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CLINICAL TRIAL

Non-sentinel axillary tumor burden applying the ACOSOG Z0011 eligibility criteria to a large routine cohort

Fabian Riedel[1] · Jörg Heil[1] · Manuel Feißt[2] · Mahdi Rezai[3] · Mareike Moderow[4] · Christof Sohn[1] · Florian Schütz[1] · Michael Golatta[1] · André Hennigs[1]

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Abstract

Purpose In the ACOSOG Z0011 trial, patients with primary breast cancer (BC) and 1–2 tumor-involved sentinel lymph nodes (SLN) undergoing breast-conserving surgery gained no benefit from completing axillary lymph node dissection (cALND). This paper reports cALND rates performed in clinical routine on patients who would meet the Z0011 criteria. Further, patients still received cALND were analyzed concerning the number of non-sentinel metastases (NSM) to estimate occult axillary tumor burden.

Methods Data were retrospectively analyzed from patients treated in 179 German breast centers between 2008 and 2015. Time-trend rates were determined for cALND regarding the presence of axillary macrometastases or micrometastases. Descriptive statistics were used to report the number of NSM depending on the number of SLN removed, tumor-involved SLN, tumor stage (pT1–2), and immunohistochemical subtype. Factors associated with NSM were identified using multivariable logistic regression.

Results Altogether, data for 188,909 patients were available, of whom 13,741 (7.3%) were identified eligible for the Z0011 criteria. For these patients, the cALND rate for macrometastases declined from 96.4% in 2008 to 49.7% in 2015, for micrometastases from 86.7 to 5.9%. In total 9773 patients still received cALND, 33.4% of whom had NSM. The NSM rates were: 38.8% for pN(1/1sn), 28.6% for pN(1/2sn), and 50.9% for pN(2/2sn). Hormone receptor (HR) positive/HER2+ showed the highest NSM rate (41.6%), HR−/HER2− the lowest rate (29.4%).

Conclusions The rate of cALND for ACOSOG Z0011 eligible patients has decreased substantially in routine care in our nationwide cohort. Our data reveal a relatively high prevalence of additional axillary NSM tumor burden.

Keywords Breast cancer · Axillary lymph node dissection · Sentinel lymph node dissection · Non-sentinel metastasis · ACOSOG Z0011

Introduction

Surgical management of early breast cancer (BC) involves margin-free removal of the tumor from the breast and evaluation of axillary lymph nodes. Lymph node status has prognostic value for estimating the likelihood of cancer recurrence following adjuvant therapy [1–3]. Lymph node sampling as a diagnostic assessment can be performed either by the selective removal of sentinel lymph node(s) (SLN) or by a systematic axillary lymph node dissection (ALND) along anatomic compartments. During the past decade, the focus of risk assessment for patients' individual treatment recommendations has shifted toward tumor biology [4, 5]. Consequently, the information value gained from lymph node status has decreased [6].

✉ André Hennigs
andre.hennigs@med.uni-heidelberg.de

1 Department of Gynecology and Obstetrics, Heidelberg University Hospital, Im Neuenheimer Feld 440, 69120 Heidelberg, Germany

2 Institute of Medical Biometry and Informatics, Heidelberg University Hospital, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

3 European Breast Center, Luisen Hospital, Luise-Rainer-Str. 6-10, 40235 Düsseldorf, Germany

4 West German Breast Center Ltd, Bahlenstr. 180, 40589 Düsseldorf, Germany

For several decades, ALND was the standard procedure for assessing pathological nodal status. Since the beginning of this century, the degree of radical surgery to the axilla has been reduced through implementation of axillary staging via SLN dissection (SLND). SLND has become standard of care for patients with clinically node-negative (cN0) BC [7, 8]. For patients with affected SLN(s), a subsequent completing ALND (cALND) was previously recommended. Paresthesia, pain, and motor neuropathy are more frequent in patients undergoing ALND than SLND. Lymphoedema and restriction of movement causes a substantial decrease in quality of life; it occurs in around 20% of patients undergoing ALND versus < 5% after SLND [9].

In 2010, the ground-breaking results from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial called into question the concept of cALND [10]. In a multicenter, randomized trial, the impact of omitting cALND in clinically node-negative early BC patients with tumors size < 5 cm and 1 or 2 positive SLN(s) was assessed. These patients were treated with breast-conserving therapy (BCT) followed by radiation and adjuvant systemic therapy according to recent guidelines. In the ACOSOG Z0011 trial, SLND alone resulted in loco-regional control, disease-free survival, and overall survival rates equivalent to the results seen after cALND, at a 10-year follow-up [11, 12]. Remarkably, the cALND group contained 97 out of 355 patients (27.3%) with additional non-sentinel metastasis (NSM) in lymph nodes removed by cALND. This implied that unremoved tumor-affected axillary lymph nodes are not prognostically relevant for many patients when receiving guideline-adherent adjuvant treatment. Thus, the identification of occult metastases does not appear to result in improved oncological outcome. That led to a paradigm shift in the understanding of BC [13].

