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CLINICAL TRIAL

Extracapsular extension in the positive sentinel lymph node: a marker of poor prognosis in cT1-2N0 breast cancer patients?

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Abstract

Objective This study aims to evaluate whether extracapsular extension (ECE) in the sentinel lymph node (SLN) is associated with involvement of ≥4 lymph node metastases at completion axillary lymph node dissection (ALND) and the effect on 5-year disease-free survival (DFS) and 10-year overall survival (OS).

Summary background data ECE in a SLN is usually a contraindication for omitting completion ALND in cT1-2N0 breast cancer patients treated with breast-conserving therapy and 1–2 positive SLN(s).

Methods All cT1-2N0 breast cancer patients with 1–3 positive SLN(s) who underwent ALND between 2005 and 2008 were selected from the Netherlands Cancer Registry. Logistic regression analysis was used to determine the association between ECE and ≥4 lymph node metastases. Five-year DFS and 10-year OS were analyzed using Kaplan–Meier survival analysis. Cox regression analysis was performed to correct for other prognostic factors.

Results A total of 3502 patients were included. Information on ECE was available for 2111 (60.3%) patients, consisting of 741 (35.1%) patients with and 1370 (64.9%) without ECE. The incidence of ≥4 lymph node metastases was 116 (15.7%) in the ECE group vs. 80 (5.8%) in the group without ECE ($p<0.001$). Five-year DFS rate was 86.4% in the ECE group compared to 88.8% in the group without ECE ($p=0.085$). 10-year OS rate was 78.6% compared to 83.0% ($p=0.018$), respectively. Cox regression analysis showed that ECE was not an independent prognostic factor for both DFS and OS.

Conclusions ECE was significantly associated with involvement of ≥4 lymph node metastases in the completion ALND group. ECE was not an independent prognostic factor for both DFS and OS.

Keywords Breast cancer · Sentinel lymph node · Axillary lymph node dissection · Extracapsular extension · Disease-free survival · Overall survival

Abbreviations

ALND	Axillary lymph node dissection
BCT	Breast-conserving therapy

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DFS	Disease-free survival
DM	Distant metastasis
ECE	Extracapsular extension
HR	Hazard ratio
IKNL	Comprehensive Cancer Organisation the Netherlands
LR	Local recurrence
NCR	Netherlands Cancer Registry
OS	Overall survival
PALGA	Pathological Anatomical National Automated Archive
RR	Regional recurrence
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy

Introduction

Extension of neoplastic cells through the nodal capsule into perinodal adipose tissue in sentinel lymph node (SLN) positive patients is called extracapsular extension (ECE) (Appendix 1) [1]. Previous studies showed that the presence of ECE is associated with the presence of additional non-sentinel lymph node metastases [2–9]. Additionally, ECE is associated with other prognostic factors, such as lymphovascular invasion and macrometastases [4, 9]. Earlier, the presence of ECE had no consequences for axillary treatment. All cT1-2N0 breast cancer patients with micro or macrometastases in the SLN were treated with an axillary lymph node dissection (ALND) or radiotherapy of the axilla, irrespective of the presence of ECE.

Currently, the value of completion axillary treatment is being questioned. The ACOSOG Z0011 and IBCSG 23-01 trials have shown that ALND can be safely omitted in cT1-2N0 breast cancer patients treated with breast-conserving therapy (BCT) and 1–2 macrometastases in the SLN [10, 11]. In both studies (macroscopic), ECE was an exclusion criterion and therefore it remains unclear whether completion axillary treatment can also be safely omitted in patients with ECE. Gooch et al. showed that the presence of ECE larger than 2 mm was significantly correlated with increased nodal tumor burden and therefore ALND might be indicated for patients with ECE > 2 mm [12].

Ongoing trials (e.g., BOOG 2013-07, POSNOC, SINODAR, and SENOMAC trial) randomize cT1-2N0 patients treated with mastectomy or BCT with a maximum of 3 macrometastases in the SLN to completion axillary treatment (consisting of ALND or radiotherapy of the axilla) or watchful waiting, irrespective of the presence of ECE [13–15]. The most important question remains whether omission of completion axillary treatment in patients with ECE affects disease-free survival (DFS) and overall survival (OS). The aim of the present study was to determine whether ECE in the SLN is associated with involvement of ≥ 4 axillary lymph node metastases after completion of an ALND in a large cohort of breast cancer patients. The secondary aim was to investigate whether patients with ECE have an inferior prognosis, with respect to local (LR), regional recurrence (RR), distant metastasis (DM), 5-year DFS, and 10-year OS.

