L'OMISSIONE DELLA STADIAZIONE ASCELLARE NEL CARCINOMA MAMMARIO ER+:

Implicazioni per la RADIOTERAPIA

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BACKGROUND

The role of axillary surgery in the management of breast cancer has changed

Sentinel-lymph-node biopsy is used to identify nodal metastases, but recognition of the lack of therapeutic benefit of this approach, coupled with the emphasis on tumor biology for decisions about systemic therapy, has led to trials examining the elimination of sentinel-lymph-node biopsy in early-stage breast cancer

Axillary lymph node dissection in breast cancer patients: obsolete or still necessary?

Gianluca Vanni,[a,] Marco Pellicciaro,[a,b] and Oreste Claudio Buonomo[a,b,c]*

Indication to adding chemotherapy to hormone treatment in luminal-like B breast cancer
Indication for regional node irradiation
Indication for abemaciclib in patients fulfilling monarchE criteria
Indication for dual anti-HER2 therapy
Indication to Olaparib in post-NeoCHT in patients BRCA+
Indication to type and duration of endocrine treatment in ER+ breast cancer

***Table 1:* Clinical conditions where adjuvant treatments are influenced by nodal status.**

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The Lancet Regional Health - Europe 2024;47: 101107

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

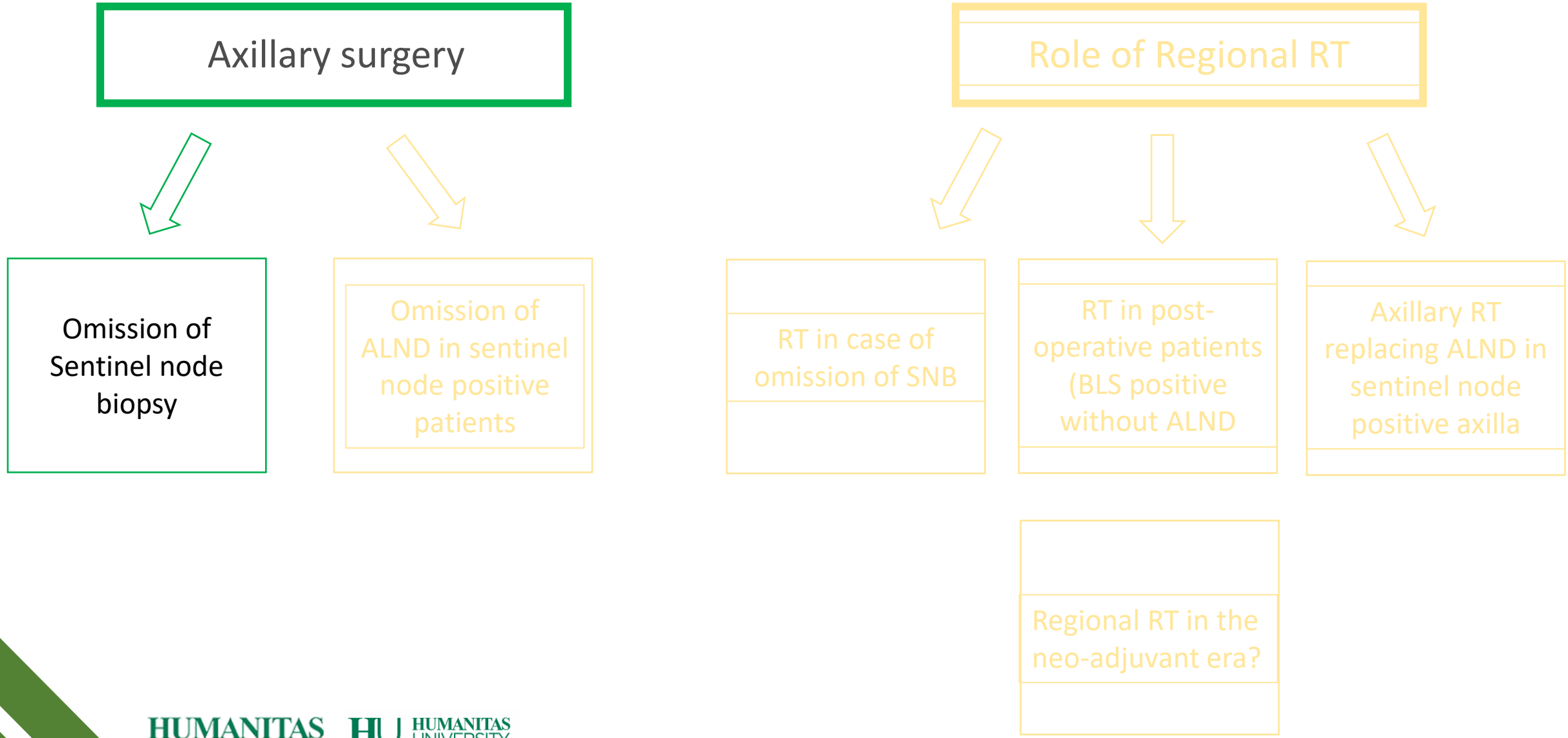
Axillary surgery

- Omission of Sentinel node biopsy
- Omission of ALND in sentinel node positive patients

Role of Regional RT

- RT in case of omission of SNB
- RT in post-operative patients (BLS positive without ALND
- Axillary RT replacing ALND in sentinel node positive axilla
- Regional RT in the neo-adjuvant era?

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?



Omission of Sentinel node biopsy

The American Board of Internal Medicine Foundation launched a national initiative called Choosing Wisely to prompt provider discussion about the appropriate use of tests, treatments, and procedures based on evidence-driven medicine.

In conjunction with the Society of Surgical Oncology in 2016, five recommendations were released.

The first recommendation stated, **“Don’t routinely use sentinel node biopsy in clinically node-negative women ≥70 years of age with early-stage hormone receptor-positive, HER2 negative invasive breast cancer.”**

Omission of Sentinel node biopsy

Prospective trials highlighting that SLNB had no impact on locoregional recurrence or breast-cancer-specific ***mortality***
(patients >70 years old with operable BC and negative clinical axillae)

Authors	Stage of disease	Axillary recurrences	BC-specific mortality
Martelli et al	T < 2 cm	15-years: 5.8% ALND 3.7% no ALND	No difference
IBCSG 10-93 trial	T < 2 cm	Improved early QOL in no ALND group	No difference
CALGB 9343 trial	T < 2 cm	ALND: 3% ipsilateral axillary recurrence No ALND: no recurrences	No difference

Martelli et al Ann Surg 2005
IBCSG 10-93 JCO 2006
CALGB 9343 trial JCO 2013

Omission of Sentinel node biopsy

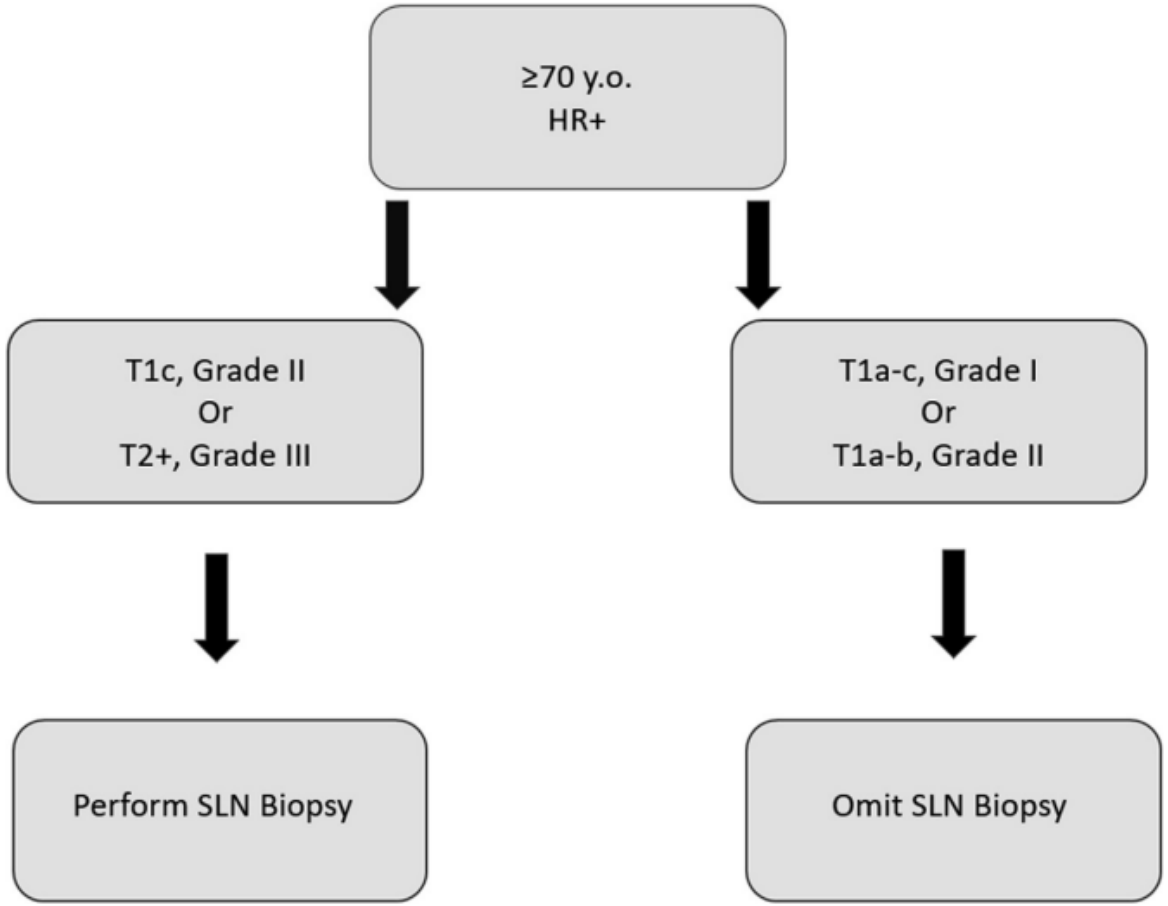


Figure 1. Algorithm for omission of sentinel lymph node biopsy in older people. *HR+*, hormone receptor positive; *SLN*, sentinel lymph node; *y.o.*, years old.