However, the ACOSOG Z0011 trial has been criticized for its low statistical power, because of slow recruitment and premature termination of the study. In addition, mainly low-risk patients were included, which may have influenced survival outcomes. Hence, the applicability of these results to a typical routine cohort and the general implementation of the trial results into clinical practice have been questioned [14–16]. Nevertheless, the concept of omission of cALND in subgroups has been analyzed by additional randomized controlled trials (RCTs): first for axillary micrometastases in the IBCSG 23-01 trial [17, 18], but also later in specific radiotherapy settings such as the AMAROS [19] or the OTOASOR trial [20]. These trials confirmed the results of ACOSOG Z0011, showing no oncological outcome benefit for cALND. Also, these prospective trials revealed a relevant rate of NSM which can be left behind without any disadvantage outcomes. The rate of NSM in the cALND group was 32.7% (220/672) in the AMAROS trial and 38.5% (94/224) in OTOASOR trial (both these rates being even higher than in ACOSOG Z0011). The results from these RCTs have been implemented into the clinical routine [21] and found their way into guidelines [22, 23].

Aim of this study is to evaluate the presence of NSM in clinical routine as an estimator for occult axillary tumor burden. In this study, we present recent clinical data from 179 breast care unites (BCU) in Germany. We extracted all patients that would have fulfilled the eligibility criteria of ACOSOG Z0011 but who nonetheless underwent cALND. Annual cALND rates were evaluated in a time-trend analysis separately for patients with micrometastases or with macrometastases in the SLN(s). The data present the axillary tumor burden of the patients still receiving cALND, according to the number of NSM depending on the number of SLN removed, tumor-involved SLN, tumor stage (pT1–2), and immunohistochemical subtype. Additionally, factors associated with NSM were identified using multivariable logistic regression analyses.

Methods

Database

Data were obtained from a voluntary benchmarking project in Germany. The participating units contributed clinical, surgical, and pathological data from patients with primary BC to the West German Breast Center Ltd (WBC), Düsseldorf, Germany. The WBC is an institution that provides quality control through an annual benchmarking report [24]. 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 post hoc analysis of registry data.

The validity and quality of the data registered in the WBC tumor documentation system are assessed through a detailed benchmarking system. Comparative quality assessment through benchmarking requires accurate recording of treatment data. The credibility of the tumor documentation is examined for validation purposes. Besides the statistical data-check procedures, in-house data monitoring by clinical research associates is performed twice per year in the participating BCUs.

Eligibility criteria

For this analysis, anonymized data from all patients with primary BC treated between 1 January 2008 and 31 December 2015 were extracted from the WBC database. A cohort of patients who would have been eligible for the ACOSOG Z0011 trial was selected for this analysis according to the trial inclusion criteria: cT1/2cN0cM0 BC with 1–2 tumor-affected SLN(s) undergoing BCT followed by radiation of

the affected breast and adjuvant systemic therapy according to guidelines. Unlike in the original ACOSOG Z0011 trial, all analyses for this cohort were conducted with the pathological tumor stage (pT) due to the inconsistent documentation of the clinical tumor (cT) stage in our database; this substitution seems reasonable due to the high concordance between the two types of staging [25].

The immunohistochemical expression of the hormone receptors (HR), i.e., estrogen (ER) and progesterone (PR), as well as the HER2 receptor, has been used to define four invasive BC subtypes [26]: (1) HR+/HER2− type (i.e., ER+ or PR+ with HER2−); (2) HR+/HER2+ type (i.e., ER+ or PR+ with HER2+); (3) HR−/HER2+ type (aka. "HER2-type"; i.e., ER− and PR− with HER2+); and (4) HR−/HER2− type (aka. "triple negative breast cancer" (TNBC); i.e., ER− and PR− with HER2−) [27].

Statistical analysis

Patient and tumor characteristics were reported as absolute and relative frequencies. Annual percentages of cALND were calculated and presented as a longitudinal time-trend analysis for the period from 2008 to 2015 for both micrometastases and macrometastases in the SLND. Multivariable logistic regression was used to determine factors associated with the existence of additional NSM in patients with pT1/2cN0cM0 BC and 1–2 tumor-affected SLN(s). Due to the large sample size of this study p values of < 0.01 were considered as statistically significant in a descriptive sense. All statistical analyses were performed with R software, version 3.4.1.

