EUROPEAN JOURNAL OF CANCER 47 (2011) 872–878

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Stage migration after introduction of sentinel lymph node dissection in breast cancer treatment in Denmark: A nationwide study

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ARTICLE INFO

Article history:
Received 26 August 2010
Received in revised form 19 November 2010
Accepted 24 November 2010
Available online 29 December 2010

Keywords:
Breast neoplasms
Sentinel lymph node biopsy
Neoplasm metastasis
Neoplasm staging

ABSTRACT

Purpose: To estimate the size and therapeutic consequences of stage migration after introduction of sentinel lymph node dissection (SLND) in breast cancer treatment in Denmark.
Patients and methods: We compared the distribution of lymph node metastases in breast cancer patients operated in 1993–1996 and 2005–2008; before and after introducing SLND. The study was based on data from the national Danish Breast Cancer Cooperative Group (DBCG) database.
Results: We included 24,051 patients in the study; 10,231 patients from the first period and 13,820 from the second period. The proportion of patients having macrometastases was not significantly different in the two periods, whereas the proportion of patients with micrometastases increased from 5.1% to 9.0% ($P < 0.0001$). However, this only resulted in an estimated change, from 7.8% to 8.8%, in the proportion of patients offered adjuvant systemic treatment due to positive nodal status as the only high-risk criterion, when using today's criteria for risk-allocation. In addition, we found that negative hormone receptor status was associated to negative nodal status when adjusted for confounders (odds ratios (OR) 0.83, $P < 0.0001$).
Conclusion: Introduction of SLND in breast cancer treatment in Denmark has resulted in a stage migration on 4% due to identification of more micrometastases. However, this stage migration has only minor impact on patients offered adjuvant systemic treatment because nodal status today is less important in risk-allocation.

1. Introduction

Axillary nodal status is the most important prognostic factor in breast cancer. Axillary lymph node dissection (ALND) has until recently been the standard procedure for staging of the axilla, but this procedure is associated with considerable morbidity[1] and is redundant for women without lymph node metastases. Sentinel lymph node dissection (SLND) has gradually replaced ALND as standard procedure, because it can accurately stage the axilla by removing in average only two lymph nodes.[2] Following SLND, patients are only recommended ALND in case of verified sentinel node metastases.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.11.022

After ALND, the removed lymph nodes are traditionally examined by standard microscopy of a few haematoxylin–eosin stained histological sections. More extensive histopathological examinations using immunohistochemical staining on multi-sections of all removed lymph nodes will identify metastasis in 9–31% of the cases considered negative by standard examination.[3] These time-consuming methods are not used routinely in ALND, but are feasible following SLND. As a result more metastases, including micrometastases, are found.[4] Hence, more patients are diagnosed as being node positive and classified as having a more advanced stage of the disease, resulting in stage migration or Will Rogers phenomenon as described by Feinstein.[5]

The magnitude of this stage migration has been investigated previously,[6–14] but only few studies have been population-based[7–9] and none have been nationwide. The consequences of stage migration on patients offered adjuvant treatment have not been systematically investigated and are basically unknown.

In Denmark, the Danish Breast Cancer Cooperative Group (DBCG) database gives us a unique opportunity for a nationwide study on stage migration.

The purpose of the present study was to estimate the size and therapeutic consequences of stage migration after introduction of SLND in breast cancer treatment in Denmark.

