present standard. Although axillary lymph node dissection provides excellent regional control, it is associated with harmful side-effects. We aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects.

Methods Patients with T1–2 primary breast cancer and no palpable lymphadenopathy were enrolled in the randomised, multicentre, open-label, phase 3 non-inferiority EORTC 10981-22023 AMAROS trial. Patients were randomly assigned (1:1) by a computer-generated allocation schedule to receive either axillary lymph node dissection or axillary radiotherapy in case of a positive sentinel node, stratified by institution. The primary endpoint was non-inferiority of 5-year axillary recurrence, considered to be not more than 4% for the axillary radiotherapy group compared with an expected 2% in the axillary lymph node dissection group. Analyses were by intention to treat and per protocol. The AMAROS trial is registered with ClinicalTrials.gov, number NCT00014612.

Findings Between Feb 19, 2001, and April 29, 2010, 4823 patients were enrolled at 34 centres from nine European countries, of whom 4806 were eligible for randomisation. 2402 patients were randomly assigned to receive axillary lymph node dissection and 2404 to receive axillary radiotherapy. Of the 1425 patients with a positive sentinel node, 744 had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy; these patients constituted the intention-to-treat population. Median follow-up was 6·1 years (IQR 4·1–8·0) for the patients with positive sentinel lymph nodes. In the axillary lymph node dissection group, 220 (33%) of 672 patients who underwent axillary lymph node dissection had additional positive nodes. Axillary recurrence occurred in four of 744 patients in the axillary lymph node dissection group and seven of 681 in the axillary radiotherapy group. 5-year axillary recurrence was 0·43% (95% CI 0·00–0·92) after axillary lymph node dissection versus 1·19% (0·31–2·08) after axillary radiotherapy. The planned non-inferiority test was underpowered because of the low number of events. The one-sided 95% CI for the underpowered non-inferiority test on the hazard ratio was 0·00–5·27, with a non-inferiority margin of 2. Lymphoedema in the ipsilateral arm was noted significantly more often after axillary lymph node dissection than after axillary radiotherapy at 1 year, 3 years, and 5 years.

Interpretation Axillary lymph node dissection and axillary radiotherapy after a positive sentinel node provide excellent and comparable axillary control for patients with T1–2 primary breast cancer and no palpable lymphadenopathy. Axillary radiotherapy results in significantly less morbidity.

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Introduction

Sentinel node biopsy has replaced axillary lymph node dissection as the standard method for assessment of axillary lymph node status in clinically node-negative breast cancer. Many studies have proven the accuracy and high negative predictive value of the sentinel node procedure.[1,2] Findings from several randomised trials showed that patients with a negative sentinel node can be spared the short-term and long-term morbidity of axillary lymph node dissection, and this translates into a better quality of life (QoL).[3–6] Axillary lymph node dissection is associated with harmful and often persistent side-effects, particularly lymphoedema and restriction in shoulder mobility.[7–9] Axillary lymph node dissection has long been regarded as standard if treatment of the axilla is indicated for patients with a positive sentinel node.[10] Recently, findings from the ACOSOG Z0011 trial[11,12] and the IBCSG 23-01 trial[13] showed that patients with limited disease in the sentinel node or nodes who are treated with breast-conserving surgery, whole breast irradiation, and

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For the **trial protocol** see http://www.eortc.be/services/doc/10981-Protocol-Version5.pdf

adjuvant systemic treatment can be spared axillary lymph node dissection without compromising locoregional control or survival. An adaptation of the strategy to omit axillary lymph node dissection in patients with low-risk axillary involvement who are treated with breast-conserving surgery, whole breast irradiation, and adjuvant systemic treatment is included in the American Society of Clinical Oncology guidelines.[14] However, for a subset of patients with sentinel node involvement, axillary treatment is still deemed useful. Further involvement of the axillary lymph nodes is suggested to be predicted on the basis of factors such as tumour size, type, grade, vascular invasion, and extracapsular extension of cancer in the sentinel nodes.[15–17] Patients with a high risk of axillary involvement still need axillary treatment.[15]

Before the introduction of sentinel node biopsy, axillary radiotherapy was described as an alternative for axillary lymph node dissection in clinically node-negative patients.[18–20] Satisfactory local control was reported with axillary radiotherapy, with fewer side-effects compared with axillary lymph node dissection.[8,20] However, axillary lymph node dissection and axillary radiotherapy have never been compared prospectively in patients with a positive sentinel node. We aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects compared with axillary lymph node dissection.

