Axillary clearance and chemotherapy rates in ER+HER2– breast cancer: secondary analysis of the SENOMAC trial

Tove Filtenborg Tvedskov,[a,b,*] Robert Szulkin,[c,d] Sara Alkner,[e,f] Yvette Andersson,[g,h] Leif Bergkvist,[h] Jan Frisell,[i,j] Oreste Davide Gentilini,[k,l] Michalis Kontos,[m] Thorsten Kühn,[n,o] Dan Lundstedt,[p,q] Birgitte Vrou Offersen,[r,s] Roger Olofsson Bagge,[t,u] Toralf Reimer,[v] Malin Sund,[w,x] Lisa Rydén,[y,z] Peer Christiansen,[aa,ab,ad] and Jana de Boniface,[j,ac,ad] on behalf of the SENOMAC Trialists' Group

[a]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[b]Department of Breast Surgery, Gentofte Hospital, Gentofte, Denmark
[c]Cytel Inc., Stockholm, Sweden
[d]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[e]Department of Oncology, Faculty of Medicine, Institution of Clinical Sciences Lund, Lund University, Lund, Sweden
[f]Skåne University Hospital, Department of Hematology, Oncology and Radiation Physics, Lund, Sweden
[g]Department of Surgery, Vastmanland Hospital Vasteras, Vasteras, Sweden
[h]Centre for Clinical Research, Uppsala University and Region Vastmanland, Vastmanland Hospital Vasteras, Sweden
[i]Breast Center Karolinska, Karolinska Comprehensive Cancer Center, Karolinska University Hospital, Stockholm, Sweden
[j]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[k]Breast Surgery, IRCCS Ospedale San Raffaele, Milano, Italy
[l]Vita-Salute San Raffaele University, Milano, Italy
[m]1st Department of Surgery, National and Kapodistrian University of Athens, Athens, Greece
[n]Die Filderklinik, Breast Center, Filderstadt, Germany
[o]Department of Gynecology and Obstetrics, University of Ulm, Germany
[p]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
[q]Department of Oncology at Sahlgrenska University Hospital, Gothenburg, Sweden
[r]Department of Oncology, Aarhus University Hospital, Aarhus University, Aarhus, Denmark
[s]Department of Experimental Clinical Oncology, Danish Center for Particle Therapy, Aarhus, Denmark
[t]Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
[u]Department of Surgery at Sahlgrenska University Hospital, Gothenburg, Sweden
[v]Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany
[w]Department of Surgery, University of Helsinki and Helsinki University Hospital, Finland
[x]Department of Diagnostics and Intervention/ Surgery, Umeå University, Sweden
[y]Department of Oncology and Surgery, Faculty of Medicine, Institution of Clinical Sciences Lund, Lund University, Lund, Sweden
[z]Skåne University Hospital Lund, Department of Gastroenterology and Surgery, Malmö, Sweden
[aa]Department of Plastic and Breast Surgery, Aarhus University Hospital, Aarhus, Denmark
[ab]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[ac]Department of Surgery, Capio St. Göran's Hospital, Stockholm, Sweden

The Lancet Regional Health - Europe 2024;47: 101083
Published Online xxx
https://doi.org/10.1016/j.lanepe.2024.101083

Summary

Background Randomized trials have shown that axillary clearance (AC) can safely be omitted in patients with sentinel lymph node-positive breast cancer. At the same time, de-escalation of chemotherapy in postmenopausal patients with ER+HER2– breast cancer may depend on detailed axillary nodal stage. The aim of this pre-specified secondary analysis of the SENOMAC trial was to investigate whether the choice of axillary staging affected the proportion of patients receiving adjuvant chemotherapy, and recurrence-free survival (RFS).

Methods Proportion receiving adjuvant chemotherapy was calculated according to AC or sentinel lymph node biopsy (SLNB) only, menopausal status, and region of inclusion, for 2168 patients with clinically node-negative ER+HER2– breast cancer and 1–2 sentinel lymph node macrometastases included in the SENOMAC trial.

Findings In premenopausal patients, 514 out of 615 patients (83.6%) received adjuvant chemotherapy with no significant difference between randomization arms. In postmenopausal patients, the proportion receiving chemotherapy varied considerably by region and country (36.0–82.4%). In Denmark, where 194 out of 539 postmenopausal patients (36.0%) received adjuvant chemotherapy, rates differed significantly between the AC and the SLNB only arm (41.3%

*Corresponding author. Department of Breast Surgery, Gentofte Hospital, 2900, Hellerup, Denmark.
E-mail address: tove.holst.filtenborg.tvedskov@regionh.dk (T.F. Tvedskov).
[ad]Shared last authorship.

vs 31.4%, p = 0.019). After a median follow-up of 44.88 months for Danish postmenopausal patients, no significant difference was seen in 5-year RFS, which was 91% (85.6%–96.6%) for the SLNB only and 90.9% (86.3%–95.6%) for the AC arm (p = 0.42).

Interpretation When omitting axillary clearance, and thus reducing the risk of long-term arm morbidity, potential under-treatment of postmenopausal patients with ER+HER2– breast cancer may require the development of new predictive and imaging tools.

Funding Swedish Research Council, Swedish Cancer Society, Nordic Cancer Union, Swedish Breast Cancer Association.

Keywords: Breast cancer; Axillary staging; Adjuvant treatment

Research in context

Evidence before this study

We searched PubMed on 12th of December 2023 and again on 4th of March 2024 for English-language studies presenting results from randomized trials investigating omission of axillary clearance (AC) in patients with breast cancer with axillary lymph node macrometastases. Trial names were then searched for studies presenting data on the impact of omitting AC on adjuvant systemic treatment. Only three studies were identified: the AMAROS trial, the OTOASOR trial and the TAXIS trial. None of these studies found a significant difference in proportion of patients receiving adjuvant systemic treatment according to axillary treatment, but no subgroup analyses were done according to menopausal status and breast cancer subtype.

