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**Phase III randomized equivalence trial of early breast cancer treatments
with or without axillary clearance in post-menopausal patients
Results after 5 years of follow-up**

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Running head: Axillary clearance in early breast cancer

Results will be partially presented at ESSO 2010.

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Abstract

Background: Axillary lymph node clearance (ALNC) improves locoregional control and provides prognostic information for early breast cancer treatment, but effects on survival are controversial. This multicentre, randomized pragmatic equivalence trial compares outcomes for post-menopausal early invasive breast cancer patients after locoregional treatment with ALNC and adjuvant therapies to outcomes after locoregional treatment without ALNC and adjuvant therapies.

Methods: From 1995-2005, women aged ≥ 50 years with early breast cancer (tumor ≤ 10 mm) and clinically-negative axillary nodes were randomized to receive treatment with ALNC (Ax) or without (no-Ax). Adjuvant therapies were prescribed according to hormonal receptor status and individual histological results. The primary endpoint was overall survival (OS); secondary endpoints were event-free survival (EFS) and functional outcomes. The trial was terminated due to lack of equivalence and low accrual after first interim analyses. Trial registration: NCT00210236.

Results: Of 625 patients, 297 no-Ax and 310 Ax patients were maintained for final per-protocol analyses. OS and EFS at five years were not equivalent (Ax vs. no-Ax: 98% vs. 94% and 96% vs. 90% respectively). Recurrence was higher for no-Ax, particularly in the first five years after surgery. Axillary nodes were positive for 14% Ax patients but only 2% no-Ax patients experienced axillary node recurrence. Functional impairments were greater after ALNC.

Conclusion: Our results fail to demonstrate equivalence of outcomes when ALNC is omitted from postmenopausal early breast cancer patient treatment. However the low locoregional recurrence rates warrant further examination over a longer duration, in particular to consider whether these would impact on survival.

Keywords: axillary dissection; early breast cancer; axillary clearance; breast cancer surgery, axillary lymph nodes.

Introduction

Background

Axillary lymph node clearance (ALNC) in patients with early breast cancer reduces axillary recurrence^{1,2} and provides accurate and useful prognostic information.³ It is also especially useful when adjuvant therapy will be determined based on pathological results.^{4,5} However, ALNC is invasive and results in postoperative morbidity,⁶ and there is ongoing controversy about the impact of axillary treatment itself on breast cancer survival.^{2,7} Consequently, several publications since the 1990's have concluded that ALNC can be omitted from standard treatments for early breast cancer^{3,8-12} and most recently with the NSABP-B-32 trial for clinically node-negative breast cancer patients¹³. Developments in early mammographic screening resulting in earlier diagnosis and reduced numbers of involved nodes per patient have also strengthened the idea that ALNC can be omitted, as have studies reporting that even when involved nodes are left in place (without clearance), the risk of axillary recurrence is low.^{9,10,14,15}

The omission of ALNC has been promoted by randomized controlled trials. The International Breast Cancer Study Group (IBCSG)⁶ and Martelli¹¹ found similar overall and breast cancer mortality for patients for whom ALNC was not performed. Sanghani's meta-analysis² concludes that performing ALNC does not confer a survival benefit in early clinically node-negative breast cancer, although it is associated with a reduced risk for axillary recurrence.

However, not all reports have agreed with these findings, with doubts being expressed regarding the removal of lymph nodes without deliberate ALNC in the Martelli trial and the potential inadequacy of the statistical power for measuring such small differences in survival rates.³ Orr's⁴ meta-analysis of six trials comparing

standard treatment including ALNC to treatment without ALNC undertaken between 1950 and 1990 concluded just the opposite results; that ALNC improves OS. In this context, it remains unclear whether the omission of ALNC from the standard treatment of early breast cancer confers a survival advantage, or disadvantage, or neither.