Methods

Study design and patients

In 2001, the European Organisation for Research and Treatment of Cancer (EORTC) initiated the 10981-22023 AMAROS trial, a randomised, multicentre, open-label, phase 3 non-inferiority trial in patients with T1–2 primary, unifocal, invasive breast cancer, with no palpable lymphadenopathy. The study design of the AMAROS trial has been described previously.[21] Patients with tumours of up to 3 cm diameter were eligible. Bilateral breast cancer was not an exclusion criterion and there was no protocol-specified age limit. Included patients had to be fit to undergo any of the treatment procedures and be able to comply with the follow-up schedule. Patients were not eligible if they had a medical history of previous malignancy, had received neoadjuvant systemic treatment for the primary breast cancer, or had received treatment of the axilla by surgery or radiotherapy. After a protocol amendment on Feb 22, 2008 to adjust to developments in clinical practice, the eligibility criteria were broadened to include tumours up to 5 cm diameter or multifocal disease, or both. Furthermore, sentinel nodes with only isolated tumour cells were no longer regarded as sentinel node positive.

Patients provided written informed consent before registration in the trial. Consent for any patients under the age of 18 years had to be obtained according to national laws. The independent data monitoring committee reviewed accrual, safety, and maturity every 6 months. The AMAROS trial was approved by the local ethical committees of all the participating centres.

Randomisation and masking

Patients were randomly assigned (1:1) by a computer-generated allocation schedule at the EORTC headquarters to axillary lymph node dissection or axillary radiotherapy before sentinel node biopsy. Stratification was done by institution using a minimisation method. There were three reasons for undertaking randomisation before the sentinel node biopsy. First, this strategy prevented a selection bias, for instance by inclusion of patients with limited tumour deposit in the sentinel node. Second, after randomisation to axillary lymph node dissection, a one-stage procedure with sentinel node biopsy, frozen section and, in case of a positive sentinel node, immediate axillary lymph node dissection could be done. Third, omitting axillary treatment in a non-selected group of patients with a negative sentinel node could be prospectively analysed.

Procedures

Before participating in the trial, every centre had to fulfil the surgical quality control criteria, as described previously.[22] The sentinel node procedure had to be done with a radioactive isotope, preferably combined with blue dye (patent blue dye). Local treatment of the breast consisted of breast-conserving treatment including whole-breast radiotherapy or mastectomy with or without irradiation of the chest wall. The use of adjuvant systemic treatment was applied at the discretion of the treating multidisciplinary team.

Collection of patient, tumour, and treatment characteristics and analysis of the data was done at the EORTC headquarters. At the time of the design of the trial, the risk of axillary recurrence was thought to be determined by the presence of a positive sentinel node. For this reason, data on tumour biology, such as hormonal status, lymphovascular invasion, and extranodal extension of the sentinel nodes, were not recorded.

Axillary treatment for patients with a tumour-positive sentinel node had to start within 12 weeks after the sentinel node biopsy. Consequently, systemic treatment, if indicated, was administered after completing the axillary treatment. Axillary lymph node dissection had to be done according to the manual of the EORTC Breast Cancer Group[23] and was defined as a dissection of at least anatomical levels I and II including at least ten nodes. Axillary radiotherapy included the contents of all three levels of the axilla and the medial part of the supraclavicular fossa. The prescribed dose was 25 fractions of 2 Gy. Adjuvant axillary radiotherapy after axillary lymph node dissection was allowed when at least four positive nodes were found. Further information about surgery and radiotherapy guidelines and quality assurance has been published previously.[21,22,24]

Patients were assessed for disease recurrence according to standard clinical practice. Annual patient history,

physical examination, and mammography were required; additional testing was done on indication.

Assessments of lymphoedema and shoulder mobility were done at baseline and at 1, 3, 5, and 10 years by study clinicians. This assessment included recording any sign of lymphoedema. Furthermore, arm circumference 15 cm above the medial epicondyle (upper arms) and 15 cm below the medial epicondyle (lower arms) was measured at 1, 3, 5, and 10 years by study clinicians. An increase in arm circumference of at least 10% in the lower arm or the upper arm, or both, compared with the contralateral arm at the same timepoint was judged to be clinically significant lymphoedema.