Added value of this study

The present analysis is the first to report on differences in chemotherapy rates in ER+HER2– breast cancer after omission of AC, taking menopausal status and country of inclusion into account. We did show that omission of AC leads to lower rates of chemotherapy administration in postmenopausal patients in European countries where detailed nodal stage is part of the treatment decision algorithm for adjuvant chemotherapy.

Implications of all the available evidence

The prognostic significance of potential adjuvant systemic undertreatment when omitting AC needs to be investigated once longer follow-up is available, and the need for chemotherapy in postmenopausal patients with ER+HER2– breast cancer should be critically evaluated. When omitting AC, predictive and imaging tools are needed to facilitate selection for adjuvant chemotherapy. Future studies on omitting axillary surgery should include results on the impact on adjuvant treatment to forego the risk of undertreatment, when concurrently de-escalating treatment in surgery and oncology.

Introduction

Axillary nodal status is one of the most important prognostic factors in breast cancer and guides decisions for adjuvant systemic treatment. In patients with ER+HER2– breast cancer, de-escalation of adjuvant chemotherapy has received increasing attention during recent years. The benefit from adjuvant chemotherapy in patients with 1–3 positive lymph nodes has been questioned by the RxPONDER trial and the MINDACT trial.[1,2] Based on these results, the St Gallen, ESMO, and ASCO guidelines no longer recommend the routine use of adjuvant chemotherapy in postmenopausal patients with ER+HER2– breast cancer and 1–3 lymph node metastases and a low genomic risk signature.[3–5] This is, however, not the case if four or more lymph node metastases (pN2-3) are identified. As a consequence, adjuvant chemotherapy can potentially be omitted in up to 60% of postmenopausal patients with ER+HER2– breast cancer.[6] National and regional guidelines have gradually implemented this de-escalation. In Denmark, genomic risk signatures are not routinely performed for further risk stratification of postmenopausal patients with ER+HER2–, pN1 breast cancer. Instead, the Danish developed Prognostic Score Index is used. It is based on clinical and pathological risk factors, of which one is the number of positive nodes.

At the same time as de-escalation of chemotherapy is implemented, efforts to de-escalate axillary staging surgery are ongoing, with the important aim to spare patients the risk of potentially life-long arm morbidity.[7,8] Several randomized trials have shown that axillary clearance (AC) can be safely omitted in sentinel lymph node (SLN)-positive breast cancer.[9,10] This was recently confirmed by the randomized SENOMAC trial including patients with 1–2 SLN macrometastases randomized to completion AC or sentinel lymph node

biopsy (SLNB) only.[11] However, when omitting AC in these patients, the total number of positive axillary lymph nodes and thus the exact nodal stage is unknown. Therefore, the selection of patients to adjuvant chemotherapy may be hampered. The consequence of AC omission and its potential impact on survival outcomes has not been sufficiently investigated.

The aim of this pre-specified secondary analysis of the SENOMAC trial was to investigate whether the choice of axillary staging affected the proportion of patients receiving adjuvant chemotherapy, and recurrence-free survival (RFS). In addition, the nodal stage of patients with and without AC was compared.

Methods

Patients with clinically node-negative ER+HER2– breast cancer, who had been included in the randomized SENOMAC trial and received primary surgery, were selected for this analysis.[12] The SENOMAC trial was initiated in 2015 and randomly assigned patients with 1–2 macrometastases on SLNB to AC or its omission. In Denmark, a protocol amendment allowed radiotherapy to the axilla level I in patients randomized to SLNB only. A quality assessment of radiotherapy did show that axillary level I received a high dose coverage even when not intentionally included in the target.[13] Enrolment closed after the randomization of 2766 patients in December 2021. The per-protocol population included 2540 patients randomized in Sweden (N = 1553), Denmark (N = 804), Germany (N = 87), Greece (N = 52), and Italy (N = 46). The indication for adjuvant chemotherapy was not described in the protocol but was given according to local or national guidelines. Patients offered neoadjuvant treatment were excluded from this analysis.

The primary endpoint of this analysis was the proportion of patients receiving adjuvant chemotherapy in each randomization arm. As secondary endpoints, the mean number of positive lymph nodes as well as the proportion of patients identified as having pN2-3 disease per randomization arm were calculated. Finally, 5-year RFS was compared between randomization arms for Danish postmenopausal patients. The definition of RFS followed the updated Standardized Definitions for Efficacy End Points (STEEP) criteria and included invasive in-breast, locoregional or distant recurrence as well as death from breast cancer, non-breast cancer and unknown causes.[14]

Guidelines for adjuvant chemotherapy differ between countries and regions and depend on menopausal status. Accordingly, analyses were stratified for pre- and postmenopausal status and for different countries and regions within countries. Since menopausal status was not registered in the SENOMAC trial, the type of adjuvant endocrine treatment was chosen as a surrogate variable for menopausal status, where users of aromatase inhibitors (AI) were defined as postmenopausal and users of Tamoxifen or AI in combination with a GnRH agonist as premenopausal. In addition, a sensitivity analysis was made using age ≤50 years vs >50 years as a surrogate variable for menopausal status.

Since few patients were included in Germany, Italy, and Greece, only patients from Sweden and Denmark were included in subanalyses on the proportion of patients offered chemotherapy in the randomization arms.

Statistical analysis

Continuous variables are described with means, standard deviations (SD), median, minimum, and maximum values. Categorical variables are summarized with frequencies and percentages of each category.