At the time the present study was started, the SLN practice had not yet been introduced into standard clinical practices and ALNC was almost systematically performed. This pragmatic trial was thus designed to evaluate whether survival outcomes after a treatment program involving surgery (with no clearance) + adjuvant treatments for clinically node-negative early breast cancer in postmenopausal women, would be equivalent to survival outcomes after treatment involving surgery + ALNC + adjuvant treatments. Secondary objectives were to examine functional impairments of the two groups and to examine the rates of axillary node events when nodes are left intact, i.e. for patients not receiving ALNC.

Methods

Participants

Eligible patients were post-menopausal women aged 50 and older with early invasive breast cancer (tumor size ≤ 10 mm). Baseline exclusion criteria were: inflammation, palpable axillary nodes (N+), metastasis, prior contralateral invasive cancer or another carcinoma, or limited survival prognosis (<10 years). All patients gave informed, written consent according to the regional ethics committee and legal requirements in France at the time.

Randomization

Randomization was performed by block, stratified by center and by operation time: either histological diagnosis was known and randomization was performed after histological analysis; or, randomization was performed intra-operatively and was based on histological extemporaneously-assessed size. They were randomized into two groups: no-Ax that received surgery and adjuvant treatment and Ax (reference treatment) that received surgery, standard ALNC and adjuvant treatment.

Interventions

Standard surgery was performed following the same technique for all eligible patients; either a Radical Modified Mastectomy or lumpectomy involving an excision ≥ 10 mm surrounding the tumor with section slices for histological analysis to ensure free margins. For the Ax group, ALNC was standard and limited to nodes inferior to the axillary vein (Berg levels I and II). Radiotherapy was administered to all lumpectomy patients and most mastectomy patients as indicated (i.e. with involved nodes) via the same method: 50 Gy over the whole breast or the chest wall with no axillary irradiation. Receptor positivity was established either by immunohistochemistry ($>10\%$) or immunoradiologically ($>10\text{mg/ml}$). For patients in both groups with estrogen- or progesterone- positive receptors or unknown status, 20mg tamoxifen was prescribed daily from surgery for 3 years for patients randomized before 23 September 2002 and for 5 years for patients randomized after this date. For negative receptor patients in both groups, no endocrine therapy was prescribed but adjuvant chemotherapy was prescribed as indicated. If histologically or biologically indicated, adjuvant chemotherapy was prescribed after surgery according to the practices in each center. Follow-up by clinical examination was performed every three months in the first two years and subsequently with a clinical examination and bilateral mammogram every year.

Endpoints

The primary endpoint was OS at five years. OS was defined as time from random assignment to death of any cause. Secondary outcomes were event-free survival (EFS) measured as time from randomization to first event and functional outcomes. First events were considered as: any recurrence (local, locoregional, axillary or metastatic), contralateral breast cancer, other cancer or death of any cause. We also examined functional impairments and axillary node progressions (associated or not with metastasis). The rate of axillary recurrence was evaluated every six months to ensure that it had not risen over 10%, a condition that would result in an immediate discontinuation of the trial.

Statistical methods

This two-sided equivalence trial was designed to compare OS in the no-Ax group to the Ax group (estimated at 95% based on previous published data).^{12,16} Using a two-sided 0.10-level test, 105 events (1 612 patients) were required for 90% power over five years. The equivalence margin was set at 3%, that is, equivalence will be admitted if HR is inferior to 1.6, or if OS in the no-Ax group is not less than 92%.

Survival outcomes were estimated by the Kaplan-Meier method and compared using Hazard Ratios and confidence intervals (90%CI) in per protocol (PP) analyses to minimize the risk of falsely claiming equivalence.¹⁷ Intention to treat (ITT) analyses and Treatment-Received (TR) (all patients treated in protocol, regardless of randomization) were used to substantiate findings. Survival data were censored at five years.