2. Patients and methods

In Denmark, clinical and histopathological data as well as information on treatment and follow-up status of women with breast cancer have been prospectively registered in a national database managed by DBCG since 1977. Furthermore, DBCG describes guidelines for breast cancer treatment in Denmark. Today the database contains information on more than 80,000 breast cancer patients.[15]

SLND was introduced in Denmark in 1997 and completely implemented in all Danish surgical departments by the end of 2004.[16] Today, SLND is a standard procedure in Denmark for axillary staging of women with unifocal breast cancers without verified lymph node metastases and without history of operation in the upper lateral quadrant of the breast.[2] All removed sentinel nodes are examined according to the national DBCG guidelines with at least two step sections 500 μm apart of the bivalved sentinel node. In case of no metastases found by haematoxylin–eosin staining, immunohistochemical cytokeratin staining is performed. Lymph nodes removed by ALND are examined by bisectioning and haematoxylin–eosin staining. Metastases are classified as described by the American Joint Committee on Cancer (AJCC)[17] in combination with cell counts defining metastases with between 10 and 100 tumour cells as micrometastases and with less than 10 cells as isolated tumour cells.[2] In the primary tumour, hormone receptor status is defined from percentage of stained tumour cells where patients with staining for either oestrogen or progesterone receptors in $\geqslant$10% of the cells are considered as being hormone receptor positive.

We estimated the size of stage migration by comparing the distribution of lymph node metastases in breast cancer patients operated in two different periods of 4 years: from 1993 to 1996 and from 2005 to 2008. Data on lymph node metastases, age at diagnosis, hormone receptor status, tumour size, histological type and malignancy grade were retrieved from the DBCG database. All registered patients, regardless of inclusion in specific treatment protocols, were included in the study to avoid selection bias. We collected missing information on nodal status manually from the original pathology file when possible. Altogether, 1617 patients were excluded: 53 patients from the first period due to missing information on nodal status and 1038 patients from the first and 526 patients from the second period due to missing information of the number of lymph nodes removed or less than four lymph nodes removed by ALND.

To investigate if the introduction of SLND had changed the proportion of patients offered adjuvant systemic treatment, we divided patients from the two periods into risk groups according to the risk criteria described at the 10th St. Gallen International Expert Consensus Meeting 2007 (Table 2).[18] Accordingly, negative nodal status, tumour size $\leqslant$ 2 cm, positive or unknown hormone receptor status, age $\geqslant$ 35 years and ductal carcinoma malignancy grade I or unknown grade were considered as low risk criteria. Furthermore, non-ductal carcinoma was considered as a low risk criterion, because only ductal carcinomas were graded histologically in the first period. HER2 status and peritumoural vascular invasion were not included as risk criteria when comparing the two periods because these parameters were only measured in the last period.

The study was approved by the Ethical Committees of the Capital Region, protocol no. H-4-2009-087, and by the Danish Data Protection Agency.

2.1. *Statistical analysis*

The DBCG Data Centre was responsible for data collection and data analysis. Associations between pairs of variables were analysed by the χ^2-test (excluding unknowns). Univariate and multivariate logistic regression models were applied to examine the effect of age at diagnosis, tumour size, histological type and grade, hormone receptor status and period on nodal status. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and the Wald test was used to test the overall significance of each parameter. For departments of pathology involved in both periods, a multivariate model including interaction terms of departments and period was set up to test heterogeneity using the Wald test. Two-tailed P-values were applied and level of significance was set to 5%. All statistical analyses were done using SAS 9.1 (SAS Institute, Cary, NC, USA).

3. Results

We included a total of 24,051 patients in the study; 10,231 patients were operated between 1993 and 1996, and 13,820 patients were operated between 2005 and 2008. Patient and tumour characteristics are described in Table 1. In 2005–2008, we identified 307 patients having only isolated tumour cells in their lymph nodes. These patients are considered as node negative when staged according to the AJCC[17] and were

Table 1 – Patient and tumour characteristics by period of diagnosis among 24,051 breast cancer patients in Denmark.

