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EPIDEMIOLOGY

Which patients with sentinel node-positive breast cancer after breast conservation still receive completion axillary lymph node dissection in routine clinical practice?

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Abstract

Purpose In the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, patients with 1 or 2 tumour-involved sentinel lymph nodes (SLNs) gained no benefit from completion axillary lymph dissection (cALND). We examined implementation of evidence from this trial into routine clinical management.

Methods Data were included from patients diagnosed with primary breast cancer in German breast cancer units between 2008 and 2015 and analysed retrospectively from a prospective maintained database. Descriptive analyses assessed time-trend changes in axillary surgery. Factors associated with cALND in patients with 1 or 2 positive SLNs were identified using multivariable logistic regression analysis.

Results Overall, 179 breast cancer units provided data for 188,909 patients, of whom 13,741 (7.3%) had pT1/2cN0M0 invasive breast cancer with 1 or 2 tumour-involved SLNs and underwent breast-conserving surgery and adjuvant radiotherapy. cALND use decreased from 94.6% in 2008 to 46.9% in 2015 ($p < 0.001$). In multivariable analyses, the following factors were associated with cALND: fewer removed SLNs; two tumour-affected SLNs; younger age; lower annual case volume per hospital; higher tumour grade and lymphovascular invasion. No statistically significant influence was detected for hormone receptor or HER2 status.

Conclusion In our cohort, 7.3% of patients with primary breast cancer met the ACOSOG Z0011 inclusion criteria and could potentially have been spared the morbidity of cALND. cALND tended to be performed in patients with a higher axillary tumour burden. This study shows a shift towards less extensive axillary surgery through rapid implementation of new clinical trial evidence into routine clinical practice.

Keywords Breast cancer · Axillary lymph node dissection · Mastectomy · ACOSOG Z0011 · Time-tend analysis · Sentinel lymph node dissection · Tumour-involved sentinel lymph node

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Introduction

The surgical management of breast cancer involves the removal of the tumour from the breast and surgical excision of axillary lymph nodes. Lymph node status has prognostic value for estimating the likelihood of breast cancer relapse following adjuvant therapy [1–3]. This diagnostic assessment can be performed either by the selective removal of sentinel lymph node(s) (SLNs) or an axillary lymph node dissection (ALND). However, during the past decade the focus of risk assessment for patients' individual treatment recommendations has shifted towards tumour biology as the most relevant prognostic marker [4, 5]. Consequently, the importance of lymph node status has diminished [6].

For several decades, ALND was the standard procedure for assessing pathological nodal status. Since the beginning of the new millennium, the degree of radical surgery to the axilla has been reduced through implementation of axillary staging via SLN dissection (SLND), which has become the standard of care for patients with clinically node-negative breast cancer [7, 8]. However, for patients with a tumour-affected SLN, completion ALND (cALND) was still recommended. Paraesthesia, pain and motor neuropathy are more frequent in patients undergoing ALND than SLND. Lymphoedema with arm swelling and restriction of movement causing a substantial decrease in quality of life occurs in 20% of patients undergoing ALND versus < 5% after SLND [9].

In 2010, results from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial called into question the concept of cALND [10]. This randomised, prospective, multicentre trial investigated the impact of omitting cALND in clinically node-negative patients with T1/2 tumours and 1 or 2 positive SLNs who had undergone breast-conserving treatment followed by radiation of the affected breast and systemic therapy according to guidelines. In the ACOSOG Z0011 trial, SLND alone resulted in equivalent locoregional control, disease-free survival and overall survival rates compared with those seen after cALND [11, 12]. These results led to broad discussion and reassessment of the surgical management of breast cancer in patients with tumour-affected SLNs. Traditionally, cALND was performed not only to evaluate the number of tumour-affected lymph nodes for the selection of systematic therapy and radiotherapy, but also with the aim of improving prognosis, based on the assumption that removal of affected lymph nodes reduces tumour burden. Results of the ACOSOG Z0011 trial challenged this concept. However, the ACOSOG Z0011 trial has been criticised for its low statistical power because slow recruitment led to premature study termination. In addition, only low-risk patients were eligible, which may have influenced survival outcomes. Hence, the applicability of these results to a typical breast cancer cohort and the general implementation of the trial results into clinical practice have been questioned [13–15].

Here we report the impact of ACOSOG Z0011 evidence on the axillary management of patients with breast cancer treated in Germany between 2008 and 2015. Furthermore, we examine factors influencing the decision to perform cALND in clinical routine management in patients meeting the ACOSOG Z0011 inclusion criteria.