Unadjusted comparison between randomization arms, AC vs SLNB only, for the primary and secondary outcomes were performed in all patients and subsequently stratified by menopausal status. A further stratification focused on differences between countries and regions and was limited to patients enrolled in Sweden and Denmark. Group differences were assessed with t-tests for continuous variables and Chi-square-tests or Fisher's exact tests (in small sub-groups) for categorical variables. Group differences for number of removed lymph nodes, number of positive nodes and duration of chemotherapy were assessed with the Mann Whitney test. RFS was defined as time from randomization to first invasive recurrence (contralateral breast cancer not included) or death. Follow-up time was censored at the last event-free visit. The RFS proportion was estimated with the Kaplan–Meier method and group differences were evaluated with the log-rank test. A significance level of 0.05 was used in all statistical tests. All statistical analyses were performed using R version 4.2.2.

Role of the funding source

Financial support for work related to the SENOMAC trial has been obtained from the Swedish Research Council (grant numbers 2015-00760 and 2021-02128), the Swedish Cancer Society (grant numbers CAN 2015/437 and 22 2061 Pj), the Nordic Cancer Union (grant numbers R217-A13260 and R241-A14982), and the Swedish Breast Cancer Association. The funding parties had no part in the design, performance, analysis, or reporting of the trial.

Results

Out of 2168 patients selected from the SENOMAC trial for the present analysis, 1010 had AC and 1158 SLNB only (Fig. 1). Patient, tumor, and treatment characteristics are shown in Table 1. In the AC arm, a significantly higher mean number of lymph nodes was removed (15.45 vs 2.31, $p < 0.001$) and accordingly, the

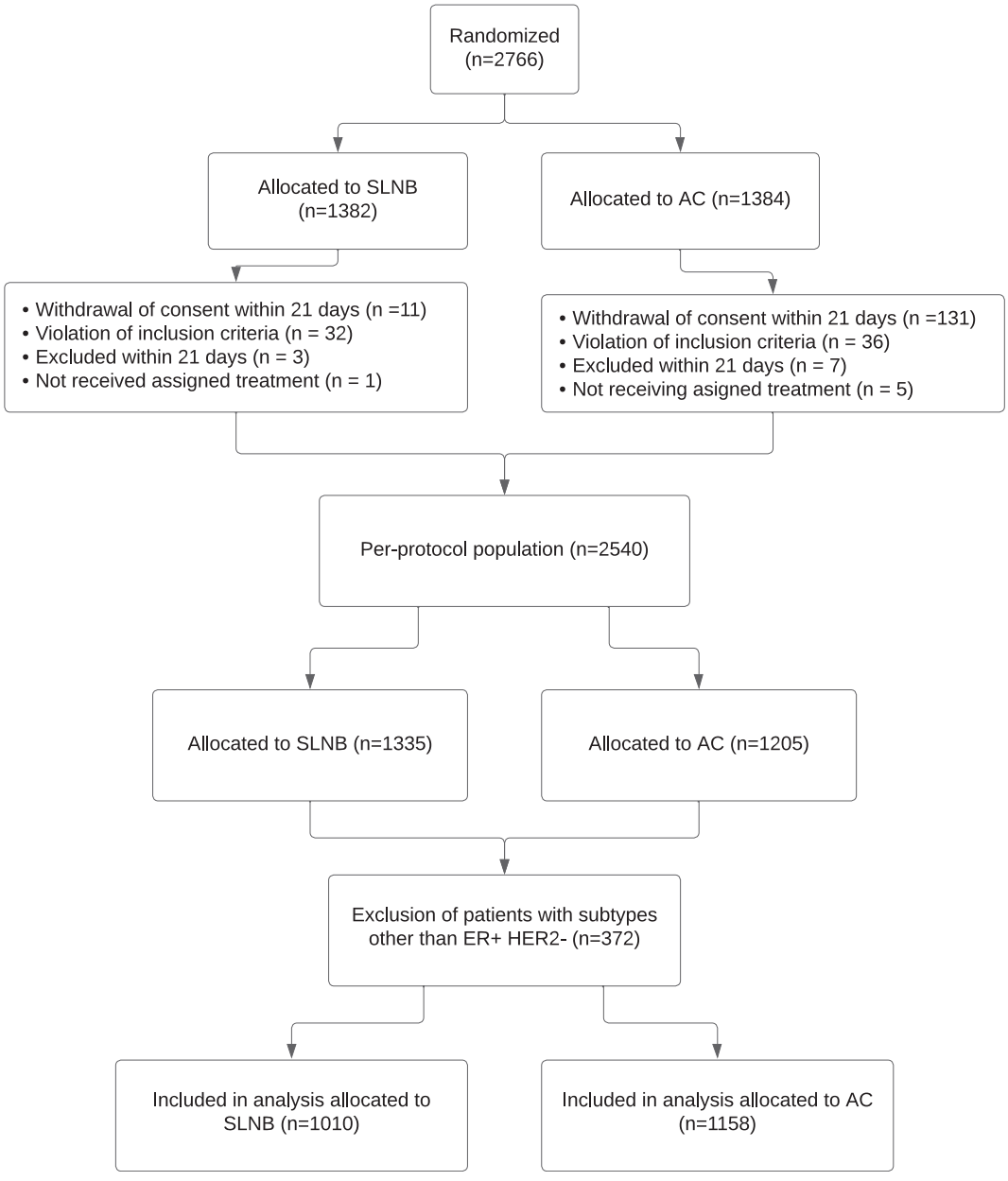

Fig. 1: **CONSORT diagram over inclusion of SENOMAC trial patients into the present analysis.**

mean number of lymph node metastases was significantly higher (2.34 vs 1.29, $p < 0.001$). As final nodal stage, 13.7% of patients had pN2-3 status after completion AC, but only 0.6% in the SLNB only arm ($p < 0.001$), where nodal metastases exceeding the permitted 1–2 macrometastases were found on randomly excised lymph nodes which did not fulfill the criteria for a sentinel lymph node. According to type of endocrine treatment, 1492 patients (68.8%) were considered as postmenopausal and 615 (28.4%) as premenopausal. Information on type of endocrine treatment was missing in 61 patients (2.8%).