For shoulder mobility, the range of motion in both arms was measured in four excursions: abduction, adduction, anteversion, and retroversion. For each of the excursions, the range of movement was compared between arms. The four relative excursions were combined in a multivariate composite endpoint at 1 and 5 years.

QoL was assessed using the EORTC quality-of-life questionnaire (EORTC-QLQ-C30; version 3) and breast cancer module (QLQ-BR23). The selected scales were pain, body image, and arm symptoms. The arm symptoms scale was composed of three items: pain in arm or shoulder, swollen arm or hand, and difficulties moving arm. Questionnaires were completed at baseline and at years 1, 2, 3, 5, and 10. All outcome data at 10 years will be presented in a future report.

Outcomes

The primary endpoint in the group of patients with a positive sentinel node was 5-year axillary recurrence, defined as tumour recurrence in lymph nodes in the ipsilateral axilla, infraclavicular fossa, or interpectoral area. Supraclavicular lymph node recurrences were classed as distant metastases. Recurrences had to be confirmed with histological or fine needle examination. Additionally, in the group of patients with a negative sentinel node, the axillary recurrence rate was analysed (prespecified analysis).

Secondary endpoints were axillary recurrence-free survival, disease-free survival (DFS), overall survival, shoulder mobility, lymphoedema, and QoL. Axillary recurrence-free survival was defined as the time to axillary recurrence or death from any cause. DFS was defined as any sign of disease progression including second malignancy (contralateral breast or non-breast cancer) or death.

Statistical analysis

The clinical cutoff date for this analysis was Oct 31, 2012. A complete statistical analysis plan was designed and approved before any analysis was done. All analyses were done with SAS 9.3. All described analyses are restricted to the patients with a positive sentinel node, unless otherwise specified.

For the efficacy endpoints 5-year axillary recurrence, DFS, axillary recurrence-free survival, and overall survival, patients without an event were censored at the last date known alive. We assessed 5-year axillary recurrence using the cumulative incidence method, with death as a competing risk; for the other endpoints, we used the Kaplan-Meier approach.

The primary objective of the trial was to show non-inferiority of axillary radiotherapy compared with axillary lymph node dissection with respect to 5-year axillary recurrence in patients with a positive sentinel node. 5-year axillary recurrence of 2% was assumed in the axillary lymph node dissection group and non-inferiority was defined as an axillary recurrence not higher than 4% in the axillary radiotherapy group. With a one-sided log-rank test for the hazard ratio (HR) for non-inferiority (non-inferiority margin of 2) with α of 0·05, 52 events were needed to ensure a power of 80% under the latter assumptions. Because of a low event rate, we realised that the projected number of events would probably never occur. Therefore, the independent data monitoring committee gave permission for the timing of the final analysis, with a data cutoff of Oct 31, 2012, leaving the primary non-inferiority test underpowered. We fitted a multivariate Cox proportional hazards model for DFS to assess the effect of important covariates on the main analysis (appendix). Additionally, we did a prespecified subgroup analysis to assess whether the results would be applicable to different subgroups (appendix).

See Online for appendix

Since this is a non-inferiority trial, all efficacy analyses were done in both the per-protocol population, which excluded patients with a sentinel node that contained only isolated tumour cells, and the intention-to-treat population, which included patients with isolated tumour cells only in the sentinel node who were randomly assigned before the protocol amendment.

We analysed the 1-year, 3-year, and 5-year lymphoedema endpoints using Fisher's exact test. For the composite shoulder mobility endpoints, we did a multivariate ANOVA on the basis of Hotelling's T^2 test on the log scale. We set a significance level of 5% for all tests. All safety analyses were done for the safety population, defined as those patients with a positive sentinel node who received at least the randomised treatment.

The main QoL objective was to compare the QoL scales over time between the two groups for all patients with a positive sentinel node. We fitted a linear mixed model with treatment, a (linear) time effect, and a time–treatment interaction as fixed effects, and patient-specific random effects. We obtained from the model a general F test for differences between the two treatment groups at all timepoints after baseline. Differences of at least 10 points (on a 0–100 scale) were classified as clinically relevant,[25] with the study being more than adequately powered to detect such differences.

For the **full statistical analysis plan** see http://www.eortc.be/services/doc/10981SAP_FARv1.pdf

The AMAROS trial is registered with ClinicalTrials.gov, number NCT00014612.

Role of the funding source
The funding source had no role in study design or conduct, data collection, data management, data analysis, data interpretation, or writing of the report. MD, LS, NJD, CC, JB, and EJTR had full access to all the data in the study, and EJTR had final responsibility for the decision to submit for publication.