Materials and methods

Data collection

For this population-based study, the Netherlands Cancer Registry (NCR) and the Pathological Anatomical National Automated Archive (PALGA) were used. The NCR contains data on all newly diagnosed malignancies in the Netherlands. Trained data managers of the Comprehensive Cancer Organisation the Netherlands (IKNL) gather data from patients' records in all hospitals based on a notification by PALGA.

Data on patient and tumor characteristics, surgical, radiation, and systemic treatment were obtained, as well as follow-up data on first breast cancer events and survival.

First breast cancer event was registered as new primary ipsilateral breast cancer, contralateral breast cancer, LR, RR, or DM. The vital status was obtained through linkage to the Municipal Personal Records Database. Data on pathology, e.g., presence of ECE, size (micro or macrometastasis), number of positive SLN(s) and/or ALND, and total number of removed axillary lymph nodes during sentinel lymph node biopsy (SLNB) and/or ALND, were retrieved from the PALGA. This is a nationwide network, which registers all histo and cytopathology reports generated by all pathology laboratories in the Netherlands [16].

Study population

This study focused on study populations similar to the previously mentioned randomized controlled trials, involving breast cancer patients with a clinically T1-2 tumor, clinically node-negative status and positive SLN(s) treated BCT or mastectomy. From the NCR, all patients diagnosed between 2005 and 2008 with primary invasive epithelial cT1-2N0 breast cancer were included, with 1–3 micro/macrometastases at SLNB, who underwent completion ALND. Patients with distant metastasis at diagnosis (or within 91 days), an incomplete 5-year follow-up, or patients treated with primary systemic treatment were excluded. Subsequently, selected patients were linked to data of the PALGA. In case of incomplete registered SLN and/or ALND results (e.g., presence of ECE, number of positive SLN/ALND and total number of removed axillary lymph nodes), patients were excluded.

Locoregional treatment

All patients were treated according to the Dutch breast cancer guidelines of 2005 [17]. Locoregional treatment consisted of BCT (lumpectomy and whole breast radiotherapy) or mastectomy combined with a SLNB in clinically node-negative breast cancer. Clinically node negative was based on physical examination (axillary ultrasound was common but not mandatory). Contraindications for SLNB were previous axillary surgery and multiple tumors. Patients with a positive SLN were treated with either ALND or axillary radiotherapy, in context of the AMAROS trial. For the present study, patients treated with axillary radiotherapy were excluded. If indicated, patients received adjuvant systemic treatment (e.g., chemotherapy, hormone therapy, and/or immunotherapy) or adjuvant radiotherapy [17].

Endpoints

ECE was defined as extension of neoplastic cells through the nodal capsule into perinodal adipose tissue of the axilla [1]. DFS was defined as the absence of any first LR, RR, or contralateral recurrence, DM or death within 5 years. OS was defined as the time interval between date of diagnosis and date of death or date of emigration.

LR was defined as any invasive breast cancer in the ipsilateral breast (including skin, biopsy tract, and surgical scar) or on the ipsilateral thoracic wall including the mastectomy scar, i.e., both LR and new primary ipsilateral breast cancer were counted for the analysis. RR was defined as recurrence in an ipsilateral axillary, infraclavicular, supraclavicular, internal mammary/parasternal, or intramammary lymph node. DM was defined as breast cancer in any organ other than breast, excluding LR and RR and second primary breast cancer [18]. Events after 91 days were regarded as a recurrence (LR, RR, DM, new primary ipsilateral breast cancer, or contralateral breast cancer). Events between 0 and 91 days after diagnosis were regarded as synchronous with the primary tumor. Patients were censored at the date of their first event, at the date of last follow-up, or at the date of death. Data about recurrences were up-to-date for 5 years of follow-up.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, NY, USA). Baseline characteristics between subgroup with and without ECE were compared using Chi-squared test for categorical data and Mann Whitney U-test/ independent *t*-test for continuous data.

