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EPIDEMIOLOGY

Prognostic significance of axillary dissection in breast cancer patients with micrometastases or isolated tumor cells in sentinel nodes: a nationwide study

Tove Filtenborg Tvedskov[1] · Maj-Britt Jensen[2] · Bent Ejlertsen[3] · Peer Christiansen[4] · Eva Balslev[5] · Niels Kroman[1]

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Abstract We estimated the impact of axillary lymph node dissection (ALND) on the risk of axillary recurrence (AR) and overall survival (OS) in breast cancer patients with micrometastases or isolated tumor cells (ITC) in sentinel nodes. We used the Danish Breast Cancer Cooperative Group (DBCG) database to identify patients with micrometastases or ITC in sentinel nodes following surgery for primary breast cancer between 2002 and 2008. A Cox proportional hazard regression model was developed to assess the hazard ratios (HR) for AR and OS between patients with and without ALND. We identified 2074 patients, of which 240 did not undergo further axillary surgery. The 5-year cumulated incidence for AR was 1.58 %. No significant difference in AR was seen between patients with and without ALND. The age adjusted HR for AR if ALND was omitted was 1.79 (95 % CI 0.41–7.80, $P = 0.44$) in patients with micrometastases and 2.21 (95 % CI 0.54–8.95, $P = 0.27$), in patients with ITC after a median follow-up of 6 years and 3 months. There was no significant difference in overall survival between patients with and without ALND, when adjusting for age, comorbidity, tumor size, histology type, malignancy grade, lymphovascular invasion, hormone receptor status, adjuvant systemic treatment and radiotherapy, with a HR for death if ALND was omitted of 1.21 (95 % CI 0.86–1.69, $P = 0.27$) in patients with micrometastases and 0.96 (95 % CI 0.57–1.62, $P = 0.89$) in patients with ITC after a medium follow-up on 8 and 5 years. In this nationwide study, we found a low risk of AR on 1.58 % and we did not find a significantly increased risk of AR if ALND was omitted in patients with micrometastases or ITC in sentinel nodes. Furthermore, no significant difference in overall survival was seen between patients with and without ALND when adjusting for adjuvant treatment.

Keywords Breast cancer · Micrometastases · Sentinel node · Isolated tumor cells · ALND

✉ Tove Filtenborg Tvedskov
tft@dadlnet.dk

[1] Department of Breast Surgery, Copenhagen University Hospital, Afs 4124, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Copenhagen, Denmark

[2] Danish Breast Cancer Cooperative Group, Copenhagen University Hospital, Copenhagen, Denmark

[3] Department of Clinical Oncology and Danish Breast Cancer Cooperative Group, Copenhagen University Hospital, Copenhagen, Denmark

[4] Breast Surgery Unit, Department of Surgery, Aarhus University Hospital/Randers Regional Hospital, Aarhus, Denmark

[5] Department of Pathology, Herlev Hospital, Copenhagen, Denmark

Background

Results from the randomized American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, where no difference in axillary recurrence and survival was found between sentinel node (SN) positive patients with and without axillary lymph node dissection (ALND), has put ALND in SN positive breast cancer patients under debate [1, 2]. Especially, the benefit from ALND in patients with micrometastases or isolated tumor cells (ITC) in the SN is now questioned and has been abandoned in many centers. Generally, only about 15–20 % of patients with micrometastases [3] and 10–15 % of patients with ITC [4] in the SN have metastatic spread to non-SNs, and it is now evident that only some of these non-SN metastases will

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become clinical relevant. It has been shown that despite a false negative rate of the SN procedure on about 5 %, the regional recurrence rate is less than 1 % after 8 years of follow-up in patients with a negative SN [5, 6].

Studies investigating the impact of ALND on survival and loco-regional recurrence in patients with micrometastases or ITC in the SN are few and the majority are limited by short follow-up, small sample sizes, lack of multivariate analyses, or missing information on adjuvant treatment [7–10] and the results are conflicting. Some studies show that patients with micrometastases or even only ITC in the SN have a worse outcome if ALND is omitted [11, 12] while others can not show any difference [13–18]. Larger studies on the prognostic significance of ALND in patients with micrometastases or ITC in the SN, allowing a multivariate design with adjustments for adjuvant radiotherapy and adjuvant systemic treatment and with longer follow-up, is therefore needed to ensure the safety of the increasing trend towards omitting ALND in these patients.

