Research

JAMA Oncology | Original Investigation

Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes

The SOUND Randomized Clinical Trial

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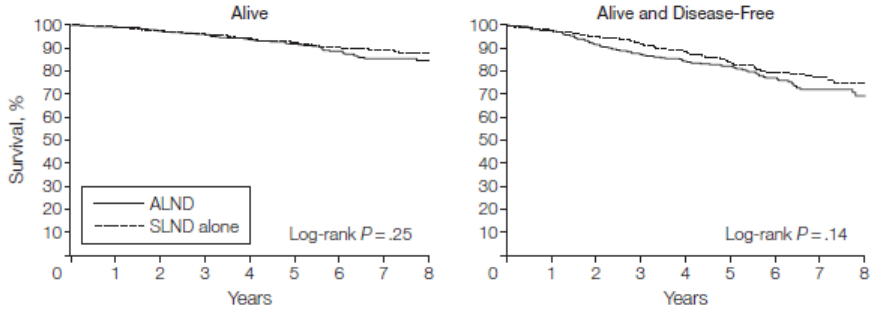
DECLARATION OF INTERESTS

Compensation for speaker, consultancy and advisory role: MSD, Astra-Zeneca, BD, Bayer, Eli Lilly

OS and DFS in the Z0011 trial

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Giuliano et al. JAMA 2011

Summary of ongoing randomized trials

Study	Inclusion Criteria		Randomization	Arms
POSNOC	• uni- or multifocal cT_{1-2} N0 • 1–2 macrometastatic SNs • BCS or mastectomy	1900	1:1	1. AD or RT 2. No further local treatment
SINODAR ONE	• 40–75 year old women • unifocal cT1-2 N0 • 1–2 macrometastatic SNs • BCS or mastectomy	2000	1:1	1. AD 2. No further axillary surgery
SENOMAC	• uni- or multifocal cT_{1-3} N0 • 1–2 macrometastatic SNs • BCS or mastectomy	3500	1:1	1. AD 2. No further axillary surgery
SOUND	• unilateral cT_1 N0 • BCS	1560	1:1	1. SLNB 2. No axillary surgery
INSEMA	• >18 year-old women • unilateral cT_1 N0 • BCS	6740	1:4	1. SLNB 2. No axillary surgery
	If macrometastatic 1–3 SNs	1640	1:1	1A. AD 1B. No further axillary surgey
BOOG 2013-08	• unilateral cT_1 N0 • BCS		1:1	1.SLNB 2.No axillary surgery
NSABP B-51	• $T_{1-3}N_1M0$ undergoing NAC • ypN0 (i+, mic+, mol+), regardless of the kind of axillary staging (AD, SLNB or both)		1:1	1. No regional node RT a. BCS group: Whole breast RT only b. Mastectomy group: No regional node or chest wall RT 2. Regional node RT a. BCS group: whole breast RT b. Mastectomy group: Regional node RT + Chest wall RT
Alliance A11202	• $T_{1-3}N_1M0$ undergoing NAC • ycN0 at post-NAC examination (no US required) • ypN + after SLNB (<6 nodes removed)		1:1	1. AD + regional node RT 2. Axillary and regional node RT

Esposito, Di Micco, Gentilini. The Breast 2017

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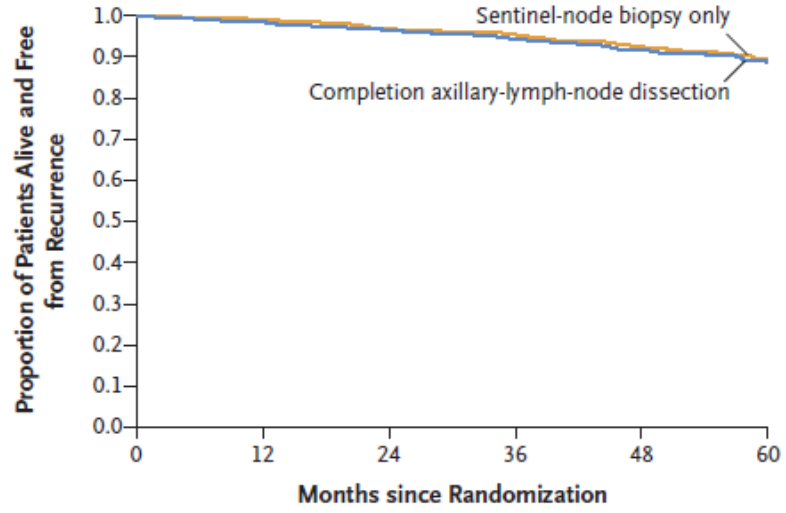
Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

