Improvements in locoregional treatment of breast cancer
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AXILLARY LYMPH NODE DISSECTION VERSUS AXILLARY RADIOTHERAPY; A DETAILED ANALYSIS OF MORBIDITY. RESULTS FROM THE EORTC 10981-22023 AMAROS TRIAL

Manuscript in preparation
ABSTRACT

Background
In breast cancer patients with a tumor-positive sentinel node, axillary lymph node dissection (ALND) and axillary radiotherapy (ART) provide both comparable and excellent axillary control. For determination of the optimal treatment, information about morbidity is crucial. The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) phase III trial compares ALND and ART in early breast cancer patients with a tumour-positive sentinel node biopsy (SNB). In this safety analysis, we studied morbidity of ALND compared to ART and identified risk factors for morbidity.

Patients and methods
Of the 4823 patients enrolled between 2001 and 2010, the 1274 patients with a tumour-positive SNB who received axillary treatment were included in this analysis. Patients were randomized to undergo ALND or ART including the medial part of the supraclavicular fossa. The incidence of surgical complications was analyzed, as well as the presence of paraesthesia of the arm. Lymphedema and shoulder mobility were analyzed at 1 and 5 years follow-up, by treatment received (at one year for edema; ART: n= 406, ALND: n= 387, ALND+ART: n=27). Lymphedema was analyzed as reported by the investigator (yes/no). Shoulder mobility was analyzed using the range of motion (anteversion, retroversion, abduction and adduction), comparing the ipsilateral side to the contralateral side. The predictive value of patient related factors as well as treatment factors (extent of ALND, the addition of radiation to ALND) was analyzed in a multivariate model.

Results
Surgical complications were observed in 23% of the patients in the ALND-group versus 9% in the ART-group (P<0.001). Paraesthesia of the arm was observed in 10% of the patients in the ALND-group and 9% in the ART-group. Lymphedema at 1 year post-treatment in patients treated with ART, ALND and ALND+ART was recorded in 15%, 25% (p<0.001 vs ART), and 59% (P<0.001 vs ART) of the patients respectively. After 5 years these rates were 10%, 21% (P<0.001 vs ART) and 58% (P<0.001 vs ART). Independent risk factors for the development of lymphedema within the first year were treatment with ALND (vs ART; OR 2.2) or ALND+ART (vs ART; OR 7.6), a BMI > 25, pre-menopausal status and treatment on the dominant side. Shoulder mobility decreased temporarily, in particular during the first year in both treatment arms. Independent risk factors for reduced abduction, anteversion and/or retroversion at 1 year post-treatment were the addition of supraclavicular radiotherapy after ALND, and an extensive ALND (level I+II+III). An ALND level I+II showed a better shoulder function compared to ART.

Conclusions
Post-operative complications and lymphedema were significantly higher after ALND than after ART. Combining ALND and ART further increased the risk of lymphedema. Patient-related factors contributed to a higher risk of lymphedema, but not to reduced shoulder mobility. The latter was influenced by the type and extent of the axillary treatment. ART is the preferred treatment over ALND in patients with a tumor-positive SNB. The combination of axillary surgery and radiation should, if possible, be avoided.
INTRODUCTION

Since the end of the last century, sentinel lymph node biopsy (SNB) has become the standard procedure to stage the axilla in breast cancer patients. Several trials have shown that patients with a tumour-negative SNB can be spared axillary treatment with its associated morbidity. However, in patients with a tumour-positive SNB and indication for axillary treatment, an axillary lymph node dissection (ALND) has long been the standard therapy. Although an ALND provides excellent locoregional control in these patients, it is associated with significant morbidity with high rates of lymphedema, peripheral neuropathy and restricted arm mobility. This has led investigators to search for more conservative strategies of treating the axilla after a tumour-positive SNB. Before the introduction of the SNB, axillary radiotherapy (ART) has been shown to provide satisfying locoregional control in patients without palpable lymphadenopathy, and this locoregional control was not inferior to that of an ALND in those patients.

The European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Group therefore initiated a trial comparing ALND with ART in patients with a tumour-positive SNB: the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial (EORTC 10981-22023 trial). This non-inferiority trial was designed to compare the 5-years axillary recurrence rate in both groups. The first results showed that with a median follow-up of 6.1 years, both ALND and ART provided excellent and comparable locoregional control. No significant differences were seen in axillary recurrence rate or survival. For both treatments, knowledge of incidence and magnitude of side effects could guide us towards optimal axillary treatment in those patients. Therefore the secondary objective of the AMAROS trial was to compare morbidity associated with ALND versus ART.