In total, 59.8% of patients received adjuvant chemotherapy. No statistically significant difference in the proportion of patients treated by adjuvant chemotherapy was found between randomization arms (AC: 61.7% vs SLNB: 58.1%, $p = 0.09$). The median duration of chemotherapy was 16 weeks, with no significant difference between randomization arms in pre- and postmenopausal patients.

In premenopausal patients, the proportion given adjuvant chemotherapy was 83.6% with no statistical difference between randomization arms, neither for all SENOMAC patients nor for the cohort restricted to

	Completion AC	SLNB only	Total	p-value
Total number of patients, N	1010	1158	2168	
Total number of lymph nodes removed				<0.001
Mean (SD)	15.45 (7.08)	2.31 (1.51)	8.43 (8.22)	
Median [min–max]	14.00 [1.00–51.00]	2.00 [1.00–15.00]	4.00 [1.00–51.00]	
Number of positive lymph nodes				<0.001
Mean (SD)	2.34 (3.09)	1.29 (0.54)	1.78 (2.21)	
Median [min–max]	1.00 [1.00–42.00]	1.00 [1.00–5.00]	1.00 [1.00–42.00]	
Nodal stage, N (%)				<0.001
pN1	872 (86.3)	1151 (99.4)	2023 (93.3)	
pN2	108 (10.7)	7 (0.6)	115 (5.3)	
pN3	30 (3.0)	0 (0.0)	30 (1.4)	
Breast surgery performed, N (%)				0.491
Breast-conserving surgery	665 (65.8)	745 (64.3)	1410 (65.0)	
Mastectomy	345 (34.2)	413 (35.7)	758 (35.0)	
Adjuvant endocrine treatment, N (%)				0.680
No	6 (1.6)	24 (2.1)	40 (1.8)	
Yes	986 (97.6)	1126 (97.2)	2112 (97.4)	
Drop-out prior to FU1	7 (0.7)	7 (0.6)	14 (0.6)	
Missing	1 (0.1)	1 (0.1)	2 (0.1)	
Adjuvant radiotherapy, N (%)				0.555
None	53 (5.2)	46 (4.0)	99 (4.6)	
Nodal field only	8 (0.8)	12 (1.0)	20 (0.9)	
Breast or chest wall only	59 (5.8)	78 (6.7)	137 (6.3)	
Breast and nodal fields	881 (87.2)	1012 (87.4)	1893 (87.3)	
Drop-out prior to FU1	7 (0.7)	7 (0.6)	14 (0.6)	
Missing	2 (0.2)	3 (0.3)	5 (0.2)	
Adjuvant chemotherapy, N (%)				0.092
Yes	623 (61.7)	673 (58.1)	1296 (59.8)	
No	379 (37.5)	477 (41.2)	856 (39.5)	
Missing	8 (0.8)	8 (0.7)	16 (0.7)	
Duration of chemotherapy, weeks[a]				0.815
Mean (SD)	16.34 (4.10)	16.42 (3.87)	16.38 (3.98)	
Median [min–max]	17.37 [0.00–30.40]	17.37 [0.00–52.11]	17.37 [0.00–52.11]	
Missing (%)	23 (3.7)	26 (3.9)	49 (3.8)	
Country of inclusion, N (%)				0.781
Sweden	612 (60.6)	694 (59.9)	1306 (60.2)	
Denmark	323 (32.0)	381 (32.9)	704 (32.5)	
Germany	30 (3.0)	41 ((3.5)	71 (3.3)	
Italy	22 (2.2)	19 (1.6)	41 (1.9)	
Greece	23 (2.3)	23 (2.0)	46 (2.1)	
Age				0.914
Mean (SD)	61.15 (11.47)	61.09 (12.01)	61.12 (11.76)	
Median[min–max]	61.00 [34.00–90.00]	61.00 [20.00–94.00]	61.00 [20.00–94.00]	
Menopausal status, N (%)				0.302
Premenopausal	278 (27.5)	337 (29.1)	615 (28.4)	
Postmenopausal	713 (70.6)	779 (67.3)	1492 (68.8)	
Missing	19 (1.9)	42 (3.6)	61 (2.8)	
Age				0.405
Age ≤50 years, N (%)	208 (20.6)	260 (22.5)	468 (21.6)	
Age > 50 years, N (%)	802 (79.4)	898 (77.5)	1700 (78.4)	
Histological tumor type, N (%)				0.248
Ductal	765 (75.7)	843 (72.8)	1608 (74.2)	
Lobular	212 (21.0)	267 (23.1)	479 (22.1)	
Other	33 (3.3)	48 (4.1)	81 (3.7)	

(Table 1 continues on next page)

	Completion AC	SLNB only	Total	p-value
(Continued from previous page)				
Multifocality, N (%)				0.256
Yes	262 (25.9)	327 (28.2)	589 (27.2)	
No	746 (73.9)	830 (71.7)	1576 (72.7)	
Missing	2 (0.2)	1 (0.1)	3 (0.1)	
Tumor size, mm				0.298
Mean (SD)	23.92 (16.81)	24.65 (15.68)	24.31 (16.21)	
Median [min–max]	19.00 [1.10–155.00]	20.00 [1.70–155.00]	20.00 [1.10–155.00]	
Histological grade, N (%)				0.490
Grade 1	206 (20.4)	239 (20.6)	445 (20.5)	
Grade 2	647 (64.1)	719 (62.1)	1366 (63.0)	
Grade 3	152 (15.0)	195 (16.8)	347 (16.0)	
Missing	5 (0.5)	5 (0.4)	10 (0.5)	
Profileration, Ki67 (%)				0.773
Mean (SD)	22.01 (15.14)	22.20 (14.71)	22.11 (14.91)	
Median [min–max]	20.00 [1.00–90.00]	20.00 [1.00–92.00]	20.00 [1.00–92.00]	
Missing, no (%)	12 (1.2)	11 (1.0)	23 (1.1)	

Abbreviations: ER: estrogen receptor, AC: axillary clearance, SLNB: sentinel lymph node biopsy, FU1: 1 year follow-up. [a]In patients treated with chemotherapy.