Results

Study sample

The entire study cohort comprised $n = 188{,}909$ patients with primary, non-metastatic BC treated between 2008 and 2015 in 179 BCUs in Germany, of whom 13,741 (7.3%) were identified with pT1/2cN0cM0 BC and 1–2 tumor-affected SLN(s) (Z0011-eligible cohort) (Table 1). From this Z0011-eligible cohort, only SLND was performed in $n = 3968$ (28.9%) patients, whereas $n = 9773$ (71.1%) still received cALND after histological confirmation of metastases in 1–2 SLN(s). The cALND cohort did not differ substantially from the Z0011-eligible cohort: most cases were HR+ (ER: 89.9%, PR: 80.8% vs. ER: 90.7%, PR: 81.4%), HER2− (89.2% vs. 90.1%) and had an intermediate tumor grading (63.6% vs. 64.1%). Tumor stage distribution was also balanced with 56.7% pT1 and 43.3% pT2 in the cALND cohort and 58.2% pT1 and 41.8% pT2 in the Z0011-eligible cohort. Micrometastasis were less present in the cALND cohort (10.3%) than in the Z0011-eligible cohort (18.0%). Table 1 presents detailed patient and tumor characteristics.

cALND time-trend analyses for macrometastases and micrometastases

The cALND rate was evaluated with a time-trend analysis in the Z0011-eligible cohort, i.e., in patients with pT1/2cN0cM0 BC and 1–2 tumor-affected SLN(s) (Fig. 1a, b). The annual cALND rate for the subgroup with micrometastases declined for pT1 patients from 86.7% in 2008 to 7.3% in 2015 and for pT2 patients from 86.7% in 2008 to 2.8% in 2015 (Fig. 1a). This reduction was less pronounced for the macrometastases subgroup: here the cALND rate declined for pT1 patients from 95.4% in 2008 to 46.8% in 2015 and for pT2 patients from 97.8% in 2008 to 52.7% in 2015 (Fig. 1b).

Non-sentinel metastases in the cALND cohort

In the cALND cohort of our patients eligible for ACOSOG Z0011, 3264 out of 9773 (33.4%) cases were found to have additional NSM in the axillary lymph node dissection specimens (Table 2; Fig. 2a). The number of NSMs strongly depends on the combination of the number of involved SLNs and the number of removed SLNs (i.e., 1–2 affected out of 1–2 removed SLN; pN(1–2/1–2sn). Independently from the pT stage, further axillary lymph node involvement was seen for pN(1/1sn) in 38.8% of cases, for pN(1/2sn) in 28.6% of cases, and for pN(2/2sn) in 50.9% of cases. In most cases, only one additional NSM was affected: in 16.1% of the pN(1/1sn) cases and in 14.8% of the pN(1/2sn) cases. Nonetheless, five or more NSMs were affected in 7.4% of pN(1/1sn) cases and in 14.0% of pN(2/2sn). There was a higher rate of NSM for pT2 (38.7%) than for pT1 (29.3%). Concerning subtype, it becomes evident that the HR+/HER2− with 33.2% and HR−/HER− (i.e., TNBC) with 29.6% have the lowest rate of further lymph node affection, whereas the HR−/HER+ type was found to have the highest rate of NSM with 41.6% (Table 3, Fig. 2b). Patients with 3 or more removed SLNs of which 1–2 were affected [i.e., pN(1–2/≥ 3sn)] had the lowest rates of further NSM (25.9%), independent from pT stage or subtype (Tables 2, 3).

Factors associated with additional non-sentinel metastases

In multivariable analyses, the greatest influence on the presence of additional NSMs was the size category of the SLN metastasis, i.e., micrometastasis versus macrometastases (OR 6.1, $p < 0.001$). Further significant variables were lobular histology (ductal vs. lobular; OR 1.5, $p < 0.001$), intermediate (OR 1.2, $p < 0.023$) and high (OR 1.3, $p < 0.004$) grading, lymphovascular invasion (OR 1.6,

Table 1 Characteristics of the entire study cohort, of patients meeting the ACOSOG Z0011 inclusion criteria (Z0011-eligible cohort), and of the subgroup of patients with a completing axillary lymph node dissection (cALND cohort)

