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The Dilemma After an Unforeseen Positive Sentinel Node in Primary Breast Cancer: Is Completion Axillary Dissection Necessary?

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Abstract

Background In the majority of cases, the sentinel node is the only positive node in the axilla and completion ALND (cALND) is a futile procedure. However, refraining from cALND will lead to less accurate staging and, possibly, undertreatment. To help resolve this dilemma, we examined the clinical value of cALND in staging and determining adjuvant treatment.

Methods In a retrospective cohort, all consecutive patients over a five-year period with primary breast cancer who received ALND were identified and grouped based on timing of ALND. Total nodal yield and positive lymph nodes were defined and factors with possible impact identified. In the case of cALND, N-status upstaging and possible impact on adjuvant treatment were studied in detail.

Results A total of 280 patients were selected of whom 204 underwent primary ALND (pALND) and 76 cALND. pALND resulted in a significantly higher total nodal yield and more positive nodes when compared to cALND ($p = 0.003$, and $p < 0.001$, respectively). Neoadjuvant chemotherapy (NAC) had no effect on total nodal yield ($p = 0.413$), but resulted in fewer positive nodes ($p < 0.001$). Due to the results of cALND, only 11 patients (14%) had upstaging of N-status. All these patients were advised more extensive adjuvant radiotherapy.

Conclusion In the majority of patients, cALND does not lead to upstaging. cALND should be performed only after a careful discussion with the patient about the pros and cons of this procedure, and most probably only in the presence of multiple risk factors for axillary disease in the absence of systemic therapy.

Introduction

In the current management of primary breast cancer, axillary nodal status forms a guide to adjuvant treatment, since it is one of the most important prognostic factors [1–3]. To define this nodal status, sentinel lymph node biopsy (SLNB) has become a standard of care. SLNB alone is an accepted therapy in the case of a negative sentinel lymph node. However, in the case of a positive axillary lymph node, detected either by SLNB or preoperatively on ultrasound and cytology, treatment of the axilla is desirable [1–3].

Axillary lymph node dissection (ALND) is historically the treatment of choice for both maintaining regional control and achieving the most adequate staging [1, 4, 5]. It may be performed in either a primary or a completion setting: primary when preoperatively the nodal status of the axilla has been assessed pathologically as positive, i.e., by either fine-needle aspiration or core biopsy (cN1 or higher), or as a completion procedure after an unforeseen positive SLNB (cN0) [1, 6].

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Always performing completion ALND (cALND) after a positive SLNB will ultimately result in a futile procedure for a substantial number of cases since it has been established that in the vast majority of cases the sentinel node (SN) is the only positive lymph node in the axilla [4, 5, 7, 8]. However, refraining from cALND will undoubtedly lead to a less accurate staging and, possibly, to undertreatment of the patient. To help to resolve this dilemma, we conducted this study to determine the clinical value of cALND in staging and in determining the need for adjuvant treatment according to national protocols. Furthermore, we examined the results for potential differences between primary and completion clearance in detail.

Methods

Patient selection

The study was conducted as a single-center retrospective cohort study. Patients with primary breast cancer who received ALND in a five-year period (January 2013–December 2017) were identified. The database consisted of all records of patients who received ALND in the management of breast cancer. Patient, tumor, and treatment-related variables were gathered from electronic medical records of institutional databases including age, type of surgery, tumor histology, and adjuvant treatment. In order to prevent missing or accidentally false information, all electronic medical records were checked by two authors individually.

Patients were included when they received an ALND for primary breast cancer. In our hospital, all patients received preoperative axillary ultrasound and fine-needle aspiration cytology (FNAC) of suspicious nodes [2]. Patients with preoperatively proven axillary metastasis received pALND. Patients with multifocal and/or larger (cT3) tumors were also offered pALND according to the guidelines in the study period even in the absence of preoperatively proven axillary metastasis. All other patients were scheduled for SLNB. Intraoperative examination of the sentinel node (SN) was not performed. Those patients with a positive SN were offered cALND [2]. Patients were divided into two groups based on the timing of the ALND: group 1 patients who received pALND and group 2 patients who received cALND.