Patients and methods

Tumour documentation

Data were obtained from a voluntary benchmarking project in Germany. The participating breast cancer units (BCUs) contributed clinical, surgical and pathological data from patients with primary breast cancer to the West German Breast Center Ltd (WBC), Düsseldorf, Germany. The WBC is an institution that provides quality control through an annual benchmarking report [16]. The data are also used for the German Cancer Society's periodical re-certification process for certified BCUs. Collaborating BCUs collected the data prospectively. Thus, this is a retrospective analysis of a prospectively maintained database.

The validity and quality of the data registered in the WBC tumour documentation system are assessed through a

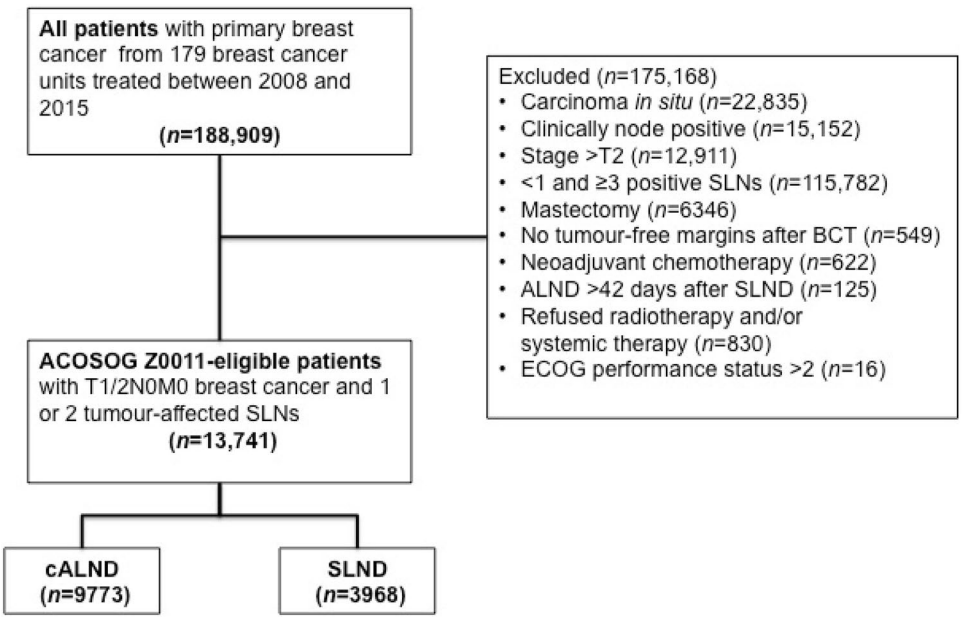


Fig. 1 CONSORT diagram. *cALND* completion axillary lymph node dissection, *ECOG* Eastern Cooperative Oncology Group, *SLN* sentinel lymph node, *SLND* sentinel lymph node dissection

Table 1 Patient characteristics in the entire study cohort, in patients meeting the ACOSOG Z0011 inclusion criteria and in the SLND-only group of the ACOSOG Z0011 trial

Characteristic	Entire study cohort ($n=188,909$)	Z0011-eligible patients ($n=13,741$)	SLND-only arm of Z0011 ($n=436$)
Age, years			
Median (range)	62 (18–100)	60 (23–95)	54 (25–90)
Missing	0	0	10
Age group, *n* (%)			
≤ 50 y	41,127 (21.8)	3307 (24.1)	160 (37.6)
> 50 y	147,782 (78.2)	10,434 (75.9)	266 (62.4)
pT stage, *n* (%*)			
pT0	3548 (1.9)	–	–
pT1	93,389 (49.5)	7998 (58.2)	303 (70.6)
pT2	56,463 (29.9)	5740 (41.8)	126 (29.4)
pT3/4	13,607 (7.2)	–	–
pTis Is	21,656 (11.5)	–	–
Missing	246	0	7
Hormone receptor status, *n* (%*)			
ER+/PR+	133,549 (71.3)	11,046 (80.5)	270 (68.9)
ER+/PR-	22,645 (12.1)	1408 (10.3)	54 (13.8)
ER−/PR+	2337 (1.2)	130 (0.9)	4 (1.0)
ER−/PR−	28,723 (15.3)	1147 (8.3)	64 (16.3)
Missing	1655	10	44
ER status, *n* (%*)			
Positive	156,248 (83.4)	12,455 (90.7)	332 (83.0)
Negative	31,072 (16.6)	1277 (9.3)	68 (17.0)
Missing	1589	9 (0.07)	36
PR status, *n* (%*)			
Positive	135,903 (72.6)	11,177 (81.4)	274 (69.9)
Negative	51,372 (27.4)	2555 (18.6)	118 (30.1)
Missing	1634	9	44
Lymph invasion, n(%*)			
Yes	36,769 (22.2)	5423 (42.7)	113 (35.2)
No	128,851 (77.8)	7277 (57.3)	208 (64.8)
Missing	23,289	1041	115
Modified Bloom–Richardson grade, *n* (%*)			
I	27,019 (14.6)	1841 (13.4)	81 (25.6)
II	104,665 (56.7)	8793 (64.1)	148 (46.8)
III	52,853 (28.6)	3089 (22.5)	87 (27.5)
Missing/unknown	4372	18	120
Tumour type, *n* (%*)			
Infiltrating ductal	135,106 (71.5)	11,961 (87.1)	356 (84.0)
Infiltrating lobular	22,776 (12.1)	1488 (10.8)	36 (8.5)
Other	8192 (4.3)	292 (2.13)	32 (7.5)
Carcinoma *in situ*	22,835 (12.1)	0	0
Missing	0	0	12

