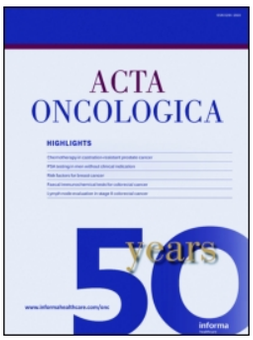

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RESEARCH ARTICLE

Risk of non-sentinel node metastases in patients with symptomatic cancers compared to screen-detected breast cancers

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ABSTRACT

Background: Symptomatic breast cancers may be more aggressive as compared to screen-detected breast cancers. This could favor axillary lymph node dissection (ALND) in patients with symptomatic breast cancer and positive sentinel nodes.

Method: We identified 955 patients registered in the Danish Breast Cancer Cooperative Group (DBCG) Database in 2008 – 2010 with micrometastases (773) or isolated tumor cells (ITC) (182) in the sentinel node. Patients were cross-checked in the Danish Quality Database of Mammography Screening and 481 patients were identified as screen-detected cancers. The remaining 474 patients were considered as having symptomatic cancers. Multivariate analyses of the risk of non-sentinel node metastases were performed including known risk factors for non-sentinel node metastases as well as method of detection.

Results: 18% of the patients had metastases in non-sentinel nodes. This was evenly distributed between patients with symptomatic and screen-detected cancers; 18.5% vs 17.5% (OR 1.07; 95% CI 0.77–1.49; $p = 0.69$). In patients with micrometastases 21% had non-sentinel node metastases in the group with symptomatic cancers compared to 19% of patients with screen-detected cancers. This difference was not significant (OR 1.16; 95% CI 0.81–1.65, $p = 0.43$). Neither the multivariate analysis showed an increased risk of non-sentinel node metastases in patients with symptomatic cancers compared to screen-detected cancers (OR 1.12, CI 0.77–1.62, $p = 0.55$). In patients with ITCs 8% of patients with symptomatic cancers had non-sentinel node metastases compared to 13% of patients with screen-detected cancers. This difference was not significant (OR 0.58; 95% CI 0.22–1.54, $p = 0.27$). In the multivariate analysis, the risk of non-sentinel node metastases was still not significantly increased in patients with symptomatic cancers compared to screen-detected cancers (OR 0.45; 95% CI 0.16–1.27, $p = 0.13$).

Conclusion: We did not find any clinically relevant difference in the risk of non-sentinel node metastases between patients with symptomatic and screen-detected cancers with micrometastases or ITC in the sentinel node.

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Today, sentinel lymph node dissection (SLND) has replaced axillary lymph node dissection (ALND) as standard procedure for staging of the axilla in clinically node negative breast cancer. Until recently, ALND has been recommended to all sentinel node positive breast cancer patients. However, the results from a randomized trial from American College of Surgeons Oncology Group (ACOSOG) (Z0011) have put the benefit from ALND in sentinel node positive patients under debate [1,2]. In the trial on patients undergoing breast conserving surgery, there were no difference in axillary recurrence rate or survival between patients with up to two positive sentinel nodes with or without ALND. As a result, the presence of micrometastases and isolated tumor cells (ITC) in the sentinel node were no longer considered as indication for ALND at the 12th St. Gallen Consensus Conference in 2011 [3]. Since 2012, ALND is no longer performed as a routine in Denmark in breast cancer patients with only micrometastases or ITC in the sentinel node. In case of more than two micrometastatic sentinel nodes or macrometastases, ALND is still recommended.

In the ongoing debate on mammographic screening it has been stated that screening leads to detection and treatment of breast cancers that would otherwise never have been detected because they grow very slow and therefore are clinically irrelevant [4]. Still, around 20% of patients with screen-detected breast cancers have sentinel node metastases at time of diagnosis [5]. If screen-detected cancers include a subgroup of clinically insignificant, slower growing cancers,

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dissemination beyond the sentinel node would be less likely compared to symptomatic cancers. This could advocate for a more aggressive axillary treatment in patients with symptomatic cancers.

In a recent study from Lund University, Grabau et al. have shown a five-fold increased risk of non-sentinel node metastases in symptomatic cancers with micrometastases in the sentinel node compared to screen-detected cancers in a multivariate design [6]. However, the results are based on only 140 breast cancer patients.

In Denmark, a national breast cancer screening program was introduced between 2007 and 2010, where mammographic screening was offered free of charge to all Danish women between the age of 50 and 70 years every second year [7].

The aim of this study was to investigate whether patients with symptomatic breast cancers have a higher risk of non-sentinel node metastases compared to patients with screen-detected cancers in a population of Danish patients with micrometastases or ITC in the sentinel node who underwent ALND.