J. de Boniface, T. Filtenborg Tvedskov, L. Rydén, R. Szulkin, T. Reimer, T. Kühn, M. Kontos, O.D. Gentilini, R. Olofsson Bagge, M. Sund, D. Lundstedt, M. Appelgren, J. Ahlgren, S. Norenstedt, F. Celebioglu, H. Sackey, I. Scheel Andersen, U. Hoyer, P.F. Nyman, E. Vikhe Patil, E. Wieslander, H. Dahl Nissen, S. Alkner, Y. Andersson, B.V. Offersen, L. Bergkvist, J. Frisell, and P. Christiansen, for the SENOMAC Trialists' Group*

Recurrence free survival in the SENOMAC trial



	No. of Events	Recurrence-free Survival (95% CI)
		percent
Sentinel-Node Biopsy Only	89	89.7 (87.5–91.9)
Dissection	91	88.7 (86.3–91.1)

Hazard ratio for recurrence or death, 0.89 (95% CI, 0.66–1.19)
P<0.001 for noninferiority

No. at Risk						
Sentinel-node biopsy only	1335	1276	1069	832	577	307
Dissection	1205	1159	1009	772	544	274

Figure 2. Recurrence-free Survival (Per-Protocol Population).
Shown are Kaplan–Meier curves for the secondary end point of recurrence-free survival.

De Boniface et al. NEJM 2024

Considerations

- “Lymph node metastases are indicators and not governors of survival”
- SLNB lost much of its importance
- Imaging may play a relevant role in axillary staging
- Adjuvant treatment recommendations are more and more tailored on the biological features rather than on the risk of recurrence

B. Cady

Is SLNB necessary?

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Viewpoints and debate

Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: **S**entinel node vs **O**bservation after axillary **U**ltraSou**ND**)

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VIEWPOINTS AND DEBATES

Sentinel lymph node biopsy (SLNB) is the standard approach for axillary staging in patients with early breast cancer. Recent data showed no outcome difference in patients with positive sentinel node between axillary dissection vs no further axillary surgery, raising doubts on the role of SLNB itself. Therefore, a new trial was designed comparing SLNB vs observation when axillary ultra-sound is negative in patients with small breast cancer candidates to breast conserving surgery.

Gentilini O, Veronesi U. Breast 2012

Will imaging replace surgery for axillary staging?

VIEWPOINT

Staging the Axilla in Early Breast Cancer
Will Imaging Replace Surgery?

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In the not-so-distant past, removing axillary nodes seemed unavoidable to surgeons who dealt with breast cancer. As physicians and surgeons, we learned that when you excised a cancer in the breast, it was also necessary to remove lymph nodes from the axilla—either all or some—or maybe just 1—but axillary nodes had to go. This attitude derived from the historically later presentation of breast cancer, when overt spreading to the axillary nodes was almost always present. From that time on, breast and axillary surgery became almost indivisibly wed.

The first attempts to avoid removal of axillary nodes was documented with the National Surgical Adjuvant Breast and Bowel Project B-04 trial.[1] This trial clearly regardless of nodal status. In patients with negative SLNB findings, the axillary recurrence rate is about 1%, even though the expected rate should be higher considering the false-negative rate of the procedure (5%-10%).[6] In the IBCSG 23-01 trial,[7] patients with micrometastases of the sentinel lymph nodes who did not receive ALND had an incidence of axillary nodal recurrence of about 1% despite the rate of additional nonsentinel nodes involved being 13% in the ALND arm. In the ACOSOG Z0011[4] and AMAROS[5] trials, recurrence was again about 1%. Is there a sort of predetermined and somehow fixed rate of overt axillary metastases after modern multimodality treatments?