Predetermined interim analyses were scheduled for after the first 15 patient deaths, then at 30 deaths and after every following 30 deaths. After the first interim analysis, an Interim Data Monitoring Committee (IDMC) was convened on 4 November 2005

at which it was decided to stop enrolment due to the lack of equivalence of outcomes, the slower-than-anticipated inclusion rates (600 instead of 1600 expected), the changes in adjuvant endocrine therapy and the arrival of the SLN practice. In this light, continuing inclusions was deemed unethical by the IDMC. At this time, the IDMC recommended delaying the publication of results until longer follow-up was obtained. Currently, we present results for all patients with five years follow-up since the last inclusion.

Results

Participant flow

Figure 1 displays patient inclusions and exclusions in the trial. From 27 October 1995 to 14 October 2005, 625 patients were included: no-Ax: 312 and Ax: 313. Minor protocol deviations were observed for 1 patient aged < 50 years (49 years and menopausal) in the Ax group and for 33 patients who had tumors > 10 mm (14 no-Ax, 19 Ax). These patients were maintained for analyses after discussions with clinicians due to the variations in tumor size measurements according to randomization methods: when patients were included preoperatively after a radiological judgment of tumor size this was often adjusted post-operatively with a histological measure of tumor size. Major protocol deviations were observed for 9 no-Ax patients that received ALNC and for one Ax patient who did not receive ALNC (these patients are only included in the TR analyses), for 4 patients not receiving radiotherapy after a lumpectomy and for 4 no-Ax patients receiving axillary irradiation. These patients were excluded from PP and TR analyses as shown in Figure 1.

Baseline data

As shown in Table 1, baseline characteristics of patients on inclusion such as age, initial surgical treatment and tumor size were balanced across groups. Ninety-six percent of patients had a lumpectomy and four percent had a mastectomy. Histological tumor size was, for the majority (over 65%), between 6-10mm, with the same mean tumor size across groups (7.1 no-Ax vs 7.25mm Ax). For over 70% of patients that underwent ALNC, more than 10 nodes were removed in accordance with recommendations¹⁸ and on average 12 were examined. Under 8 nodes were cleared for 14% of patients. Positive nodes were found for 42 Ax patients (14%) and for 28 (67%) of these, only one node was involved. While these initial inclusion characteristics were balanced, the proportions of patients receiving adjuvant therapies were not balanced as may be expected in a pragmatic trial^{17,19} where adjuvant treatments changed over time and according to standard practices in each center. Almost all no-Ax patients received adjuvant endocrine therapy compared to two thirds of Ax patients and only 6 received adjuvant chemotherapy compared to 26 Ax patients, as chemotherapy was prescribed only in cases of histologically-proven positive lymph nodes. Radiotherapy was balanced across groups.

Survival outcomes

As Figure 2 shows, at five years, OS per protocol in the no-Ax group (94%) was not equivalent to OS in the Ax group (98%) HR=3.07, 90%CI: 1.40-6.70, p=1. Data across the full follow up duration mirror this pattern with OS lower for no-Ax (92%) than for Ax (97%) HR=2.56, 90%CI: 1.37-4.78. ITT analyses mirror this pattern with OS lower for no-Ax (94%) than for Ax (98%) HR=2.91, 90%CI: 1.33-6.36 at five years and OS lower for no-Ax (92%) than for Ax (97%) HR=2.49, 90%CI: 1.34-4.63. Equivalence between treatment strategies is not demonstrated due to a higher than

expected OS in our reference treatment group (Ax 98% vs. 95% expected) and lack of statistical power. Similarly for EFS at five years, equivalence was not demonstrated: no-Ax = 90%, Ax = 96%, HR = 2.26, 90%CI 1.32-3.86. Although non-censored data tend towards significance for equivalence, no-Ax EFS is not equivalent to Ax EFS over full follow-up: no-Ax 85%, Ax 90%; HR=1.61, 90%CI: 1.10-2.37. ITT analyses match these patterns with no demonstration of equivalence, despite an attenuation of the difference when the non-censored data are considered. As shown in Table 2, at 31 December 2008, there were 33 deaths: 23 patients without clearance and 10 patients with clearance. Most no-Ax patient deaths were caused by other events. More no-Ax patients died of breast cancer and other causes than Ax patients.