Patients and methods

Between 2002 and 2010, a total number of 2801 breast cancer patients with micrometastases or ITC in the sentinel node and a completion ALND, were registered in the Danish Breast Cancer Cooperative Group (DBCG) database; 2316 with micrometastases and 485 with ITC. In that period, metastases were classified according to the American Joint Committee on Cancer (AJCC) staging manual [8] 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 [9]. Information on age at diagnosis, tumor size, histology type, malignancy grade, hormone receptor status, HER2 status, number of removed sentinel nodes, number of positive sentinel nodes, lymphovascular invasion, location of tumor in the breast and presence of non-sentinel node metastases have been retrieved from the DBCG database. Data have been validated, and missing information has been collected if possible, using the original pathology files. Based on information from these patients two models have previously been developed and validated for the prediction of non-sentinel node metastases in patients with micrometastases or ITCs in the sentinel node, respectively [10,11]. Large tumor size, high proportion of positive sentinel nodes, lymphovascular invasion, negative hormone receptor status and location of tumor in the upper lateral quadrant of the breast were in a multivariate analysis found to be associated with increased risk of non-sentinel node metastases in patients with micrometastases in the sentinel node. Large tumor size, young age and high proportion of positive sentinel nodes were found to be associated with the risk of non-sentinel node metastases in patients with ITCs in the sentinel node. Method of detection of the breast cancer was not included in these initial models.

Registration of information on screen-detected breast cancers in the nationwide Danish Quality Database of Mammography Screening was initiated during 2007 [7]. Nine hundred and fifty-five of the 2801 patients from the initial cohort were operated between 2008 and 2010, after introduction of the national mammographic screening program, and belonged to the screening population, with age between 50 and 70 at time of surgery. Information on method of detection for these 955 patients was retrieved from the nationwide Danish Quality Database of Mammography Screening. Patients not registered in the Danish Quality Database of Mammography Screening as having screen-detected cancers were considered as having symptomatic cancers.

Statistical analyses

The risk of non-sentinel node metastases in patients with symptomatic cancer compared to patients with screen-detected cancer was analyzed in univariate and multivariate logistic regression models, including the factors identified previously to be statistical significant predictors. Unadjusted and adjusted odds ratio and 95% confidence intervals for non-sentinel node metastases according to method of detection was calculated. The Wald test was used to test the significance of the variables. For ITC, tumor size (>2 vs. $\leq$2 cm) and proportion of positive sentinel nodes (100% vs. <100%) were included, whereas young age (<40) was not included, because only patients between 50 and 70 years were included in the study. For micrometastases, tumor size (cm, trend), proportion of positive sentinel nodes (100% vs. <100%), lymphovascular invasion, hormone receptor status (negative vs. positive) and location of tumor in upper lateral quadrant of the breast were included. Associations between detection method and the characteristics listed in Table I were analyzed by χ^2-test, excluding unknowns. SAS version 9.4 was used for statistical analyses.

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

Results

Of the 955 patients in the screening population, 773 had micrometastases and 182 had ITC in the sentinel node. Half of the patients (481) were identified in the nationwide Danish Quality Database of Mammography Screening as having screen-detected cancers. The remaining 474 patients were considered as having symptomatic cancers. Due to the gradual introduction of the screening program, there was an uneven distribution of cancers detected by screening during the period, with the lowest rate in the first year. Cancers detected by screening were significantly smaller, had lower malignancy grade, lower risk of lymphovascular invasion, and were more often hormone receptor positive than symptomatic cancers. In addition, they had a higher proportion of positive sentinel nodes; 48% of patients with screen-detected breast cancers had metastases in all removed sentinel nodes compared to only 39% of patients with symptomatic cancers ($p < 0.05$). These findings could be explained by the higher proportion of patients with screen-detected cancers with only one sentinel node removed ($p = 0.02$). Patient and tumor characteristics of the 955 included patients are shown in Table I.

A total of 18% of patients had metastases in non-sentinel nodes. This was evenly distributed between patients with

Table I. Patient and tumor characteristics of 955 Danish breast cancer patients with micrometastases or ITC in the sentinel node, operated between 2008 and 2010 and age 50–70 at the time of surgery.