PATIENTS AND METHODS

This multicenter, phase III randomized non-inferiority trial included patients with primary invasive breast cancer up to 5 cm and a clinically negative axilla. The study design was previously described. Patients were not eligible in case of previous treatment of the axilla or a history of cancer, except for adequately treated basal cell cancer. Bilateral breast cancer was not an exclusion criterion. Patients were randomized centrally at the EORTC headquarters in a 1:1 ratio between ALND and ART if they were found to have a tumour-positive SNB. Local treatment of the breast consisted of breast-conserving surgery or mastectomy. Use of adjuvant systemic treatment was not specified in the protocol and this treatment was given at the discretion of the treating physician. The institutional ethical committees approved the AMAROS trial, and informed consent was obtained from all patients. This trial is registered with Clinicaltrials.gov Identifier: NCT00014612.

Axillary treatment

Axillary treatment had to start within twelve weeks after the SNB. ALND had to be performed according to the manual of the EORTC Breast Cancer Group and was defined as an anatomically level I and II dissection including at least 10 nodes. Level III dissection was optional. All three levels of the axilla together with the medial part of the supraclavicular fossa were considered ART clinical target volume. The prescribed dose to the axilla was 50 Gy in 25 fractions of 2 Gy, 5 days a week. Postoperative axillary irradiation in patients undergoing ALND was allowed in patients with
≥4 tumour-positive nodes and applied according to the institutional protocols. Further information about surgery and radiotherapy guidelines and quality assurance has been provided previously.7-10

Clinical measurements

Postoperative adverse effects for all surgical procedures were assessed. These complications were a result of surgical treatment of the breast and SNB with or without ALND. Complications related to axillary radiotherapy were not collected. The presence of long-term complications was determined and recorded by the treating physician.

Lymphedema was reported in two ways. Any sign of lymphedema, and treatment for lymphedema irrespective of the magnitude, was assessed at baseline (before surgery), and at the 1, 3, 5 and 10-year follow-up. An unblinded clinician carried out this clinical assessment. During the same assessment, the arm circumference 15 cm above the medial epicondyle (upper arm) and 15 cm below the medial epicondyle (lower arm) was measured on both arms. An increased arm circumference of the ipsilateral arm ≥10% compared to the contralateral arm at the same time moment was defined as severe lymphedema. Besides these measurements, early lymphedema of the arm (onset within 3 months after surgery) was recorded.

The maximum shoulder range of movement in both arms was measured in four directions: abduction, adduction, anteversion and retroversion. The patient was asked to stand straight and to move the arm in the maximal excursion without assistance. Measurements on both arms had to be performed at baseline and after 1, 3, 5, and 10-year follow-up. The maximal range of movement on the affected side was compared to the contralateral side at any time point to exclude inter-observer variation and physiological changes in flexibility. Furthermore, the presence of winged scapula was recorded.

The analysis of lymphedema and shoulder function excluded patients who also had received therapy on the contralateral side. The 10-year follow-up assessments of lymphedema and shoulder function are not part of this analysis, since there is still insufficient follow-up data.

Statistical analysis

The safety endpoints included post-operative complications, range of shoulder movement and lymphedema. These safety analyses are performed in the safety population, which is defined as those patients who received at least the randomized treatment.

Short term (1-year) and long-term (5-year) lymphedema and shoulder movement endpoints were defined as secondary trial endpoints in the statistical analysis plan. Lymphedema was analyzed using Fisher’s exact test. The four relative shoulder directions were combined in a multivariate (composite) endpoint on the log scale. A multivariate analysis of variance (MANOVA) was performed based on Hotelling’s T test. For all tests, results <0.05 were considered significant.