Patients who received ALND in the case of recurrence of disease or progression of known local disease were excluded. Patients were also excluded in the case of an occult invasive breast tumor or if only a part of the axillary lymph nodes were removed (partial ALND). Lastly, patients were excluded when the indication for ALND did not match the national oncologic guidelines (rare cases).

Surgical technique

All operations were carried out by five experienced and certified breast cancer surgeons. In this study, patient selection was made based on the operation report: ALND was defined as the complete clearance of axillary levels 1 and 2, i.e., until the level of the axillary vein. In the case of a mastectomy, the ALND was performed using the mastectomy incision. However, in the case of breast-conserving surgery (BCS) a second incision was made in the majority of cases to perform the ALND.

pALND was defined as an ALND at the moment of the primary operation in the management of breast cancer, without SLNB prior to ALND. cALND was defined as an ALND performed at a later stage due to a positive SLNB.

Statistical analysis

Patient and tumor characteristics were analyzed using descriptive statistics presented as mean with standard deviation, median with range, and/or numbers with percentages. No imputations were performed for missing data.

The total nodal yield was calculated as the sum of nodes cleared by pALND or combined cALND and SLNB. The total positive nodal yield was defined as the sum of positive axillary nodes by pALND or combined cALND and SLNB.

To identify variables with an impact on the total nodal yield and on the number of positive lymph nodes, univariate and multivariate analyses were performed. Univariate analysis was performed with Chi-square or Mann–Whitney *U* test. Multivariate analysis of the total nodal yield was performed using multiple linear regression with indication (primary vs completion), surgery (BCS vs mastectomy), NAC (with vs without), and age as independent variables. The positive nodal yield was analyzed using negative binomial regression with indication (primary vs completion), surgery (BCS vs mastectomy), NAC (with vs without), and age as independent variables.

The multivariate analysis gives a coefficient in the multiple linear regression and a rate ratio in the negative binomial regression. The coefficient is an additive number. (One variable outcome serves as a reference and is set to zero.) The rate ratio is a multipliable number. (One variable outcome serves as a reference and is set to one.)

All statistical tests were two-sided with a significance level of 0.05. All statistical analyses were performed using the statistical software IBM SPSS version 24.

Results

Patients

In the management of breast cancer, 326 patients received ALND of whom 280 met the inclusion criteria: 204 (73%) patients received pALND, and 76 (27%) patients received cALND (Fig. 1). Neoadjuvant chemotherapy (NAC) was part of the treatment in 58 (28%) patients of group 1 and only in 6 (8%) patients of group 2 ($p < 0.001$). In group 1, NAC resulted in 17 patients in pN0. No patients received radiotherapy prior to ALND. The tumor grade and nodal status of patients receiving pALND were higher as compared to patients receiving cALND ($p = 0.016$ and $p < 0.001$, respectively). Group 1 contained 24 (12%) multifocal tumors as compared to group 2 which contained 15 (20%) multifocal tumors ($p = 0.019$). No significant differences were found between the groups with respect to age, sex, type of breast surgery, histologic subtypes, and tumor size (Table 1).

cALND and upstaging N-status

Subsequent to SLNB, 76 patients received cALND of whom 65 (86%) patients had no upstaging and 11 (14%) had upstaging of N-status because of the pathologic findings at cALND. When comparing patients with and without N-status upstaging, a difference was observed in median total macrometastases identified in SLNB ($p = 0.032$). No significant differences were found with respect to age, surgery, and other histologic characteristics (Table 2).

Of the 76 patients who received cALND, 52 (68%) had no more involved nodes in the cALND. N-status upstaging concerned five (45%) patients after BCS and six (55%) after mastectomy. Eight patients were upstaged to N2- and three patients to N3-disease. Because of upstaging in N-status, all patients subsequently underwent dissemination evaluation. In no case (0%), M1-disease was established.