Table 1: **Patient, tumour, and treatment characteristics among patients with ER+HER2− breast cancer included in the SENOMAC trial according to randomized assignment.**

those enrolled in Denmark or Sweden (Table 2). In postmenopausal patients, 50.6% received adjuvant chemotherapy, with a higher proportion in the AC arm (52.9% vs 48.5%). This difference was, however, not statistically significant (p = 0.09).

A large variation was observed in the proportion of postmenopausal patients receiving chemotherapy per country (p < 0.001) with the lowest proportion in Denmark (36.0%) and the highest in Greece (64.3%). The proportion treated by chemotherapy was 43.9% in Germany, 36.4% in Italy, and 60.0% in Sweden. Significant regional variations were observed in Sweden (43.4%–82.4%, p < 0.001) but without any difference between randomization arms (p = 0.65). Differences in proportion of patients offered chemotherapy according to randomization arm in different regions in Sweden are shown in the Supplementary Table S2a. In contrast, only 36.0% of postmenopausal patients included in

	Premenopausal patients (N = 615)			Postmenopausal patients (N = 1492)		
	Completion AC	SLNB only	p-value	Completion AC	SLNB only	p-value
Total number of patients, N	278	337		713	779	
Total number of lymph nodes removed			<0.001			<0.001
Mean (SD)	14.94 (6.97)	2.55 (1.75)		15.59 (7.06)	2.21 (1.37)	
Median [Min-Max]	14.00 [1.00–51.00]	2.00 [1.00–15.00]		14.00 [1.00–50.00]	2.00 [1.00–12.00]	
Number of positive lymph nodes			<0.001			<0.001
Mean (SD)	2.45 (3.51)	1.29 (0.53)		2.30 (2.92)	1.29 (0.54)	
Median [Min-Max]	2.00 [1.00–37.00]	1.00 [1.00–4.00]		1.00 [1.00–42.00]	1.00 [1.00–5.00]	
Adjuvant chemotherapy, N (%)			0.248			0.0923
Yes	238 (85.6)	276 (81.9)		337 (52.9)	378 (48.5)	
No	39 (14.0)	60 (17.8%)		334 (46.8)	401 (51.5)	
Missing	1 (0.4)	1 (0.3%)		2 (0.3%)	0 (0)	
Duration of chemotherapy[a] (weeks)			0.885			0.642
Mean (SD)	16.62 (3.78)	16.67 (3.50)		16.20 (4.13)	16.27 (4.01)	
Median [Min-Max]	17.37 [0.00–26.06]	17.37 [0.00–30.40]		17.37 [0.00–30.40]	17.37 [0.00–52.11]	
Missing, N (%)	12 (5.0)	10 (3.6)		11 (2.9)	14 (3.7)	

Abbreviations: ER: estrogen receptor, AC: axillary clearance, SLNB: sentinel lymph node biopsy. [a]In patients treated with chemotherapy.

Table 2: **Nodal status and proportion receiving chemotherapy among patients with ER+HER2− breast cancer included in the SENOMAC trial according to randomized assignment and menopausal status according to type of endocrine treatment.**

Denmark received adjuvant chemotherapy, with significantly more patients having chemotherapy in the AC arm than the SLNB only arm (41.3% vs 31.4%, p = 0.019).

When using age ≤50 vs > 50 years as surrogate variable for menopausal status, 90% of patients with age <50 received adjuvant chemotherapy with no difference between randomization arms. In patients with age ≥50, 51.6% received adjuvant chemotherapy; 54.9% in the AC arm and 48.8% in the SLNB only arm. This difference was statistically significant (p = 0.0151). In Sweden, 61.1% of patients with age ≥50 had adjuvant chemotherapy, with no significant difference between randomization arms while in Denmark, only 37.1% received adjuvant chemotherapy, with significantly more patients in the AC arm compared to the SLNB arm (44.4% vs 30.4%, p < 0.001) (Supplementary Table S2b).

Considering the observed difference in chemotherapy rates in postmenopausal patients in Denmark, we compared 5-year RFS for the two randomization arms in this subgroup (N = 539). After a median follow-up of 44.88 months (45.97 in the AC arm and 43.01 in the SLNB only arm), no significant difference was seen, with a 5-year RFS on 91.0% (85.6%–96.6%) in the SLNB only arm and 90.9% (86.3%–95.6%) in the AC arm (p = 0.42) (Fig. 2). No locoregional recurrences were seen in postmenopausal Danish patients in the study period.

Discussion

In this pre-specified secondary analysis of patients with ER+HER2– breast cancer included in the randomized SENOMAC trial,[12] no significant difference in the overall proportion of patients receiving adjuvant chemotherapy was found despite significantly more positive lymph nodes identified in the AC arm. In Denmark, however, a significantly lower proportion of postmenopausal patients received adjuvant chemotherapy if completion AC had been omitted, without detectable deterioration of 5-year RFS.