Period of diagnosis	1993–1996		2005–2008	
	No.	%	No.	%
Number of patients	10,231	100	13,820	100
Removed LN(lymph nodes) by ALND (axillary lymph node dissection)				
4–9 removed LN	3302	32.3	510	6.9
⩾10 removed LN	6929	67.7	6893	93.1
Nodal status				
Node negative	5565	54.4	6952[a]	50.3
Node positive: macrometastases	4144	40.5	5630	40.7
Node positive: micrometastases	522	5.1	1238	9.0
Age (years)				
⩽34	193	1.9	217	1.6
35–39	441	4.3	501	3.6
40–49	1933	18.9	1885	13.6
50–59	2761	27.0	3539	25.6
60–69	2729	26.7	4433	32.1
⩾70	2174	21.2	3245	23.5
Tumour size (mm)				
1–10	1521	14.9	2223	16.1
11–20	4000	39.1	5701	41.3
21–50	3935	38.5	5278	38.2
⩾51	519	5.1	512	3.7
Unknown	256	2.5	106	0.8
Histological type and grade				
Ductal grade I	2746	26.8	3281	23.7
Ductal grade II	3378	33.0	4914	35.6
Ductal grade III	1651	16.1	2963	21.4
Ductal grade unknown	287	2.8	219	1.6
Lobular grade I–III	1232	12.0	1391	10.1
Other	937	9.2	1052	7.6
Hormone receptor status				
Positive	6820	66.7	11,375	82.3
Negative	2260	22.1	2376	17.2
Unknown	1151	11.3	69	0.5
Risk allocation				
High-risk	7276	71.1	10,058	72.8
Low risk	2802	27.4	3731	27.0
Allocation not possible	153	1.5	31	0.2

[a] The number includes 307 patients with only isolated tumour cells in the lymph nodes.

Table 2 – Criteria for risk allocation.

	Danish high-risk criteria 2007	St. Gallen intermediate- or high-risk criteria 2007	High-risk criteria used in the present study
Nodal status	Positive	Positive	Positive
Tumour size	>2 cm	>2 cm	>2 cm
Age at diagnosis	<35 years	<35 years	<35 years
Grade	Ductal grade 2–3 Lobular grade 3	Grade 2–3	Ductal grade 2–3
Hormone receptor status	Negative	Negative	Negative
HER2 status	Positive	Positive	Not used
Peritumoural vascular invasion	Not used	Present	Not used

included in the group of node negative patients. No patients with only isolated tumour cells were registered in the first period. The distribution of nodal status, age at diagnosis, tumour size, hormone receptor status, histological type and grade changed significantly over time. From the first to the second period we found an increasing age at diagnosis ($P < 0.0001$), increasing grade ($P < 0.0001$), increasing proportion of patients having ductal carcinomas ($P < 0.0001$),

increasing proportion of patients having hormone receptor positive tumours ($P < 0.0001$) and a decreasing tumour size ($P < 0.0001$) (Table 1).

The overall number of node positive patients increased significantly from 45.6% before to 49.7% after introduction of SLND; the proportion of patients with micrometastases increased from 5.1% to 9.0% ($P < 0.0001$), whereas the proportion of patients having macrometastases was unchanged. In a univariate analysis the risk of being node positive was significantly increased after introduction of SLND compared to before (OR 1.18; CI 1.12–1.24, $P < 0.0001$). Furthermore, the risk of being node positive was significantly related to histological type and grade, increasing tumour size and younger age. There was no significant difference in the risk of having lymph node metastases between patients with positive or negative hormone receptor status (Table 3).

In a multivariate analysis, adjusting for changes in tumour size, age at diagnosis, hormone receptor status, histological type and grade, the risk of being node positive when operated in the last period compared to the first remained significantly increased (OR 1.20; CI 1.14–1.28, $P < 0.0001$) (Table 3). When specifying this analysis according to the risk of having either macrometastases or micrometastases, we found an even more increased risk for having micrometastases after introduction of SLND compared to before (OR 1.85; CI 1.65–2.07, $P < 0.0001$) while the risk of having macrometastases was unchanged (OR 1.01; CI 0.95–1.07, $P = 0.77$). In the multivariate analysis younger age, increasing tumour size and histological grade remained significantly related to node positive disease ($P < 0.0001$), but in contrast to the results of the univariate analysis, negative hormone receptor status turned out to be significantly related to negative nodal status (OR 0.83; CI 0.77–0.90, $P < 0.0001$). Patients with unknown hormone receptor status were found to be significantly related to negative nodal status as well (OR 0.81; CI 0.71–0.92; $P < 0.0001$). However, this group represented only 5% of all patients and negative hormone receptor status remained significantly related to negative nodal status when compared to the common group of patients with either positive or unknown hormone receptor status (OR 0.85; CI 0.79–0.91; $P < 0.0001$).