Gentilini O, Veronesi U. JAMA Oncol 2015

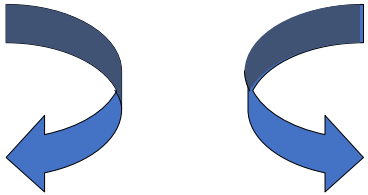
SOUND trial
(**S**entinel node vs **O**bservation after axillary **U**ltra-sou**ND**)

- Sponsor: European Institute of Oncology, Milan
- The primary outcome was distant disease-free survival (DDFS), analysed by intention to treat. The log-rank test was used to test DDFS differences between groups. The trial was designed on the basis of an expected 5-year DDFS of 96.5% in the SLNB group, with 80% power to exclude a 2.5% decrease in DDFS (non-inferiority margin) in the no axillary surgery group; non-inferiority was shown if the upper limit of the two-sided 90% confidence interval (CI) for the hazard ratio (HR) for no axillary surgery versus SLNB was less than 1.74.
- The trial is registered with ClinicalTrials.gov, NCT02167490
- Fundings: Umberto Veronesi Foundation, AVON Running

SOUND trial study design

Patients with breast cancer ≤2 cm
Any age, Breast conserving therapy
Negative U.S. of the axilla
negative FNAC of a single doubtful axillary node

Randomization



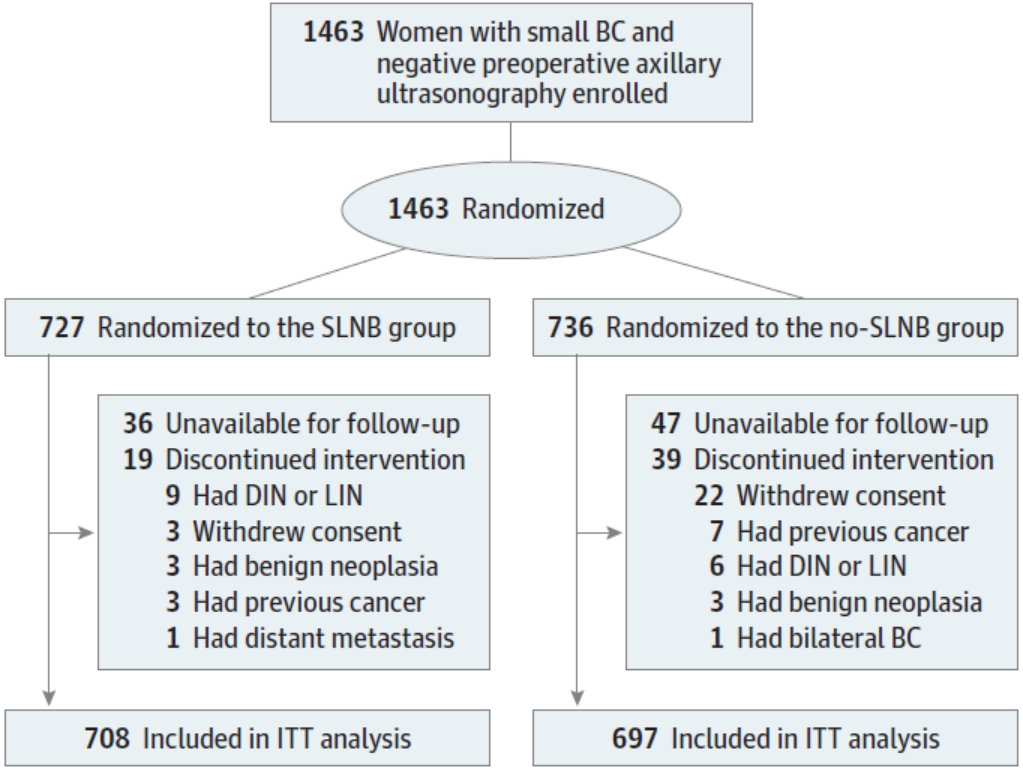
SNB policy

n=780

No axillary surgery

n=780

Figure 1. Flow Diagram



BC indicates breast cancer; DIN, ductal intraepithelial neoplasia; ITT, intention to treat; LIN, lobular intraepithelial neoplasia; and SLNB, sentinel lymph node biopsy.