ER oestrogen receptor, *PR* progesterone receptor, *SLND* sentinel lymph node dissection

*For the calculation of the relative frequencies, the missing values were not included

detailed benchmarking system. Comparative quality assessment through benchmarking requires accurate recording of treatment data. Credibility of the tumour documentation is examined for validation purposes. Besides the statistical data-check procedures, in-house data monitoring by clinical research associates is performed twice a year in the

participating BCUs. Random verification of original data is performed. After addressing documentation discrepancies, the results are used to optimise documentation processes to enhance the validity of quality indicators.

Eligibility criteria

For this analysis, anonymised data from all patients with primary breast cancer treated between 1 January 2008 and 31 December 2015 were extracted from the WBC database. As the objective of the study was to analyse the impact of the ACOSOG Z0011 results on the axillary management of breast cancer, the cohort was selected according to the trial inclusion criteria: T1/2N0M0 breast cancer with 1 or 2 tumour-affected SLNs undergoing breast-conserving treatment followed by radiation of the affected breast and adjuvant systemic therapy according to guidelines.

In the ACOSOG Z0011 trial, staging was assessed clinically. In the benchmarking database, the clinical tumour stage was not part of the benchmarking report and therefore not documented consistently. Thus in the WBC database, clinical staging (cT) information was available for only 3986 (29.0%) of the patients meeting ACOSOG Z0011 eligibility criteria. However, clinical and pathological tumour (pT) stage showed very good concordance: 3162 (79.3%) patients had the same tumour stage by clinical and pathological assessment. pT stage was higher than cT stage (overestimation) in 14.6% and lower (underestimation) in 6.1%. Thus, it was considered reasonable to use the pT stage for our analysis as a surrogate for cT stage.

Statistical analysis

Baseline characteristics in the various populations were reported as medians with corresponding ranges or as absolute and relative frequencies, as appropriate. Group comparisons were performed by chi-squared tests for categorical variables and *t* tests for continuous variables. Annual percentages of cALND use were calculated and presented as a longitudinal time-trend analysis for the period from 2008 to 2015. We defined the period before publication of ACOSOG Z0011 (January 2008 to October 2010) as a reference period and determined the point of permanent deviation from the respective 95% confidence interval (CI) as the beginning of a significant reduction in cALND use. Multivariable logistic regression was used to determine factors associated with performing a cALND in patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected SLNs. A p value of <0.05 was considered statistically significant. All statistical analyses were performed with R software, version 3.4.1.

Results

Analysis population

The entire study cohort comprised 188,909 patients with primary, non-metastatic breast cancer treated between 2008 and 2015 in 179 BCUs in Germany; of these, 13,741 (7.3%) met the ACOSOG Z0011 inclusion criteria (Fig. 1). Table 1 shows baseline patient and tumour characteristics from the entire study cohort, together with the subgroup of patients meeting the ACOSOG Z0011 inclusion criteria