In the case of upstaging of N-status due to cALND, ten (91%) had SN containing macrometastases, eight (73%) had a T2 or T3 tumor, six (55%) had a multifocal tumor in their surgical specimen, and two (18%) had extranodal growth (Table 3). Based on the results of the cALND, all 11 patients with an upstaging of N-status were advised more extensive adjuvant radiotherapy. All but one finally received more extensive radiotherapy (i.e., by national protocol: radiation of the thoracic wall and infra- and supraclavicular regions). The one who did not receive adjuvant radiotherapy was aged 82 years and was diagnosed of having a synchronous colon carcinoma that came

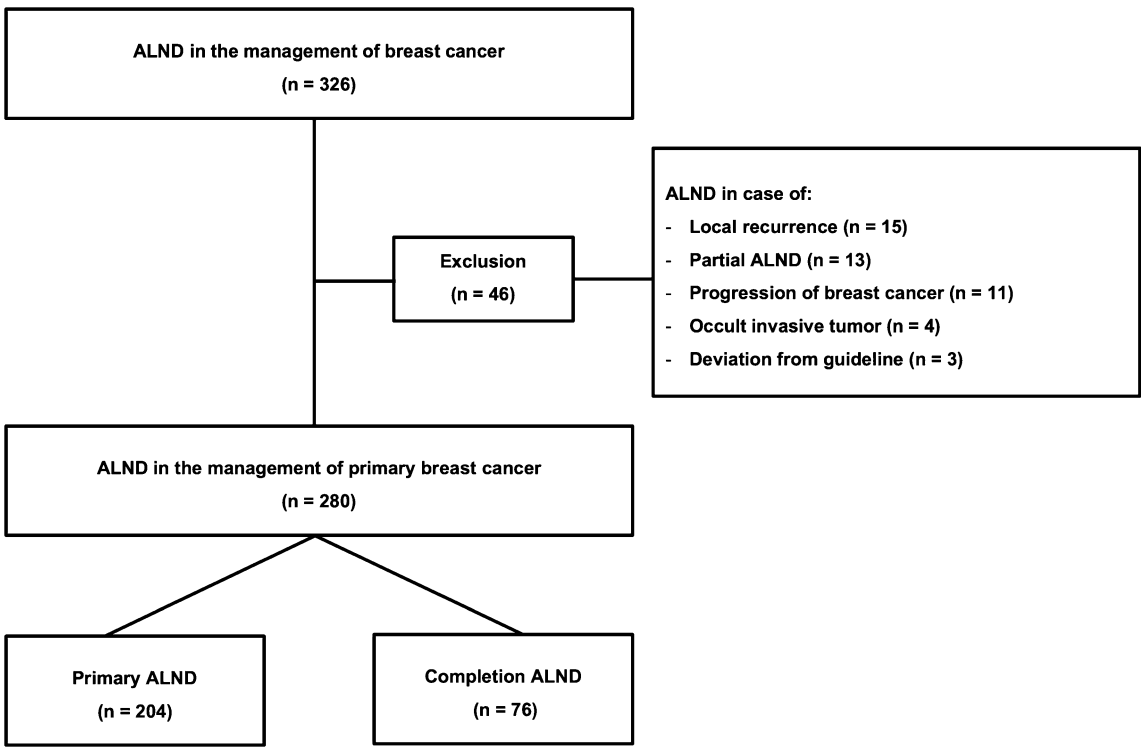

Fig. 1 Patient selection and management for patients who received ALND in the management of breast cancer