For edema a multivariate Logistic regression model fitted for clinical sign of edema yes/no after 1 year. For the shoulder mobility, separate linear models are fitted for each of the 4 relative excursions on log scale. In the multivariable analyses, factors that may affect morbidity were analyzed including age, menopausal status, tumour size on pathology, location of tumour, local treatment of the breast and the axilla (local therapy, ART/ALND/ART+ALND, type of ALND, supraclavicular RT if no ART), total number of nodes removed (SNB + ALND), treatment on the dominant site versus contralateral, adjuvant chemotherapy, and BMI at baseline. BMI was not collected but estimated via the formula: BMI= 1.10*upper arm circumference-6.7.11 Backward model selection (significance level = 5%) was performed only on those variables that were significant at the 20% level in the univariate model. ‘Axillary treatment/combination received’ is kept in the multivariate model at all times.
A longitudinal analysis for relative arm circumference was performed. We investigated whether the presence and the severity of lymphedema differed between the groups in the follow up. A linear mixed model was fitted on the relative arm circumference measurements (the maximum of that of the lower and upper arm). Including only those patients that were reported as having edema (by local clinical assessment, excl baselin edema) and restricted to all measurements after onset for that patient. A fixed treatment effect, linear time effect, linear time-treatment interaction effect and patient specific random intercepts will be fitted. For the spatial covariance structure the simple, power, exponential, and Gaussian type were considered. The exponential type was selected based on Akaike’s Information Criterion (AIC).

SAS version 9.3 was used for all analyses. Analyses were restricted to those patients with non-missing assessments.

RESULTS

Treatment outcomes

Basic patient, tumour, and treatment characteristics were reported in the previous chapter in the intent-to-treat population (ALND: n=744, ART: n=681). No significant baseline differences were observed between the ALND and ART groups. The median ages in the ALND and ART-group were 56 and 55 years, respectively.

In both treatment groups the median number of removed sentinel nodes was 2 (interquartile range [IQR], 1-3) and the median number of positive sentinel nodes was 1 (IQR, 1-1). In the ALND-group, 210 patients (31.3%) underwent a level I+II dissection and 459 patients (68.3%) a level I+II+III dissection. In the majority of these dissections (60%), between 10 and 19 additional nodes were removed.

In the ALND-group, 672 (out of 744) patients received at least the randomized treatment, compared to 602 (out of 681 patients) in the ART-group. In the ALND-group, The combination of both axillary treatments (ALND followed by ART) was administered to 41 patients (6.1%) in the ALND-group and to 12 patients (2.0%) in the ART-group. In the ALND-group, the majority of patients treated with additional ART after ALND received this treatment because of the presence of ≥4 tumour-positive lymph nodes as allowed per protocol. In the ART-group, these were all but one patients who crossed over to the ALND-group, after which ART was added. Isolated radiotherapy of the periclavicular nodes (in absence of radiotherapy of the other nodal fields in the axilla) after ALND was administered...
to 70 (10.4%) patients. In 17 of the 602 patients (2.8%) in the ART-group the radiation treatment was interrupted for more than 1 week. For 11 of these patients this interruption was due to toxicity. For 2 patients the ART was never completed due to toxicity.

Surgical complications
Adverse effects after surgery were observed in 152 of the 672 patients (23%) in the ALND-group compared to 54 of the 602 patients (9%) in the ART-group, due to the SNB. The complications occurring most often were infection and persistent seroma (Table 1). There was no difference in the overall complication rate when the SNB and ALND were performed in the same session, versus SNB followed by ALND at a later date.

Long-term complications
Radiation pneumonitis was observed in 9 patients in the ALND-group (1.3%) and 20 patients in the ART-group (3.3%). Neuropathy of the ipsilateral arm was noted in 65 patients (9.7%) in the ALND-group and in 56 patients (9.3%) in the ART-group.

Lymphedema of the ipsilateral arm
Some sign of lymphedema in the first 5 years after treatment was observed in 26.0% of patients after ALND, in 13.1% of patients after ART (p<0.001) and in 58.3% of the patients after ALND+ART (p<0.001).

Table 2. Lymphedema
Abbrevations: LE: Lymphedema; ALND = axillary lymph node dissection; ART = axillary radiotherapy
Figure 1. The (A) relative circumference of the lower arm, and (B) relative circumference upper arm
ALND = axillary lymph node dissection; ART = axillary radiotherapy; SNB = Sentinel Node Biopsy
After 5 years of follow-up, lymphedema as a clinical observation was observed in 20.8%, 10.3%, and 58.3% of the patients respectively (Table 2). 50 out of the 130 (38%) edema cases at 3 years and 17 out of the 107 (16%) cases at 5 years (by clinical assessment) were reported for the first time.