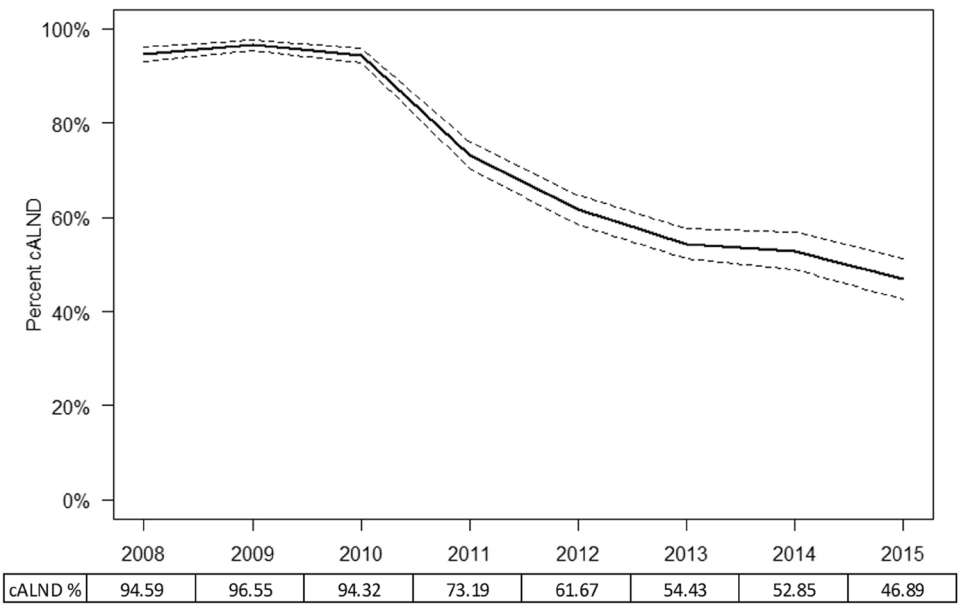


Fig. 2 Patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected sentinel lymph nodes receiving cALND between 2008 and 2015. The dashed line shows the 95% confidence interval. *cALND* completion axillary lymph node dissection

(Z0011-eligible patients) and, for comparison, patients from the original ACOSOG trial (SLND-only arm). Compared with the ACOSOG Z0011 trial cohort, the Z0011-eligible patients in our nationwide cohort were older and included a higher proportion with hormone receptor-positive tumours. Additionally, the Z0011-eligible patients included a smaller proportion of patients with grade III tumours and a larger proportion with a higher T stage. Overall, the tumour and patient characteristics of the SLND-only arm of the ACOSOG Z0011 trial seem similar to a typical breast cancer cohort meeting the inclusion criteria for the trial.

cALND time-trend analysis

In patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected SLNs, cALND was performed in 95.2% of patients presenting between January 2008 and November 2010. The time-trend analysis showed the first significant decrease of cALND in December 2010 to a rate of 90.2%. The proportion of patients undergoing cALND declined further over time from 73.2% in 2011 to 46.9% in 2015 ($p < 0.001$) (Fig. 2).

Table 2 compares baseline characteristics in Z0011-eligible patients undergoing cALND versus SLND alone. The proportion of patients with pT2 tumours was higher in the cALND cohort than the SLND-only cohort. Furthermore, lymphovascular invasion and grade III tumours were more frequent in the cALND than the SLND-only group. Other patient and tumour characteristics were equally distributed in the two cohorts.

Further analysis between the different BCUs showed considerable variation between institutions, as illustrated in Fig. 3. The rate of cALND for patients with 1 or 2 tumour-affected SLNs ranged from 80.1 to 3.5% in 2015.

Factors associated with cALND

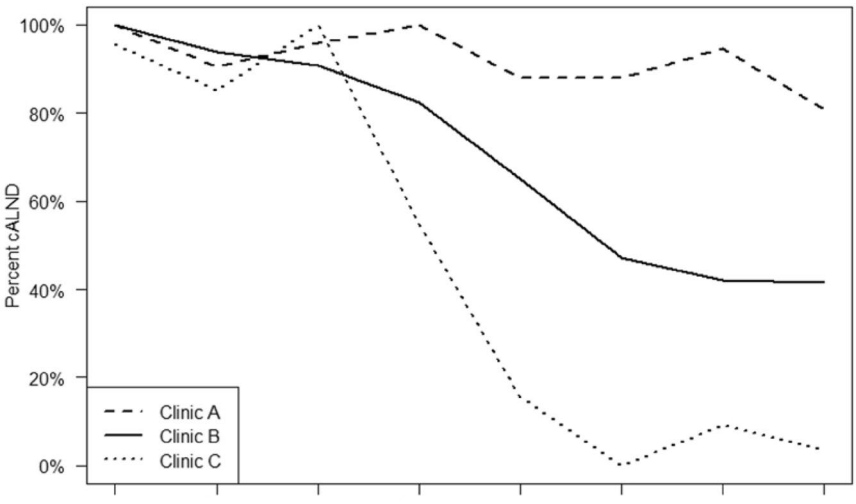
A multivariable logistic regression analysis was used to determine factors influencing the decision to perform cALND in routine clinical management of patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-involved SLNs. The following factors were associated with performing cALND: fewer SLNs removed, a higher number of tumour-affected SLNs, lower case volume per hospital, higher tumour grade and lymphovascular invasion (Table 3). No statistically significant influence of histology, hormone receptor status or HER2 status was detected in multivariable analysis. Figure 4 shows the rate of cALND according to the number of involved SLNs and the number of SLNs removed.