The impact of de-escalated axillary surgery on adjuvant chemotherapy rates has been investigated in secondary analyses of previous randomized trials. The AMAROS trial randomized patients with metastases on SLNB to completion AC or axillary radiotherapy.[9] In a subgroup analysis on 566 randomized patients conducted after the enrollment of the first 2000 patients, 12% of patients in the AC arm had pN2-3 disease and none in the axillary radiotherapy arm. There was no significant difference in the proportion of patients who were treated with adjuvant chemotherapy; 58% in the AC arm vs 61% in the axillary radiotherapy arm.[15] Likewise, the per-protocol population of the OTOASOR trial included 474 patients with metastasis on SLNB, who were randomized to either completion AC or axillary radiotherapy.[16] Fifty-four out of 244 patients (22%) in the AC arm had pN2-3 disease. While a larger proportion of patients was treated by chemotherapy in the AC arm than the axillary radiotherapy arm (78% vs 69%; p = 0.020), a subgroup analysis found that this was associated with a higher percentage of premenopausal patients and larger tumors in the AC arm and not related to nodal stage. None of the two trials found any differences in axillary recurrence and survival. No

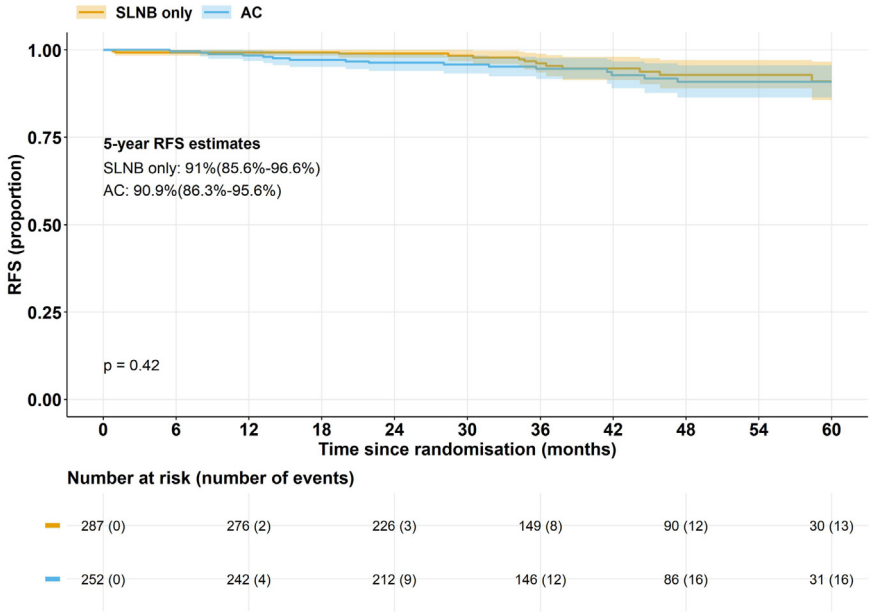

Fig. 2: **Recurrence-free survival for Danish postmenopausal patients with ER+HER2– breast cancer included in the SENOMAC trial according to randomized assignment; completion AC vs SLNB only.**

subgroup analysis was done according to menopausal status in these studies.

More recently, the TAXIS trial, randomizing patients with biopsy-proven node-positive breast cancer to AC or tailored axillary surgery (TAS) with subsequent axillary radiotherapy, investigated the impact of de-escalating axillary surgery on adjuvant chemotherapy rates in 296 patients with ER+HER2– disease and primary surgery. Similar to the present study, significantly more lymph node metastases were found in the AC arm which, however, did not result in a larger proportion of patients receiving adjuvant chemotherapy (TAS: 55.9% vs AC: 60.3%; adjusted odds ratio 0.72; 95% CI, 0.19–2.67).[17] While this is in line with our results for all patients with ER+HER2– breast cancer, no subgroup analysis according to menopausal status was done, which could have revealed unidentified differences. In addition, patients with clinically node-positive breast cancer such as enrolled in the TAXIS trial should have a significantly higher axillary nodal burden than patients with clinically node-negative breast cancer such as enrolled in the SENOMAC trial.[18] Thus, results cannot be directly compared.[3] Consequently, the present analysis is the first to report on differences in chemotherapy rates in ER+HER2– breast cancer in specific, taking menopausal status into account.

Based on results from the randomized MINDACT trial [2]and RxPONDER trial,[19] the St Gallen guidelines have since 2021 no longer recommended adjuvant chemotherapy to postmenopausal patients with ER+HER2– breast cancer with metastases to 1–3 lymph nodes and an intermediate risk profile, while chemotherapy is still recommended to patients with four or more lymph node metastases.[3] Likewise, the current ESMO guidelines do not recommend chemotherapy to postmenopausal patients with ER+, HER2–, T1—T 2, N1 disease with low-risk genomic score and/or lower-risk features on traditional pathological analysis including lower-grade histology and lower measures of proliferation.[4] Finally, the ASCO guidelines recommend the use of Oncotype DX, MammaPrint, Breast Cancer Index, or EndoPredict to guide adjuvant chemotherapy in ER+HER2– postmenopausal patients with 1–3 positive nodes.[5] Adherence to these guidelines has been gradually introduced in national guidelines with varying degree of de-escalation of chemotherapy. A Portuguese study from 2023 tested 154 mostly postmenopausal patients with ER+HER2– breast cancer with 1–3 positive lymph nodes with the 21-gene recurrence score assay and found that a low score allowed safe de-escalation of adjuvant chemotherapy in 65% of the patients.[6]

In an attempt to de-escalate chemotherapy in postmenopausal patients with ER+, HER2– breast cancer in Denmark, the Danish Breast Cancer Group (DBCG) introduced the Prognostic Score Index (PSI) in their guidelines in 2013.[20] The results are clearly reflected in the lower chemotherapy rates when comparing with e.g., rates in Sweden. The PSI replaced previously used high-risk criteria for postmenopausal patients with ER+HER2– breast cancer. The PSI is automatically calculated in the DBCG database after entry of clinical and pathological information and is based on age, type of surgery (mastectomy or lumpectomy), indication for radiotherapy, tumor size, histological type, ER positivity, grade, lymphovascular invasion, and number of positive lymph nodes. Patients with a low PSI are recommended adjuvant endocrine treatment only while patients with a high PSI are recommended adjuvant chemotherapy prior to endocrine treatment. In 2017, genetic testing by PAM50 was introduced for patients with an intermediate PSI to guide adjuvant chemotherapy decisions: Patients with a luminal B genomic profile are recommended chemotherapy while those with a luminal A genomic profile are recommended adjuvant endocrine treatment only. Since the exact number of positive lymph nodes is an integral part of the PSI score, omission of AC would be expected to affect chemotherapy rates, as confirmed in the present analysis.