LR, RR, DM, DFS, and OS for both subgroups were calculated with Kaplan–Meier curves and compared with the log-rank test. Prognostic factors of DFS and OS were examined using univariable and multivariable Cox proportional hazards regression, to estimate crude and adjusted Hazard Ratios (HR's) and corresponding 95% confidence intervals. P-values (two-sided) ≤ 0.05 were considered statistically significant.

Results

A total of 3502 patients with clinically T1-2N0 breast cancer and 1–3 positive SLN(s) who underwent a completion ALND were included. Of these, information on ECE was available for 2111 patients (60.3%), consisting of 741 patients with ECE (35.1%) and 1370 without ECE (64.9%) (Fig. 1). Patient and tumor characteristics of patients with and without ECE were compared (Table 1). Compared to patients without ECE, patients with ECE had more often a macrometastasis in the SLN (63.4% vs. 53.2%, $p < 0.001$), ≥ 4 additional lymph node metastases at completion ALND (15.7 vs. 5.8, $p < 0.001$), and received more often hormone therapy in case of estrogen receptor positive (93.9% vs. 89.8%, $p < 0.001$). The presence of ECE was a predictor of ≥ 4 additional lymph node metastases in the ALND (OR 2.8 95%CI 1.936–4.270, $p < 0.001$) (Table 2). Other predictors of ≥ 4 additional lymph node metastases in the ALND were clinical tumor size (OR 1.652 95% CI 1.119–2.438, $p = 0.012$) and SLN size (macro vs. micrometastases) (OR 3.262 95%CI 1.611–6.605, $p = 0.001$).

Recurrence

Locoregional recurrence (LRR) occurred rarely within 5 years after diagnosis. Only 2.2% (47/2111) of the patients was diagnosed with LR as a first event and RR occurred in only 1.0% (22/2,111) of the patients. Subgroup analyses showed that LR occurred in 1.6% (12/741) of the patients with ECE and in 2.6% (35/1370) of the patients without ECE ($p = 0.196$). RR occurred in 0.9% (7/741) and in 1.1% (15/1370) ($p = 0.788$), respectively. Distant metastasis was diagnosed in 9.0% (190/2111) of the patients, whereof 12.2% (83/741) in patients with ECE and 7.8% (107/1370) of the patients without ECE ($p = 0.008$).

Disease-free survival

Within five years after diagnosis, 12.1% (255/2111) of the patients were diagnosed with LR, RR, DM or were deceased. This resulted in a five-year DFS of 87.9% (1856 of 2111) for all patients. Subgroup analyses showed a 5-year DFS of 86.4% (640/741) with ECE and 88.8% (1216/1370) in patients without ECE ($p = 0.085$) (Fig. 2).

Table 1 Patient demographics and tumor characteristics (n = 2111)