Table 2 Patients from the entire study cohort with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected lymph nodes meeting the ACOSOG Z0011 inclusion criteria and undergoing either cALND or SLND alone in routine clinical practice

Characteristic	cALND ($n = 9773$)	SLND alone ($n = 3968$)
Age, years		
Median (range)	60 (23–91)	61 (25–95)
Age group, *n* (%)		
≤ 50 years	2436 (24.9)	871 (22.0)
> 50 years	7337 (75.1)	3097 (78.0)
pT stage, *n* (%*)		
pT1	5544 (56.7)	2454 (61.8)
pT2	4228 (43.3)	1512 (38.2)
Missing	1 (< 0.1)	2 (0.1)
Hormone receptor status, *n* (%*)		
ER+/PR+	7792 (79.8)	3254 (82.0)
ER+/PR−	992 (10.2)	416 (10.5)
ER−/PR+	98 (1.0)	32 (0.8)
ER−/PR−	882 (9.0)	265 (6.5)
Missing	9	1
ER status, *n* (%*)		
Positive	8785 (90.0)	3670 (92.5)
Negative	980 (10.0)	297 (7.5)
Missing	8	1
PR status, *n* (%*)		
Positive	7891 (80.8)	3286 (82.8)
Negative	1874 (19.2)	681 (17.2)
Missing	8	1
Lymph invasion, *n* (%*)		
Yes	4055 (45.5)	1368 (36.1)
No	4858 (54.5)	2419 (63.9)
Missing	860	181
Modified Bloom–Richardson grade, *n* (%*)		
I	1200 (12.3)	641 (16.2)
II	6214 (63.6)	2579 (65.2)
III	2352 (24.1)	737 (18.6)
Missing/unknown	7	11
Tumour type, *n* (%)		
Infiltrating ductal	8533 (87.3)	3428 (86.4)
Infiltrating lobular	1028 (10.5)	460 (11.6)
Other	212 (2.2)	80 (2.0)

cALND completion axillary lymph node dissection, *ER* oestrogen receptor, *PR* progesterone receptor, *SLND* sentinel lymph node dissection

*For the calculation of the relative frequencies, the missing values were not included



	2008	2009	2010	2011	2012	2013	2014	2015
Clinic A cALND %	100	90.48	96	100	88	88	94.74	80.1
Clinic B cALND %	100	93.75	90.9	82.35	65	47.06	42.11	41.67
Clinic C cALND %	95.65	85.19	100	54.84	15.63	0	9.1	3.45

Fig. 3 Rate of cALND in patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected sentinel lymph nodes between 2008 and 2015: examples from three breast cancer clinics. *cALND* completion axillary lymph node dissection

Discussion

In this study, we aimed to assess the impact of ACOSOG Z0011 results on the treatment of patients with breast cancer to understand how new evidence from a prospective, randomised trial has been implemented into routine clinical practice. The ACOSOG Z0011 trial is often called a practice-changing trial. Our nationwide study cohort including more than 185,000 patients from 179 BCUs from all areas in Germany can be assumed to be representative of a typical breast cancer population. Every patient with primary breast cancer diagnosed and treated at one of the participating BCUs was included in this survey. Our results show that the ACOSOG Z0011 inclusion criteria (pT1/2cN0M0 tumours and 1 or 2 affected lymph nodes) applied to 7.3% of all patients with primary breast cancer. In our nationwide study population, almost 10,000 patients could potentially have been spared cALND and the associated arm morbidity without compromising oncological outcome.

The ACOSOG Z0011 trial has also altered our understanding of cALND primarily as a staging procedure rather than a procedure to improve locoregional control and overall survival [11, 12]. The exact number of tumour-involved lymph nodes determined by ALND is of prognostic value but is seldom needed to plan appropriate adjuvant therapy [3, 17]. The ACOSOG Z0011 trial demonstrated that removal of all affected lymph nodes, especially in cases with a low axillary tumour burden, does not lead to improved survival at 10-year follow-up.