In Denmark, clinical and histopathological data, as well as information on treatment and follow-up status of women with breast cancer, has been registered in a national database managed by the Danish Breast Cancer Cooperative Group (DBCG) since 1978. Today the database contains information on more than 100,000 breast cancer patients [19]. This gives a very large and nationwide data material for a study of prognostic significance of ALND in patients with micrometastases or ITC in the SN.

DBCG describes guidelines for treatment of breast cancer in Denmark. Until 2012 the standard treatment of patients with micrometastases or ITC in the SN was ALND. Although, in selected patients this standard treatment has not been performed.

The aim of the present study was based on data from the DBCG database, to estimate whether omission of ALND in patients with micrometastases or ITC in the SN had any impact on the risk of axillary recurrence and the overall survival.

Materials and methods

Between 2002 and 2008 a total number of 2074 women with primary breast cancer and either micrometastases or ITC in the SN were registered in the DBCG database. Since 2005 micrometastases and ITC have been registered according to the American Joint Committee on Cancer (AJCC) staging manual 6th edition [20] in combination with cell count, where metastases between 10 and 100 tumor cells were defined as micrometastases and less than 10 cells were defined as ITC [21]. Until the end of 2004, micrometastases and ITC were registered together. A re-evaluation of the specimens from this period was done by two breast trained pathologist at the Department of Pathology, Herlev Hospital, in order to obtain a uniform distinction between micrometastases and ITC.

Information on age at diagnosis, tumor size, histology type, malignancy grade, lymphovascular invasion, hormone receptor status, nodal status, surgical treatment, radiotherapy, adjuvant systemic treatment, axillary recurrence, and overall survival was retrieved from the DBCG database and validated using the original patient and pathology files. Adjuvant systemic treatment was defined as any kind of adjuvant systemic treatment; either as chemotherapy and/or anti-estrogen treatment, regardless of whether treatment had been completed or not. Loco-regional radiotherapy was defined as any kind of radiotherapy, including breast-conserving radiotherapy, regardless of whether treatment had been completed or not. Axillary recurrence was defined as recurrence in ipsilateral axillary or in infra- or supra-clavicular lymph nodes as first event. Death was defined as death from all causes.

Information on co-morbidity up to 10 years before breast cancer diagnosis was retrieved from the National Patient Health Register. Co-morbidity was scored using the Charlson co-morbidity Index.

A total of 156 patients were excluded due to missing information, identification of macrometastases or no metastases in the SN.

Statistics

The DBCG data center undertook central review, querying, and analysis of data. Associations between SN status, ALND, and clinicopathological variables (excluding unknowns) were assessed by χ^2 and Fisher exact test. Follow-up time was quantified in terms of a Kaplan–Meier estimate of potential follow-up. The risk of axillary recurrence as a first event was estimated as cumulative incidence in the presence of competing risk with the time from surgery to first event, taking local recurrence, distant metastases, new primary invasive cancer, or death as competing events. A complete follow-up on vital status until January 1, 2015 was obtained for all patients through linkage to the Danish Central Population Registry. Overall survival was estimated using the Kaplan–Meier method, calculating the time from date of surgery until death, irrespective of cause of death, or end of follow-up. The effects of ALND on axillary recurrence and overall survival were quantified in terms of hazard ratios (HRs), estimated unadjusted and adjusted using the Cox proportional hazards model. For axillary recurrence, adjustment was restricted to age (trend < 40, 40–49, 50–59, 60–69, 70+) due to low number of events. For overall survival, multivariate analyses included age at diagnosis (<40, trend 40–49, 50–59, 60–69, 70–79, 80+), Charlson co-morbidity

score (trend 0, 1, 2, 3+) tumor size (trend cm), histology type (ductal, lobular, other), malignancy grade (I, II, III), lymphovascular invasion, and hormone receptor status. The multivariate analyses further included adjuvant systemic treatment, loco-regional radiotherapy, and type of surgery. Adjuvant systemic treatment was grouped as any kind of adjuvant systemic treatment, no adjuvant systemic treatment, and no information on whether adjuvant systemic treatment was given. Loco-regional radiotherapy was grouped as any kind of radiotherapy, no radiotherapy, and no information on whether radiotherapy was given. The assumption of proportional hazards was assessed by formal tests and plot of Schoenfeld residuals. Test for interaction between effect of ALND, adjuvant treatment, and SN group (ITC vs. micrometastases) was done using the Wald test. Tests of statistical hypotheses were done on the two-sided 5 % level of significance. Statistical analyses were done with the SAS 9.4 statistical software (SAS Institute, Inc., Cary, NC).