Martelli et al Ann Surg 2005
IBCSG 10-93 JCO 2006
CALGB 9343 trial JCO 2013

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Omission of Sentinel node biopsy

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

Oreste Davide Gentilini, MD; Edoardo Botteri, PhD; Claudia Sangalli, BSc; Viviana Galimberti, MD; Mauro Porpiglia, MD; Roberto Agresti, MD; Alberto Luini, MD; Giuseppe Viale, MD; Enrico Cassano, MD; Nickolas Peradze, MD; Antonio Toesca, MD; Giulia Massari, MD; Virgilio Sacchini, MD; Elisabetta Munzone, MD; Maria Cristina Leonardi, MD; Francesca Cattadori, MD; Rosa Di Micco, PhD; Emanuela Esposito, PhD; Adele Sgarella, MD; Silvia Cattaneo, MD; Massimo Busani, MD; Massimo Dessena, MD; Anna Bianchi, MD; Elisabetta Cretella, MD; Francisco Ripoll Orts, MD; Michael Mueller, MD; Corrado Tinterri, MD; Badir Jorge Chahuan Manzur, MD; Chiara Benedetto, PhD; Paolo Veronesi, MD; for the SOUND Trial Group

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)
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)
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)

(continued)

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)

Abbreviation: SLNB, sentinel lymph node biopsy.

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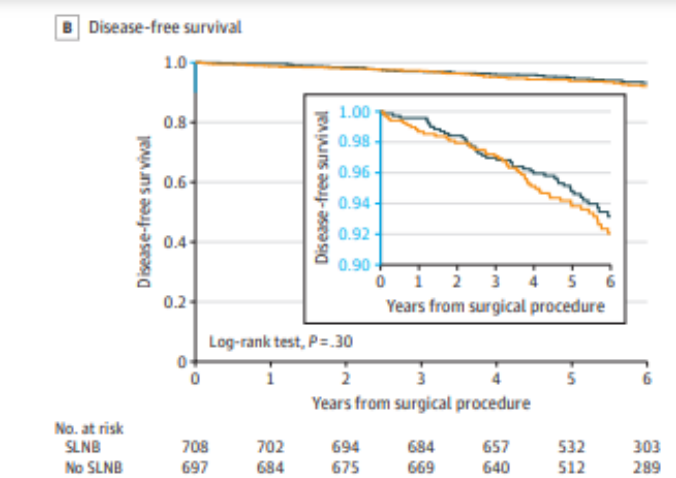
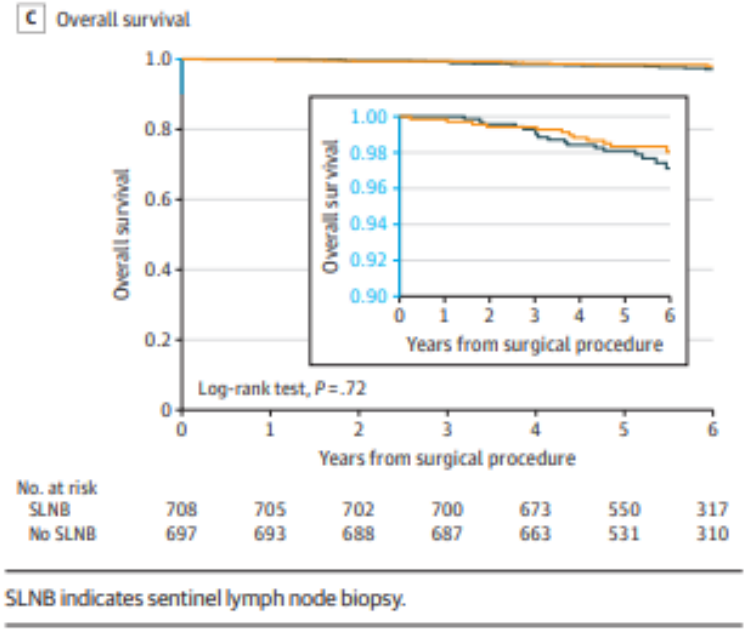
Gentilini et al. JAMA Oncol. 2023 Nov 1;9(11):1557-1564

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Omission of Sentinel node biopsy





SLNB indicates sentinel lymph node biopsy.

Gentilini et al. JAMA Oncol. 2023 Nov 1;9(11):1557-1564

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Omission of Sentinel node biopsy

The NEW ENGLAND JOURNAL of MEDICINE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

Authors: Toralf Reimer, Ph.D., Angrit Stachs, Ph.D., Kristina Veselinovic, M.D., Thorsten Kühn, Ph.D., Jörg Heil, Ph.D., Silke Polata, M.D., Frederik Marmé, Ph.D., +15, and Bernd Gerber, Ph.D. Author Info & Affiliations

Published December 12, 2024 | N Engl J Med 2025;392:1051-1064 | DOI: 10.1056/NEJMoa2412063

- A total of 5502 eligible patients (90% with clinical T1 cancer and 79% with pathological T1 cancer) underwent randomisation in a 1:4 ratio
- **962 were assigned to undergo treatment without surgical axillary staging (the surgery-omission group), and 3896 to undergo sentinel lymph node biopsy (the surgery group)**.
- The median follow-up was 73.6 months.

The estimated 5-year iDFS rate was 91.9% (95% confidence interval [CI] 89.9 to 93.5) among patients in the surgery-omission group and 91.7% (95% CI 90.8 to 92.6) among patients in the surgery group, with HR of 0.91 (95% CI 0.73 to 1.14), which was below the pre-specified non-inferiority margin.

The analysis of the first primary outcome events (occurrence or recurrence of invasive disease or death from any cause), which occurred in a total of 525 patients (10.8%), showed apparent differences between the surgery-omission group and the surgery group in the incidence of axillary recurrence (1.0% versus 0.3%) and death (1.4% versus 2.4%).