To examine whether different departments of pathology in Denmark contributed equally to the increase in the amount of node positive patients after introduction of SLND, sub-analyses were made for single departments of pathology. Nine departments were no longer part of a breast unit in the last period because of centralisation of breast cancer treatment in Denmark. For the remaining 16 departments multivariate analyses adjusting for changes in tumour size, age at diagnosis, hormone receptor status, histological type and grade were made to investigate interactions between department and period. A total of 21,276 patients were included in these sub-analyses; 7478 operated in 1993–1996, and 13,798 in

Table 3 – Probability of positive axillary lymph nodes (macro- or micrometastases) among 24,051 breast cancer patients in Denmark treated in 1993–1996 or 2005–2008.

	Univariate analysis			Multivariate analysis		
	OR (odds ratio)	95% CI (confidence interval)	P-value	OR	95% CI	P-value
Period of diagnosis			<0.0001			<0.0001
1993–1996	1			1		
2005–2008	1.18	1.12–1.24		1.20	1.14–1.28	
Age at diagnosis (years)			<0.0001			<0.0001
⩽34	1.46	1.20–1.79		1.34	1.08–1.66	
35–39	1.31	1.14–1.50		1.26	1.09–1.46	
40–49	1.28	1.19–1.39		1.26	1.16–1.37	
50–59	1.18	1.10–1.27		1.21	1.13–1.30	
60–69	1			1		
⩾70	1.15	1.08–1.24		0.96	0.89–1.04	
Tumour size (mm)			<0.0001			<0.0001
1–10	0.41	0.38–0.45		0.43	0.39–0.47	
11–20	1			1		
21–50	2.29	2.16–2.43		2.31	2.18–2.46	
⩾51	6.57	5.57–7.74		6.91	5.84–8.17	
Unknown	1.38	1.12–1.70		1.81	1.45–2.25	
Type and grade			<0.0001			<0.0001
Ductal grade I	0.57	0.53–0.61		0.73	0.68–0.78	
Ductal grade II	1			1		
Ductal grade III	1.14	1.06–1.23		0.98	0.90–1.06	
Ductal grade unknown	0.55	0.46–0.66		0.69	0.57–0.84	
Lobular grade I–III	0.84	0.77–0.91		0.75	0.69–0.83	
Other	0.36	0.33–0.40		0.39	0.35–0.43	
Hormone receptor status			<0.0001			<0.0001
Positive	1			1		
Negative	1.05	0.99–1.12		0.83	0.77–0.90	
Unknown	0.72	0.64–0.82		0.81	0.71–0.92	

2005–2008. Odds ratios for being node positive in 2005–2008 compared to 1993–1996 did not vary significantly between the single departments of pathology ($P = 0.11$).