Characteristic	ECE negative $n = 1370$	ECE positive $n = 741$	p value
Age, years			
Mean	56	57	0.073
Range	24-91	25–88	
Tumor type, n (%)			
Invasive carcinoma of NST	1,034 (75.5)	591 (79.8)	0.13
Lobular	173(12.6)	78 (10.5)	
Mixed or other	90 (6.6)	44 (5.9)	
Unknown	73 (5.3)	28 (3.8)	
Grade (Bloom-Richardson), *n* (%)			
I	276 (20.1)	179 (24.2)	0.053
II	630 (46.0)	341 (46.0)	
III	417 (30.5)	198 (26.7)	
Unknown	47 (3.4)	23 (3.1)	
cT-stage, *n* (%)			
cT1	924 (67.4)	490 (66.1)	0.539
cT2	446 (32.6)	251 (33.9)	
pT-stage, *n* (%)			
pT1	759 (55.4)	355 (47.9)	**0.011**
pT2	576 (42.0)	370 (49.9)	
pT3	30 (2.2)	12 (1.6)	
pT4	2 (0.2)	2 (0.3)	
Unknown	3 (0.2)	2 (0.3)	
Subtype, *n* (%)			
ER+PR+Her2−	789 (57.6)	484 (65.3)	**< 0.001**
ER+PR−Her2−	143 (10.4)	77 (10.4)	
ER+Her2+	109 (7.9)	59 (8.0)	
ER−Her2+	68 (5.0)	18 (2.4)	
Triple negative	120 (8.8)	34 (4.6)	
Unknown	141 (10.3)	69 (9.3)	
Surgical treatment, *n* (%)			
Mastectomy	594 (43.4)	338 (45.6)	0.319
Lumpectomy	776 (56.6)	403 (54.4)	
Outcome SLN, *n* (%)			
Micrometastasis	343 (25.0)	50 (6.8)	**< 0.001**
Macrometastasis	729 (53.2)	470 (63.4)	
Unknown	298 (21.8)	221 (29.8)	
Number of positive additional lymph nodes in ALND, *n* (%)			
01–3	1290 (94.2)	625 (84.3)	
≥4	80 (5.8)	116 (15.7)	**< 0.001**
Radiotherapy in case of lumpectomy, *n* (%)			
Yes	769 (99.1)	397 (98.8)	0.403
No	7 (0.9)	6 (0.2)	
Chemotherapy, *n* (%)			
Yes	865 (63.1)	483 (65.2)	
No	505 (36.9)	258 (34.8)	0.351
Hormone therapy in case of ER+, *n* (%)			
Yes	1033 (89.8)	630 (93.9)	**< 0.001**
No	117 (10.2)	41 (6.1)	
Trastuzumab and chemotherapy in case of HER2+, *n* (%)			
Yes	134 (89.3)	54 (87.1)	0.125
No	16 (10.7)	8 (12.9)	

Table 1 (continued)

N Number of cases, *NST* invasive carcinoma of no special type, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *cT* clinical tumor stage, *pT* pathological tumor stage

Table 2 Logistic regression analysis ≥ 4 positive lymph nodes in the ALND

	OR (95%CI)	p value
ECE vs. no ECE	2.875 (1.936–4.270)	< 0.001
Age (per year increment)	1.003 (0.987–1.018)	0.755
Grade		
III vs. I–II	1.005 (0.648–1.559)	0.982
cT-stage		
cT2 vs. cT1	1.652 (1.119–2.438)	0.012
SLN size		
Macro vs. micrometastasis	3.262 (1.611–6.605)	0.001
Triple negative subtype		
Yes vs. no	1.552 (0.785–3.071)	0.207

In multivariable Cox regression analyses, the effect of ECE on DFS was not significant (HR 1.302, 95%CI 0.930–1.823, $p = 0.125$). Grading (HR 1.998, 95%CI 1.439–2.772, $p < 0.001$), clinical tumor stage (HR 2.155, 95%CI 1.572–2.953, $p < 0.001$), and ≥ 4 additional lymph node metastases in the ALND (HR 1.983, 95%CI 1.277–3.078, $p = 0.002$) were identified as significant predictors for decreased DFS and endocrine therapy for increased DFS (HR 0.473, 95%CI 0.305–0.732, $p = 0.001$) (Table 3).

Overall survival

After ten years of follow-up, 81.6% (1722/2,111) of all patients were alive. This concerned 78.9% (585/741) of patients with ECE and 83.0% (1137/1370) without ECE ($p = 0.018$). In multivariable cox regression analyses, the effect of ECE on OS was not statistically significant (HR 1.168, 95%CI 0.881–1.548, $p = 0.281$). Significant predictors for decreased OS were age (HR 1.047, 95%CI 1.031–1.063, $p < 0.001$), grading (HR 2.158, 95%CI 1.616–2.881, $p < 0.001$), triple-negative breast tumors (HR 2.564, 95%CI 1.195–5.499, $p = 0.016$), clinical tumor size (HR 1.594, 95%CI 1.204–2.110, $p < 0.001$), and ≥ 4 positive lymph node metastasis in the ALND (HR 1.992, 95%CI 1.368–2.901, $p < 0.001$) (Table 4).