Characteristics	Entire study cohort ($n=188,909$)	Z0011-eligible cohort ($n=13,741$)	cALND cohort ($n=9773$)
Age, years			
Median (range)	62 (18–100)	60 (23–95)	60 (23–91)
Missing	0	0	0
Age group, *n* (%)			
≤ 50 years	41,127 (21.8)	3307 (24.1)	2436 (24.9)
> 50 years	147,782 (78.2)	10,434 (75.9)	7337 (75.1)
ECOG score, *n* (%)			
0	141,063 (83.8)	11,093 (89.4)	7904 (90.3)
1	22,275 (13.2)	1219 (9.8)	792 (9.0)
2	4261 (2.5)	96 (0.8)	56 (0.6)
≥ 3	697 (0.4)	0	0
Missing	20,633	1333	1021
pT stage, *n* (%*)			
pT0	3548 (1.9)	–	–
pT1	93,389 (49.5)	7998 (58.2)	5544 (56.7)
pT2	56,463 (29.9)	5740 (41.8)	4228 (43.3)
pT3/4	13,607 (7.2)	–	–
is	21,656 (11.5)	–	–
Missing	246	0	0
pN stage, *n* (%*)			
0	119,432 (68.3)	115 (0.8)	–
1	30,837 (17.6)	9824 (71.5)	8431 (86.6)
1mi	4937 (2.8)	2470 (18.0)	1000 (10.3)
2	11,918 (6.8)	1037 (7.5)	1024 (10.5)
3	7625 (4.4)	288 (2.1)	286 (2.9)
Missing	14 160	7	32
ER status, *n* (%*)			
Positive	156,248 (83.4)	12,455 (90.7)	8785 (89.9)
Negative	31,072 (16.6)	1277 (9.3)	980 (10.1)
Missing	1589	9	8
PR status, *n* (%*)			
Positive	135,903 (72.6)	11,177 (81.4)	7891 (80.8)
Negative	51,372 (27.4)	2555 (18.6)	1874 (19.2)
Missing	1634	9	8
HER2 status *n* (%*)			
Positive	22,573 (13.1)	1346 (9.9)	1035 (10.8)
Negative	149,374 (86.9)	12,199 (90.1)	8586 (89.2)
Missing	16,962	196	152
Lymphovascular invasion, *n* (%*)			
Yes	36,769 (22.2)	5423 (42.7)	4055 (45.5)
No	128,851 (77.8)	7277 (57.3)	4858 (54.5)
Missing	23,289	1041	860
Grading, *n* (%*)			
G1 (low)	27,019 (14.6)	1841 (13.4)	1200 (12.3)
G2 (intermediate)	104,665 (56.7)	8793 (64.1)	6214 (63.6)
G3 (high)	52,853 (28.6)	3089 (22.5)	2352 (24.1)
Missing	4372	18	7
Histological tumor type, *n* (%*)			
Infiltrating ductal	135,106 (71.5)	11,961 (87.1)	8533 (87.3)
Infiltrating lobular	22,776 (12.1)	1488 (10.8)	1028 (10.5)

Table 1 (continued)

Characteristics	Entire study cohort ($n=188,909$)	Z0011-eligible cohort ($n=13,741$)	cALND cohort ($n=9773$)
Other	8192 (4.3)	292 (2.1)	212 (2.2)
Carcinoma in situ	22,835 (12.1)	0	–
Missing	0	0	0

pT tumor stage, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen, *PR* progesterone

*The missing values were not included in the calculation of the relative frequencies

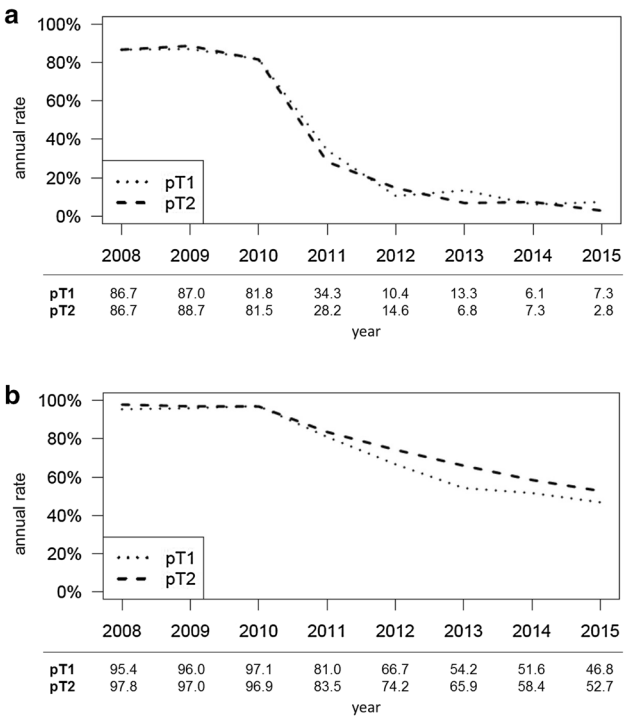

Fig. 1 **a** Rate of cALND (2008–2015) in patients with micrometastasis in 1–2 sentinel lymph nodes and pT1/2 cN0 invasive breast cancer treated with breast-conserving therapy, differentiated into pT1–2 [in %]. **b** Rate of cALND (2008–2015) in patients with macrometastasis in 1–2 sentinel lymph nodes and pT1/2 cN0 invasive breast cancer treated with breast-conserving therapy, differentiated into pT1–2 [in %]