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Axillary surgery

Omission of Sentinel node biopsy

Role of Regional RT

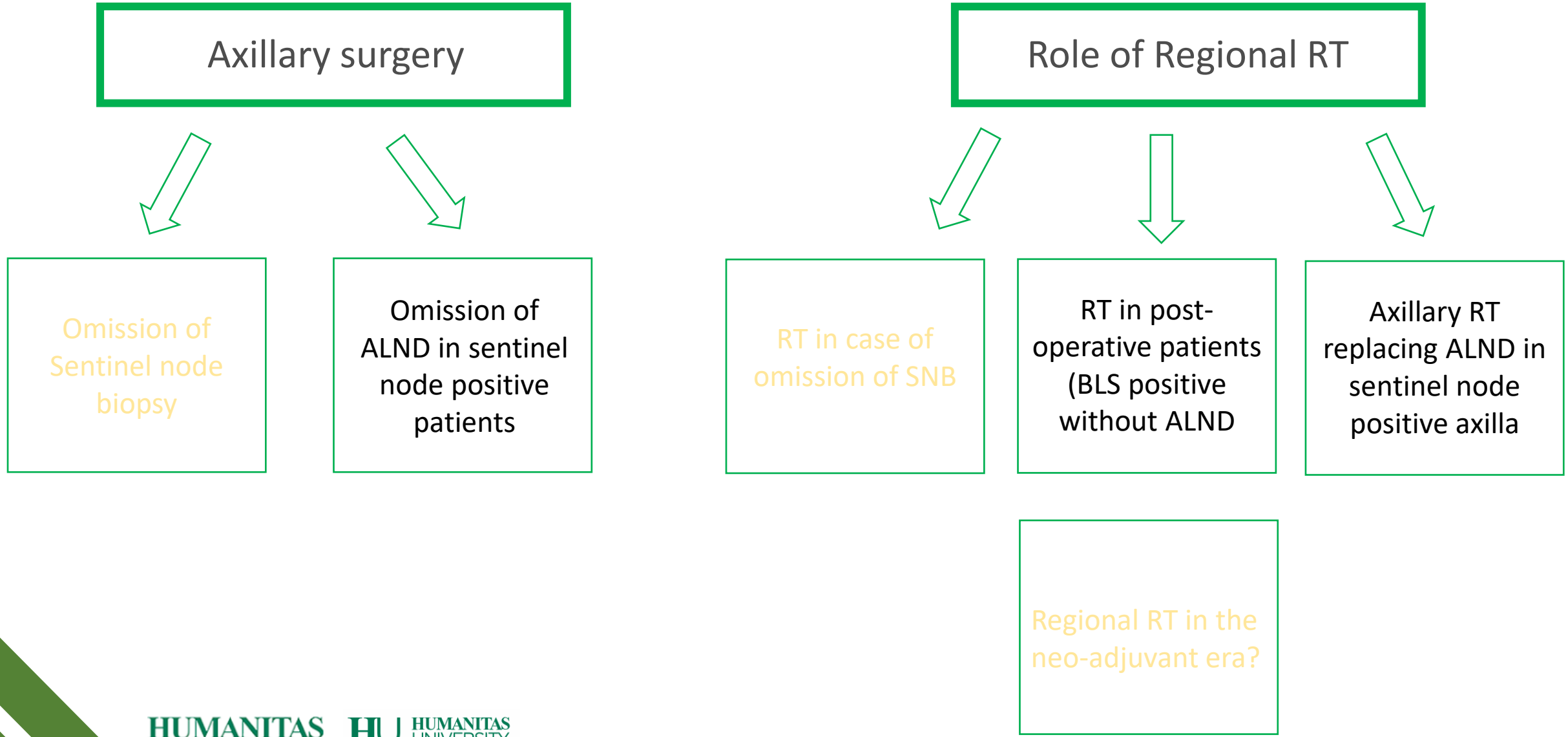
Whole Breast RT

INSEMA trial
SOUND trial

Pazienti candidabili ad omissione della chirurgia ascellare:

- post-menopausa
- T < 2 cm
- G1-G2
- Luminal A

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?



Omission of ALND in sentinel node positive patients

Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis:

The ACOSOG Z0011 (Alliance) Randomized Clinical Trial

T1-2 tumours and 1/2 positive sentinel nodes after breast-conserving therapy: ALND vs NO ALND

891/1900 enrolled pts (closed early with only 50% accrual)
Unbalanced baseline characteristics
Missing radiotherapy details (available only for 228 pts)

Ten-year regional recurrence did not differ significantly between the 2 groups
10-year disease-free survival was 80.2% in the SLND alone group and 78.2% in the ALND group
10-year overall survival was 86.3% in the SLND alone group and 83.6% in the ALND group (non-inferiority p = .02)

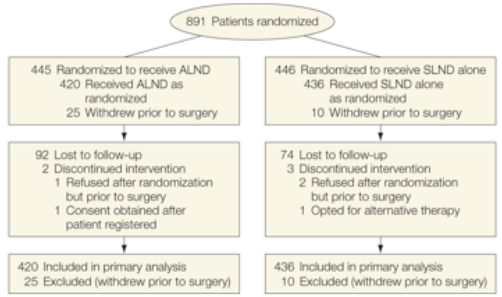


Figure Legend:

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

Giuliano et al. Jama Oncology 2011

Omission of ALND in sentinel node positive patients

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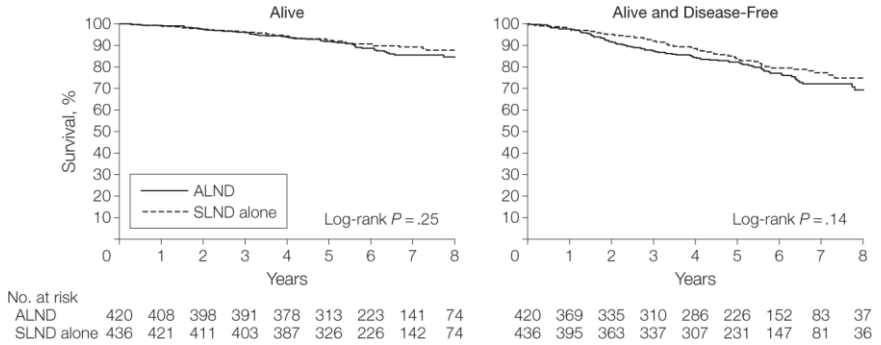
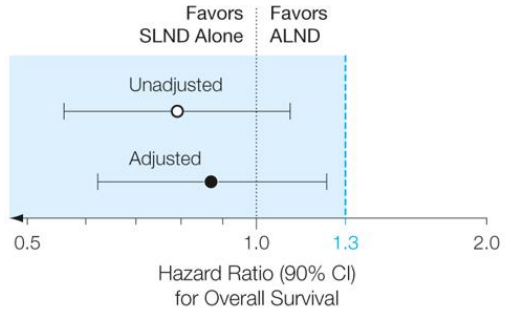




Giuliano et al. Jama Oncology 2011

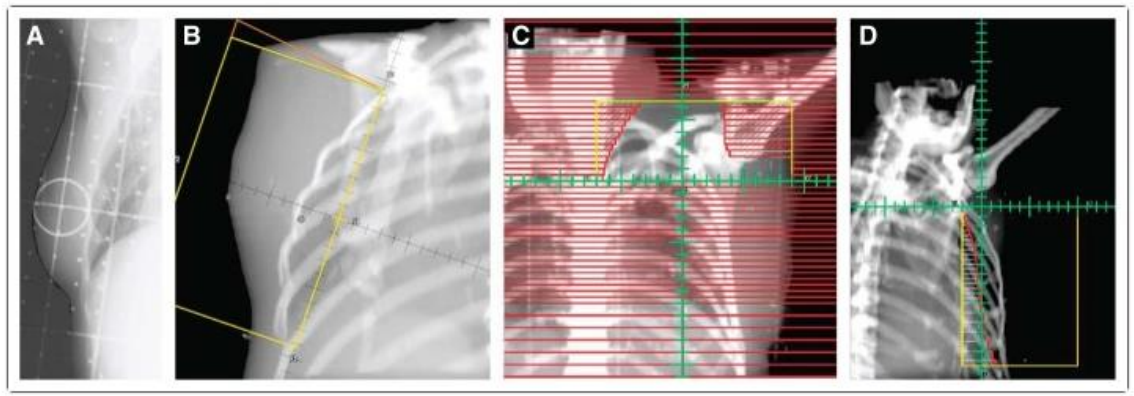
Omission of ALND in sentinel node positive patients

ACOSOG Z0011 (Alliance) Trial uncertainties:

- ❑ Under-recruitment
- ❑ Premature closure of the study
- ❑ Large noninferiority margin
- ❑ Short follow up
- ❑ Irradiated nodal volumes?

Giuliano AE, Jagsi et al. JCO 2014

Omission of ALND in sentinel node positive patients



Representative examples of detailed radiation treatment records received and classified as receiving standard tangents, high tangents, or third-field treatment. (A) Standard tangents. (B) High tangents. (C and D) Third-field and matched tangents from a single patient.

- ❑ RT administration were available for 605 patients
- ❑ 540/605 pts (89%) were noted to have received whole-breast RT.
- ❑ 89/605 patients (15%) were recorded as also receiving treatment to the supraclavicular region

Giuliano AE, Jagsi et al. JCO 2014

Omission of ALND in sentinel node positive patients

Ann Surg Oncol (2022) 29:5732–5744
https://doi.org/10.1245/s10434-022-11866-w

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

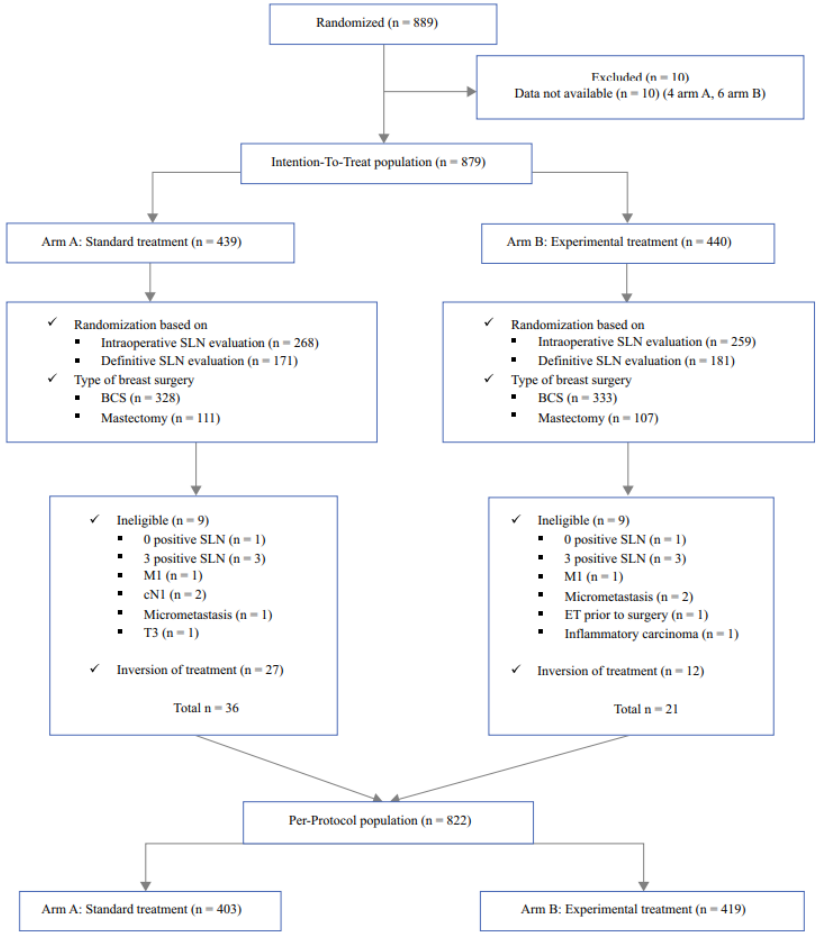
ORIGINAL ARTICLE – BREAST ONCOLOGY

Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1–2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial

T1-2 tumours and 1/2 positive sentinel nodes after BCS or mastectomy (24.8%): ALND vs NO ALND

889 enrolled pts (trial enrollment closed early because of poor accrual rates and fewer than anticipated events)

The **3-year** survival and relapse rates of BC pts treated with SLNB only, and adjuvant therapy, were not inferior to those of patients treated with ALND



Tinterri et al. Annals Surg Oncology 2022

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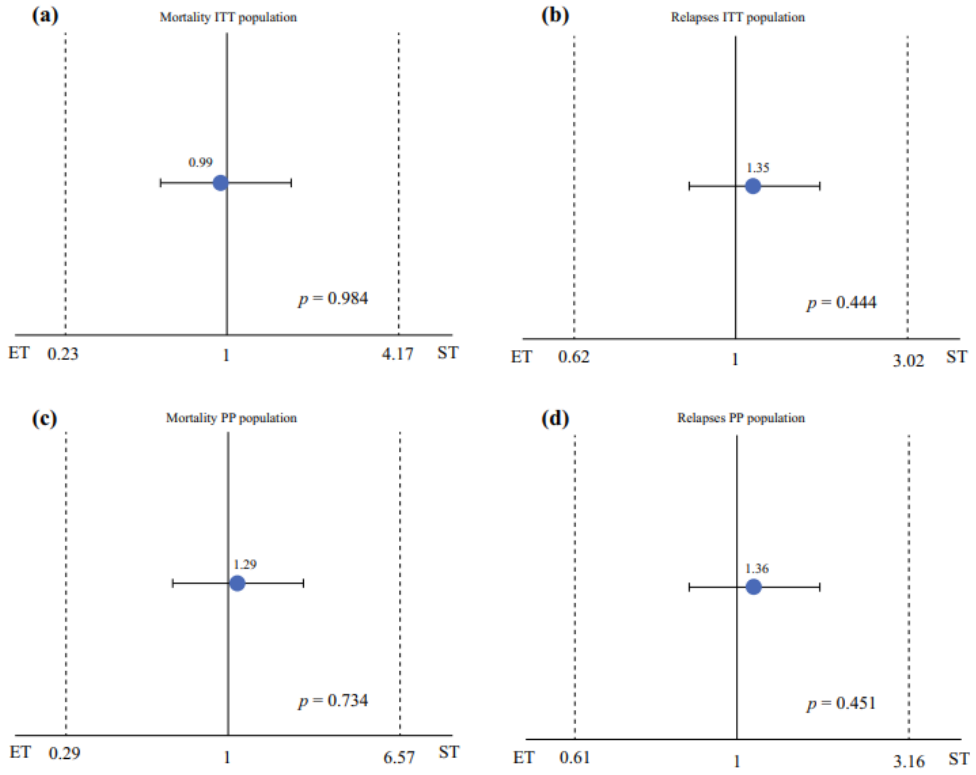

FIG. 4 Testing noninferiority between treatment arms (standard versus experimental), showing noninferiority outcomes in terms of mortality and relapses rates of the experimental treatment (sentinel lymph node biopsy only) compared with the standard treatment (axillary dissection) in both the ITT (**a**, **b**) and PP population (**c**, **d**). *ITT* intention-to-treat, *PP* per-protocol, *ET* experimental treatment, *ST* standard treatment

Tinterri et al. Annals Surg Oncology 2022

Omission of ALND in sentinel node positive patients

146 (PB-053) Poster

The radiotherapy omission within the Sinodar One protocol: Survival and Relapse Outcomes and dosimetric analysis

R. Spoto[1], A. Bertolini[1], D. Franceschini[1], L. Dominici[1], F. Lobefalo[1], C. Tintern[2], M. Scorsetti[3]. *[1]IRCCS Humanitas Research Hospital, Department of Radiotherapy and Radiosurgery, Rozzano, Italy; [2]IRCCS Humanitas Research Hospital, Breast Unit, Rozzano, Italy; [3]Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Italy*

Background: We conducted a re-analysis of the data from the SINODAR-ONE phase III randomized trial, focusing on the omission of radiotherapy. The primary objectives of the study were overall survival (OS) and locoregional relapse (LRR). We performed a dosimetric analysis of the dose to the axilla.

Materials and Methods: Patients with T1-2 breast cancer and 1–2 macrometastatic sentinel lymph nodes were randomly assigned in a 1:1 ratio to either undergo removal of ≥10 axillary level I/II non-sentinel lymph nodes followed by adjuvant radiotherapy (ARM 1) or receive no further axillary treatment (ARM 2). We collected radiotherapy data and compare the outcomes. We contoured retrospectively all four axillary levels and internal mammary chain in order to perform a dosimetric analysis of the dose distribution to that regions.

Results: From 2015 to 2020, a total of 889 patients were enrolled and randomized. The median follow-up period was 34.0 months. Radiotherapy data were available for 355 patients. In study arm, no axillary dissection was performed, and locoregional radiotherapy was administered 17pts that represent a major deviation. In ARM 1 and ARM 2, we observed 0 and 2 deaths, and the relapse were 2 and 4, respectively. Statistical analysis did not reveal any significant differences between the two arms. The dosimetric analysis performed on 72 pts (56 treated with VMAT and 16 treated with 3D conformal technique) revealed that the median mean dose to the first level of axilla is half of prescription dose.

Conclusion: In T1-2 breast cancer patients with 1–2 macrometastatic sentinel lymph nodes treated with sentinel lymph node biopsy alone, the 3-year survival and relapse rates were not inferior to those of patients treated with axillary lymph node dissection plus or minus locoregional radiotherapy. The dose to axilla can't influence these results.

No conflict of interest.

European Journal of Cancer 200S1 (2024) 113720
https://doi.org/10.1016/j.ejca.2024.113720

A dosimetric analysis performed on 72 pts revealed that a median mean dose to the I Level of axilla is 50% of prescription dose

Spoto R et al. EJC 2024

Omission of ALND in sentinel node positive patients

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*

T1-3 tumours and 1/2 positive sentinel nodes (ECE was allowed) after BCS (64%) or mastectomy (36%): ALND vs NO ALND

2540 enrolled pts (1335 BLS – 1205 ALND)
Use of RT followed national guidelines
(RNI in 90% BLS group and 88% ALND group)

Five-year recurrence-free survival did not differ significantly between the 2 groups

Table 1. (Continued.)

Characteristic	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Tumor subtype — no. (%)¶		
ER-positive, HER2-negative	1166 (87.3)	1034 (85.8)
ER-positive, HER2-positive	84 (6.3)	88 (7.3)
ER-negative, HER2-positive	23 (1.7)	34 (2.8)
ER-negative, HER2-negative	57 (4.3)	46 (3.8)
Missing data	5 (0.4)	3 (0.2)
Ki-67 proliferation index		
Mean — %	24.6±17.2	24.8±17.7
Median (range) — %	20 (1–98)	20 (1–98)
Missing data — no. (%)	13 (1.0)	18 (1.5)

SENOMAC trial
De Boniface J et al. NEJM 2024

Omission of ALND in sentinel node positive patients

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

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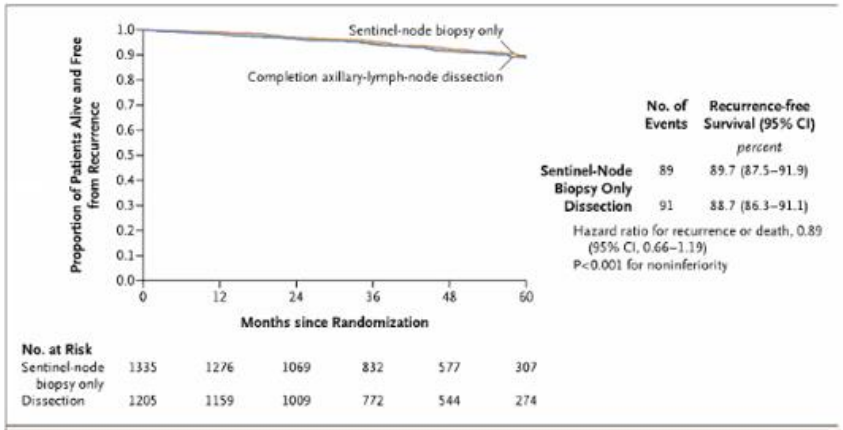

Figure 2. **Recurrence-free Survival (Per-Protocol Population).**
Shown are Kaplan–Meier curves for the secondary end point of recurrence-free survival.