Gentilini et al. JAMA Oncol 2023

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	Patients, No. (%)	
	SLNB (n = 708)	No axillary surgery (n = 697)
Age at surgery, y		
<40	10 (1.4)	10 (1.4)
40-49	114 (16.1)	128 (18.4)
50-64	324 (45.8)	298 (42.8)
≥65	260 (36.7)	261 (37.4)
Median (IQR)	60 (52-68)	60 (51-68)
Menopausal status[a]		
Premenopausal	145 (20.6)	154 (22.3)
Perimenopausal or postmenopausal	558 (79.4)	538 (77.7)
Histotype		
Ductal	551 (77.8)	543 (77.9)
Lobular	61 (8.6)	59 (8.5)
Tubular	27 (3.8)	33 (4.7)
Other	69 (9.7)	62 (8.9)
Pathological tumor size		
pT1mic or pT1a	71 (10.0)	61 (8.8)
pT1b	251 (35.5)	240 (34.4)
pT1c	355 (50.1)	361 (51.8)
pT2	31 (4.4)	35 (5.0)
Median (IQR), cm	1.1 (0.8-1.5)	1.1 (0.8-1.5)
No. of positive SLNs		
0	599 (84.6)	12 (1.7)
1	83 (11.7)	10 (1.4)
≥2	14 (2.0)	0
SLNB not performed	12 (1.7)	675 (96.8)
No. of positive LNs		
0	599 (84.6)	12 (1.7)
1-3	93 (13.1)	9 (1.3)
4-9	2 (0.3)	1 (0.1)
≥10	2 (0.3)	0

Gentilini et al. JAMA Oncol 2023

Table 1. Baseline Patient and Tumor Characteristics (continued)

Characteristic	Patients, No. (%)	
	SLNB (n = 708)	No axillary surgery (n = 697)
Pathological node status		
pNx	12 (1.7)	675 (96.8)
pN0	584 (82.5)	12 (1.7)
pN0(i+)	15 (2.1)	0
pN1mi	36 (5.1)	4 (0.6)
pN1	57 (8.1)	5 (0.7)
pN2	4 (0.6)	1 (0.1)
Grade[b]		
1	194 (27.7)	204 (29.9)
2	377 (53.8)	356 (52.2)
3	130 (18.5)	122 (17.9)
ER status		
0	56 (7.9)	44 (6.3)
>0	652 (92.1)	653 (93.7)
PgR status		
0	108 (15.3)	95 (13.6)
>0	600 (84.7)	602 (86.4)
Ki-67 index[c]		
<20	455 (64.4)	439 (63.2)
≥20	252 (35.6)	256 (36.8)
Median (IQR)	15 (10-23)	15 (10-24)

Gentilini et al. JAMA Oncol 2023

Table 1. Baseline Patient and Tumor Characteristics (continued)

Characteristic	Patients, No. (%)	
	SLNB (n = 708)	No axillary surgery (n = 697)
ERBB2 overexpression		
Not overexpressed	660 (93.2)	650 (93.3)
Overexpressed	48 (6.8)	47 (6.7)
Surrogate subtype		
Luminal *ERBB2*-negative	617 (87.1)	617 (88.5)
ERBB2-enriched	48 (6.8)	47 (6.7)
Triple-negative	43 (6.1)	33 (4.7)

Gentilini et al. JAMA Oncol 2023

Table 2. Final Surgical Treatment and Recommended Adjuvant Therapy

Treatment	Patients, No. (%)		*P* value
	SLNB (n = 708)	No axillary surgery (n = 697)	
Surgery			
Breast-conserving	12 (1.7)	675 (96.8)	NA
Breast-conserving and SLNB	646 (91.2)	13 (1.9)	
Breast-conserving, SLNB, and AD	45 (6.4)	5 (0.7)	
Mastectomy and SLNB	5 (0.7)	4 (0.6)	
Hormone therapy			
No	66 (9.3)	49 (7.0)	.12
Yes	642 (90.7)	648 (93.0)	
Hormone therapy in ER-positive cases[a]			
No	14 (2.1)	7 (1.1)	.12
Yes	638 (97.9)	646 (98.9)	
Chemotherapy			
No	566 (79.9)	575 (82.5)	.22
Yes	142 (20.1)	122 (17.5)	
Hormone therapy and chemotherapy			
Neither hormone therapy nor chemotherapy	17 (2.4)	11 (1.6)	.35
Hormone therapy without chemotherapy	549 (77.5)	564 (80.9)	
Chemotherapy without hormone therapy	49 (6.9)	38 (5.5)	
Both hormone therapy and chemotherapy	93 (13.1)	84 (12.1)	
Radiotherapy			
No	14 (2.0)	17 (2.4)	.56
Yes	694 (98.0)	680 (97.6)	
Trastuzumab			
No	661 (93.4)	651 (93.4)	.98
Yes	47 (6.6)	46 (6.6)	
Trastuzumab in overexpressed *ERBB2*-positive cases[b]			
No	3 (6.2)	1 (2.1)	.62
Yes	45 (93.8)	46 (97.9)	