Results

Between Feb 19, 2001, and April 29, 2010, 4823 patients were enrolled at 34 centres from nine European countries, which included affiliates of the ALMANAC Trialists Group and the Dutch Breast Cancer Trialists Group. 17 patients were excluded because they did not provide informed consent, leaving 4806 patients for further analysis (figure 1). 2402 patients were randomly assigned to receive axillary lymph node dissection and 2404 to receive axillary radiotherapy. 1425 patients (30%) were found to be sentinel node positive; 744 of whom had been randomly assigned to the axillary lymph node dissection group and 681 to the axillary radiotherapy group. In 132 patients the sentinel node was not identified, resulting in an identification rate of 4674 (97%) of 4806 patients. Since a sentinel node was defined as a lymph node that was radioactive or blue, or both, nodes that were only suggestive of disease on palpation were excluded. Inclusion of those nodes as sentinel nodes would not have changed the results (data not shown).

Because the results of both the intention-to-treat and per-protocol analyses were qualitatively the same for the primary and all secondary efficacy endpoints, only the intention-to-treat results are reported here and the per-protocol results are reported in the appendix.

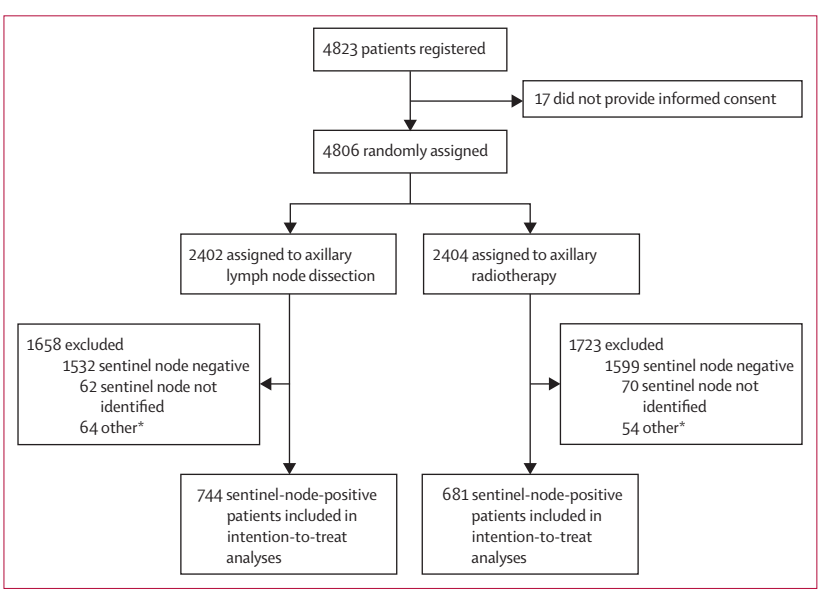

Figure 1: **Trial profile**
*Includes patients who did not undergo sentinel node biopsy or the sentinel node results were unknown (12 in the axillary lymph node dissection group and 12 in the axillary radiotherapy group), had only a positive non-sentinel node (16 and six), had a positive sentinel node that was not located in the axilla (nine and 13), or only isolated tumour cells in the sentinel node after the protocol amendment (27 and 23).

Patient and disease baseline characteristics were well balanced between the two treatment groups (table 1). In 859 (60%) of 1425 patients with a positive sentinel node, preoperative staging of the axilla included ultrasound examination. Median follow-up was 6·1 years (IQR 4·1–8·0) in the patients who were sentinel node positive and 5·1 years (3·9–6·3) in those who were sentinel node negative (forms were only collected up to 5 years in the latter group).

A median of two (IQR 1–3) sentinel nodes were removed in both treatment groups. A median of one (IQR 1–1) sentinel node had proven metastasis, including isolated tumour cells in both treatment groups. Most patients in both treatment groups had a macrometastasis in the sentinel node (table 1).

In the axillary lymph node dissection group, a median of 15 (IQR 12–20) additional nodes were removed besides the sentinel node; histological examination revealed additional lymph nodes with metastases in 220 (33%) of 672 patients who underwent axiliary lymph node dissection, 52 (8%) of whom had four or more additional metastatic nodes. Combined axillary treatment (axillary lymph node dissection followed by axillary radiotherapy) was administered to 41 patients randomly assigned to the axillary lymph node dissection group and 12 patients in the axillary radiotherapy group.