$p<0.001$), and higher pT stage (pT1 vs. pT2; OR 1.3, $p<0.001$). Immunohistochemical parameters such as positivity for HR or HER2 receptor as well as age at diagnosis were not significant associated with NSM (Table 4).

Discussion

In this study, we showed the decreasing rates of cALND in the routine treatment of patients with pT1/2cN0cM0 BC with 1–2 tumor-involved SLN undergoing BCT. The implementation of omitting cALND (as recommended by several RCTs) leads to a substantial number of patients with NSM left behind in the axilla whose oncological outcomes are nonetheless no worse.

Time trend rate of cALND

We analyzed the rates of cALND as an example of the rapid adoption of new findings from RCTs into routine management. Since the presentation of the ACOSOG Z0011 trial results in 2010 at the Annual Meeting of the American Society of Clinical Oncology (ASCO), a rising number of patients in our cohort have been treated accordingly to those results. The rate of cALND for macrometastases has decreased from 96.4% in 2008 to 49.7% in 2015. A study by Dengel et al. implies that a subsequent cALND could be avoided according to the ACOSOG Z0011 inclusion criteria for approximately 85% of patients with clinically node-negative disease who underwent BCT in routine clinical practice and were found to have positive SLNs [28]. The remaining patients with either gross extracapsular extension or ≥ 3 positive SLNs are at high risk for extensive residual axillary disease, so a cALND is still warranted for them. An analysis using the National Cancer Data Base (NCDB) with $n=74,309$ patients eligible for ACOSOG Z0011 criteria showed a decline of the cALND rate from around 77% in 2009 to 44% in 2011 [29]. A decrease in cALND has also been reported from European countries, for example in a Dutch registry (cALND rate: 75% in 2011 to 17% in 2015) [30]. Discrepancies within European countries concerning implementation at the beginning of the ACOSOG Z0011 era have been described [31].

In our cohort, cALND for micrometastases in the SLN decreased earlier and much more sharply than for macrometastases, as it was studied in the IBCSG 23-01 trial [17, 18]. It had previously been assumed that micrometastases or isolated tumor cells in axillary lymph nodes do not have a relevant impact on the overall outcome [32], so the omission of cALND for micrometastases of the SLN(s) was implemented in the guidelines already in 2011 [33].

Table 2 Non-sentinel metastases after completing axillary lymph node dissection (in ACOSOG Z0011-eligible patients) in total and regarding initial results from sentinel lymph node dissection, differentiated for pT stage [in %]

Number of NSM after cALND—in total and regarding initial results from SLND in % ($n=9773$)										
pT stage	Total		pN(1/1sn)		pN (1/2sn)		pN(2/2sn)		pN(1–2/≥3sn)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
pT1 ($n=5544$)										
0	3919	70.7	1183	66.6	891	74.6	284	51.3	1561	77.3
1	755	13.6	273	15.4	165	13.8	60	10.8	257	12.7
2	350	6.3	113	6.4	62	5.2	69	12.5	106	5.3
3	147	2.7	64	3.6	23	1.9	25	4.5	35	1.7
4	118	2.1	33	1.9	23	1.9	36	6.5	26	1.3
5	49	0.9	18	1.0	9	0.8	11	2.0	11	0.5
>5	206	3.7	92	5.1	22	1.8	69	12.5	23	1.1
Any	1625	29.3	593	33.4	304	25.4	270	48.7	458	22.7
pT2 ($n=4228$)										
0	2590	61.3	736	54.1	575	66.9	245	46.8	1034	69.6
1	669	15.8	232	17.0	140	16.3	73	14.0	224	15.1
2	308	7.3	101	7.4	65	7.6	45	8.6	97	6.5
3	168	4.0	68	5.0	23	2.7	32	6.1	45	3.0
4	110	2.6	42	3.1	14	1.6	25	4.8	29	2.0
5	91	2.2	43	3.2	11	1.3	21	4.0	16	1.1
>5	292	6.9	139	10.3	31	3.6	82	15.7	40	2.7
Any	1719	38.7	625	45.9	284	33.1	278	53.2	451	30.4
pT1–2 ($n=9773$)										
0	6509	66.6	1919	61.2	1466	71.4	529	49.1	2595	74.1
1	1425	14.6	506	16.1	305	14.8	133	12.3	481	13.7
2	658	6.7	214	6.8	127	6.2	114	10.6	203	5.8
3	315	3.2	132	4.2	46	2.2	57	5.3	80	2.3
4	228	2.3	75	2.4	37	1.8	61	5.7	55	1.6
5	140	1.4	61	1.9	20	1.0	32	3.0	27	0.8
>5	498	5.1	231	7.4	53	2.6	151	14.0	63	1.3
Any	3264	33.4	1219	38.8	588	28.6	548	50.9	909	25.9