A criticism of the ACOSOG Z0011 trial was a putative selection bias including only a low-risk patient population, leading to concerns about the applicability of the results to routine clinical practice. However, although the rate of locoregional failure is partly influenced by local surgical treatment, breast cancer subtype and adjuvant therapy also have an impact [4, 5, 17]. For example, triple-negative breast cancer generally has a higher rate of locoregional failure independent of the extent of surgery [18]. Furthermore, adjuvant therapy (endocrine and/or chemotherapy) lowers the risk of locoregional failure [1, 19, 20]. Z0011-eligible patients in our nationwide study cohort were older and more likely to have hormone receptor-positive tumours than patients in the SLND-only arm of the Z0011 trial, thus representing a similar or even slightly lower risk population than in ACOSOG Z0011. Several subsequent clinical trials have called into question the paradigm of compulsory cALND in the presence of positive SLNs. For example, the IBCSG 23-01 study by Galimberti et al. showed that cALND could be avoided in patients with micrometastasis in SLNs [21]. The AMAROS trial by Donker et al. showed similar locoregional control rates for patients with T1/2N0M0 tumours with a positive SLN who were treated with only radiotherapy of the axillary region as an alternative to cALND [22]. Other prospective trials and observational studies showed similar results [23–25].

The ACOSOG Z0011 trial was first presented in June 2010 and published in September 2010, initially including only locoregional recurrence results [10, 26]. Before this publication, 95.2% of patients in our cohort of ACOSOG Z0011-eligible patients underwent cALND. The time-trend analysis shows the first significant decrease in cALND in December 2010 to a rate of 90.2%. Thereafter, the rate of cALND decreased further from 73.2% in 2011 to 46.9% in 2015 ($p > 0.001$). This demonstrates rapid

Table 3 Multivariable analysis on factors potentially influencing cALND in patients with pT1/2cN0M0 breast cancer and 1 or 2 tumour-affected SLNs

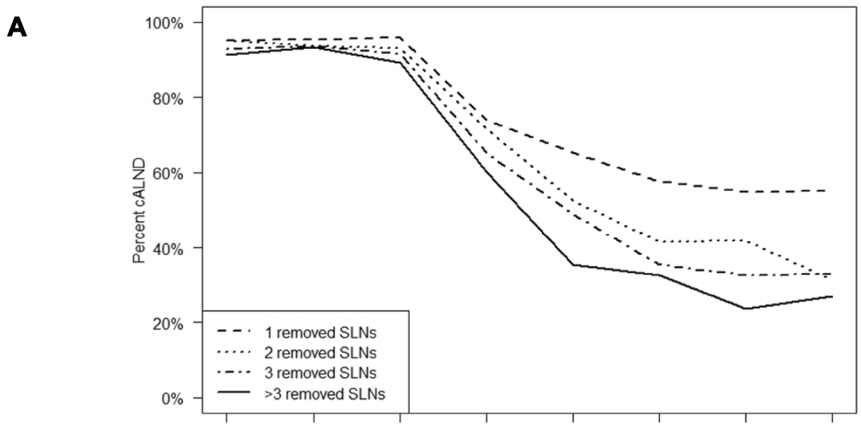
Variable	Odds ratio (95% CI)	*p* value
Type of hospital		
Academic teaching	Reference	
General	0.808 (0.728–0.896)	< 0.001
University	0.922 (0.745–1.142)	0.456
Hospital caseload per year		
< 150	Reference	
150–249	1.046 (0.922–1.186)	0.485
≥ 250	0.741 (0.654–0.841)	< 0.001
Age, y	0.986 (0.981–0.990)	
pT status		
1	Reference	
2	1.310 (1.181–1.454)	< 0.001
No. of SLNs removed		
1	Reference	
2	0.636 (0.556–0.724)	< 0.001
3	0.476 (0.411–0.556)	< 0.001
≥ 4	0.262 (0.231–0.313)	< 0.001
SLN metastasis		
1	Reference	
2	3.679 (3.199–4.238)	< 0.001
Modified Bloom–Richardson grade		
1	Reference	
2	1.201 (1.033–1.840)	0.017
3	1.527 (1.267–1.532)	< 0.001
Lymphovascular invasion		
No	Reference	
Yes	1.381 (1.245–1.135)	< 0.001
Histologic subtype		
Ductal	Reference	
Lobular	0.968 (0.825–1.135)	0.686
Other	1.106 (0.781–1.571)	0.572
HER2 status		
Negative	Reference	
positive	1.147 (0.959–1.375)	0.135
Surgical procedure		
BCS with re-excision	Reference	
BCS only	0.652 (0.564–0.752)	< 0.001
ECOG performance status		
0	Reference	
1	0.771 (0.650–0.914)	0.003
2	0.824 (0.487–1.388)	0.465
Hormone receptor status		
Negative	Reference	
Positive	0.906 (0.736–1.112)	0.356