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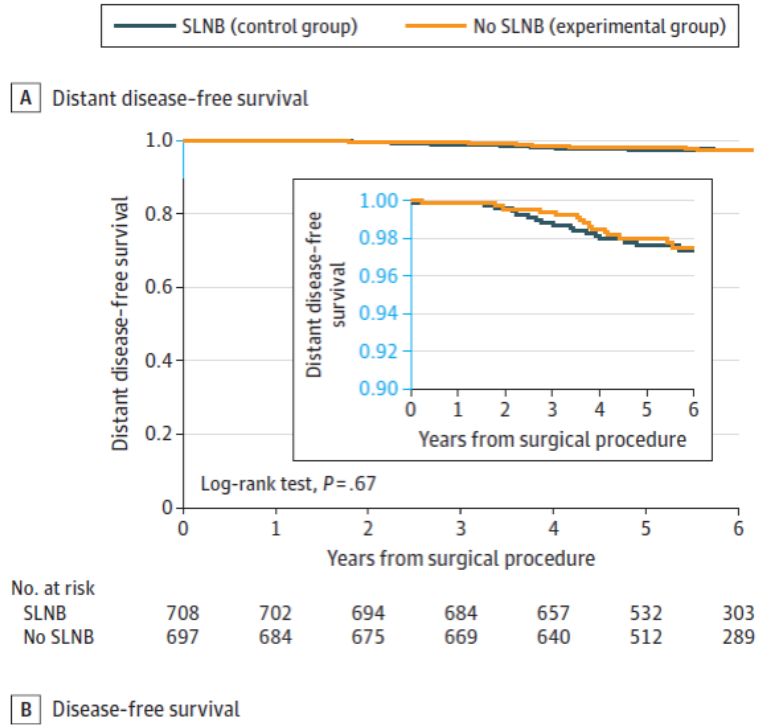
Table 3. Summary of First Events, Deaths, and Follow-Up Time

Outcome	Events, No. (%) SLNB (n = 708)	No axillary surgery (n = 697)
First events		
Ipsilateral breast recurrence	7 (1.0)	6 (0.9)
Axillary recurrence	3 (0.4)	5 (0.7)
Ipsilateral breast and axillary recurrence	2 (0.3)	0
Distant metastasis	13 (1.8)	14 (2.0)
Contralateral breast cancer	5 (0.7)	7 (1.0)
Nonbreast primary tumors	17 (2.4)	22 (3.2)
Death from breast cancer	0	0
Death from cause other than breast cancer	5 (0.7)	6 (0.9)
Death from unknown cause	1 (0.1)	1 (0.1)
Follow-up, median (IQR), y	5.7 (5.0-6.8)	5.7 (5.0-6.6)
All deaths, cause		
Breast cancer	7 (1.0)	4 (0.6)
Cause other than breast cancer	10 (1.4)	12 (1.7)
Unknown cause	4 (0.6)	2 (0.3)
Follow-up, median (IQR), y	5.8 (5.0-6.9)	5.8 (5.0-6.8)

Figure 2. Kaplan-Meier Estimates of Distant Disease-Free Survival, Disease-Free Survival, and Overall Survival



Five-year DDFS was 97.7% in the SLNB arm and 98.0% in the no axillary surgery arm (Log-rank test P=0.665; HR 0.84; 90% CI 0.45-1.54; non-inferiority P=0.024).