The incidence of axillary recurrence in patients with either micrometastases or ITC in the SN is reported to be 1–2 % after 5 years of follow-up [22, 23]. Detection of a clinically relevant difference in recurrence rate on 5 % with a power of 80 % and a significance level of 0.05 will require a sample size on at least 1408 patients with a distribution between patients with and without ALND on 10–1 and (SSP software—Java applet for sample size and power authored by Marc Bacsa).

Results

A total number of 2074 patients were eligible for the study, 1673 had micrometastases in the SN and 401 had ITC. 240 patients did not undergo ALND; 136 with micrometastases and 104 with ITC. Patient and tumor characteristics as well as registered treatment are shown in Table 1. Patients without ALND were significantly older ($P < 0.0001$) and had a higher degree of co-morbidity ($P = 0.01$) than patients with ALND. Patients without ALND were in average 71 years old compared to 58 years for patients with ALND. In addition, patients without ALND had more often lobular carcinomas ($P = 0.002$).

The estimated potential median follow-up was 6 years and 3 months for axillary recurrence, where patients were followed until first event of local ($N = 61$), axillary ($N = 34$) or distant recurrence ($N = 118$), contralateral breast cancer ($N = 30$) or death ($N = 140$). In total, only 34 patients (1.6 %) had an axillary recurrence; 1.50 versus 1.47 % in the group with micrometastasis with and without ALND, and 2.0 versus 2.9 % in the group with ITC with and without ALND. Recurrences were evenly distributed in the follow-up period, no clear peak could be identified, and

Table 1 Patient, tumor, and treatment characteristics of 2074 Danish breast cancer patients with micrometastases or isolated tumor cells in the sentinel node treated between 2002 and 2008

	Micrometastases				Isolated tumor cells			
	ALND				ALND			
	Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%
Patients	1537	100	136	100	297	100	104	100
Age (years)								
<40	66	4.3	2	1.5	21	7.1	1	1.0
40–49	281	18.3	7	5.2	52	17.5	9	8.7
50–59	468	30.5	7	5.2	84	28.3	16	15.4
60–69	495	32.2	23	16.9	98	33.0	28	26.9
≥70	227	14.8	97	71.3	42	14.1	50	48.1
Co-morbidity (CCI)								
0	1209	78.7	93	68.4	252	84.9	77	74.0
1	194	12.6	21	15.4	24	8.1	16	15.4
2	85	5.5	13	9.6	14	4.7	5	4.8
3+	49	3.2	9	6.6	7	2.4	6	5.8
Tumor size (cm)								
≤1	239	15.6	17	12.5	36	12.1	14	13.5
>1 – ≤2	770	50.1	61	44.9	131	44.1	41	39.4
>2 – ≤3	374	24.3	41	30.2	83	28.0	32	30.8
>3	133	8.7	14	10.3	44	14.8	16	15.4
Unknown	21	1.4	3	2.2	3	1.0	1	1.0
WHO type								
Ductal	1320	85.9	108	79.4	205	69.0	71	68.3
Lobular	144	9.4	15	11.0	73	24.6	26	25.0
Other	62	4.0	12	8.8	17	5.7	7	6.7
Unknown	11	0.7	1	0.7	2	0.7	0	0
Grade								
Grade I	506	34.6	50	40.65	74	26.6	32	33.0
Grade II	696	47.5	56	45.5	133	47.8	39	40.2
Grade III	242	16.5	17	13.8	64	23.0	23	23.7
Unknown	20	1.4	0	0	7	2.5	3	3.1
LVI								
Yes	160	10.4	11	8.1	19	6.4	3	2.9
No	1353	88.0	123	90.4	273	91.9	97	93.3
Unknown	24	1.6	2	1.5	5	1.7	4	3.9
Hormone receptor status								
Positive	1341	87.3	130	95.6	251	84.5	86	82.7
Negative	183	11.9	6	4.4	45	15.2	18	17.3
Unknown	13	0.9	0	0	1	0.3	0	0
Type of surgery								
Mastectomy	591	38.5	68	50.0	124	41.8	39	37.5
BCS	946	61.5	68	50.0	173	58.2	65	62.5
Loco-regional radiotherapy								
Yes	1060	69.0	47	34.6	198	66.7	54	51.9
No	460	29.9	77	56.6	94	31.6	46	44.2
Unknown	17	1.1	12	8.8	5	1.7	4	3.9