SENOMAC trial
De Boniface J et al. NEJM 2024

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

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Table 2. Recurrence-free Survival Analyses (Per-Protocol Population).*

Variable	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Recurrence — no. (%)		
Local	12 (0.9)	10 (0.8)
Regional	6 (0.4)	6 (0.5)
Distant	44 (3.3)	53 (4.4)
Death — no. (%)	62 (4.6)	69 (5.7)
Cause of death — no./total no. (%)		
Breast cancer	24/62 (39)	31/69 (45)
Other cause	30/62 (48)	30/69 (43)
Unknown	8/62 (13)	8/69 (12)
Recurrence or death as first event — no. (%)		
No	1240 (92.9)	1109 (92.0)
Yes	95 (7.1)	96 (8.0)

SENOMAC trial
De Boniface J et al. NEJM 2024

Omission of ALND in sentinel node positive patients

Radiation Field Design in the SENOMAC Trial

The use of Radiation Therapy followed national guidelines, which led to ahigh proportion of pts undergoing nodal field irradiation, which is the standard of care in Sweden and Denmark

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Axillary surgery

Omission of ALND in sentinel node positive patients

Role of Regional RT

Whole breast radiotherapy +/- boost following BCS

SINODAR-ONE trial
ZOO11 trial

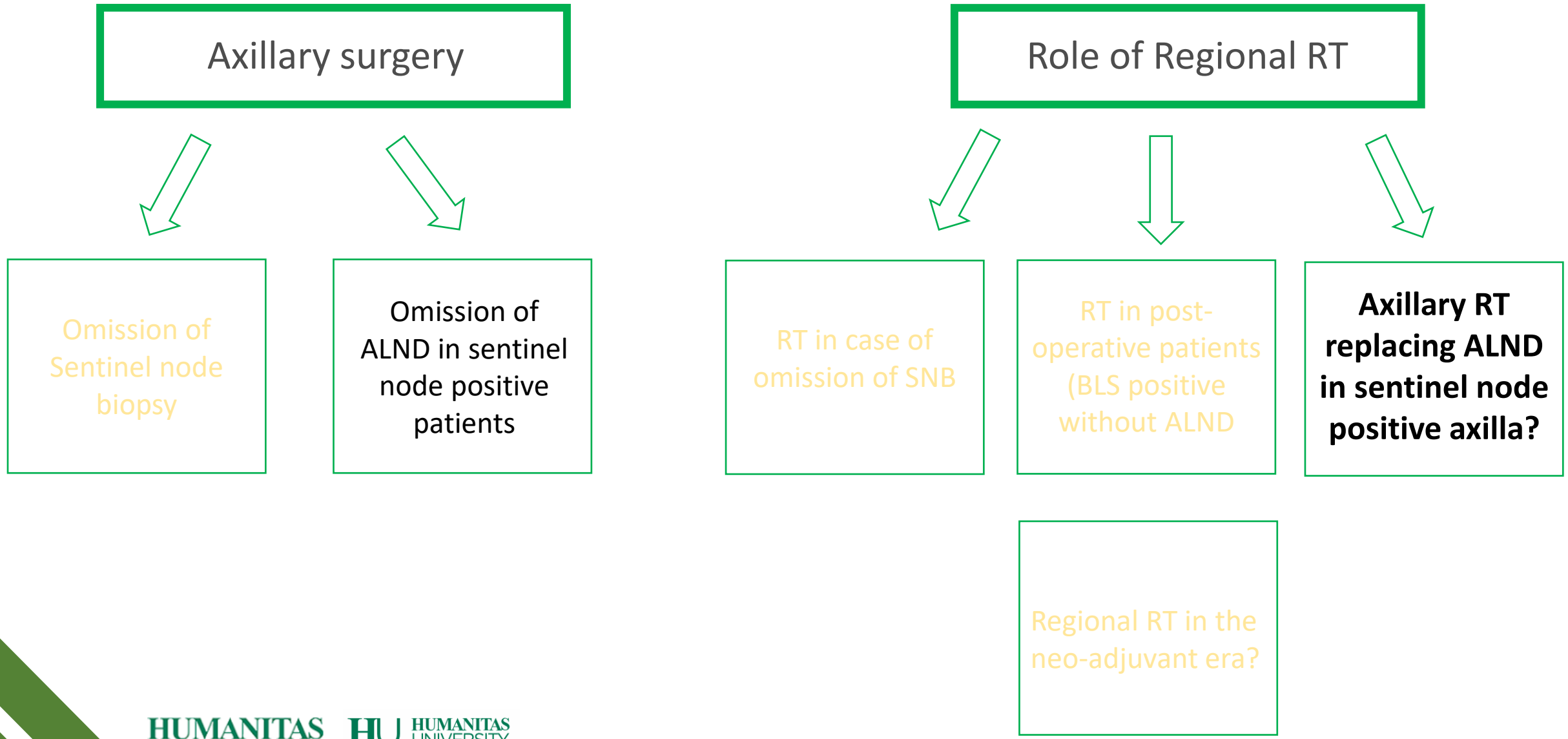
All patients diagnosed with at least one lymph node macrometastasis had an indication for locoregional RT

SENOMAC trial
De Boniface J et al. NEJM 2024

Omission of ALND in sentinel node positive patients

ACOSOG Z0011	SINODAR-ONE	SENOMAC
sentinel-node micrometastases: 40% of the trial population	sentinel-node micrometastases: 7% of the trial population	None (pT3 disease included)
matted nodes and gross extranodal disease were an exclusion criterion	extracapsular extension was not reported	allowed sentinel-node extracapsular extension
mastectomy was not an eligible intervention	mastectomy was included (24.4% of pts)	more than one third of the patients underwent mastectomy

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?



Omission of ALND in sentinel node positive patients

Axillary RT replacing ALND in sentinel node positive axilla

Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer:
A randomized, single centre, phase III, non-inferiority trial

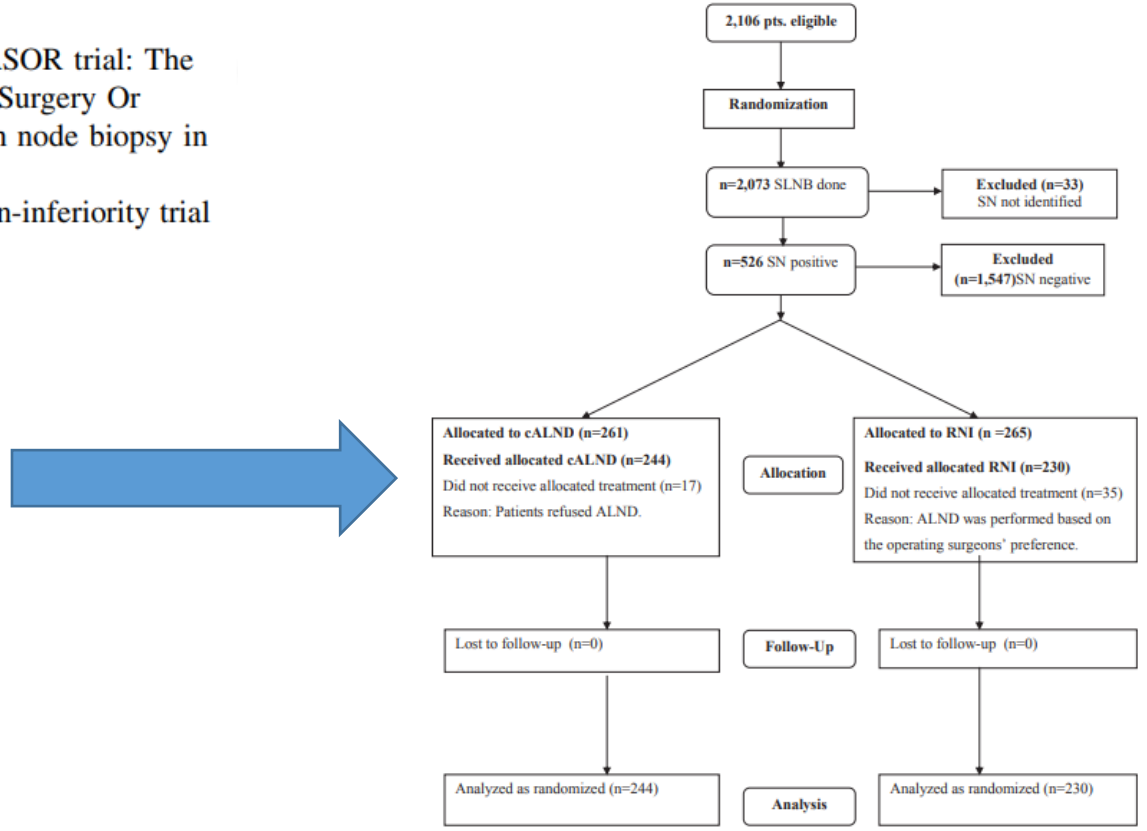


Figure 1. **Patients flow chart of study protocol and number of enrolled cases** SLNB – sentinel lymph node biopsy, cALND – completion axillary lymph node dissection, RNI – regional nodal irradiation.