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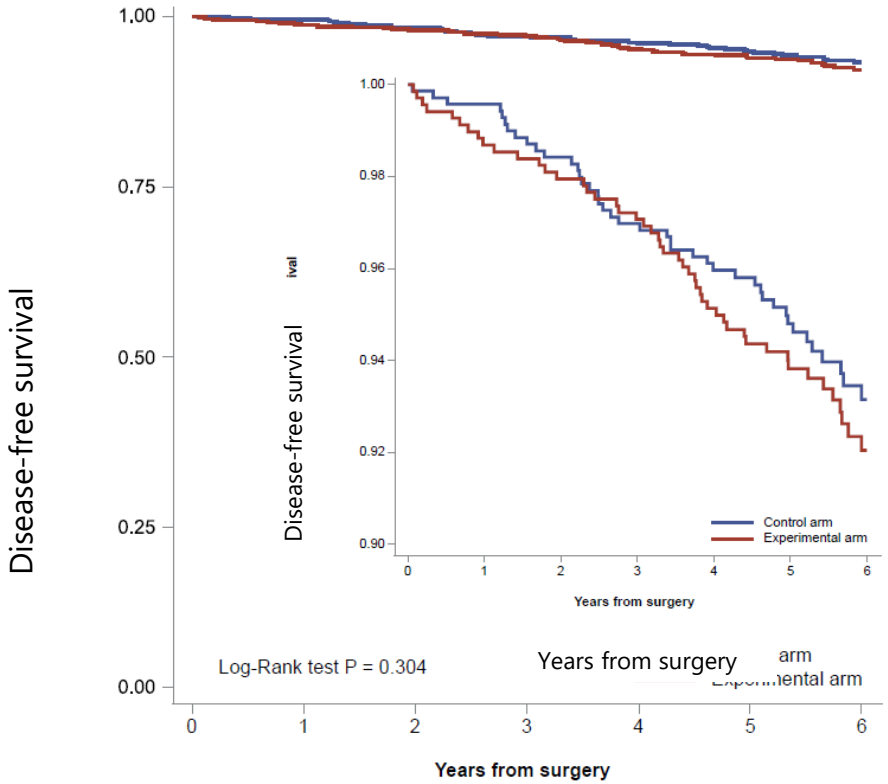
SOUND trial: DFS



Number of subjects at risk							
Control arm	708	702	694	684	657	532	303
Experimental arm	697	684	675	669	640	512	289

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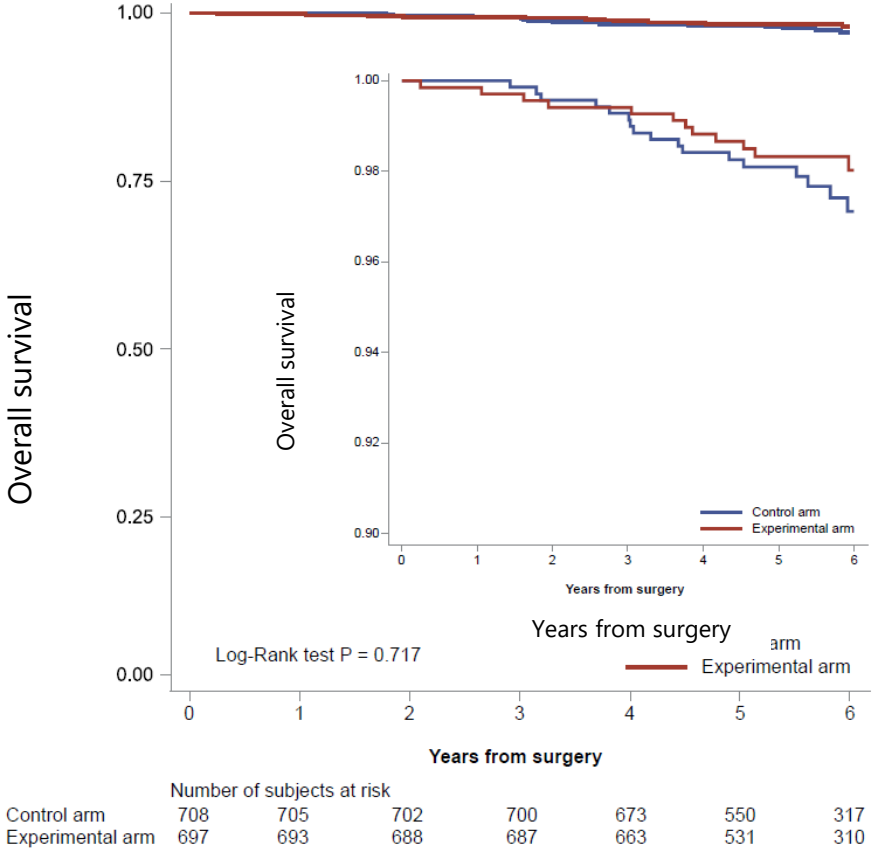
SOUND trial: OS