Table 1 continued

	Micrometastases				Isolated tumor cells			
	ALND				ALND			
	Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%
Adjuvant systemic treatment								
Yes	1461	95.1	115	84.6	237	79.8	69	66.4
No	56	3.6	9	6.6	54	18.2	26	25.0
Unknown	20	1.3	12	8.8	6	2.0	9	8.6

ALND axillary lymph node dissection, *CCI* Charlsons co-morbidity index, *LVI* lymphovascular invasion, *BCS* breast-conserving surgery, *BRT* breast radiotherapy

recurrence was seen as long as 8 years after primary surgery. 5 years cumulated incidence for axillary recurrence as first event is shown in Table 2. Albeit a tendency towards an increased age adjusted HR for axillary recurrence was seen if ALND was omitted (HR 1.99; CI 0.72–5.50, $P = 0.18$), the risk was neither significantly increased in patients with micrometastases (HR 1.79; 95 % CI 0.41–7.80, $P = 0.44$), nor in patients with ITC (HR 2.21, 95 % CI 0.54–8.95, $P = 0.27$) (Table 3).

The estimated potential median follow-up for overall survival was 8.5 years. In total, 383 patients were dead by end of follow-up and the 5-year overall survival for the whole cohort was 91.0 %. Overall survival for the different groups is shown in Table 2. In the groups of patients with ALND, overall survival was over 90 %, while it was between 79 and 88 % for patients without ALND. Accordingly, the crude HR for death when ALND was omitted compared to patients with ALND was significantly increased to 2.92 (95 % CI 2.18–3.91, $P < 0.0001$) for patients with micrometastases, 1.68 (95 % CI 1.03–2.79, $P = 0.04$) for patients with ITC and 2.52 (95 % CI 1.94–3.26, $P < 0.0001$) for the common group of patients with micrometastases or ITC. However, when adjusting for age at diagnosis, co-morbidity, tumor size, histology type, malignancy grade, lymphovascular invasion and hormone receptor status the HR was no longer significantly increased. The adjusted HR for death when ALND was omitted was 1.32 (95 % CI 0.95–1.84, $P = 0.10$) for patients with micrometastases, 1.00 (95 % CI 0.59–1.68, $P = 0.99$) for patients with ITC and 1.22 (95 % CI 0.91–1.63, $P = 0.18$) for the two groups together (Table 3).

The majority of the included patients (90.7 %) were treated by adjuvant systemic treatment; 94 % of patients with micrometastases and 76 % of patients with ITC. 93 % of patients in the group with ALND did receive adjuvant systemic treatment compared to only 77 % of patients without ALND ($P < 0.0001$).

66 % of the included patients did receive loco-regional radiotherapy; 66 % of patients with micrometastases and 63 % of patients with ITC. A significantly larger proportion of patients with ALND did receive radiotherapy compared to patients without ALND; 69 versus 47 % ($P < 0.0001$). In 62 (3 %) patients, information on adjuvant systemic treatment and radiotherapy were missing.

When adjusting for adjuvant systemic treatment and loco-regional radiotherapy, in addition to adjustment for age, co-morbidity, tumor size, histology type, malignancy grade, lymphovascular invasion, and hormone receptor status, there was still no significant difference in overall survival between patients with and without ALND. HR for death if ALND was omitted was 1.13 (95 % CI 0.84–1.52, $P = 0.41$) in the common group of patients, 1.21 (95 % CI 0.86–1.69, $P = 0.27$) in patients with micrometastases and 0.96 (95 % CI 0.57–1.62, $P = 0.89$) in patients with ITC (Table 3).