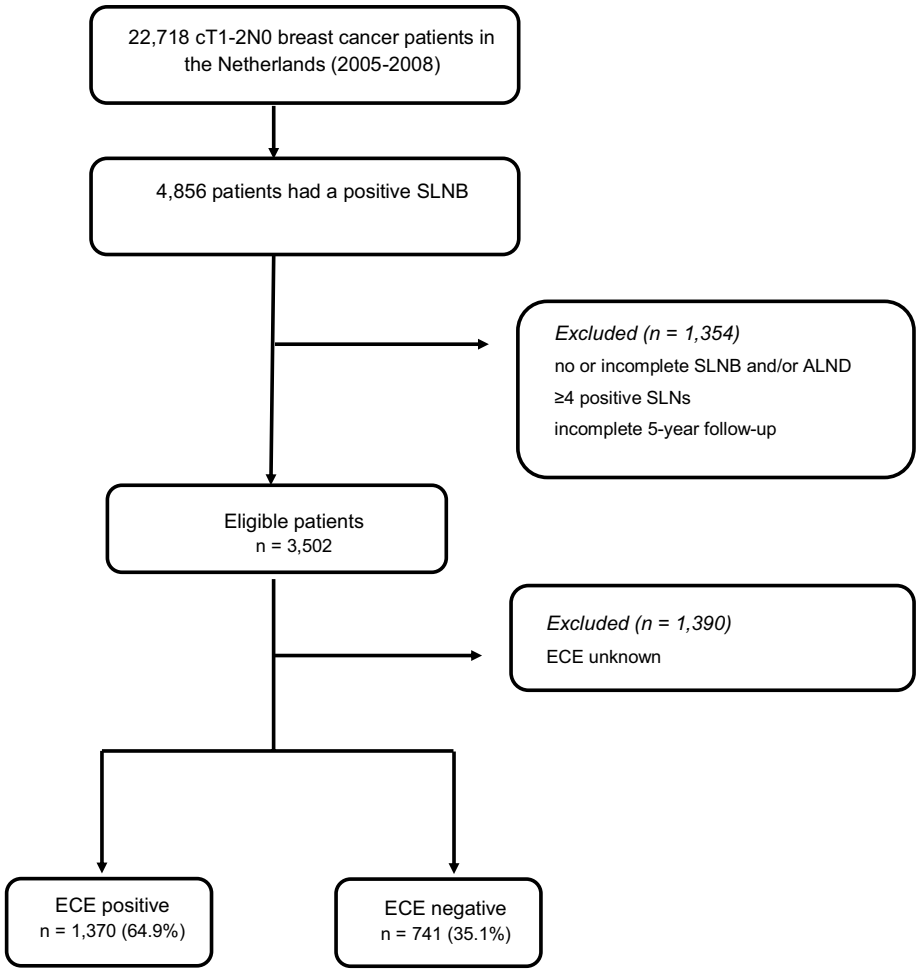


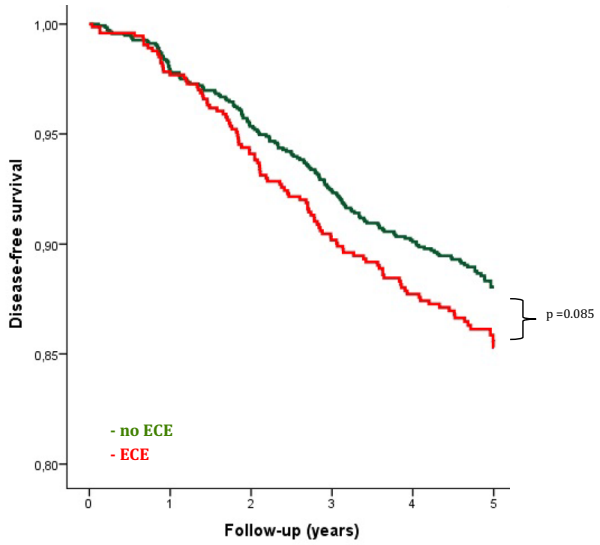
Fig. 1 Flow diagram

Discussion

This large population-based study of more than 2,000 breast cancer patients showed that the presence of ECE in the SLN is associated with the presence of ≥4 additional lymph node metastases in the ALND (15.7% vs. 5.8%, $p<0.001$), which is in agreement with several studies, which showed that the presence of ECE was a predictor for the presence of non-SLN metastases [2, 5, 7, 19]. Previous studies also investigated that the presence of ECE was significantly associated with a higher incidence of N2 disease (20–47.6%) compared to the group without ECE (2.7–9.2%) [6, 12, 20]. Gooch et al. also showed that size of ECE was important, where >2 mm had significantly more often N2 disease compared to ECE ≤2 mm (33% vs. 9%, $p<0.001$) [12].