BCS breast-conserving surgery, *cALND* completion axillary lymph node dissection, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *SLN* sentinel lymph node

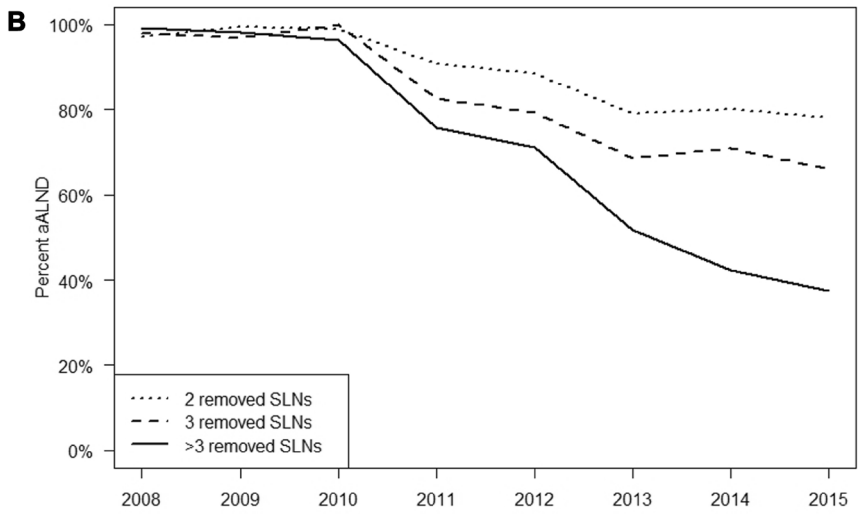
implementation of new evidence from a practice-changing trial into routine clinical practice. Of note, implementation of the ACOSOG Z0011 results differed considerably between the BCUs, with cALND rates ranging from 3.5 to 80.1% in 2015. The recommendation to omit ALND was not included in the S3-German Breast Cancer Guideline until December 2017 [27]. Before that date, omission of cALND for patients with tumour-involved SLNs was considered only as an option. To omit a cALND in patients meeting the ACOSOG Z011 eligible criteria, a comprehensive patient information was required. Therefore, the decision whether to invest this additional effort with the aim of reducing patients' morbidity based on new evidence from a single clinical trial was left to each institution's discretion.

We also analysed factors influencing the decision to perform cALND in routine clinical practice despite evidence from prospective clinical trials. Notably, in multivariable analysis, only grading of 3 but neither hormone receptor nor HER2 status was statistically significantly associated with cALND. This suggests that tumour biology had only little impact on clinical decision-making despite the significant influence of hormone receptor status on locoregional recurrence in univariable analysis of the ACOSOG Z0011 trial [11]. The most important factor influencing treatment decisions in our dataset was the nodal tumour burden, determined by the number of involved SLNs and the number of removed SLNs. In routine clinical practice, physicians were more comfortable with omitting cALND in patients with one rather than two tumour-affected SLNs and more removed SLNs, suggesting a higher likelihood of no further non-sentinel metastasis. Of note, the number of affected SLNs was not predictive of locoregional recurrence in the ACOSOG Z0011 study [11].

Although the present study reported a large dataset with cases from all over Germany, some limitations have to be considered. First, we cannot exclude a possible selection bias because not all breast cancer units participated in the voluntary benchmarking. As there is no nationwide clinical cancer registry, we cannot guarantee the representativeness of all breast cancer patients in Germany. A second limitation is the infrequent reporting of some variables, which are not part of the benchmarking report and therefore not documented consistently. In particular, the documentation of the cT stage is not part of the systematic validation process and is missing in 71% of the cases. This led to the use of the pT stage rather than cT stage to determine whether patients met the ACOSOG Z0011 inclusion criteria. However, this approach was considered reasonable because for the majority of patients in our cohort with evaluable data, the pT and cT stage were concordant.