Since 2019, and thus during the enrolment phase in the SENOMAC trial, Swedish guidelines recommend chemotherapy for patients with a luminal B breast cancer and a tumor size >10 mm or lymph node metastases. If no more than 1–3 lymph node metastases and no other risk factors are found, endocrine treatment only is considered. Patients in an intermediate risk group (grade 2 or intermediate Ki67) are recommended gene expression analysis for risk stratification and treatment guidance. In Sweden, different genetic tests have been introduced after the completion of the SENOMAC trial, including Oncotype DX, PAM50 and Single Sample Predictor.[21]

Our results show a large variation between countries and regions in the proportion of ER+HER2– postmenopausal patients who receive adjuvant chemotherapy, reflecting a gradual implementation of de-escalating guidelines. In Denmark, the use of adjuvant chemotherapy has been reduced considerably for the postmenopausal group of patients. In the present study, a further reduction was observed in the SLNB arm, indicating that complete nodal stage is an important factor in treatment decision for chemotherapy when a de-escalating algorithm like the PSI score is used. Thus, if the use of AC and its related high risk of late sequelae is to be reduced, new tools for predicting the axillary nodal stage and thus the benefit of chemotherapy in postmenopausal patients with ER+HER2– breast cancer are needed.

The significantly lower number of positive lymph nodes identified in the group of patients without AC reflects an underdiagnosis of patients with pN2-3 disease by the preoperative evaluation mainly based on ultrasound. According to the St Gallen, ESMO and, ASCO guidelines,[3–5] adjuvant chemotherapy is always recommended in these patients regardless of

menopausal status, and in some guidelines, like the Danish, the recommendation is 8 cycles of chemotherapy, in contrast to only six cycles for postmenopausal patients with pN1 disease and a high–risk profile. We found no significant difference in the duration of chemotherapy between randomization arms, neither for premenopausal nor postmenopausal patients. However, it is not known to what extent the duration of chemotherapy is mirroring interruption of treatment due to toxicity. Duration of chemotherapy was only registered as month for start and end of treatment, so the results should be interpreted with caution.

In addition to chemotherapy, also the selection of patients who might benefit from adjuvant treatment with the CDK4/6 inhibitor abemaciclib depends on complete axillary nodal stage. Abemaciclib was not a part of standard adjuvant treatment in Denmark and Sweden in the period for inclusion in the SENOMAC trial, and any consequences of undertreatment with abemaciclib cannot thus not be investigated. The potential consequences of performing a completion AC for the identification of candidates for adjuvant abemaciclib, however, have recently been described.[22]

The present analysis is limited by missing information on precise menopausal status. The MINDACT trial used 50 years of age as a cut-off for postmenopausal status,[2] but since the average age for menopause in the Nordic countries is 52 years, the type of endocrine treatment was considered a better surrogate for menopausal status. A sensitivity analysis using 50 years of age as a cut-off for menopausal status did not change the main results. Another limitation is the multicenter design since indications for adjuvant chemotherapy vary both nationally and locally. Analyzing the complete data set can thus mask an effect of omitting AC on adjuvant chemotherapy, as shown when analyses were made for Denmark and Sweden separately.

The lower proportion of postmenopausal patients treated by adjuvant chemotherapy in the SLNB only arm did so far not translate into a deterioration of 5-year RFS, which could question the need for chemotherapy in these patients. Median follow-up was, however, only 3.7 years resulting in few events and broad confidence intervals indicating low precision of the estimates. Considering that events occur gradually over the first 10–15 years in ER+HER2– breast cancer,[23] longer follow-up is needed to substantiate the results.

In conclusion, the lower proportion of patients with lymph node metastases identified if AC was omitted did affect the chemotherapy rates in postmenopausal patients. To avoid completion AC with its associated risk of long-term arm morbidity,[7] new tools for determining chemotherapy indications are needed. More precise imaging procedures like MRI or Contrast-enhanced spectral mammography may be useful for nodal staging. However, tumor biology might be a much better indicator for the need for adjuvant chemotherapy than counting positive nodes, calling for more genetic testing. Until then, comprehensive patient information leading to shared decision-making for omitting AC, which may lead to less information on nodal stage and thus potential undertreatment by chemotherapy, weighed against the risk of arm morbidity from AC, could be the solution.

Contributors

Tove Filtenborg Tvedskov: Conceptualization, Investigation, Methodology, Project administration, Resources, Visualization, Writing—original draft, Robert Szulkin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing—review & editing, Sara Alkner: Investigation, Resources, Writing—review & editing, Yvette Andersson: Investigation, Resources, Writing—review & editing, Leif Bergkvist: Investigation, Resources, Writing—review & editing, Jan Frisell: Investigation, Resources, Writing—review & editing, Oreste Davide Gentilini: Investigation, Resources, Writing—review & editing, Michalis Kontos: Investigation, Resources, Writing—review & editing, Thorsten Kühn: Investigation, Resources, Writing—review & editing, Dan Lundsted: Investigation, Resources, Writing—review & editing, Birgitte Vrou Offersen: Investigation, Resources, Writing—review & editing, Roger Olofsson Bagge: Investigation, Resources, Writing—review & editing, Toralf Reimer: Investigation, Resources, Writing—review & editing, Malin Sund: Investigation, Resources, Writing—review & editing, Lisa Rydén: Investigation, Resources, Writing—review & editing, Peer Christiansen: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing—review & editing, Jana de Boniface: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing—review & editing.