Table 1 Patient demographics

	Primary ALND (n = 204)	Completion ALND (n = 76)	p-value
Mean age ± SD, years	61. ± 14.9	59.0 ± 9.9	0.321[a]
Sex			1.000[c]
Male	2 (1.0%)		
Female	202 (99.0%)	76 (100%)	
NAC			**<0.001[b]**
No	146 (71.6%)	70 (92.1%)	
Yes	58 (28.4%)	6 (7.9%)	
Type of breast surgery			0.129[b]
Mastectomy	160 (78.4%)	53 (69.7%)	
BCS	44 (21.6%)	23 (30.3%)	
Histology tumor			0.386[b]
Invasive ductal carcinoma	174 (85.3%)	60 (78.9%)	
Invasive lobular carcinoma	26 (12.7%)	13 (17.1%)	
Other histologic subtypes	4 (2.0%)	3 (3.9%)	
Multiple tumors			**0.030[b]**
No	180 (88.2%)	63 (81.6%)	
Yes, 2 tumors	19 (9.3%)	15 (18.4%)	
Yes, >2 tumors	5 (2.5%)		
Tumor grade[d]			**0.016[b]**
Determination not possible		1 (1.3%)	
Bloom Richardson I	24 (14.1%)	15 (19.7%)	
Bloom Richardson II	74 (43.5%)	42 (55.9%)	
Bloom Richardson III	72 (42.4%)	18 (23.7%)	
Mean tumor size ± SD, cm[d]	3.2 ± 2.3	2.5 ± 1.3	0.065[a]
pN (after first operation)			**<0.001[b]**
N0	24 (11.8%)		
N1	91 (44.6%)	74 (94.9%)	
N2	52 (25.5%)	2 (2.6%)	
N3	37 (18.1%)		
pN (definitive)			**<0.001[b]**
N0	24 (11.8%)		
N1	91 (44.6%)	63 (82.9%)	
N2	52 (25.5%)	10 (13.2%)	
N3	37 (18.1%)	3 (3.9%)	
In the case of cALND, upgrading of N-status			
No		65 (85.5%)	
Yes		11 (14.5%)	

Statistically significant values ($p < 0.05$) are given in bold

[a]Mann–Whitney U test, [b]Pearson Chi-square, [c]Fisher's exact test, [d]in the case of multiple tumors, the biggest size and highest grade were used

to light by the PET-CT performed because of upstaging. All adjuvant systemic therapy was administered by protocol, and no changes were made based on the results of cALND. Two patients were not upstaged because they were already staged as having N2-disease at SLNB.

Axillary total nodal yield

pALND resulted in a significantly higher total nodal yield as compared to cALND (median 16.0 versus 14.0, respectively). The positive nodal yield in pALND significantly differed from a cALND (median 3.0 vs 2.0, respectively).

Table 2 Patients with *N*-change after cALND compared to no *N*-change after cALND

	No *N*-change after cALND ($n = 65$)	N-change after cALND ($n = 11$)	*p*-value
Mean age ± SD, years	58.5 ± 10.0	62.3 ± 9.2	0.265
Type of surgery			0.726
BCS	19 (29.2%)	4 (36.4%)	
Mastectomy	46 (70.8%)	7 (63.6%)	
Presence of macrometastases in SLNB			1.000
No	8 (12.3%)	1 (9.1%)	
Yes	57 (87.7%)	10 (90.9%)	
Median total nodes SLNB [IQR]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.913
Median positive nodes SLNB [IQR]	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.099
Median macrometastases in SLNB [IQR]	1.0 [1.0–1.0]	2.0 [1.0–2.0]	**0.032**
Presence of extranodal growth in SLNB			0.446
No	53 (81.5%)	8 (72.2%)	
Yes	12 (18.5%)	3 (27.3%)	
Tumor grade			0.185
Grade I	13 (20.0%)	2 (18.2%)	
Grade II	38 (58.5%)	4 (36.4%)	
Grade III	13 (20.0%)	5 (45.5%)	
Determination of grade not possible	1 (1.5%)		
Presence of angioinvasion in surgical specimen			0.102
No	30 (46.2%)	4 (36.4%)	
Doubtfully	3 (4.6%)	1 (9.1%)	
Yes	10 (15.4%)	5 (45.5%)	
No invasive carcinoma is present	2 (3.1%)		
Missing	20 (30.8%)	1 (9.1%)	

Statistically significant value ($p < 0.05$) is given in bold

IQR interquartile range

Patients who received NAC had significantly fewer positive lymph nodes (median 1.0) as compared to those who did not receive NAC (mean 2.0). NAC, however, had no significant impact on the total nodal yield. Patients who received a mastectomy had significantly more positive lymph nodes (median 3.0) compared to those who received BCS (mean 2.0). Operation type, however, had no impact on the total nodal yield (Table 4).