NSM non-sentinel metastases, *cALND* completing axillary lymph node dissection, *SLND* sentinel lymph node dissection, *pT* tumor stage

Non-sentinel metastases in cALND

In the cALND arm of the ACOSOG Z0011 trial, 27.3% of the patients were found to have additional involved NSMs and 13.7% had even ≥ 4 NSMs [10]. In our study, we found a slightly higher rate of NSM in the cALND cohort with 33.4% but a lower rate of 9.0% for ≥ 4 NSM. Higher rates of NSM in the control groups with cALND have been reported in other randomized trials that compared the omission of cALND with radiotherapeutic interventions. The NSM rate in the AMAROS trial was 32.7% (and 8.3% for ≥ 4 NSM) [19], and it was even 38.5% in OTOASOR [20]. Our overall NSM rate of 33.4% is quite average compared to routine clinical data reported from American cohorts, which ranged between 27% [34] and 45% [35].

When interpreting NSM rates in this study, it must be kept in mind that a relevant proportion (28.6%, $n=3968$) of the ACOSOG Z0011 eligible cohort of $n=13{,}741$ patients has been treated by SLND only. In routine decision making, these were patients with a higher number of removed SLNs and micrometastasis, as previously shown [25]; thus, they were less likely to have additional lymph nodes affected by tumor. This possible selection bias might have led to an overestimation of NSM rates in our cohort.

Non-sentinel metastases in high-risk subtypes

Varying rates of NSM have been reported for different subtypes. Multiple studies have demonstrated that TNBC patients are significantly less likely than those with other tumor subtypes to have metastases in four or more lymph nodes [36]. That is confirmed by our data (HR−/HER2− ≥ 4 NSM: 6.4%; Fig. 2b), so more aggressive local therapy seems unjustified [37]. Studies suggest that HER2+ patients are more like to have a heavier nodal burden [38]. A recent study on 2967 patients undergoing