Recurrence

As seen in Table 2, no-Ax patients had higher rates of metastatic events, contralateral breast cancer and axillary events, particularly in the first five years after surgery. Ax patients had no axillary events but twice as many breast/parietal events as for no-Ax patients. The combined rate of breast or axillary events was the same for no-Ax patients (12 events) as for Ax patients (12 events).

Histological examination of the lymph nodes dissected during initial clearance showed that the cancer had involved the axillary nodes for 42 (14%) patients receiving clearance. Assuming similar nodal involvement in the no-Ax group, and combining this with the low rate of axillary recurrence observed (6 patients, 2%), this indicates that leaving involved lymph nodes intact (i.e. not performing ALNC) is only accompanied by clinical consequences (axillary recurrence) for 14% (6/42) of patients with positive nodes.

Functional impairments

At 31st December 2008, functional evaluations were recorded for 543 patients. Table 3 shows that less than one in ten no-Ax patients experienced any functional impairments whereas one in four Ax patients experienced moderate to severe functional impairments, with the most common impairments being arm paresthesia , lymphedema, upper arm fatigue and reduced shoulder mobility.

Discussion

Survival outcomes

The equivalence of survival outcomes for post menopausal early breast cancer patients treated with or without ALNC was not demonstrated for several reasons. Firstly, outcomes in our reference group (ALNC) were higher than expected and higher than for our proposed treatment group. Secondly, we did not obtain the number of patients required to conclude equivalence (or the absence of) statistically. Thirdly, this is a pragmatic trial that despite starting with balanced groups, compares two treatment strategies that differ in more ways than just the inclusion or omission of ALNC (i.e., more no-Ax patients received endocrine therapy).

Yet, with over 600 patients randomized, clear differences in morbidity rates and interesting locoregional recurrence data, we can propose some interpretations to our results. The higher than predicted survival outcomes in the reference treatment group suggest that survival outcomes after ALNC are better than outcomes after treatment without ALNC. Several interpretations are possible for the slight advantage in OS at five years for ALNC patients: support for the efficacy of ALNC, a positive effect of the chemotherapy received by 8% Ax patients (vs. 2% of no-Ax patients), or as adverse effects of the endocrine therapy received by the majority of the no-Ax group. This last

interpretation may be supported by the cause of death results showing four times as many deaths due to 'other events' for no-Ax patients (12 vs. 3) and by research indicating a link between Tamoxifen treatments and thromboembolic complications,²⁰ particularly for women >50 years.²¹ On closer analysis, in the no-Ax group who were in majority treated by tamoxifen we observe two deaths related to pancreatic cancer and one death due to vascular complications attributed to tamoxifen. However, recent contrasting results suggest that one of the few factors impacting on survival for a similar patient group is the (lack of) adjuvant systematic therapy²².

In terms of beneficial effects of chemotherapy, although our groups differ slightly in rates of patients receiving chemotherapy, this difference of 20 patients can hardly explain a difference of 10 more deaths in the no-Ax group. In fact, when we use the adjuvant online program²³ to investigate the actual benefit of first generation chemotherapy on OS, we find an absolute benefit of only 2%. As a result, the differences in outcomes we observed cannot be attributed to the different rates of patients receiving chemotherapy.