Axillary recurrence occurred in four of 744 patients in the axillary lymph node dissection group and seven of 681 in the axillary radiotherapy group over the entire follow-up period. Two of the four recurrences in the axillary lymph node dissection group and two of the seven recurrences in the axillary radiotherapy group were isolated axillary recurrence as a first event. The axillary recurrences occurred with a previous or concurrent local recurrence in one patient in the axillary lymph node dissection group and two patients in the axillary radiotherapy group. 5-year axillary recurrence was 0·43% (95% CI 0·00–0·92) in the axillary lymph node dissection group and 1·19% (0·31–2·08) in the axillary radiotherapy group. The one-sided 95% CI for the underpowered non-inferiority test on the HR was 0·00–5·27, with a non-inferiority margin of 2. In the group of 3131 patients with a negative sentinel node, 25 axillary recurrences occurred during the entire follow-up period (axillary recurrence rate 0·72%, 95% CI 0·39–1·04).

There were no significant differences between treatment groups in DFS and overall survival. 124 disease-free survival events occurred in the axillary lymph node dissection group and 134 in the axillary radiotherapy group. 5-year DFS was 86·9% (95% CI 84·1–89·3) in the axillary lymph node dissection group and 82·7% (79·3–85·5) in the axillary radiotherapy group (HR 1·18, 95% CI 0·93–1·51; p=0·18; figure 2A). 71 (10%) of 744 patients in the axillary lymph node dissection group and 76 (11%) of 681 in the axillary radiotherapy group died.

Death due to breast cancer occurred in 53 (7%) patients in the axillary lymph node dissection group and 54 (8%) in the axillary radiotherapy group. 5-year overall survival was 93·3% (95% CI 91·0–95·0) in the axillary lymph node dissection group and 92·5% (90·0–94·4) in the axillary radiotherapy group (HR 1·17, 95% CI 0·85–1·62; p=0·34; figure 2B). Because of the low number of axillary recurrences, axillary recurrence-free survival is analogous to overall survival and is not reported. In patients who were sentinel node negative, 5-year DFS was 87·9% (95% CI 86·6–89·1) and overall survival was 95·4% (94·4–96·1). No significant differences in DFS were noted in the subgroup analyses (appendix).

Information on lymphoedema and arm circumference increases were collected from 1241 (98%) of 1265 patients at baseline, 820 (65%) of 1255 at 1 year, 714 (62%) of 1154 at 3 years, and 614 (69%) of 895 at 5 years. Lymphoedema was noted significantly more often after axillary lymph node dissection than after axillary radiotherapy at every measured timepoint (table 2). An increase in arm circumference by at least 10% was reported in a numerically greater proportion of patients in the axillary lymph node dissection group compared with the axillary radiotherapy group; however, the difference was only significant at 5 years. 39 (6%) of 655 patients in the axillary lymph node dissection group and 11 (2%) of 586 patients in the axillary radiotherapy group received both radiation and surgery to the axilla. Lymphoedema was significantly more frequently reported in this subgroup compared with patients who were treated with axillary lymph node dissection or axillary radiotherapy only.[26] When those patients who received

	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
Baseline characteristics		
Age, years	56 (48–64)	55 (48–63)
Menopausal status		
Premenopausal	283 (38%)	289 (42%)
Postmenopausal	449 (60%)	384 (56%)
Missing	12 (2%)	8 (1%)
Preoperative ultrasound axilla		
Done	440 (59%)	419 (62%)
Not done	304 (41%)	262 (38%)
Tumour on dominant side		
Yes	377 (51%)	329 (48%)
No	352 (47%)	336 (49%)
Bilateral	8 (1%)	2 (<1%)
Missing	7 (1%)	14 (2%)
Clinical tumour size		
Median (mm; IQR)	17 (13–22)	18 (13–23)
0–2 cm	612 (82%)	533 (78%)
2–5 cm	132 (18%)	143 (21%)
>5 cm	0 (0%)	1 (<1%)
Missing	0 (0%)	4 (1%)
Tumour type		
Infiltrating ductal	563 (76%)	515 (76%)
Infiltrating lobular	100 (13%)	99 (15%)
Other	81 (11%)	66 (10%)
Missing	0 (0%)	1 (<1%)
Grade		
I	179 (24%)	154 (23%)
II	356 (48%)	311 (46%)
III	192 (26%)	200 (29%)
Missing	17 (2%)	16 (2%)
Type of breast surgery		
Breast-conserving surgery	609 (82%)	557 (82%)
Mastectomy	127 (17%)	121 (18%)
Missing	8 (1%)	3 (<1%)