Data sharing statement

Data will be transferred via an encrypted data sharing tool once a request for data is accepted by the trial committee. This can only be the case once all ethical and regulatory requirements are fulfilled, and the primary endpoint of the SENOMAC trial has been published. Any request should be addressed to the principal investigator at jana.de-boniface@ki.se.

Declaration of interests

Dr. RO Bagge declares research grants from BMS, Endomagnetics Ltd, Skyline Dx and NeraCare GmbH as well as participation in advisory board for Amgen, BD/BARD, Bristol-Myers Squibb (BMS), Cansr.com, Merck Sharp & Dohme (MSD), Novartis, Roche and Sanofi Genzyme and stock or stock options in SATMEG Ventures AB. Thorsten Kuehn has payment or honoraria for presentations from MSD, Novartis, Lilly, Exact Sciences, Merit Medical, Sirius Medical and EndoMag and support for attending meetings from MSD, Lilly. All other authors declare no competing interests.

Acknowledgements

The SENOMAC Trialists' Group consists of the international steering committee represented in its entirety in the list of authors. We thank the Clinical Trials Office at Karolinska University Hospital for data monitoring and management, the local investigators and study nurses and other supporting staff at participating hospitals, and the patients who participated in the trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101083.

References

1 LeVasseur N, Sun J, Fenton D, et al. Impact of the 21-gene recurrence score assay on the treatment of estrogen receptor-positive, HER2-negative, breast cancer patients with 1-3 positive nodes: a prospective clinical utility study. *Clin Breast Cancer*. 2022;22(1):e74–e79. https://doi.org/10.1016/j.clbc.2021.09.004.

2 Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22:476–488.

3 Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen international consensus guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021;32:1216–1235.

4 Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(2):159–182. https://doi.org/10.1016/j.annonc.2023.11.016.

5 Andre F, Ismaila N, Allison KH, et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2022;40(16):1816–1837. https://doi.org/10.1200/JCO.22.00069.

6 Martins-Branco D, Cristóvão Ferreira S, Gouveia E, et al. Adjuvant chemotherapy de-escalation with genomic assay protocol in patients with early breast cancer: a single-centre prospective cohort study. *Acta Med Port*. 2023;36:487–495.

7 Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302:1985–1992.

8 Appelgren M, Sackey H, Wengström Y, et al. Patient-reported outcomes one year after positive sentinel lymph node biopsy with or without axillary lymph node dissection in the randomized SENOMAC trial. *Breast*. 2022;63:16–23. https://doi.org/10.1016/j.breast.2022.02.013.

9 Donker M, van Tienhoven G, Straver ME, et al. 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. *Lancet Oncol*. 2014;15:1303–1310.

10 Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569–575.

11 de Boniface J, Filtenborg Tvedskov T, Rydén L, et al. Omitting axillary dissection in breast cancer with sentinel-node metastases. *N Engl J Med*. 2024;390:1163–1175.

12 de Boniface J, Frisell J, Andersson Y, et al. Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. *BMC Cancer*. 2017;17:379.

13 Alkner S, Wieslander E, Lundstedt D, et al. Quality assessment of radiotherapy in the prospective randomized SENOMAC trial. *Radiother Oncol*. 2024;197:110372.

14 Tolaney SM, Garrett-Mayer E, White J, et al. Updated standardized definitions for efficacy end Points (STEEP) in adjuvant breast cancer clinical trials: STEEP version 2.0. *J Clin Oncol*. 2021;39:2720–2731.

15 Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol*. 2010;28(5):731–737. https://doi.org/10.1200/JCO.2008.21.7554.

16 Savolt A, Péley G, Polgár C, et al. 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. *Eur J Surg Oncol*. 2017;43:672–679.

17 Weber WP, Matrai Z, Hayoz S, et al. Association of axillary dissection with systemic therapy in patients with clinically node-positive breast cancer. *JAMA Surg*. 2023;158:1013–1021.

18 Verheuvel NC, Voogd AC, Tjan-Heijnen VCG, Siesling S, Roumen RMH. Different outcome in node-positive breast cancer patients found by axillary ultrasound or sentinel node procedure. *Breast Cancer Res Treat*. 2017;165:555–563.

19 Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385:2336–2347.

20 Ejlertsen B, Jensen MB, Mouridsen HT. Excess mortality in post-menopausal high-risk women who only receive adjuvant endocrine therapy for estrogen receptor positive breast cancer. *Acta Oncol*. 2014;53:174–185.

21 Staaf J, Häkkinen J, Hegardt C, et al. RNA sequencing-based single sample predictors of molecular subtype and risk of recurrence for clinical assessment of early-stage breast cancer. *NPJ Breast Cancer*. 2022;8:94.

22 de Boniface J, Appelgren M, Szulkin R, et al. Completion axillary lymph node dissection for the identification of pN2–3 status as an indication for adjuvant CDK4/6 inhibitor treatment: a post-hoc analysis of the randomised, phase 3 SENOMAC trial. *Lancet Oncol*. 2024;25(9):1222–1230. https://doi.org/10.1016/S1470-2045(24)00350-4.

23 Pagani O, Price KN, Gelber RD, et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: a therapeutic target for a quarter of a century. *Breast Cancer Res Treat*. 2009;117(2):319–324. https://doi.org/10.1007/s10549-008-0282-0.