Advanced age of our patients (median over 60, 18% of 70) must also be considered when interpreting the patient death rates as most deaths were not breast cancer-related. This concurs with research demonstrating that although death from breast cancer remains substantial for patients 70 and older, death from other causes becomes increasingly important with age.^{3,12,24}

Recurrence

Recurrence rates are consistent with previous findings showing relatively low recurrence rates overall. While lymph node recurrence was more frequent for no-Ax patients, breast events were more frequent for Ax patients. An interpretation may be that after ALNC, malignant cells can no longer freely circulate beyond this area and

are somehow 'blocked' at the breast/parietal level, although this remains to be investigated in further research. Further, in line with previous research,^{6,14,15,25} we observed only a very small rate of axillary recurrence given the assumed rate of nodal involvement. In the Ax group, pathological results confirmed that 13.5% of patients had positive lymph nodes but the recurrence rate was only 2% for no-Ax patients. These results are similar to those of Park who estimated the risk of residual axillary disease at 9% but observed axillary recurrence at only 2%. Similarly, in the two studies with comparable methodologies to ours, the IBCSG⁶ found axillary recurrences for 3% of patients without ALNC compared to an observation of 27% positive lymph nodes in the reference group receiving ALNC. Others observed metastatic lymph nodes for 33% of ALNC patients and only 1.8% recurrences for no ALNC patients¹⁴ or relapse of 1.7% and 2% for T1a and T1b tumors respectively.²⁵ This finding can only partially be explained by a lack of follow up as patients were followed for more than 15 years¹⁴ and overall it appears that positive lymph nodes are not always followed by an evolution, at least at this stage of the disease.²⁶ It should also be noted that our results demonstrate that there were never more than five positive nodes found, although more than eight nodes were removed in the clearance procedure for a large majority of patients (86.1%). This offers support for 'limited' ALNC, for small tumors, even for positive SLN patients as recently demonstrated in the ACOSOG trial although it did not reach full recruitment^{22,27}.

Functional impairments

In terms of morbidity, we observed a higher rate of functional impairment for ALNC patients. Incidences were similar to other reported rates of complications.^{28,29} Our overall rate of 9% of patients experiencing functional impairments in the no-Ax group should be understood as the sum of pre-existing conditions, (not measured in our

series but estimated around 5% in the literature),^{28,29} plus the consequences of the lumpectomy/mastectomy and radiotherapy procedures. The difference between 9% of no-Ax patients and 28% of Ax patients experiencing functional impairments can be understood as the consequences of the ALNC.

Conclusions

Overall, this research presents mixed results, indicating low rates of axillary recurrence even when involved nodes are left intact but, despite early termination of the trial, an indication of more deaths and lower overall and event-free survival when ALNC is not performed. This may partially be explained by the higher rates of locoregional recurrence in the no-Ax group, particularly in the first five years after treatment. We do not believe that these relatively large differences can be attributed to the slight differences in patients receiving chemotherapy or endocrine therapy. This research and growing evidence indicates that positive nodes do not always translate into locoregional recurrence, however the question of survival remains unanswered.

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Conflicts of Interest statement

There are no conflicts of interest to be declared by any authors.

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Figure legends

Fig 1. Consort diagram of exclusions and inclusions for 3 study populations in AXIL95.

Fig 2. (A) Overall survival (OS) and (B) Event-free survival (EFS) according to treatment group per protocol censored at five years (No-Ax: no axillary lymph node clearance; Ax: axillary lymph node clearance, HR, Hazard Ratio; CI, confidence interval).

Conflicts of Interest statement

There are no conflicts of interest to be declared by any authors.

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Table 1. Patient characteristics at inclusion and treatment received in AXIL95 by Per-Protocol