The whole breast plus all 3 levels of the axilla and the supraclavicular fossa were considered target volume

Savolt et al. OTOASOR trial EJSO 43 (2017) 672e679

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

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OTOASOR (Optimal Treatment Of the Axilla e Surgery Or Radiotherapy) single centre randomized controlled clinical trial to compare cALND to RNI in patients with sentinel lymph node-positive (micro- and macrometastases) primary invasive breast cancer

Table 1
Patient and treatment characteristics according to treatment arms.

Characteristic		Arm A (cALND) (n = 244) No. (%)	Arm B (RNI) (n = 230) No. (%)	p-value
Age (years) 0.602[a]	Mean (range)	54.7 (26–74)	55.2 (27–74)	
Menopausal Status	Pre	83 (34)	62 (27)	0.095
	Post	161 (66)	168 (73)	
Surgery	Breast-conserving	200 (82)	200 (84)	0.164
	ROLL (non-palpable)	71 (29)	76 (33)	
	Mastectomy	44 (18)	30 (16)	
cT category	cT1	152 (62)	157 (68)	0.173
	cT2 (<3 cm)	92 (38)	73 (32)	
pT category	pT1	105 (44)	138 (60)	0.003
	pT2	123 (50)	87 (38)	
	pT3	16 (6)	5 (2)	
Histology	Ductal	193 (79)	188 (82)	0.397
	Lobular	40 (16)	28 (12)	
	Other	11 (5)	14 (6)	
Histologic grade	I	38 (16)	50 (22)	0.221
	II	125 (51)	111 (48)	
	III	81 (33)	69 (30)	
Multifocality	Yes	26 (10)	27 (12)	0.708
	No	218 (90)	203 (88)	
ER status	Positive	203 (83)	194 (84)	0.734
	Negative	41 (17)	36 (16)	
PR status	Positive	178 (73)	168 (73)	0.982
	Negative	66 (27)	62 (27)	
HER-2 status	Positive	28 (12)	40 (17)	0.066
	Negative/UK	216 (88)	190 (83)	

cALND – completion axillary lymph node dissection, RNI – regional nodal irradiation, ROLL – radio-guided occult lesion localization, cT – clinical tumor size, pT – pathological tumor size, ER – estrogen receptor, PR – progesterone receptor; UK = unknown. Data presented as number of patients and percentage in parentheses, unless otherwise noted.

[a] Mann–Whitney two sample test (all other variables were tested with the chi-square test).

OTOASOR trial EJSO 43 (2017) 672e679

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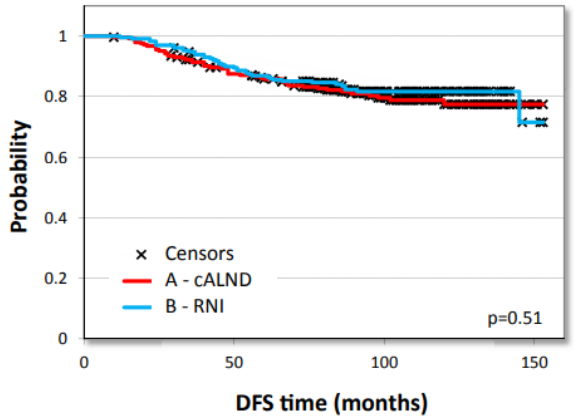

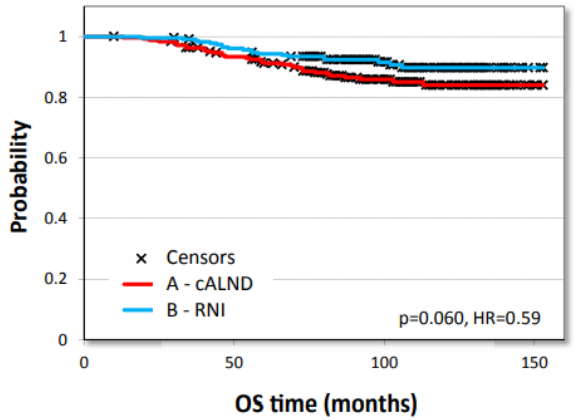

OTOASOR trial EJSO 43 (2017) 672e679

Omission of ALND in sentinel node positive patients

Axillary RT replacing ALND in sentinel node positive axilla

clinical trial updates

Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial

Sanne A.L. Bartels, MD, PhD, MSc[1,2]; Mila Donker, MD, PhD[2,3]; Coralie Poncet, MSc[1]; Nicolas Sauvé, MSc[1]; Marieke E. Straver, MD, PhD[4]; Cornelis J.H. van de Velde, MD, PhD[5]; Robert E. Mansel, MD, MS[6]; Charlotte Blanken, MD, PhD[7]; Lorenzo Orzalesi, MD, PhD[8]; Jean H.G. Klinkenbijl, MD, PhD[9]; Huub C.J. van der Mijle, MD, PhD[10]; Grard A.P. Nieuwenhuijzen, MD, PhD[11]; Sanne C. Veltkamp, MD, PhD[12]; Thijs van Dalen, MD, PhD[13]; Andreas Marinelli, MD, PhD[4]; Herman Rijna, MD, PhD[14]; Marko Snoj, MD, PhD[15]; Nigel J. Bundred, MD, PhD[16]; Jos W.S. Merkus, MD, PhD[17]; Yazid Belkacemi, MD, PhD[18,19]; Patrick Petignat, MD[20]; Dominic A.X. Schinagl, MD, PhD[21]; Corneel Coens, MSc[1]; Geertjan van Tienhoven, MD, PhD[22]; Frederieke van Duijnhoven, MD, PhD[2]; and Emiel J.T. Rutgers, MD, PhD[2]

ALND included at least anatomic level I and II and >10 nodes

ART was 25 fractions of 2 Gy or a biologically equivalent dose to all three levels of the axilla as well as the medial part of the supraclavicular fossa

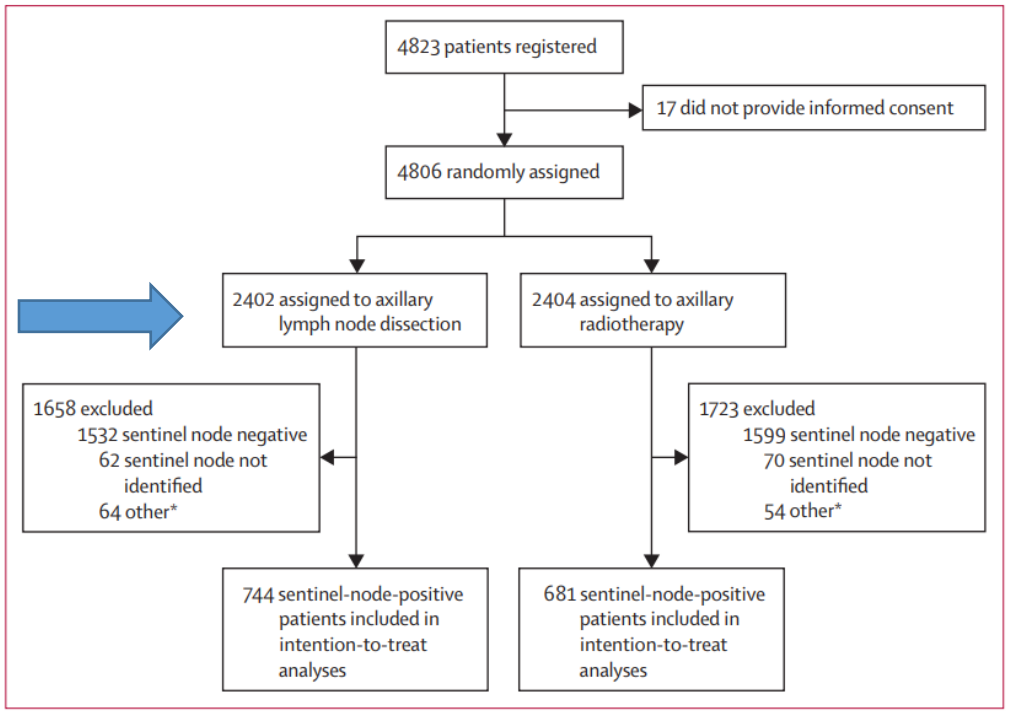

Figure 1: **Trial profile**

*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).