(Table 1 continues on next page)

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	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
Adjuvant radiotherapy		
Breast	597 (80%)	546 (80%)
Chest wall	34 (5%)	51 (7%)
Internal mammary chain	72 (10%)	65 (10%)
Systemic treatment administered		
Any systemic treatment	666 (90%)	612 (90%)
Chemotherapy	453 (61%)	418 (61%)
Hormonal therapy	585 (79%)	525 (77%)
Immunotherapy	45 (6%)	44 (6%)
Sentinel node characteristics		
Number of sentinel nodes removed		
1	332 (45%)	293 (43%)
2	201 (27%)	217 (32%)
3	127 (17%)	105 (15%)
≥4	84 (11%)	66 (10%)
Number of positive sentinel nodes		
1	581 (78%)	512 (75%)
2	127 (17%)	134 (20%)
3	29 (4%)	27 (4%)
≥4	7 (1%)	8 (1%)
Size of the largest sentinel node metastasis		
Macrometastasis	442 (59%)	419 (62%)
Micrometastasis	215 (29%)	195 (29%)
Isolated tumour cells	87 (12%)	67 (10%)
Number of positive additional nodes (besides sentinel node)		
0	451/672 (67%)*	26/69 (38%)†
1–3	168/672 (25%)*	24/69 (35%)†
≥4	52/672 (8%)*	17/69 (25%)†
Missing	1/672 (<1%)*	2/69 (3%)†

Data are median (IQR) or number (%). Some percentages do not total 100 because of rounding. *72 patients did not have axillary lymph node dissection. †Additional metastatic lymph nodes in the axillary radiotherapy group were found in a group of patients who crossed over from axillary radiotherapy to axillary lymph node dissection and are thus not representative of the number of additional nodes in the whole group.

Table 1: **Baseline and treatment characteristics**

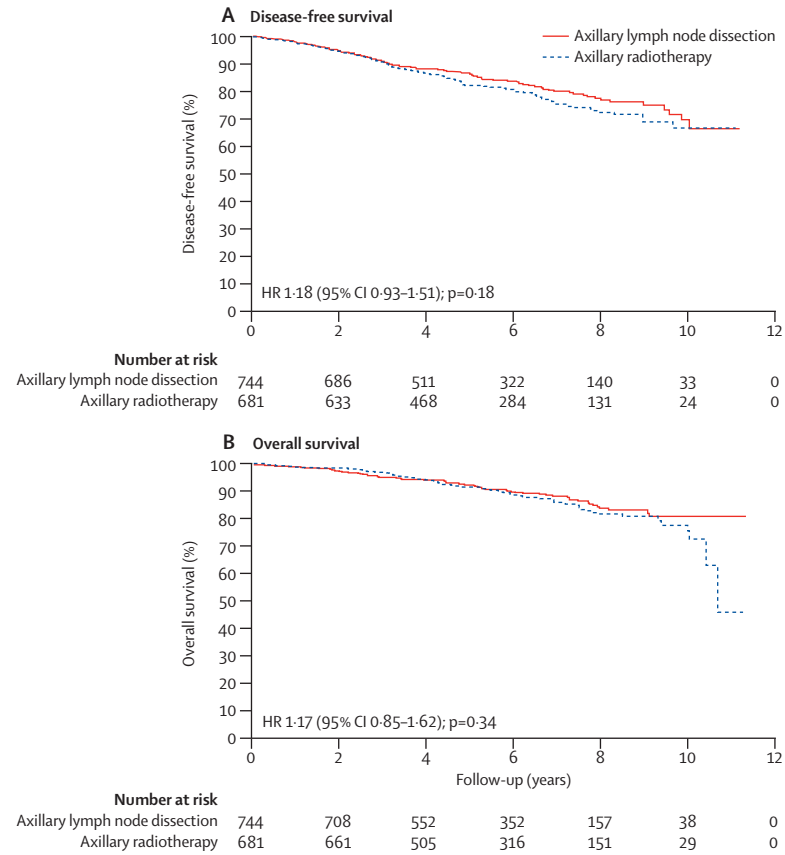

Figure 2: **Disease-free survival and overall survival**
HR=hazard ratio.