	No-Ax (N=297)		Ax (N=310)	
	N	%	N	%
Age, years				
Median (range)	62.6 (50-81)		61.6 (50-87)	
Histological tumor size				
Mean (mm)	7.1		7.25	
1 to 5 mm	86	(29)	82	(27)
6 to 10 mm	196	(66)	208	(67)
>10mm	9	(3)	19	(6)
Missing	6	(2)	1	(0)
Histology				
Invasive ductal carcinoma	232	(78)	236	(76)
Invasive lobular carcinoma	23	(8)	28	(9)
Other	42	(14)	45	(15)
ER/PR Receptor status*				
Both Negative	19	(6)	20	(7)
At least one positive†	235	(79)	264	(85)
Unknown	43	(15)	26	(8)
Surgical Intervention				
Lumpectomy	287	(97)	295	(95)
Mastectomy	10	(3)	15	(5)
Radiotherapy	288	(97)	298	(96)
Post-lumpectomy	287	(100)	295	(99)
Breast boost	187	(65)	195	(65)
Post- mastectomy	1	(0)	3	(1)
Axilla	39	(14)	56	(19)
Supraclavicular nodes	22	(8)	50	(17)
Internal mammary chain	35	(12)	60	(20)
Adjuvant Endocrine therapy	270	(91)	203	(66)
Missing	2	(1)	7	(2)
Adjuvant Chemotherapy	6	(2)	26	(8)

*ER: Estrogen receptors, PR: Progesterone receptors. † Positive by Immunohistochemistry = >10% cells or by Immunoradiology: ER Positivity = >10 fmol/mg protein, PR positivity = >15 fmol/mg protein.

Table 2. Distribution of first events in AXIL95 and cause of death by Per-Protocol

	no-Ax N = 297		Ax N = 310	
	Within five years	After five years	Within five years	After five years
Patients with events*	29	15	14	17
Axillary event	4	2	0	0
Breast/Chest wall event	5	0	4	8
Lymph node event (excl. axillary)	1	0	na	na
Metastatic event	4	2	1	2
Contralateral breast cancer	2	2	1	1
Other site cancer	5	5	5	4
Death as first event	8	4	3	2
Cause of death (over all events)	17	6	6	4
Breast cancer	5	2	1	1
Other cancer	4	–	1	2
Hormonotherapy adverse effects	1	–	–	–
Other event	7	4	3	–
Unknown	–	–	1	1

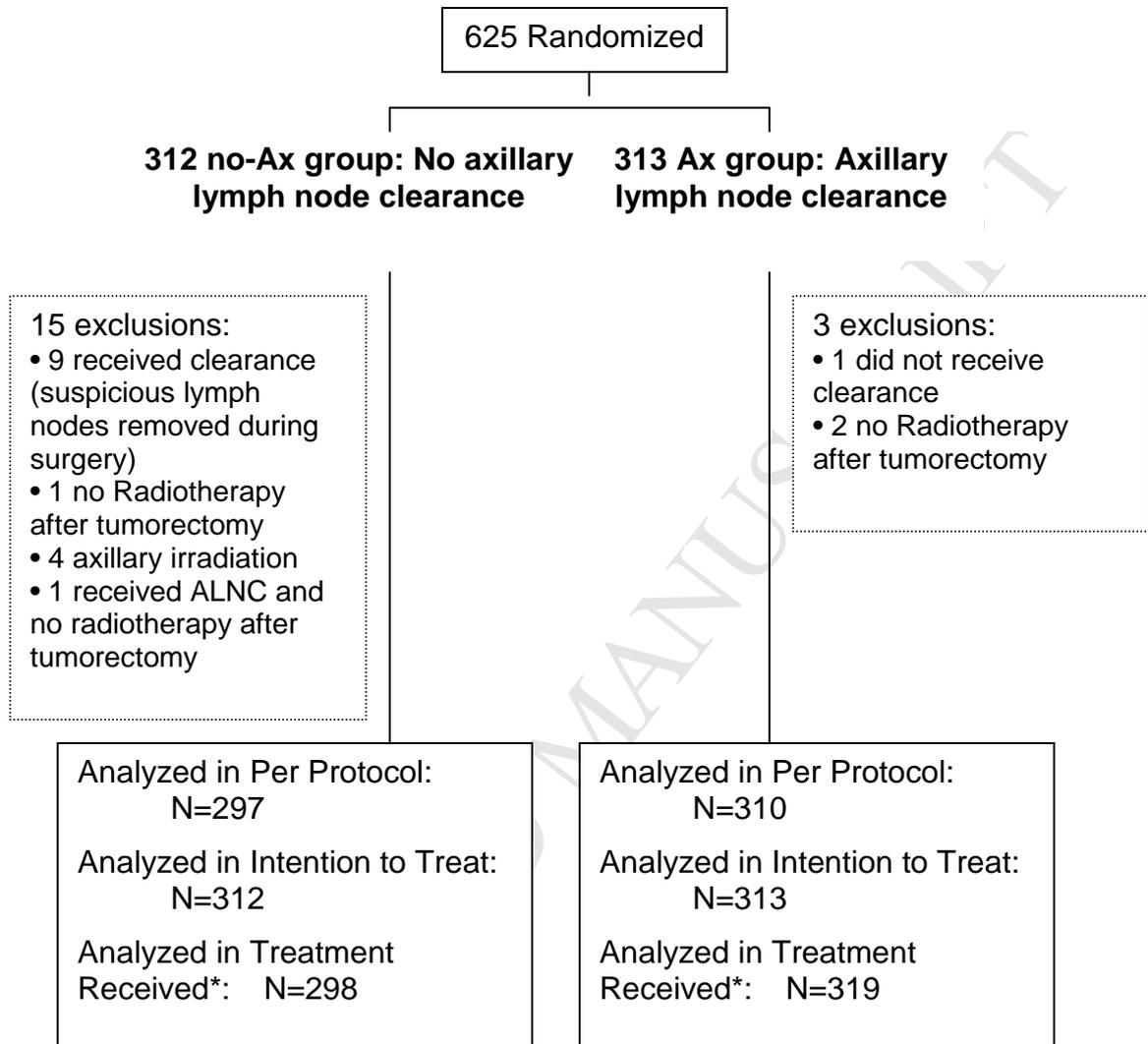
* Contralateral and other site recurrences not included