The effect of breast-conserving radiotherapy on the axilla could be questioned. Therefore, an additional multivariate analysis with separate adjustments for axillary radiotherapy and type of surgery was made. In this analysis there was still no significant difference in overall survival between patients with and without ALND with a HR of 1.23 (95 % CI 0.91–1.65, $P = 0.18$) in the common group of patients, HR of 1.33 (95 % CI 0.95–1.87, $P = 0.10$) in patients with micrometastases and HR of 1.00 (95 % CI 0.59–1.69, $P = 0.99$) in patients with ITC.

There was no significant interaction between adjuvant treatment and ALND.

Table 2 Axillary recurrence and overall survival in 2074 Danish breast cancer patients with micrometastases or ITC in the sentinel node treated between 2002 and 2008

5 years cumulated incidence	Micrometastases		Isolated tumor cells	
	ALND		ALND	
	Yes	No	Yes	No
Axillary recurrence	1.44 (0.09–2.15)	1.04 (0.09–5.11)	1.90 (0.71–4.15)	3.96 (1.04–10.2)
OS (95 % CI)	91.8 (90.3–93.1)	79.4 (71.6–85.3)	93.3 (89.8–95.6)	87.3 (79.1–92.4)

ITC isolated tumor cells, *ALND* axillary lymph node dissection, *OS* overall survival

Table 3 Adjusted Cox proportional hazard ratios for axillary recurrence and death if ALND is omitted compared to patients with ALND in 2074 Danish breast cancer patients with micrometastases or ITC in the sentinel node treated between 2002 and 2008

	Axillary recurrence			Death		
	HR[a]	95 % CI	*P* value	HR[b]	95 % CI	*P* value
Micrometastases $n = 1673$	1.79	0.41–7.80	0.44	1.21	0.86–1.69	0.27
ITC $n = 401$	2.21	0.54–8.95	0.27	0.96	0.57–1.62	0.89
Micrometastases or ITC $n = 2074$	1.99	0.72–5.50	0.18	1.13	0.84–1.52	0.41

ITC isolated tumor cells, *ALND* axillary lymph node dissection, *HR* hazard ratio, *CI* confidence interval

[a] Adjustment for age

[b] Adjustment for age, tumor size, histology type, malignancy grade, lymphovascular invasion, hormone receptor status, nodal status, co-morbidity, adjuvant systemic treatment, and adjuvant radiotherapy

Discussion

In this nationwide study, the axillary recurrence rate among women with micrometastases or ITC was generally low. There was a trend towards an increasing risk of axillary recurrence if ALND was omitted, especially in patients with ITC. However, because of the generally low recurrence rate, this can be considered without clinical relevance and did not affect survival. An impaired survival was seen in the selected group of patients without ALND, but after adjusting for risk factors, co-morbidity and adjuvant systemic and loco-regional treatment no significant difference was seen in overall survival between patients with and without ALND.

The results were based on data from the national DBCG database. Data have been prospectively collected and registered on standardized forms in the DBCG database. In addition, extensive validation was done by cross checking data with the original corresponding files. The nationwide material resulted in a large sample size on 2074 patients, more than sufficient to show a clinically relevant difference in axillary recurrence and survival between patients with and without an ALND. In addition the sample size made a multivariate design possible regarding survival. In contrast to other large databases [22], the DBCG database contains information on adjuvant loco-regional radiotherapy and adjuvant systemic treatment as well as follow-up status. In addition, information on co-morbidity was collected from a national registry. Adjustments for these factors are important to get a valid result. Finally, a median follow-up on 6–8 years allowed sufficient time for a recurrence to develop. Development of axillary recurrence from minimal metastatic disease left in the axilla may take longer that what is experienced after macrometastatic disease. A study of long-term outcome of patients with hematoxylin-eosin negative SNs, where patients with occult metastases did not receive ALND, showed a medium time to any disease recurrence on 4.8 years [24]. Hence, a follow-up on in average 5 years, as seen in previous studies [12, 18], may not be sufficient for an axillary recurrence to develop.