Finally, we estimated the impact of the increased proportion of node positive patients on the proportion offered adjuvant systemic treatment. Patients from the two periods were divided into risk groups according to the modified St. Gallen risk criteria as described (Table 2). By doing this, we estimated that 71% of the patients in the first period and 73% of the patients in the second period would have been high-risk patients according to the risk-criteria of today (Table 1), and out of those only 788 patients (150 with micrometastases, 638 with macrometastases) in the first period, corresponding to 7.8% of the patients, and 1217 patients (361 with micrometastases, 856 with macrometastases) in the last period, corresponding to 8.8% of the patients, became high-risk patients because of positive nodal status as the only high-risk criterion. The majority became high-risk patients regardless of nodal status but due to the existence of other high-risk criteria. The minor increase in high-risk patients caused by nodal status, from 7.8% to 8.8%, was, however, significant ($P = 0.006$). In the last period, 75% of the included patients (10,433 patients) underwent SLND. If we used all available risk-criteria defined at the 10th St. Gallen International Expert Consensus Meeting 2007,[18] including HER2 status, peritumoural vascular invasion and histological grading of lobular carcinomas, the proportion of high-risk patients increased even further to 80% of the patients (8334 patients) and still only a minor proportion, 7.9% (820 patients), had nodal status as the only high-risk criterion.

4. Discussion

In this nationwide study, we examined the influence of introducing SLND on the proportion of lymph node positive patients in 24,051 breast cancer patients. Our results provide support for an absolute increase in the proportion of node positive patients on nearly 4% points, exclusively due to more women diagnosed with micrometastases. However, this stage migration resulted in only 1% absolute increase in the proportion of patients who, according to current guidelines, would be offered adjuvant systemic treatment.

This study has some potential limitations. First, misclassification could arise if the pathologists were not consistent in how they evaluated nodal metastases.[19] In this study, the Danish departments of pathology reported the results of nodal examination prospectively during the study period using a standardised form. To examine whether heterogeneity between departments had any impact on our results we calculated odds ratios for being node positive for every single department of pathology. This revealed no significant differences in odds ratios between the departments. Thus, the DBCG data on nodal status, used in this study, are not significantly affected by minor local differences in pathology procedures and can be considered as quite uniform.

Second, we found a significant drift in risk factors for having lymph node metastases over time which made it difficult to compare different periods. A decrease in average tumour size over time as well as an increase in oestrogen receptor positive tumours and age at diagnosis have been shown earlier,[20–22] and could be explained by the introduction of mammography screening in some Danish counties.[21,22] It may also represent a trend towards an overall biologically less aggressive disease, but at the same time, an increase in malignancy grade was seen, pointing in the opposite direction. These opposite trends resulted in a basically unchanged proportion of high-risk patients (Table 1). Malignancy grading is to some degree a subjective measurement and changes in registrational practice could theoretically explain the trend towards increasing grade. Still, there have been no change in Danish grading guidelines between the two periods[22] and furthermore, a large intraobserver agreements in malignancy grading have been shown.[23] Further studies are needed to evaluate the observed increase in grade.

After adjustment for the described changes, when estimating the size of stage migration, the risk of being node positive after introduction of SLND remained significantly increased compared to the period before. The risk was still only increased in the group of patients with micrometastases. That implies that the increase in micrometastases after introduction of SLND is actually the result of a more extensive lymph node examination and cannot be explained by changes in age at diagnosis, tumour size, hormone receptor status and malignancy grade over time.

The strengths of our study include its large sample size of more than 24,000 breast cancer patients and its population-based approach including 94% of all breast cancer patients registered in the national DBCG database in the two periods. Data in the DBCG database have been prospectively collected from all Danish women with breast cancer and more than 95% concordance with the Danish Cancer Register and the National Pathology Register, which are considered close to complete, has been shown.[15] Accordingly, existing discrepancies in the proportion of node positive patients and in tumour size between the DBCG database and national databases from other contries[24] are not likely to be caused by incomplete registration but could rather be explained by differences in population and breast cancer screening policies.