Discussion

ALND has been the primary tool for axillary staging in breast cancer for decades. It is, however, infamous, for carrying the risk of seroma, infection, and lymphedema [1, 4, 9]. Particularly after the introduction of SLNB, the use of ALND in the management of breast cancer declined dramatically since SLNB proved to be a non-inferior staging procedure [10–14]. Furthermore, cALND as a standard procedure after a positive SLNB became a matter of debate since it showed no survival benefit [4, 5, 8, 15]. Recently, axillary radiotherapy has been introduced as an alternative treatment to the axilla after a positive SLNB [4, 16]. We studied the clinical relevance of cALND based on data in a period that cALND in national protocols was the standard procedure after a positive SLNB. We also examined our results for potential differences in nodal yield between primary and completion clearance.

First, we found that cALND did not alter N-stage, and the need for adjuvant treatment in the vast majority of cases (86%). If cALND would have been omitted, someone in seven patients would not have been upstaged to N2/N3-disease and, consequently, would not have received more extensive radiotherapy.

Second, we found that patients with an upstaging of N-stage had a combination of characteristics (multifocal disease, high grade, and larger (T2/T3) tumors). Therefore, in the case of omission of cALND the combination of these characteristics in itself, indicating a risk of extended

Table 3 Patient characteristics of patients with *N*-change after ALND

Patient	Type of breast surgery	SLNB total nodes	SLNB positive nodes	SLNB macrometastases	SLNB extranodal growth	T- and G-status	Hormone status	Additional findings	ALND positive nodes	N-change
1	BCS	1	1	Yes	No	T2 GIII	ER + PR + Her2−	DCIS grade III (Tmult)	3	N1 → N2
2	BCS	1	1	Yes	No	T1c GIII	Triple negative		9	N1 → N3
3	Mastectomy	3	2	Yes	No	T2 GII	ER + PR − Her2−	1 Positive non-SN lymph node with macrometastases and extranodal growth	4	N1 → N2
4	BCS	3	3	Yes	No	T1c GII	ER + PR − Her2−		4	N1 → N2
5	Mastectomy	1	1	Yes	Yes	T2 GIII	Triple positive	DCIS grade II	9	N1 → N3
6	Mastectomy	3	2	Yes	Yes	T1b (2) GI			10	N1 → N3
7	Mastectomy	1	1	Yes	No	T2 GII	ER + PR + Her2−	DICS grade III	6	N1 → N2
8	BCS	3	3	Yes	No	T2 GIII	ER + PR + Her2−	DCIS grade III	6	N1 → N2
9	Mastectomy	2	2	Yes	No	T2 GI	ER + PR − Her2−	1 Positive non-SN lymph node with macrometastases	3	N1 → N2
10	Mastectomy	3	2	Yes	Yes	T2 GII	ER + PR + Her2−		2	N1 → N2
11	BCS	1	1	No	No	T3 GIII	ER + PR − Her2−	DCIS grade III	4	N1 → N2

Table 4 Univariate and multivariate analysis of total nodal yield and positive nodal yield

		Univariate analysis			Multivariate analysis	
	n	Median nodal yield [IQR]	*p*-value	Coefficient or rate ratio[b]	95% confidence interval	*p*-value
Total nodal yield						
Age (at diagnosis)	280			0.004	−0.053–0.062	0.880
Indication			**0.008**			**0.003**
Primary	204	16.0 [12.0–21.0]		*		
Completion	76	14.0 [10.0–18.0]		−2.555	−4.237–−0.873	
NAC			0.897			0.413
No	216	15.5 [11.0–20.0]		*		
Yes	64	16.0 [12.0–20.5]		−0.800	−2.721–1.120	
Operation type			0.984			0.699
BCS	67	15.0 [12.0–20.5]		*		
Mastectomy	213	16.0 [11.0–20.0]		−0.334	−2.036–1.367	
Positive nodal yield						
Age (at diagnosis)	280			1.007	0.998–1.017	0.141
Indication			**0.004**			**<0.001**
Primary	204	3.0 [1.0–7.0]		1*		
Completion	76	2.0 [1.0–3.0]		0.507	0.377–0.681	
NAC			**0.002**			**<0.001**
No	216	2.0 [1.0–6.0]		1*		
Yes	64	1.0 [0.0–5.0]		0.556	0.402–0.769	
Operation type			**0.002**			**0.001**
BCS	67	2.0 [1.0–3.0]		1*		
Mastectomy	213	3.0 [1.0–7.0]		1.641	1.212–2.223	