Nevertheless, this is a cohort study without the advantages of randomization. Patients without ALND is a highly selected group of patients with older age, higher degree of co-morbidity, and less aggressive adjuvant treatment. The low number of axillary recurrences did not allow us to adjust for any other risk factors than age, or adjustment for adjuvant treatment, when calculating the risk of axillary recurrence. It cannot be excluded that such an adjustment would have changed the results. Finally, information on adjuvant treatment was divided into any kind of adjuvant systemic treatment and any kind of radiotherapy. We did not distinguish between chemotherapy and anti-estrogen therapy, or between patients completing or not completing therapy.

Previous studies have investigated the impact of ALND on axillary recurrence and overall survival in patients with micrometastases or ITC in the SNs. Most studies are however small without multivariate analysis and with limited follow-up. Only one study, including 273 patients, showed a decreased overall survival in patients with ITC after omission of ALND [11], while other studies have not been able to show an increase in axillary recurrence or mortality if ALND is omitted in patients with micrometastases [14–17] or ITC [13] in the SN. However, these studies only included between 45 and 81 patients and the event rate was low [13–17]. With the low incidence of axillary recurrence in patients with micrometastases or ITC in the SN on only 1–2 % after 5 years of follow-up [9, 22, 23, 25] a large sample size on more than 1400 patients is needed to gain enough power to show a difference. Only about 9 % of breast cancer patients have micrometastases and 2 % have ITC in the SN [26] making it difficult to get such a large sample size in a single institution.

Two larger register studies exist of SLNB alone versus SLNB + ALND in patients with micrometastases. They included 6838 and 10,259 patients, respectively [22, 23].

None of these studies could show a difference in outcome between patients with and without ALND. However, these register studies have limitations like limited data on recurrences and imprecise SN count with a median of 11 SNs removed in one of the studies [23]. Furthermore, missing information on adjuvant systemic therapy and radiation field make the results less useful to estimate the impact of ALND, because adjuvant treatment, along with ALND, plays an important role in local disease control. In fact, the recent randomized AMAROS trial showed that SN positive breast cancer patients treated by axillary radiotherapy did not have an increased risk of axillary recurrence compared to patients offered ALND [27].

In contrast to these register studies, a large Dutch cohort study, including nearly 1000 patients with micrometastases and 800 patients with ITC, reported a significantly higher 5 years axillary recurrence rate in patients with micrometastases if ALND was omitted. A similar but insignificant trend was seen for patients with ITC in a multivariate design [12]. The study included information on adjuvant treatment. Nearly half of the patients (47 %) did not receive adjuvant systemic treatment.

Two randomized trials, the IBCSG23-01 trial and the AATRN 048/13/2000 trial, has compared outcome with and without ALND in breast cancer patients with only micrometastases or ITC in the SN [18, 28]. A total number of 931 and 233 patients, respectively, were included in the trials. Both trials closed down before they met the final accrual goal. Like in our study, the risk of axillary recurrence was generally low. No difference in overall survival was seen after a median follow-up of 5 years. The results are in line with the results from the randomized ACOSOG Z011 trial for patients with breast-conserving surgery and macrometastases in the SN.

In contrast to the Dutch study [12], more than 90 % of patients in our study as well as in the IBCSG23-01 trial received adjuvant systemic treatment. It has been shown that patients with micrometastases or ITC do not have a worse prognosis compared to node negative patients if they receive adjuvant systemic treatment, in contrast to untreated patients [7, 29]. The high rate of adjuvant treatment in the IBCSG23-01 trial as well as in this study may have offset the increased risk of axillary recurrence seen in the Dutch study in patients without ALND. It is possible that especially patients without adjuvant systemic treatment would benefit from ALND. We found no interaction between ALND and adjuvant treatment. However, only a small proportion of patients did not receive any kind of adjuvant treatment and because of that the results should be taken with caution.