Number of subjects at risk

Control arm	708	705	702	700	673	550	317
Experimental arm	697	693	688	687	663	531	310

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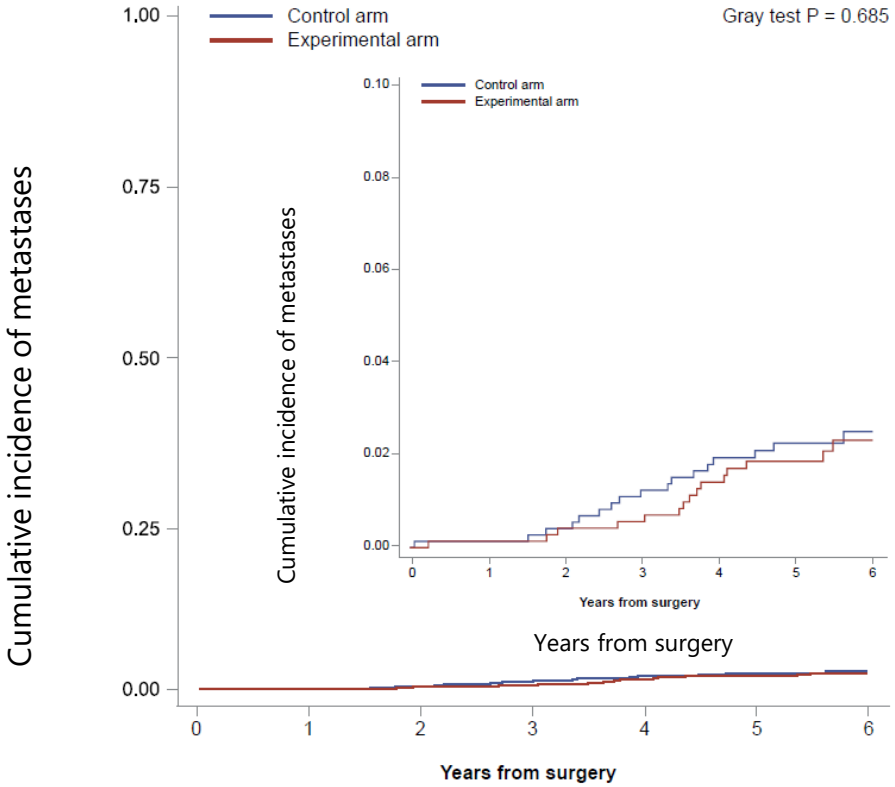
SOUND trial: cumulative incidence of distant metastases



Number of subjects at risk							
Control arm	708	702	694	684	657	532	303
Experimental arm	697	684	675	669	640	512	289