Table 3. Functional impairments in AXIL95 after surgery or surgery and clearance at three years (by Treatment-Received)

	No-Ax		Ax		Chi ²
	N	%	N	%	
Functional evaluation completed	265	(96)	278	(90)	(between first null group and moderate and/or major)
Arm fatigue					
– Null	254	(96)	249	(90)	254/4 vs. 249/24, p=0.0002
– Moderate/Severe	4	(2)	24	(9)	
– Unknown	7	(3)	5	(2)	
Shoulder mobility					
– Full	252	(95)	250	(90)	252/5 vs. 250/21, p=0.0005
– Restricted somewhat or severely	5	(2)	21	(8)	
– Unknown	8	(3)	7	(3)	
Paresthesia					
– Null	252	(95)	233	(84)	252/6 vs. 233/41, p<0.0001
– Moderate/Severe	6	(2)	41	(15)	
– Unknown	7	(3)	4	(1)	
Lymphedema					
– No difference	255	(96)	246	(88)	255/3 vs. 246/29, p<0.0001
– Minor/Major Diff	3	(1)	29	(11)	
– Unknown	7	(3)	8	(2)	
Other functional impairments					
– None	251	(95)	260	(94)	251/12 vs. 260/16, p=0.252
– Minor/Major	12	(5)	16	(6)	
– Unknown	2	(1)	2	(1)	
Nb patients with functional impairments					
– – None	242	(91)	200	(72)	242/8 vs. 200/15*, p=0.0005
– Minor	15	(6)	63	(23)	
– (At least 1) Major	8	(3)	15	(5)	