Statistically significant values ($p < 0.05$) are given in bold

*reference group, [a]IQR: interquartile range, [b]coefficient for total nodal yield and rate ratio for positive nodal yield

axillary tumor burden, should require axillary treatment (i.e., cALND or locoregional radiotherapy).

Third, we found a decrease in the total nodal yield when performing cALND (after SLNB) as compared to pALND. Although the difference is small (16 vs 14), it is significant ($p < 0.001$). This is an intriguing phenomenon, since theoretically it is an identical procedure and technically comparable. Perhaps cALND has a different surgical exposure of the axilla because of inflammatory changes and/or scarring after SLNB leading to less clearance of axillary lymph nodes [6]. Other studies, however, found no significant differences between pALND and cALND [6, 17, 18].

It must be born in mind that our study has some limitations. First, selection has taken place. Groups 1 (pALND) and 2 (cALND) are not comparable in the extent of the disease. Group 2 is small, because of the fact that most SLNBs are negative making cALND a rare treatment. The extent of disease was higher in group 1 (44% having N2/N3-disease) as compared to group 2 (17% ultimately having N2/N3-disease). Yet, this was the result of the different treatment approach, i.e., pALND or SLNB plus cALND, and, therefore, not problematic to the study question. Second, the study has limitations because of its retrospective design and its small cohort size. As a consequence of the latter, the finding that no significant differences were found with respect to age, surgery, and other histologic characteristics (Table 1) has only limited value. Also, our failure to prove a significant correlation between poor prognostic characteristics and the SLNB, such as tumor grade and tumor size and upstaging of N-status by cALND, has little value. This may be considered a type II error since predicting tumor involvement of non-sentinel lymph nodes by, e.g., tumor size and extracapsular extension of sentinel lymph node metastasis has been convincingly shown before [19, 20].

Despite these methodological restrictions, we still feel that our findings may contribute to the discussion whether it is justifiable to omit cALND which has been debated since the ACOSOG Z11 study [5, 8]. Dutch guidelines,

however, did not abandon cALND right away and cALND was considered mandatory until the publication of the results of AMAROS, where the role of radiation of the axilla was investigated as an alternative treatment of the axilla in the case of a positive SLNB [16]. Nowadays, cALND is omitted after a positive SLNB but only after BCS in the absence of certain risk factors. Since in this protocol complete axillary staging has been abandoned as a concept, it may be assumed that some patients may be undertreated in the sense that they do not receive radiation of the thoracic wall and infra- and supraclavicular regions and considered mandatory earlier. It must be noted, however, that most patients have an indication for systemic therapy already based on the positive SLNB. Although systemic therapy may not replace more extensive radiotherapy, it does have an effect on locoregional control and also has an impact on axillary status [21–23]. In our group, that was the case in 82% of those patients (9 out of 11). Of the two N-stage upgraded who did not receive systemic therapy (18%; 3% of patients receiving cALND), one (triple hormone-receptor negative) was aged 80 years at the time of cALND, leaving only one (1% of patients receiving cALND) who might have benefitted from upstaging and more extensive adjuvant treatment. This concerned a patient aged 59 years who underwent a mastectomy for multicentric disease with no indication for systemic therapy (intermediate grade pT1b).

Conclusion

In the management of breast cancer, complete axillary nodal status is important for adequate prognosis and optimal adjuvant treatment. However, cALND may be avoided. In the majority of patients, cALND does not lead to upstaging. Consequently, it does not change adjuvant treatment. So, cALND should be performed only after a careful discussion with the patient about the pros and cons of this procedure and most probably only in the presence of multiple risk factors for axillary disease in the absence of systemic therapy.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Informed consent Consent was given for registration of medical data for anonymous research.

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