Among other studies investigating the magnitude of stage migration after introduction of SLND,[6–14] only three studies have been population-based.[7–9] In The Netherlands van der Heiden-van der Loo and colleagues have investigated the magnitude of stage migration in 3665 patients in the central part of the country during the introduction of SLND.[7] They found that the proportion of node positive patients increased significantly from 28% in 1997 to 38% in 2002 and this increase was mainly caused by micrometastases. In contrast, Maaskant and colleagues made a similar investigation on 17,100 patients in the south-eastern part of The Netherlands, but included the entire population in the investigated area and the complete period for the introduction of SLND. They found a much lower increase in percentage of patients having micrometastases from 1% in 1994 to 4.3% in 2005.[9] In Denmark, stage migration after introduction of SLND has been investigated in a smaller study including 2116 patients from two different counties. An increase in the proportion of node positive patients of 7.3% and 13.3%, respectively, was found from 1996–1997 to 2002–2003.[8] These variations in the size of stage migration between different studies may reflect local differences in lymph node examinations but may also be a

result of different study sizes and study periods. Our estimated size of stage migration on nearly 4% is similar to the findings of Maaskant and colleagues which is the only previous study excluding the complete period for implementing SLND in the entire population.[9] Our findings of an increase in node positive patients exclusively represented by micrometastases confirm the results of several previous studies.[7–9]

In our study, the number of lymph nodes excised increased from the first to the second period (Table 1). It has previously been shown that the proportion of node positive patients will increase with increasing number of lymph nodes examined.[25] In Denmark, removal of at least 10 lymph nodes is today required for sufficient surgery when ALND is performed,[15] but this was not the case in the first period of our study where many patients had only between 4 and 9 lymph nodes removed. It should be noted that this will tend to underestimate the number of node positive patients in the first period and consequently the magnitude of stage migration caused by the introduction of SLND alone will be lower than the estimate found in this study.

In addition to the main results, we showed that positive nodal status was related to younger age and increasing tumour size, which is in accordance to the literature.[26,27] Moreover, we showed that negative nodal status was significantly related to negative hormone receptor status, as an independent factor, despite the fact that hormone receptor negative tumours generally are considered being biologically more aggressive.[20] Reports on hormone receptor status in relation to lymph node metastases are controversial.[27,28] One of the largest studies on the subject included 18,025 patients and showed the same relation between node negative disease and negative hormone receptor status as we do, indicating that this is a true observation.[26] Still, our results are based on patients from two different time periods and a study including patients between the two periods should be performed to confirm the results.

The prognostic significance of micrometastases in the sentinel node remains unclear and identification of more micrometastases after introduction of SLND,[29] leading to stage migration, might cause overtreatment of these patients.[30] We, therefore, investigated the therapeutic consequences of this stage migration. The criteria for offering adjuvant systemic treatment have changed over years.[15,18] By allocating patients from the two periods into risk groups according to the risk criteria of today (Table 2), we showed that introduction of SLND had only minor effect on the number of patients offered adjuvant systemic treatment, with only 1% absolute increase in the proportion of patients with positive nodal status as the only high-risk criterion.

The national criteria for risk allocation used in Denmark are slightly more conservative than the modified St. Gallen criteria used in this study (Table 2).[15] Using more conservative high-risk criteria will tend to increase the effect of stage migration on patients offered adjuvant treatment. Conversely, the trend towards inclusion of several new high-risk criteria in the decision for adjuvant systemic treatment will diminish the therapeutic consequences of stage migration. In our study, several high-risk criteria were available in the last period. When using all available criteria we found that nodal status was important in risk-allocation of only 10% of high-risk patients offered SLND (820/8334 patients). This indicates that axillary nodal status is losing its significance in the decision for adjuvant systemic treatment.

In conclusion, we found a 4% absolute increase in the proportion of node positive patients after introduction of SLND. The increase was exclusively caused by identification of more micrometastases. However, this stage migration had only minor impact on the proportion of patients offered adjuvant systemic treatment, because nodal status is gradually losing its significance in risk allocation, due to introduction of other risk factors.

Conflict of interest statement

None declared.

Funding

The study was supported by IMK common foundation, HOC research initiative foundation and the Danish cancer research foundation.

Acknowledgements

The study was supported financially by IMK common foundation, HOC research initiative foundation and the Danish cancer research foundation.

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