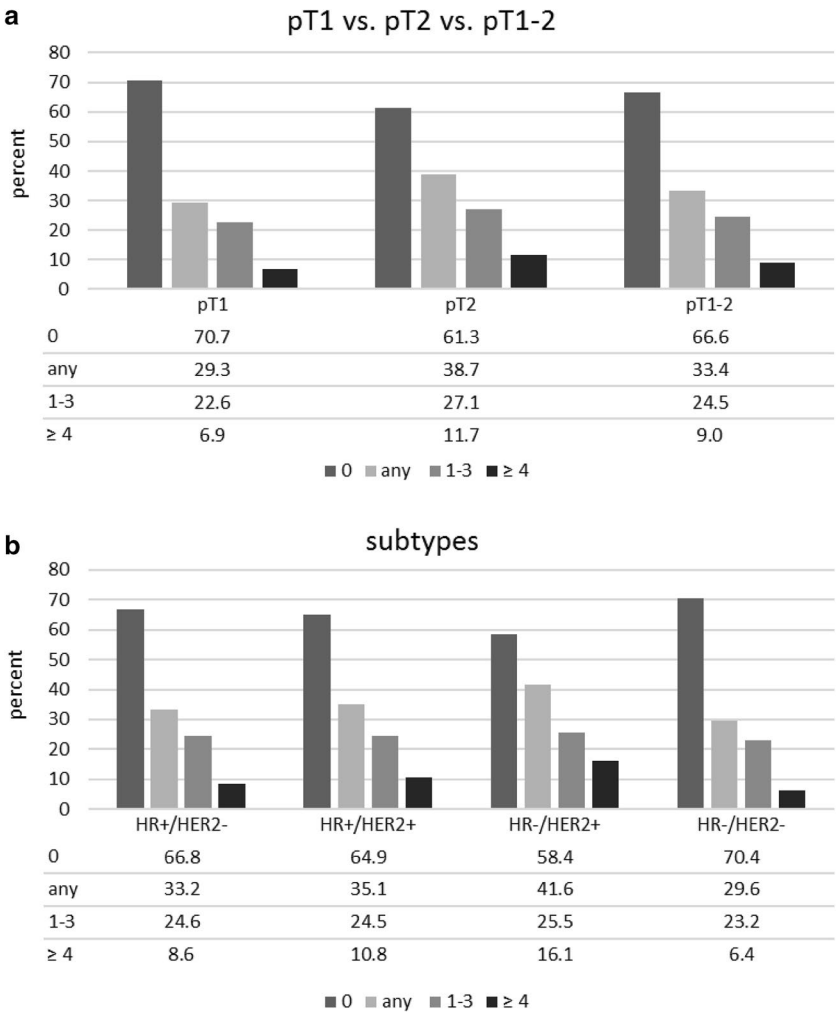

Fig. 2 **a** Non-sentinel metastases after completing axillary lymph node dissection in ACOSOG Z0011-eligible patients in four groups (none, any, 1–3, and ≥ 4 NSM), differentiated for pT stage [in %]. **b** Non-sentinel metastases after completing axillary lymph node dissection in ACOSOG Z0011-eligible patients in four groups (none, any, 1–3, and ≥ 4 NSM), differentiated for breast cancer subtype [in %]

any breast surgery with either SLNB or ALND found that 19.4% of HER2+ patients had NSMs in ≥ 4 lymph nodes, whereas TNBC cases had the lowest rate (9.4%) [39]. Those results are consistent with our study, which found a rate of 16.1% for ≥ 4 positive NSMs for HR−/HER2+ cases (Fig. 2b).

In this context, the preferred management for systemic therapy must be considered: Nowadays, most of these patients with HER2+ or TNBC will receive primary systematic therapy (PST), with rates of complete pathological remission in the breast and axilla of up to 70% [40, 41]. The ACOSOG Z0011 criteria cannot be applied to patients undergoing PST, as they were excluded from the trial.

Impact on adjuvant treatment

Although tumor biology is now a crucial factor in clinical decision making for adjuvant chemotherapy, lymph node status is an important prognostic factor and still has an influence on therapy stratification [2]. The impact of the information from cALND on adjuvant chemotherapy is controversial. One study has shown that cALND does not lead to major changes of the adjuvant systemic therapy administration [42], while another one reported a significantly higher probability of chemotherapy for these patients compared with SLND only, especially for those patients with a higher axillary lymph node tumor burden [43]. In a German single-center cohort, additional information gained from cALND led to a change to a more aggressive treatment in 17% of the patients, i.e., either chemotherapy versus none (4.5%) or the recommendation of a dose-dense regimen [44]. These patients might have improved survival from a dose-dense, dose-intense treatment [2]. This illustration of the impact of the additional information from cALND does not contradict the integration of the ACOSOG Z0011 data into clinical management of the axilla. However, it should lead to a reflection that changes of the subsequent adjuvant treatment recommendation might be possible in cases when additional NSMs were found after cALND. Additionally, the cALND results and their impact on radiotherapy and systemic therapy decisions must always be opposed to the significant increase in morbidity due to ALND [9, 45].

Table 3 Non-sentinel metastases after completing axillary lymph node dissection (in ACOSOG Z00011-eligible patients) in total and regarding results from initial sentinel lymph node dissection, differentiated for breast cancer subtype [in %]