The association of ECE to an increased nodal tumor burden is, however, less important than its potential relation to disease recurrence and survival. The present study showed that LR (2.2%) or RR (1.0%) rarely occurred during the first 5 years following diagnosis, and did not significantly differ between the group with ECE and without ECE (1.6% vs. 2.6%, $p=0.196$ and 0.9% vs. 1.1%, $p=0.788$), respectively. DM was more often diagnosed in patients with ECE compared to patients without ECE (12.2% vs. 7.8%, $p=0.008$). These results are consistent with Choi et al. that showed the presence or absence of ECE did not influence LR and RR (5.3% vs. 3.4% and 0% vs. 3.4%, respectively). Distant metastasis did occur more often in patients with ECE, but not statistically significant (10.5% vs. 2.7%, $p=0.19$) [20]. In contrast, Neri et al. showed that the presence of ECE was significantly related to an increased risk of both RR (13.4% vs. 6.6%; $p=0.037$) and distant (43% vs. 16.2%; $p<0.001$) recurrence [21].

The 5-year DFS rate in this study was 86.4% in the group with ECE compared to 88.8% in the group without ECE ($p=0.085$) and the 10-year OS rate was 78.6% and 83.0%, retrospectively, respectively ($p=0.018$). Cox regression analysis showed that ECE is not an independent prognostic factor for both 5-year DFS and OS. Other studies investigating the effect of ECE on DFS and OS are inconsistent. Neri et al. demonstrated that the presence of ECE resulted in a negative prognostic effect on DFS (HR 2.34, 95%CI 1.64–3.32, $p<0.001$) and OS (HR 2.98, 95%CI 1.89–4.66, $p<0.001$) [21]. Gruber et al. demonstrated that ECE was associated with worse OS and DFS, but did not remain significant when



	0	1	2	3	4	5
no ECE	1,370	1,353	1,307	1,268	1,238	1,216
ECE	741	712	698	670	653	640

Fig. 2 Kaplan Meier curve of 5-year DFS (red line shows curve of patients with ECE and green line the curve of patients without ECE)

the number of positive nodes was added in the multivariable analyses [22]. Despite the increased nodal tumor burden, results regarding survival remain contradictory.

The strength of the present study is the large nationwide multicenter cohort of 2,111 cT1-2N0 breast cancer patients with 1–3 positive SLN(s). This is one of the first studies reporting both the association between ECE and ≥4 additional lymph node metastases and its effect on recurrence risk and DFS and OS. A limitation of this study is its retrospective design, which may have caused many incomplete pathology reports (39.1%). A possible explanation is the lack of a standard definition and method of reporting the presence or absence of ECE. The incidence of ECE was 35.1%, within the range of 24–57% of previous studies. As a result, selection bias could have occurred since ECE is probably more often registered in the pathology report if present and not registered if not present, resulting in incomplete pathology reports. Therefore, it is likely that the incidence of ECE in this study population is overestimated, compared to the incidence in current (Dutch) breast cancer population. Furthermore, axillary ultrasound was not part of standard preoperative nodal staging then. This could have contributed to an overestimation of the presence of nodal tumor burden in the ALND, since a negative axillary ultrasound excludes the presence of advanced axillary disease (pN2–pN3), and potentially could also have led to an overestimation of ECE [23].