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0·25
1 year	114/410 (28%)	62/410 (15%)	<0·0001
3 years	84/373 (23%)	47/341 (14%)	0·003
5 years	76/328 (23%)	31/286 (11%)	<0·0001
Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0·497
1 year	32/410 (8%)	24/410 (6%)	0·332
3 years	38/373 (10%)	22/341 (6%)	0·080
5 years	43/328 (13%)	16/286 (6%)	0·0009

Data are n/N (%), unless otherwise specified.

Table 2: **Lymphoedema**

both treatments were excluded, the difference in rates of lymphoedema between the axillary lymph node dissection and axillary radiotherapy group remained significant.[26]

The range of motion in the four excursions (abduction, adduction, anteversion, and retroversion) did not differ significantly between the two treatment groups at both timepoints (1 year: p=0·29; 5 years: p=0·47).

No statistically significant and clinically relevant differences in QoL were noted between groups for any of the selected scales: arm symptoms, pain, or body image (data not shown). Sensitivity analyses, which replicated the primary analysis in the per-protocol population, using summary statistics and imputing missing data, yielded similar results to the primary analysis (data not shown). Although the arm symptom scale as a whole did not differ between the two treatment arms, a post-hoc analysis of the swelling and shoulder movement items showed that fewer patients in the axillary radiotherapy group reported a swollen hand or arm and fewer patients in the axillary lymph node dissection group reported difficulties moving the arm (appendix).

Discussion

In this phase 3 trial, axillary radiotherapy and axillary lymph node dissection both provided excellent and comparable locoregional control in patients with T1–2 primary breast cancer and no palpable lymphadenopathy who are found to have a positive sentinel node. There were no significant differences between the two groups in 5-year axillary recurrence, DFS, and overall survival, and this finding was similar in all subgroups. However, there was a significant difference in the incidence and severity of lymphoedema in favour of the axillary radiotherapy group, even when patients who received combined treatment with axillary lymph node dissection and axillary radiotherapy were excluded.[26]

These results are in accordance with findings from two randomised trials from before the introduction of sentinel node biopsy that compared axillary radiotherapy with axillary lymph node dissection in clinically node-negative patients: the NSABP-04 trial[18] and a French trial[19] initiated by the Breast Carcinoma Collaborative Group of the Institut Curie (panel). Since no sentinel node biopsy was done in these trials, axillary lymph node dissection and axillary radiotherapy were the only treatments indicated to treat the axilla. In the NSAPB-04 trial,[18] the axillary recurrence rate after a 25-year follow-up was 4% in both treatment groups. In the French trial,[19] with a 15-year follow-up, a better axillary control was noted in the axillary lymph node dissection group (1% *vs* 3% in the axillary radiotherapy group; p=0·04). Although in this trial a survival benefit was initially noted in favour of axillary lymph node dissection,[27] the long-term results of both trials did not show a significant difference in DFS and overall survival between both treatment groups.[18,19]

The results of the AMAROS trial confirm that the type of axillary management (axillary radiotherapy or axillary lymph node dissection) in patients with a positive sentinel node does not have an effect on survival. However, it can significantly affect the outcome in terms of morbidity. In this trial, signs of lymphoedema were noted at 5 years in 23% of the

patients after axillary lymph node dissection and 11% of those after axillary radiotherapy. The same pattern was noted in the NSABP-04 trial, although this trial showed higher rates of lymphoedema in both treatment groups.[8]

No significant differences in range of motion were recorded between the two treatment groups in all four excursions. A numerical but non-significant increase in restriction of arm mobility in the axillary radiotherapy group compared with the axillary lymph node dissection group at 1-year of follow-up disappeared in the following years. These lymphoedema and arm mobility results matched the patient-reported answers to the arm symptom scale, yet did not lead to differences in QoL.