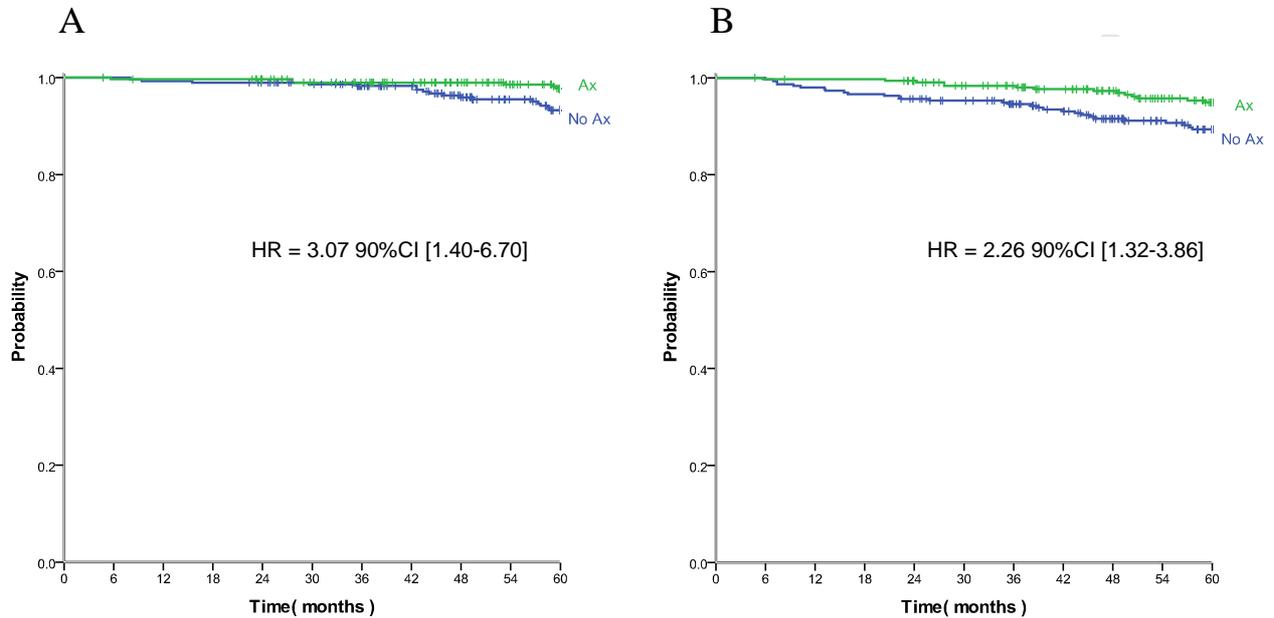
*between first group and major

Figure 1. Consort diagram of exclusions and inclusions for 3 study populations in AXIL95



*Treatment Received includes patients randomized in other treatment arm but receiving this treatment; "cross-over" patients.

Figure 2. (A) Overall survival (OS) and (B) Event-free survival (EFS) in AXIL95 according to treatment group per protocol censored at five years. (No-Ax: no axillary lymph node clearance; Ax: axillary lymph node clearance, HR, Hazard Ratio; CI, confidence interval.)



	Total Patients	Total Events	Censored N	Censored %
no-Ax	297	17	280	94.3%
Ax	310	6	304	98.1%

	Total Patients	Total Events	Censored N	Censored %
no-Ax	297	29	268	90.2%
Ax	310	14	396	95.5%

OS													
Months	0	12	24	36	48	60	Months	0	12	24	36	48	60
No-Ax							no-Ax						
At risk	297	295	291	271	236	201	At risk	297	291	280	261	226	192
Cumul. Events	0	2	3	5	11	17	Cumul. Events	0	6	13	16	24	29
Cumul. survival%	100	99.3	99	98.3	96	93.3	Cumul. survival%	100	98	95.6	94.6	91.5	89.3
Ax							Ax						
At risk	310	307	301	285	260	229	At risk	310	307	300	283	256	223
Cumul. Events	0	1	1	3	3	6	Cumul. Events	0	1	2	5	8	14
Cumul. survival%	100	99.7	99.7	99	99	97.8	Cumul. survival %	100	99.7	99	98.3	97.3	94.9