The averages and 95% confidence intervals of the logarithm of the relative arm circumference are plotted in Figure 1. The increase in arm circumference is higher in the ALND-group, although there is considerable overlap in the confidence intervals at each time point. A longitudinal analysis for relative arm circumference at onset of lymphedema and for persistent lymphedema showed that the severity of lymphedema at onset is worse for patients who received ALND compared to ART \( (p = 0.026) \). If lymphedema persisted, the severity increased over time in an equal manner for ALND and ART. Since the severity of lymphedema was worse in the ALND group at onset, it also remained worse than ART during the follow up. The area under ROC curve for clinical assessment versus arm circumference was 0.60.

In multivariable analysis for lymphedema at 1 year \((n=820)\), factors that were identified as independent risk predictors were type of axillary treatment (ALND and ALND+ART), BMI >25, pre-menopausal status and treatment on the dominant site (treatment on the right axilla in right-handed women and treatment of the left axilla in left-handed women) (Table 3).

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Table 3. Multivariate analysis for clinical lymphedema at 1 year
ALND = axillary lymph node dissection; ART = axillary radiotherapy; BMI = Body Mass Index
Shoulder function
For shoulder range of motion no significant difference between ALND and ART was seen regarding the composite endpoint of the 4 movements (p=0.29 at 1 year; p=0.47 at 5 years). The highest incidence of patients with a decreased range of motion in the treated shoulder compared to the contralateral shoulder was found at 1-year follow-up for both treatment groups (Figure 2). At this time point a trend towards a worse shoulder function in the ART-group as compared to the ALND-group was found. This difference was not significant and had largely disappeared by the 5-year follow-up.

**Figure 2.** The average (A) anteversion, (B) retroversion, (C) abduction, and (D) adduction and 95% Confidence Intervals. ALND = axillary lymph node dissection; ART = axillary radiotherapy, SNB = sentinel node biopsy
In the multivariate analysis (n=748), factors that significantly affected the range of movement at 1 year were level of ALND (I+II versus I+II+III) and inclusion of the supraclavicular fossa in the radiation field. The latter was only analyzed in the ALND-group, since this field was already included in all patients receiving ART. Effect on the range of motion was observed in anteversion, retroversion, and abduction. No effect was seen on the different aspects of axillary treatment for the range of motion for adduction.

In the multivariate analysis for anteversion, isolated irradiation of the periclavicular nodes in patients treated with ALND decreased the relative range of anteversion with on average 7.8% (model-based estimate) compared to those patients treated with an ALND without irradiation of the periclavicular nodes (7.1% for retroversion and 9.4% for abduction). Patients who were treated with an ALND including level III were found to have a decreased range of motion compared to those who underwent an ALND including only level I+II. Their average relative decrease in range of anteversion was 5.6% (model-based estimate) compared to those patients treated with an ALND level I+II (not significant for retroversion and 5.8% for abduction). Patients with ALND level I+II and no irradiation of the periclavicular nodes had a better range of motion compared to those patients treated with ART only. Their average relative increase range of anteversion was 6.1% higher (model-based estimate) compared to those patients treated with ART (3.3% for retroversion and 7.6% for abduction). For patients treated with ALND including level III the range of motion was similar compared to patients treated with ART only.

**DISCUSSION**

This study shows that, in patients with a tumour-positive SNB, ART results in fewer post-operative complications and lower incidence of lymphedema compared to ALND. Lymphedema was observed significantly more often after ALND compared to ART at every time point. Moreover, the magnitude of lymphedema increased after ALND. Thus, not only did more patients experience lymphedema after ALND, but the severity of lymphedema in terms of arm circumference also increased.

Patients treated with ALND had an estimated relative risk of developing lymphedema of 2.02 compared to ART. Moreover, additional ART after ALND increased the estimated relative risk to 3.25 compared to ART. A confounding factor for the higher risk of lymphedema after ALND+ART may be the higher tumour stage, which is generally associated with the administration of both axillary treatments. The presence of positive axillary lymph nodes in itself is identified as an independent risk factor for lymphedema. We did not include the positivity of axillary lymph nodes in our analysis since all patients had positive (sentinel) nodes and additional positive nodes could not be determined in the ART-group. In a meta-analysis of Tsai et al. the pooled risk ratios of ART as opposed to no axillary treatment was RR 2.97 (95%CI 2.06-4.28). Since no group of patients was included without axillary treatment after SNB, we cannot estimate the risk factor of ART.