In our study, a larger proportion of patients with ALND received adjuvant systemic treatment compared to patients without ALND; 93 versus 77 %. The difference in the proportion of patients offered adjuvant systemic treatment was largest in patients with ITC in the SN. Likewise, significantly more patients with ALND received loco-regional radiotherapy compared to patients where ALND had been omitted (Table 1). In Denmark loco-regional radiotherapy towards periclavicular, axillary level III and, for right side breast cancers, the internal mammary nodes is offered patients with macrometastatic spread to axillary lymph nodes as a routine. None of the included patients had macrometastases in the SN. Hence, macrometastases was only identified in patients with a completion ALND, while occult macrometastases in patients without ALND was left untreated. This difference in axillary treatment will further increase the advantage of ALND on axillary recurrence. Furthermore, half of the patients in the study received radiotherapy as a part of breast-conserving treatment, which can have affected the lower part of the axilla. Again, this treatment was offered to a larger proportion of patients in the group with ALND. It was not possible to adjust for loco-regional radiotherapy, type of surgery or adjuvant systemic treatment when calculating HR for axillary recurrence in our study, because of the low number of events. The trend towards an increased axillary recurrence rate in patients without ALND, especially seen in patients with ITC, may reflect undertreatment by radiotherapy as well as adjuvant systemic treatment of older patients and patients with co-morbidity. However, this does not seem to affect their lifespan. A similar trend towards a poorer outcome in patients with ITC if ALND, as well as adjuvant treatment, is omitted has been shown earlier [11, 30]. Again, these results indicate that omission of ALND is only safe if adjuvant systemic treatment is given. Today, the majority of patients are receiving adjuvant systemic treatment [26, 31].

The existing randomized trials, where SN positive patients are treated by ALND or no ALND, included no, or less than 10 % with mastectomies [2, 18, 28]. It has been argued that omission of ALND in SN positive patients is only safe in patients offered breast-conserving surgery, because breast-conserving radiotherapy may affect the lower part of the axilla and treat lymph node metastases if left behind. In our study, we included 859 patients (40 %) treated by mastectomy, and multivariate analysis was made with adjustment for any kind of adjuvant radiotherapy, including breast-conserving radiotherapy, or adjustment for axillary radiotherapy only. In neither of the analyses a difference was found in overall survival between patients with and without ALND. Accordingly, our results support safe omission of ALND in patients treated by mastectomy as well as breast-conserving surgery if only micrometastases or ITC are found in the SN.

In conclusion, this study adds to the increasing evidence that omission of ALND in patients with minimal metastatic

disease in the SN can safely be omitted even in patients treated by mastectomies, probably because a minor increased risk of axillary recurrences can be offset by the use of adjuvant systemic treatment.

Compliance with ethical standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the Danish Data Protection Agency (J.nr. 2009-41-3703).