AMAROS trial JCO 2023

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Omission of ALND in sentinel node positive patients

Axillary RT replacing ALND in sentinel node positive axilla

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

Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

	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)

	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
(Continued from previous page)		
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**

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Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Omission of ALND in sentinel node positive patients

Axillary RT replacing ALND in sentinel node positive axilla

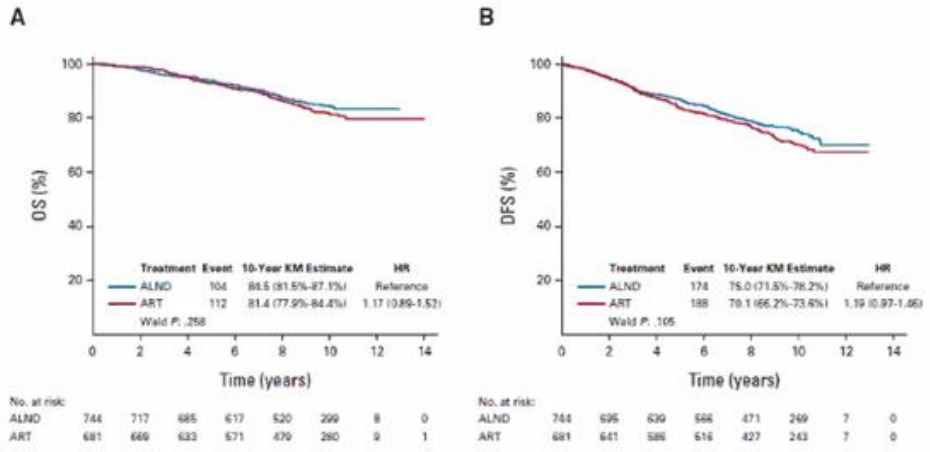
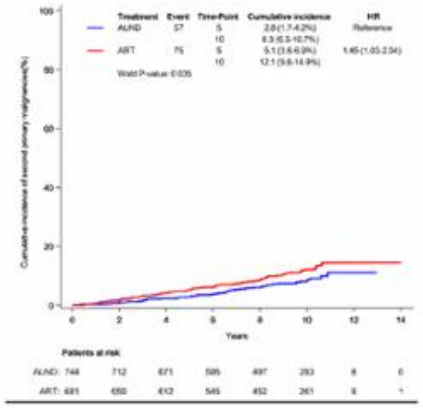


Figure S4. Cumulative incidence plot of second primary cancers



10-year cumulative incidence of LRR was 3.6% after ALND and 4.1% after ART (axillary recurrences 0.93% after ALND and 1.82% after ART)

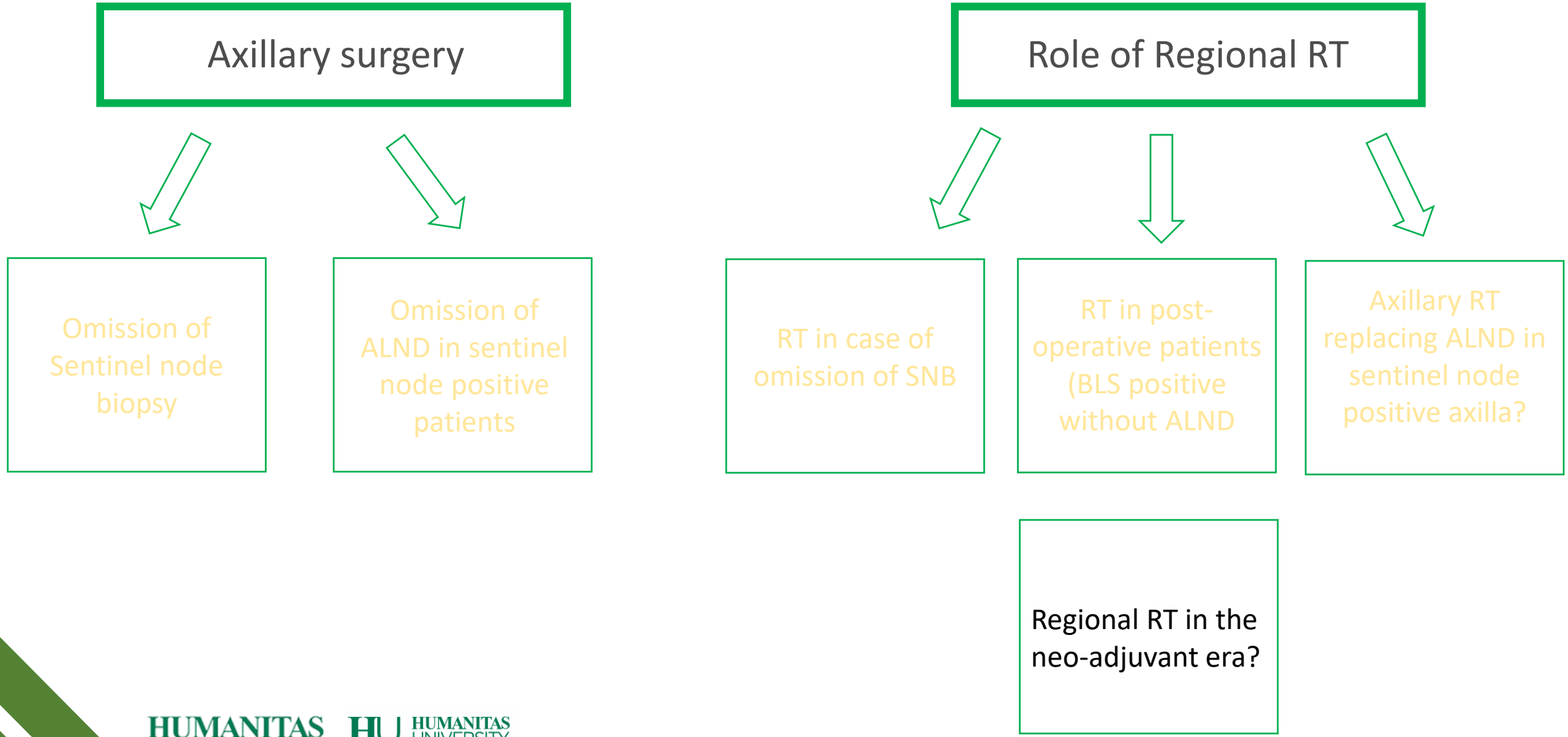
No differences in OS and DFS

Significantly lower lymphedema rate after ART at all time points
There were no differences measured in shoulder mobility and QoL

10-year cumulative incidence of second primary cancers was 12.1% after ART and 8.3% after ALND

AMAROS trial JCO 2023

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?



Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Role of regional radiotherapy in the neo-adjuvant era

There is general consensus that women who are clinically node-negative (cN0) at presentation and are found to have a negative SLN biopsy after NACT do not require any further axillary treatment.

Geng C, et al. PloS One (2016) 11:e0162605.
Mamounas EP. Ann Surg Oncol (2018) 25:2124e2126

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Role of regional radiotherapy in the neo-adjuvant era

Axillary RT (instead of ALND) may be considered for cN0 patients who are found to have fibrosis in 1 or 2 nodes and for those found to have only micro metastases or isolated tumor cells in sentinel nodes as per some guidelines

But there is no robust evidence to support these latter recommendations for axillary RT...

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Burstein HJ, et al. The St. Gallen international consensus guidelines for treatment of early breast cancer 2021

NRG Oncology/NSABP B-51/RTOG 1304: Study Design

Stratified by type of surgery (mastectomy vs lumpectomy), HR status (+/-), HER2 status (+/-), adjuvant chemotherapy (Y/N), and breast pCR status (Y/N)

Patients with clinical T1-3, N1, M0 breast cancer; axillary LN+ by FNA or core needle biopsy; completed ≥8 wk of neoadjuvant chemotherapy (+ anti-HER2 therapy if HER2+); ypN0 by SLNB (≥2 nodes excised), ALND, or both after neoadjuvant chemotherapy; mastectomy or lumpectomy (N = 1641)

No regional nodal irradiation (n = 821)
Breast radiation if breast-conserving surgery
No chest wall radiation if mastectomy

Regional nodal irradiation (n = 820)
Breast radiation if breast-conserving surgery
Chest wall radiation if mastectomy

Primary endpoint: IBCRFI (time from randomization to invasive local, regional, or distant recurrence, or death from breast cancer)
Secondary endpoints: LRRFI (locoregional recurrence without distant recurrence within 2 mo), DRFI, DFS, OS, toxicity

NRG Oncology/NSABP B-51/RTOG 1304: Baseline Characteristics

Characteristic	No RNI (n = 821)	RNI (n = 820)
Median age, yr (range)	52	52
Age, %		
▪ ≤49 yr	40	41
▪ 50-59 yr	32	33
▪ ≥60 yr	28	26
Race, %		
▪ White	69	69
▪ Black	17	18
▪ Asian	8	6
▪ Unknown/other	6	6
Ethnicity, %		
▪ Not Hispanic/Latino/a	83	82
▪ Hispanic/Latino/a	14	14
▪ Other	3	3
Clinical tumor size, %		
▪ T1	21	21
▪ T2	59	61
▪ T3	20	18