That the finding of twice as few patients in the axillary radiotherapy group having lymphoedema does not translate into a clinically significant difference in QoL is remarkable. The present QoL measures might not have been sensitive enough to detect a change in QoL resulting from lymphoedema. There is some evidence that lymphoedema simply does not affect QoL as much as anticipated.[28] Based on the arm circumference measurements, we also noted that the rate of severe lymphoedema was numerically lower than the rate of lymphoedema cases reported by the clinician. Therefore, most cases could correspond to mild oedema that is not very bothersome to the patient. Another possible explanation is a situation usually referred to as response shift in QoL. Patients adapt to their disorders and change their internal standards. Such response shifts affect QoL outcome measurement because changes over time represent not only the symptom itself, but also the coping and acceptance level of that symptom by a patient.[29]

The design and results of the AMAROS trial may raise some discussion. First, the extensive irradiation including the periclavicular area might be regarded as overtreatment since, apart from level 1 and 2, which are also treated in an axillary lymph node dissection, level 3 and the supraclavicular nodes were also treated. Axillary radiotherapy of level 1 and 2 only might have been sufficient. Second, an imbalance was noted in the distribution of sentinel-node-positive patients in the two treatment groups: more patients with a positive sentinel node were allocated to the axillary lymph node dissection group than to the axillary radiotherapy group. An independent committee approved by the independent data monitoring committee investigated this imbalance during the accrual period of the trial. No plausible cause could be identified to explain this imbalance and no suggestion of a possible bias was identified, which is shown by findings from the multivariate analysis, which confirm the randomised comparison results. Finally, 5-year axillary recurrences were far less common than what was hypothesised and therefore the trial's primary test was underpowered. The AMAROS trial was designed to test non-inferiority based on an assumption of a 2% 5-year axillary recurrence in the axillary lymph node dissection group. As per our data, that rate was an overestimation in both groups since both did better than this baseline assumption. Since axillary recurrence seems to be an early event that occurs a median of 15–30 months after treatment,[18,30] further follow-up is unlikely to result in enough axillary recurrences to create sufficient power to test for a statistically and clinically significant difference between the two treatment groups.

The excellent regional control after both treatments matches the results of the ACOSOG Z0011[11,12] and IBCSG 23-01[13] trials that showed patients with limited sentinel node metastasis who were treated with breast-conserving treatment, including whole-breast irradiation and adjuvant systemic treatment, could be spared an axillary lymph node dissection without compromising locoregional control or survival outcome. The results of these trials led to a swift change in clinical practice—patients with early breast cancer and limited sentinel node involvement who are receiving whole-breast irradiation and adjuvant systemic treatments no longer need an axillary lymph node dissection. However, in some subgroups of patients treatment of the axilla is still deemed necessary—eg, patients who do not fit into the criteria of the Z0011 trial.[15] The results of the AMAROS trial suggest that for such patients, axillary radiotherapy is a valid treatment option with less morbidity than axillary lymph node dissection.

***Panel:* Research in context**

Systematic review

At the initiation of the EORTC 10891-22023 AMAROS trial in 2001, only limited evidence existed for the value of the sentinel node procedure and no randomised trials on the topic had been published. However, before the introduction of sentinel node biopsy, several randomised trials compared axillary lymph node dissection and axillary radiotherapy in clinically node-negative breast cancer.[18,19] In the process of designing this trial, these studies,[18,19] along with non-randomised studies suggesting that axillary radiotherapy might be as effective as axillary lymph node dissection for axillary control, but less toxic,[20] provided the rationale for the AMAROS trial.

Interpretation

To our knowledge, no other trials other than the two trials[18,19] mentioned and the AMAROS trial have compared axillary lymph node dissection and axillary radiotherapy. Our results fit well with those of the NSABP-04 trial[18] and the French trial,[19] although the population of patients with clinically node-negative axilla and a positive sentinel node between 2001 and 2010 is different from the population of patients with node-negative disease in the earlier trials. Yet, all three trials seem to suggest that axillary radiotherapy is non-inferior to axillary lymph node dissection. The AMAROS trial cannot answer the remaining question of which subset of clinically node-negative, sentinel-node-positive patients still require axillary treatments. In our opinion, if further axillary treatment is needed in clinically node-negative, sentinel-node-positive patients, axillary radiotherapy could be chosen instead of axillary lymph node dissection because it provides comparable axillary control and less morbidity.

Contributors

CJHvdV and EJTR conceived and designed the trial. GvT, CJHvdV, REM, LC, AHW, JHGK, LO, WHB, HCJvdM, GAPN, SCV, PWdG, TvD, AM, HR, MS, NJB, JWSM, YB, PP, DAXS, and EJTR provided study materials or patients. MD, MES, PM, NJD, and CGMM collected and assembled data. MD, GvT, LS, CC, JB, and EJTR analysed and interpreted data. MD, GvT, LS, JB, and EJTR drafted the manuscript. All authors critically revised the manuscript.

Declaration of interests

We declare no competing interests.

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