References

1. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K (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 252:426–432
2. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569–575
3. Cserni G, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, Sandrucci S, Baltas B, Bussolati G (2004) Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 91:1245–1252
4. van Deurzen CH, de Boer M, Monninkhof EM, Bult P, van der Wall e, Tjan-Heijnen VC, van Diest PJ (2008) Non-sentinel lymph node metastases associated with isolated breast cancer cells in the sentinel node. J Natl Cancer Inst 100:1574–1580
5. Naik AM, Fey J, Gemignani M, Heerdt A, Montgomery L, Petrek J, Port E, Sacchini V, Sclafani L, VanZee K, Wagman R, Borgen PI, Cody HS III (2004) The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg 240:462–468
6. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Scarth HM, Wolmark N (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 11:927–933
7. Salhab M, Patani N, Mokbel K (2011) Sentinel lymph node micrometastasis in human breast cancer: an update. Surg Oncol 20:e195–e206. doi:10.1016/j.suronc.2011.06.006
8. Pepels MJ, Vestjens JH, de Boer M, Smidt M, van Diest PJ, Borm GF, Tjan-Heijnen VC (2011) Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review. Breast Cancer Res Treat 125:301–313
9. Erb KM, Shapiro-Wright HM, Julian TB (2010) Axillary recurrences following positive sentinel lymph node biopsy with individual tumor cells or micrometastases and no axillary dissection. Breast Dis 31:83–90
10. Francissen CM, Dings PJ, van Dalen T, Strobbe LJ, van Laarhoven HW, de Wilt JH (2012) Axillary recurrence after a tumor-positive sentinel lymph node biopsy without axillary treatment: a review of the literature. Ann Surg Oncol 19:4140–4149
11. Cox CE, Kiluk JV, Riker AI, Cox JM, Allred N, Ramos DC, Dupont EL, Vrcel V, Diaz N, Boulware D (2008) Significance of sentinel lymph node micrometastases in human breast cancer. J Am Coll Surg 206:261–268
12. Pepels MJ, de Boer M, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers MB, van Diest PJ, Borm GF, Tjan-Heijnen VC (2012) Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg 255:116–121
13. Degnim AC, Zakaria S, Boughey JC, Sookhan N, Reynolds C, Donohue JH, Farley DR, Grant CS, Hoskin T (2010) Axillary recurrence in breast cancer patients with isolated tumor cells in the sentinel lymph node [AJCC N0(i+)]. Ann Surg Oncol 17:2685–2689. doi:10.1245/s10434-010-1062-8
14. Onishi T, Jinno H, Takahashi M, Hayashida T, Sakata M, Nakahara T, Shigematsu N, Mukai M, Kitagawa Y (2010) Non-sentinel lymph node status and prognosis of breast cancer patients with micrometastatic sentinel lymph nodes. Eur Surg Res 45:344–349
15. Pernas S, Gil M, Benitez A, Bajen MT, Climent F, Pla MJ, Benito E, Guma A, Gutierrez C, Pisa A, Urruticoechea A, Perez J, Gil GM (2010) Avoiding axillary treatment in sentinel lymph node micrometastases of breast cancer: a prospective analysis of axillary or distant recurrence. Ann Surg Oncol 17:772–777
16. Fan YG, Tan YY, Wu CT, Treseler P, Lu Y, Chan CW, Hwang S, Ewing C, Esserman L, Morita E, Leong SP (2005) The effect of sentinel node tumor burden on non-sentinel node status and recurrence rates in breast cancer. Ann Surg Oncol 12:705–711
17. Rayhanabad J, Yegiyants S, Putchakayala K, Haig P, Romero L, DiFronzo LA (2010) Axillary recurrence is low in patients with breast cancer who do not undergo completion axillary lymph node dissection for micrometastases in sentinel lymph nodes. Am Surg 76:1088–1091
18. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 14:297–305
19. Moller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Hansen HB, Christiansen P, Mouridsen HT (2008) The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. Acta Oncol 47:506–524
20. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark G, Edge SB, Hayes DF, Hughes LL, Hutter RV, Morrow M, Page DL, Recht A, Theriault RL, Thor A, Weaver DL, Wieand HS, Greene FL (2002) Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 20:3628–3636
21. Christiansen P, Friis E, Balslev E, Jensen D, Moller S (2008) Sentinel node biopsy in breast cancer: five years experience from Denmark. Acta Oncol 47:561–568
22. Yi M, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, Bedrosian I, Rourke L, Hunt KK (2010) Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. Ann Surg Oncol 17:343–351
23. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, Winchester DP, Winchester DJ (2009) Comparison of sentinel lymph node biopsy alone and completion axillary

lymph node dissection for node-positive breast cancer. J Clin Oncol 27:2946–2953
24. Kapoor NS, Sim MS, Lin J, Giuliano AE (2012) Long-term outcome of patients managed with sentinel lymph node biopsy alone for node-negative invasive breast cancer. Arch Surg 16:1–7
25. Galimberti V, Botteri E, Chifu C, Gentilini O, Luini A, Intra M, Baratella P, Sargenti M, Zurrida S, Veronesi P, Rotmensz N, Viale G, Sonzogni A, Colleoni M, Veronesi U (2012) Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? Breast Cancer Res Treat 131:819–825. doi:10.1007/s10549-011-1486-2
26. Tvedskov TF, Jensen MB, Balslev E, Ejlertsen B, Kroman N (2011) Stage migration after introduction of sentinel lymph node dissection in breast cancer treatment in Denmark: a nationwide study. Eur J Cancer 47:872–878
27. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ (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 15:1303–1310. doi:10.1016/S1470-2045(14)70460-7
28. Sola M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S (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 20:120–127. doi:10.1245/s10434-012-2569-y
29. de Boer M, van Deurzen CH, van Dijck JA, Borm GF, van Diest PJ, Adang EM, Nortier JW, Rutgers EJ, Seynaeve C, Menke-Pluymers MB, Bult P, Tjan-Heijnen VC (2009) Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med 361:653–663
30. Kihara SM, Giblett NA, McNeil C, Crea P (2010) Sentinel node micrometastases in breast cancer: clinical outcome. Asia Pac J Clin Oncol 6:330–341
31. Gnant M, Harbeck N, Thomssen C (2011) St. Gallen 2011: summary of the consensus discussion. Breast Care (Basel) 6:136–141