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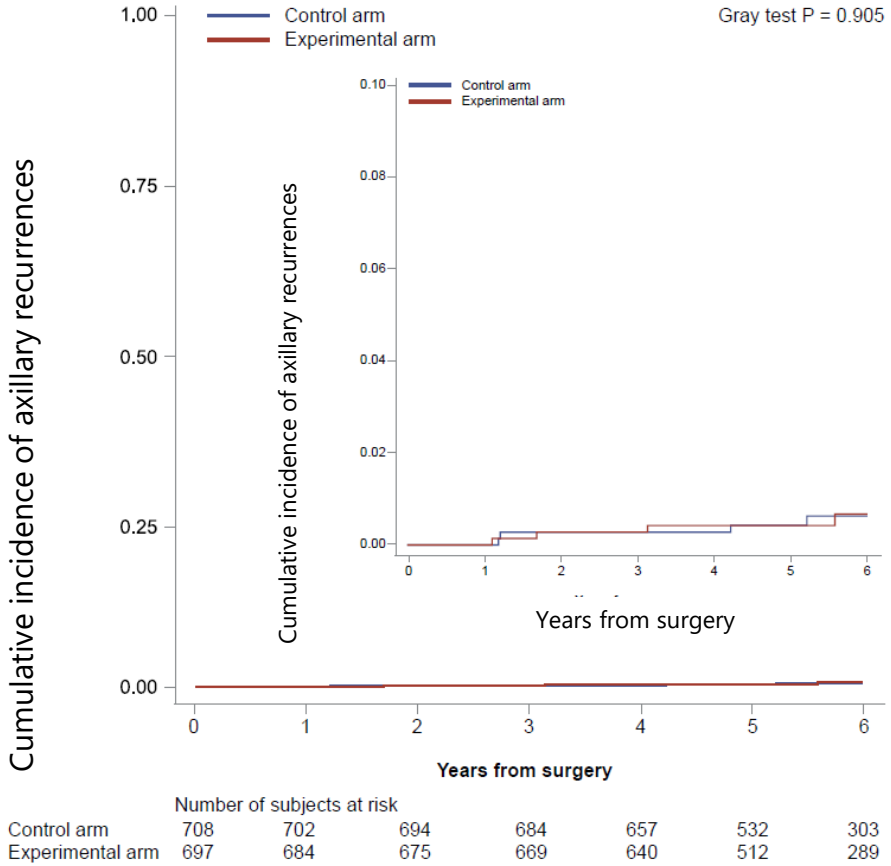
SOUND trial: cumulative incidence of axillary metastases



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SOUND trial-Conclusions

- We showed that omission of axillary surgery was non-inferior to SLNB in patients with small breast cancer and a negative ultra-sound of axillary lymph-nodes.
- Patients with these features can be safely spared any axillary surgery whenever the lack of pathologic information is not affecting the postoperative treatment plan
- Outcome of patients with SOUND criteria is excellent in the first 5 years, with an extremely low number of breast cancer-related events
- Despite the need for further research to improve imaging methods, our study supports the wide reproducibility of ultra-sound as a simple, inexpensive method to be routinely applied in the pre-operative work-up of all patients with breast cancer

SOUND trial-Conclusions

- Data from the SOUND trial indicated that adjuvant treatments were not significantly different in the two study arms, regardless of whether the pathologic information from SLNB was available or not.
- Data of this trial are in line of the Choosing Wisely Campaign that recommends to omit SLNB in patients older than 70 years with small ER+HER2- breast cancer when the adjuvant treatment plan is clear and does not include the addition of chemo to endocrine treatment.
- However, the pathologic information provided by nodal status is not completely ignored when deciding on the postoperative treatment of younger patients, especially in pre-menopausal women

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Needle Point

Lessons from the SOUND trial and future perspectives on axillary staging in breast cancer

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SOUND trial: lesson 1

- SLNB can be omitted in patients with small breast cancer and a negative pre-operative ultra-sound of the axilla without any detrimental effect in terms of DDFS at 5 years

SOUND trial: lesson 2

- Outcome of patients with SOUND-like criteria is excellent in the first 5 years, with very low risk of recurrence after a proper inter-disciplinary management

SOUND trial: lesson 3

- Number of follow up examinations can be reduced with reduced psychological distress for the patients as well as lower costs

SOUND trial: lesson 4

- Axillary ultra-sound rules out substantial nodal burden in the axilla. Patients with SOUND-like criteria have less than 1% likelihood of having 4 or more positive nodes.

SOUND trial: lesson 5

- lymph node surgery is just a staging procedure

SOUND trial: question, considerations and foresight

- what is the required level of information for the individual patient?
- in the era of biological and molecular characterization of the tumor, with an increasing role of liquid biopsies, it seems anachronistic to still rely on nodal status to tailor post-operative treatments
- axillary surgery, although perhaps not in the immediate future, will be restricted to a limited number of clinical scenarios

SOUND trial: lesson 6

- vision, coordinated planning, and international cooperation are the key elements to move forward