Number of NSM after cALND—in total and regarding initial results from SLND in % ($n=9565$*)										
Subtype	Total		pN(1/1sn)		pN (1/2sn)		pN(2/2sn)		pN(1–2/≥3sn)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
HR+/HER2− ($n=7973$)										
0	5328	66.8	1574	61.1	1196	71.5	433	49.8	2125	74.4
1	1162	14.6	415	16.1	165	13.8	103	11.6	398	13.9
2	535	6.7	177	6.9	62	5.2	94	10.8	157	5.5
3	261	3.3	108	4.2	23	1.9	49	5.6	66	2.3
4	184	2.3	60	2.3	23	1.9	50	5.8	42	1.5
5	107	1.3	51	2.0	9	0.8	24	2.7	17	0.6
>5	396	5.0	191	7.4	22	1.8	116	13.3	50	1.7
Any	2645	33.2	1002	38.9	477	28.5	436	50.2	730	25.6
HR+/HER2+ ($n=772$)										
0	501	64.9	160	61.1	113	69.3	38	34.2	190	73.4
1	112	14.5	42	16.0	26	16.0	11	12.5	33	12.7
2	49	6.3	15	5.7	10	6.1	7	7.8	17	6.6
3	26	3.7	11	4.2	3	1.8	6	6.8	6	2.3
4	14	1.8	8	3.1	1	0.6	3	3.4	2	0.8
5	18	2.3	4	1.5	3	1.8	5	5.7	6	2.3
>5	52	6.7	22	8.4	7	4.3	18	20.5	5	1.9
Any	271	35.1	102	38.9	50	30.7	50	65.8	69	26.6
HR−/HER2+ ($n=262$)										
0	153	58.4	44	55.7	33	66.0	11	30.1	65	67.0
1	37	14.1	16	20.3	6	12.0	5	13.9	10	10.3
2	21	8.0	4	5.1	3	6.0	6	16.7	8	8.2
3	9	3.4	4	5.1	2	4.0	0	0	3	3.1
4	13	5.0	2	2.5	1	2.0	4	11.1	6	6.2
5	7	2.7	2	2.5	1	2.0	1	2.8	3	3.1
>5	22	8.4	7	8.9	4	8.05	9	25.0	2	2.1
Any	3264	33.4	1219	38.8	588	28.6	548	50.9	909	25.9
HR−/HER2− (n=608)										
0	428	70.4	120	67.4	94	72.9	35	54.7	179	75.5
1	87	14.3	24	13.5	21	16.0	11	17.2	31	13.1
2	40	6.6	13	7.3	6	4.7	4	6.3	17	7.2
3	14	2.3	7	3.9	2	1.6	2	3.1	3	1.3
4	10	1.6	3	1.7	2	1.6	3	4.7	2	0.8
5	7	1.2	3	1.7	1	0.8	2	3.1	1	0.4
>5	22	3.6	8	4.5	3	2.3	7	109	4	1.7
Any	180	29.6	58	32.6	35	27.1	29	45.3	58	24.5

NSM non-sentinel metastases, *cALND* completing axillary lymph node dissection, *SLND* sentinel lymph node dissection, *HR* hormone receptor

*For $n=208$ cases (2.1%) no subtype distribution was possible due to missing immunochemistry information

Limitations

Our study is limited by its post hoc nature and missing data on outcome. Furthermore, the incomplete information of the cT stage led to the use of the pT stage to determine whether patients met the ACOSOG Z0011 inclusion criteria. We considered this approach reasonable though, because the pT stage and cT stage were concordant for most cases.

Although the results from the ACOSOG Z0011 trial results were first published in 2011, there was substantial delay before guideline recommendations for surgical axillary management were updated. In the interpretation of NSM rates for this cohort, it must be kept in mind that a

Table 4 Multivariable analysis on factors potentially influencing the existence of additional non-sentinel metastases (cALND cohort)

Variable	Odds ratio (95% CI)	*p* value
Age (in years)	1.003 (0.999–1.007)	0.086
Histology		
Ductal	Reference	
Lobular	1.523 (1.313–1.765)	< 0.001
Other	0.855 (0.612–1.118)	0.350
Grading		
G1 (low)	Reference	
G2 (intermediate)	1.192 (1.026–1.389)	0.023
G3 (high)	1.295 (1.088–1.544)	0.004
Lymphovascular invasion		
No	Reference	
Yes	1.591 (1.450–1.746)	< 0.001
pT stage		
1	Reference	
2	1.330 (1.212–1.459)	< 0.001
HER2 status		
Negative	Reference	
Positive	1.178 (0.935–1.262)	0.275
Hormone receptor status		
Negative	Reference	
Positive	1.178 (0.994–1.399)	0.060
Lymph node metastases		
Micrometastases	Reference	
Macrometastases	6.064 (5.833–7.532)	< 0.001

CI confidence interval

relevant proportion of patients with 1–2 positive SLN(s) were not treated with cALND. Thus, it is possible that there was a selection bias that led to higher rates of NSM in comparison with cohorts from before ACOSOG Z0011.

Conclusion

There was a rapid implementation of the ACOSOG Z0011 results into routine clinical practice in Germany, including a decrease in cALND. The ACOSOG Z0011 criteria applied to 7.3% of patients with primary BC in our national population-based study for the period 2008–2015. Our data reveal a high prevalence of additional axillary non-sentinel tumor burden, depending on the combination of removed and tumor-affected SLN(s). Interpreting the ACOSOG Z0011 trial results, these affected lymph nodes that were left behind seem to not compromise oncological outcome when treated under guideline-adherent conditions. Thus, these patients could potentially have been spared the morbidity of cALND. The impact of additional affected lymph nodes on adjuvant treatment should be considered in the therapy decision process.

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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 anonymized analysis of routinely collected data; consequently, the ethics committee of the University of University 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.

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