Characteristic, %	No RNI (n = 821)	RNI (n = 820)
Tumor subtype		
▪ **TNBC**	**21 %**	**23 %**
▪ **ER+ and/or PgR+/HER2-**	**22 %**	**20 %**
▪ **ER- and PgR-/HER2+**	**25 %**	**24 %**
▪ **ER+ and/or PgR+/HER2+**	**31 %**	**33 %**
Breast surgery		
▪ Lumpectomy	58	58
▪ Mastectomy	42	42
Axillary surgery		
▪ SLNB	55	56
▪ ALND (± SLNB)	45	44
pCR in breast		
▪ No	22	21
▪ Yes	78	79
Adjuvant chemotherapy		
▪ No	100	99
▪ Yes	<1	1

NSABP B-51 SABCS 2023

NRG Oncology/NSABP B-51/RTOG 1304: Efficacy

Parameter	No RNI (n = 784)	RNI (n = 772)	HR (95% CI)	*P* Value
IBCRFI events, n	59	50	0.88 (0.60-1.29)	.51
▪ 5-yr estimate of IBCRFI, %	91.8	92.7		
Isolated LRRFI events, %	11*	4†	0.37 (0.12-1.16)	.088
▪ 5-yr estimate of LRRFI, %	98.4	99.3		
DRFI events, n	48	46	1.00 (0.67-1.51)	.99
▪ 5-yr estimate of DRFI, %	93.4	93.4		
DFS events, n	83	85	1.06 (0.79-1.44)	.69
▪ 5-yr estimate of DFS, %	88.5	88.3		
	(n = 802)	(n = 800)	HR (95% CI)	*P* Value
OS events, n	45	49	1.12 (0.75-1.68)	.59
▪ 5-yr estimate of OS, %	94.0	93.6		

*2 local, 8 regional, and 1 locoregional. †All local.

- No significant difference in IBCRFI between arms for all stratification subgroups or exploratory age, race, and axillary surgery subgroups
- Significant interaction between treatment arm and tumor subtype based on small number of events and patients (*P* = .037)

Mamounas. SABCS 2023. Abstr GS02-07.

Slide credit: clinicaloptions.com

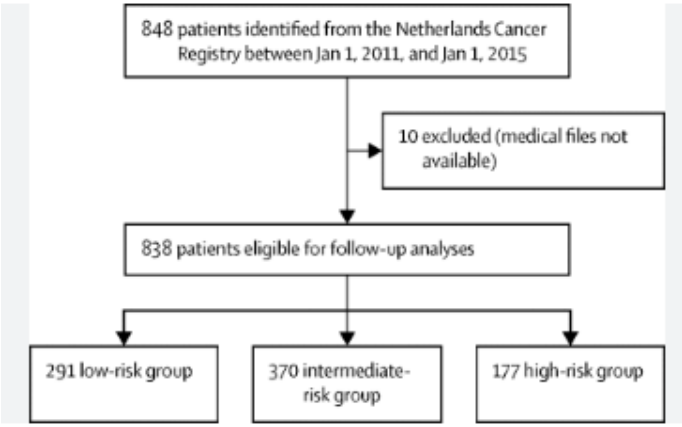
The study demonstrated that patients whose lymph nodes converted to negative status had excellent outcomes with low [recurrence] events, regardless of whether they received regional nodal radiation

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

Role of regional radiotherapy in the neo-adjuvant era

De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study

Sabine R de Wild, Linda de Munck, Janine M Simons, Janneke Verloop, Thijs van Dalen, Paula H M Elkhuizen, Ruud M A Houben, A Elise van Leeuwen, Sabine C Linn, Ruud M Pijnappel, Philip M P Poortmans, Luc J A Strobbe, Jelle Wesseling, Adri C Voogd, Liesbeth J Boersma



	Whole group* (n=838)	Low-risk group (n=291)	Intermediate-risk group (n=370)	High-risk group (n=177)	χ^2 p value
Age, years	..	..	..	..	0·0053
<40	101 (12%)	45 (15%)	45 (12%)	11 (6%)	..
40–59	58 (70%)	206 (71%)	256 (69%)	123 (69%)	..
≥60	152 (18%)	40 (14%)	69 (19%)	43 (24%)	..
Molecular subtype	..	..	..	..	<0·0001
HR+, HER2–	534 (64%)	128 (44%)	276 (75%)	139 (80%)	..
HR+, HER2+	108 (13%)	58 (20%)	38 (10%)	12 (7%)	..
HR–, HER2+	57 (7%)	35 (12·1%)	18 (5%)	4 (2%)	..
Triple negative	123 (15%)	69 (24%)	35 (9%)	19 (11%)	..
Hormone receptor missing†	7	1	3	3	..
Grade	..	..	..	..	0·0035
1	123 (19%)	36 (17%)	57 (19%)	30 (20%)	..
2	348 (53%)	92 (44%)	174 (58%)	82 (55%)	..
3	185 (28%)	79 (38%)	68 (23%)	38 (25%)	..
Unknown†	182	84	71	27	..
Lymphovascular invasion	..	..	..	..	0·0013
No	441 (81%)	145 (86%)	208 (82%)	88 (70%)	..
Yes	106 (19%)	23 (14%)	45 (18%)	38 (30%)	..
Unknown†	291	123	117	51	..
Initial tumour size, cm	..	..	..	..	0·064
≤2·0	165 (20%)	46 (16%)	84 (23%)	35 (20%)	..
2·1–5·0	657 (80%)	242 (84%)	275 (77%)	140 (80%)	..
Exact size unknown (≤5·0)†	16	3	11	2	..
Type of breast surgery	..	..	..	..	0·042
Lumpectomy	475 (57%)	175 (60%)	214 (58%)	86 (49%)	..
Mastectomy	363 (43%)	116 (40%)	156 (42%)	91 (51%)	..

(Table 2 continues on next page)

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RAPCHEM; BOOG 2010-03: 5-year follow-up results of a Dutch, prospective, registry study. Lancet Oncol (2022) 23(9):1201–10

Axillary lymph node dissection in BC patients ER+: obsolet or still necessary?

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Sabine R de Wild, Linda de Munck, Janine M Simons, Janneke Verloop, Thijs van Dalen, Paula H M Elkhuizen, Ruud M A Houben, A Elise van Leeuwen, Sabine C Linn, Ruud M Pijnappel, Philip M P Poortmans, Luc J A Strobbe, Jelle Wesseling, Adri C Voogd, Liesbeth J Boersma

	Radiotherapy after breast conserving therapy	Radiotherapy after mastectomy
Low-risk group		
ypN0 (ALND)	Whole breast radiotherapy	..
If SLNB before primary chemotherapy and no ALND: cN1mi (SLNB), no risk factor*; or if SLNB after primary chemotherapy and no ALND: ypN0 (SLNB)	Whole breast radiotherapy	..
Intermediate-risk group		
ypN1 (ALND)	Whole breast radiotherapy	Chest wall radiotherapy
If SLNB before primary chemotherapy and no ALND†: cN1mi (SLNB), ≥1 risk factor*, or cN1 (SLNB), ≤2 macrometastases, no risk factor*; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), no risk factor*	Whole breast radiotherapy; in addition axilla level I and II†	Chest wall radiotherapy; in addition axilla level I and II†
High-risk group		
ypN2–3 (ALND)	Whole breast radiotherapy; axilla level III and IV	Chest wall radiotherapy; axilla level III and IV
If SLNB before primary chemotherapy and no ALND†: cN1 (SLNB), with ≤2 macrometastases and ≥1 risk factor*, or ≥3 macrometastases; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), ≥1 risk factor*, or ypN1 (SLNB)	Whole breast radiotherapy; axilla level III and IV; in addition axilla level I and II†	Chest wall radiotherapy; axilla level III and IV; in addition axilla level I and II†

ALND=axillary lymph node dissection. SLNB=sentinel lymph node biopsy. *Risk factor: grade 3, lymphovascular invasion, tumour size more than 3 cm. †If ALND was omitted in the intermediate-risk or high-risk group, radiotherapy of the axilla (level I and II) was recommended. Radiotherapy of the axilla (level I and II) after ALND, and radiotherapy of the internal mammary chain were optional.

Table 1: **Study guideline with risk groups based on locoregional recurrence risk, and locoregional radiotherapy recommendations**

HUMANITAS GAVAZZENI HU HUMANITAS UNIVERSITY

RAPCHEM; BOOG 2010-03: 5-year follow-up results of a Dutch, prospective, registry study. Lancet Oncol (2022) 23(9):1201–10

CONCLUSION

It remains an ongoing discussion (in a multidisciplinary context) on determining the optimal approach for managing axilla in patients with node-positive (cN+) breast cancer (BC), with options including:

- ❑ limited axillary surgery
- ❑ increased use of radiotherapy (RT)
- ❑ combination of both

The crucial aspect is how to properly select pts who might benefit from de-escalation strategies