	2008	2009	2010	2011	2012	2013	2014	2015
cALND of patients with 1 removend SLN %	95.24	95.27	95.88	74.01	65.23	57.59	54.83	55.04
cALND of patients with 2 removend SLNs %	95.15	93.58	93.08	71.53	52.6	41.56	41.86	31.41
cALND of patients with 3 removend SLNs %	92.71	93.7	91.57	65.18	48.98	35.54	32.61	32.87
cALND of patients with >3 removend SLNs %	91.27	93.43	89.32	60.07	35.36	32.51	23.79	26.95



	2008	2009	2010	2011	2012	2013	2014	2015
cALND of patients with 2 removend SLNs %	97.09	99.35	98.83	90.91	88.51	79.1	80.17	78.02
cALND of patients with 3 removend SLNs %	97.83	96.84	100	82.64	79.35	68.54	70.83	66.13
cALND of patients with >3 removend SLNs %	99.11	98.21	96.4	75.86	71.05	51.69	42.31	37.35

Fig. 4 Omission of cALND between 2008 and 2015 in patients with pT1/2cN0M0 breast cancer and **a** one tumour-involved lymph node; **b** two tumour-involved lymph nodes. cALND, completion axillary lymph node dissection; SLN, sentinel lymph node

Conclusion

The ACOSOG Z0011 inclusion criteria applied to only 7.3% of patients with primary breast cancer in our national population-based study. There was rapid implementation of the ACOSOG Z0011 results into routine clinical practice in Germany, although there were considerable differences in uptake rates between centres. Of note, in routine clinical management, cALND was still performed in patients with a higher axillary tumour burden despite meeting the eligibility criteria for ACSOG Z0011. Nevertheless, over time an increasing number of patients benefited from the reduced morbidity associated with SLND compared with cALND.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interests (e.g. employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations or grants or other funding with regard to this study) for any of the authors.

Ethical approval The study was approved by the ethics committee of the University of Heidelberg and was conducted in accordance with the Declaration of Helsinki. The study was deemed to be without risk, including only anonymised analysis of routinely collected data; consequently, the ethics committee of the University of Heidelberg did not request approval for consent for this designated analysis.

Informed consent Informed consent was obtained from all individual participants within the data acquisition of the benchmarking process to analyse the anonymised data.

References

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A et al (2015) Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373(4):30716
2. Moebus V, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C et al (2010) Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. J Clin Oncol 28(17):2874–2880
3. Network NCC. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Breast Cancer 2016. 1(2016)
4. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al (2000) Molecular portraits of human breast tumours. Nature 406(6797):747–752
5. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S et al (2016) 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375(8):717–729
6. Gluz O, Nitz UA, Christgen M, Kates RE, Shak S, Clemens M et al (2016) West German Study Group phase III PlanB trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol 34(20):2341–2349
7. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V et al (2003) A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349(6):546–553
8. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP et al (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 11(10):927–933
9. DiSipio T, Rye S, Newman B, Hayes S (2013) Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 14(6):500–515
10. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM et al (2010) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 252(3):426–432; discussion 32–3
11. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P et al (2016) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. Ann Surg 264(3):413–420
12. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR et al (2017) 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. JAMA 318(10):918–926
13. Guth U, Myrick ME, Viehl CT, Schmid SM, Obermann EC, Weber WP (2012) The post ACOSOG Z0011 era: does our new understanding of breast cancer really change clinical practice? Eur J Surg Oncol 38(8):645–650
14. Shah-Khan M, Boughey JC (2012) Evolution of axillary nodal staging in breast cancer: clinical implications of the ACOSOG Z0011 trial. Cancer Control 19(4):267–276
15. Morrow M, Giuliano AE (2011) To cut is to cure: can we really apply Z11 in practice? Ann Surg Oncol 18(9):2413–2415
16. WBC, Westdeutsches Brust-Centrum GmbH. Benchmarking WBC–2014, Jahresbericht, Kennzahlen. 2015
17. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B et al (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24(9):2206–2223
18. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S (2011) Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. J Clin Oncol 29(21):2852–2858
19. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 88(21):1529–1542
20. Fisher B, Dignam J, Mamounas EP, Costantino JP, Wickerham DL, Redmond C et al (1996) Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. J Clin Oncol 14(7):1982–1992
21. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P et al (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23 – 01): a phase 3 randomised controlled trial. Lancet Oncol 14(4):297–305
22. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE et al (2014) 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 15(12):1303–1310
23. Savolt A, Peley G, Polgar C, Udvarhelyi N, Rubovszky G, Kovacs E et al (2017) 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 43(4):672–679
24. Sola M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R et al (2013) Complete axillary lymph node dissection versus

clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol 20(1):120–127
25. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY et al (2009) Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol 27(18):2946–2953
26. Giuliano AE, McCall LM, Beitsch PD, Whitworth PW, Morrow M, Blumencranz PW et al (2010) ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node. J Clin Oncol 28(18_suppl):CRA506–CRA506RA
27. Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms 12/2017. http://www.awmf.org/uploads/tx_szleitlinien/032-045OLl_S3_Mammakarzinom_2017-12.pdf