Table 3 Uni- and multivariable analysis for predictors of five-year DFS

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
ECE vs. no ECE	1.246 (0.970–1.602)	0.086	1.302 (0.930–1.823)	0.125
Age (per year increment)	1.00 (0.989–1.010)	0.959	–	–
Type				
Lobular vs. invasive carcinoma NST	1.131 (0.785–1.628)	0.509	–	–
Grade				
III vs. I–II	3.341 (2.595–4.302)	< 0.001	1.998 (1.439–2.772)	**< 0.001**
Triple negative subtype				
Yes vs. no	5.001 (3.772–6.721)	< 0.001	1.684 (0.998–2.843)	0.051
cT-stage				
cT2 vs. cT1	2.068 (1.618–2.644)	< 0.001	2.155 (1.572–2.953)	**< 0.001**
SLN size				
Macro vs. micrometastasis	1.418 (0.981–2.050)	0.063	1.337 (0.889–2.010)	0.163
ALND				
≥4 vs. 1–3	2.446 (1.782–3.357)	< 0.001	1.983 (1.277–3.078)	**0.002**
Radiation therapy				
Yes vs. no	1.271 (1.124–1.437)	< 0.001	1.007 (0.710–1.428)	0.969
Chemotherapy				
Yes vs. no	1.110 (0.854–1.443)	0.434	–	–
Endocrine therapy				
Yes vs. no	1.596 (1.396–1.824)	< 0.001	0.473 (0.305–0.732)	**0.001**
Targeted therapy				
Yes vs. no	0.932 (0.781–1.112)	0.434	–	–

Table 4 Uni- and multivariable analysis for predictors of ten-year OS

	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
ECE vs. no ECE	1.277 (1.0443–1.564)	0.018	1.168 (0.881–1.548)	0.281
Age (per year increment)	1.047 (1.038–1.056)	< 0.001	1.047 (1.031–1.063)	**< 0.001**
Type				
Lobular vs. ductal	1.009 (0.740–1.377)	0.953	–	–
Grade				
III vs. I–II	2.235 (1.822–2.742)	< 0.001	2.158 (1.616–2.881)	**< 0.001**
Triple negative subtype				
Yes vs. no	3.646 (2.790–4.765)	< 0.001	2.564 (1.195–5.499)	**0.016**
cT-stage				
cT2 vs. cT1	1.656 (1.355–2.024)	< 0.001	1.594 (1.204–2.110)	**0.001**
SLN size				
Macro vs. micrometastasis	1.306 (0.976–1.747)	0.072	1.263 (0.907–1.759)	0.167
OKD				
≥4 vs. 1–3	2.279 (1.752–2.966)	< 0.001	1.992 (1.368–2.901)	**< 0.001**
Radiation therapy				
Yes vs. no	1.559 (1.280–1.898)	< 0.001	0.772 (0.104–5.722)	0.8
Chemotherapy				
Yes vs. no	0.533 (0.437–0.651)	< 0.001	0.922 (0.613–1.387)	0.696
Endocrine therapy				
Yes vs. no	1.354 (1.206–1.521)	< 0.001	0.508 (0.220–1.170)	0.111
Targeted therapy				
Yes vs. no	1.108 (0.936–1.311)	0.232	–	–

A second limitation of this study is that we were not able to distinguish between ECE ≤ 2 mm or > 2 mm, as this not used in the Dutch clinical setting and therefore not available. However, results of Choi et al. already showed that results of both groups were comparable [20]. Furthermore, there is not yet a consensus regarding the definition of ECE. Finally, lymphovascular invasion (LVI) and multifocality of the primary tumor are other known prognostic factors for non-SLN metastases and survival. These factors were not included in our multivariable analyses, due to a large number of missing data. Yajima et al. investigated the effect of ECE in combination with other clinicopathological factors (i.e., age, tumor type, grade and size, positive lymph nodes, lymphovascular invasion, ER, PR and Her2 status) and demonstrated that patients with a combination of ECE and vascular invasion decreased their DFS [24].

In conclusion, this study showed that ECE in the SLN is associated with the presence of ≥ 4 additional lymph node metastases. Despite the increased nodal tumor burden, cT1-2N0 breast cancer patients with a positive SLN treated with either BCT or mastectomy and an ALND, did not have an inferior prognosis in multivariable analysis, in terms of inferior 5-year LR, RR, DFS, and OS. Based on results, it seems justified to include patients with ECE in the ongoing trials in order to demonstrate if omitting axillary treatment is safe in this subgroup of patients.

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Compliance with ethical standards

Conflict of interest None of the authors reported have a conflict of interest related to the outcomes of this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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