For patients with a tumour on the dominant side, the risk of lymphedema was 30% higher compared to women with a tumour on the non-dominant side. This has also been found elsewhere, although treatment on the dominant side has only been sparsely linked with increased risk of LE. The reason for this correlation is not fully understood. A higher level of physical activity with the dominant arm as opposed to the non-dominant arm is not found to be a risk factor for lymphedema. Moreover, exercise can even improve the function in the treated arm. Possibly, the correlation is due to a higher incidence of injury and infection on the dominant side.
For patients that are overweight (BMI > 25) or obese (BMI > 30) at baseline, the risk of developing lymphedema is respectively 50% and 62% higher compared to normal weight (BMI < 25) patients. This strong correlation is also found in several other studies.\textsuperscript{13, 15, 16} For premenopausal women the risk is 22% higher compared to post-menopausal women. There might be a link with increased administration of systemic treatment, since chemotherapy and hormonal therapy may alter the composition of bodily fluids. However, there is conflicting evidence about the link between systemic treatment and the occurrence of lymphedema.\textsuperscript{12-15} Furthermore, after an artificial menopause this group may experience more weight gain, which can contribute to the onset of lymphedema.

The type of breast-surgery and administration of adjuvant RT to the breast did not significantly affect the risk of lymphedema at one-year follow up. This finding is in contrast to other studies.\textsuperscript{12} An explanation for this finding might be that all patients in our study received axillary treatment in addition to a tumour-positive SNB. The effects of axillary treatment might overrule the more subtle effects from treatment to the breast. Also the number of nodes removed or the level of ALND was not an independent predictor of lymphedema. This is also in contrast to other studies.\textsuperscript{15}

A major obstacle in studies of lymphedema is the choice of an objective measurement of arm volume. Several techniques have been used to measure difference in the involved arm compared with the non-operated arm. McLaughlin and colleagues argued that several symptom assessments and objective measurements are needed to determine the true incidence of clinically significant lymphedema.\textsuperscript{17} Since the correlation between different methods of measurement is poor,\textsuperscript{18} it is important to incorporate more than one method.

The discrepancy we observed, between lymphedema as a clinical observation and lymphedema defined as an increase of > 10% in arm circumference could be influenced by several factors. For example, patients with isolated lymphedema of the hand could have been omitted, as well as patients with a normal arm circumference due to adequate treatment. Furthermore, the clinical assessment of lymphedema could also take into account patients’ symptoms and complaints of heaviness or tightness that is not reflected in the arm circumference. Moreover, a subtle increase in arm circumference might be recorded as lymphedema, while it was <10% and thus not included as increased arm circumference.

The relatively high rates of lymphedema in this study compared to other studies may be explained by several factors. First, there is only limited correlation between different methods of lymphedema assessment. This was also observed in the current trial. Studies using only one method of measurement may therefore underestimate the true magnitude of the problem. Second, a substantial number of the patients developed lymphedema after the 3-year follow-up. In studies with shorter follow-up periods, those cases would not be detected patients and the true incidence will be underestimated.\textsuperscript{19-20} Thirdly, two-thirds of the patients were treated with an ALND including level III, which is high compared to other studies. However, in this study, an ALND including level III was not a significant risk factor for lymphedema compared to an ALND level I+II.

In the ALMANAC trial, shoulder and arm morbidity was carefully ascertained at multiple time points following axillary surgery.\textsuperscript{1} ALND was associated with significant reductions in shoulder flexion and abduction at 1 month but range of movement had returned to near baseline by 12 months. Similarly, 62% of women reported arm pain or numbness at 1 month and 31% still reported these symptoms at 12 months. Clinicians rated these symptoms as severe in only 1% of the women at 12 months. Women may develop measurable arm swelling after axillary surgery without symptoms; consequently, lymphedema rates are generally higher for studies that measure arm volumes or circumferences than for studies that rely on patient-reported symptoms.\textsuperscript{5}
The present study shows a steady decrease in the incidence of lymphedema in the ART-group, while in the ALND-group women seem to recover more slowly from lymphedema. Thus it is very possible that the differences become even larger after the 10-year follow-up. The same trend was observed in the NSABP-04 where a larger decrease was noted in lymphedema over time after ART compared to ALND.\textsuperscript{21}

In conclusion, this analysis of the AMAROS trial shows that in patients with a tumour-positive SNB, treating the axilla with ART instead of ALND will result in significantly less post-operative complications and lymphedema. Combining lymph node dissection and radiotherapy further increased the risk of lymphedema and should, if possible, be avoided.
REFERENCES