	Screen-detected cancers		Symptomatic cancers		
	No	%	No	%	*p* Value
Total	474	100	481	100	
Metastasis size					0.66
Micrometastases	381	80	392	81	
ITC	93	20	89	19	
NSN metastases					0.69
Yes	83	18	89	19	
No	391	82	392	82	
Operation year					<0.0001
2008	81	17	197	41	
2009	228	48	148	31	
2010	165	35	136	28	
Tumor size					0.0001
0–10 mm	112	24	79	16	
11–20 mm	263	55	242	50	
21–30 mm	80	17	114	24	
>30 mm	18	4	40	8	
Unknown	1	0.2	6	1	
Histology type					0.30
Ductal	401	85	390	81	
Lobular	50	11	54	11	
Other	23	5	34	7	
Unknown	0	0	3	1	
Malignancy grade					<0.0001
I	200	42	116	24	
II	184	39	219	46	
III	49	10	85	18	
Unknown	41	9	61	13	
Lymphovascular invasion					0.02
Yes	45	9	70	15	
No	425	90	405	84	
Unknown	4	1	6	1	
HR receptor status					<0.0001
Neg	29	6	69	14	
Pos	444	94	410	85	
Unknown	1	0.2	2	0,4	
Location of tumor in breast					0.10
UL	265	56	241	50	
Not UL	194	41	220	46	
Unknown	15	3	20	4	
Number of removed sentinel nodes					0.02
1	198	42	151	32	
2	155	33	178	37	
3	75	16	88	18	
4	33	7	35	7	
5	13	3	25	5	
Proportion of positive sentinel nodes					0.047
≤25%	37	8	45	9	
>25–33%	58	12	67	14	
>33–99%	153	32	183	38	
100%	226	48	186	39	

HR, hormone receptor; ITC, isolated tumor cells; Neg, negative; NSN, non-sentinel node; Pos, positive; UL, upper lateral.

symptomatic and screen-detected cancers; 18.5% versus 17.5% (OR 1.07; 95% CI 0.77–1.49; $p = 0.69$). The risk of non-sentinel node metastases was higher in 2008 than in 2009–2010; 22% versus 16% ($p = 0.04$), but there was no significant difference in the risk of non-sentinel node metastases between symptomatic and screen-detected cancers within each year.

In the subgroup of patients with micrometastases in the sentinel node 21% of patients with symptomatic cancers had non-sentinel node metastases compared to 19% in the screen-detected group. This difference was not significant (OR 1.16; 95% CI 0.81–1.65, $p = 0.43$). Seven hundred and fifty-six of the 773 patients with micrometastases in the sentinel node had complete information on the risk factors for non-sentinel node metastases identified in the previously developed model for prediction of non-sentinel node metastases. These patients were included in a multivariate analysis of the risk of non-sentinel node metastases in patients with symptomatic cancers compared to screen-detected cancers (Table II). When adjusting for tumor size, proportion of positive sentinel nodes, lymphovascular invasion, hormone receptor status and location of tumor in the breast, symptomatic cancers were still not associated with a higher risk of non-sentinel node metastases compared to screen-detected cancers (OR 1.12, CI 0.77–1.62, $p = 0.55$). In the multivariate analysis, tumor size, proportion of positive sentinel nodes and lymphovascular invasion were associated with an increased risk of non-sentinel node metastases, while hormone receptor status and location of tumor in the breast were not significantly associated, although with estimates in the range found in the previous study on risk factors for non-sentinel node metastases [11].

Table II. Risk factors for NSN metastases in a multivariate analysis of 181 Danish breast cancer patients with ITC and 756 patients with micrometastases in the sentinel node from the screening population operated between 2008 and 2010.

Variable	OR	95% CI	*p*-Value
	Isolated tumor cells		
Tumor size, >2 vs. ≤2 cm	2.54	0.93–6.89	0.07
Proportion of pos SN, 100% vs. <100%	0.78	0.29–2.14	0.63
Symptomatic vs. screen-detected	0.45	0.16–1.27	0.13
	Micrometastases		
Tumor size, cm, trend	1.36	1.12–1.64	0.002
Proportion of pos SN, 100% vs. <100%	1.46	1.01–2.10	0.04
Lymphovascular invasion	1.78	1.11–2.86	0.02
Hormone receptor status, neg vs. pos	1.25	0.70–2.24	0.46
Location of tumor in upper lateral quadrant	1.41	0.97–2.06	0.07
Symptomatic vs. screen-detected	1.12	0.77–1.62	0.55

CI, confidence interval; ITC, isolated tumor cells; neg, negative; NSN, non-sentinel node; OR, odds ratio; pos, positive; SN, sentinel node.

Likewise, when looking at the 182 patients with ITCs in the sentinel node, 8% of patients with symptomatic cancers had non-sentinel node metastases compared to 13% of patients with screen-detected cancers. This difference was not significant (OR 0.58; 95% CI 0.22–1.54, $p = 0.27$). One patient did not have complete information on risk factors for non-sentinel node metastases identified in the previously developed model. In a multivariate analysis of the remaining 181 patients, including tumor size and proportion of positive sentinel nodes, no significant difference was found in the risk of non-sentinel node metastases between patients with symptomatic and screen-detected cancers (OR 0.45; 95% CI 0.16–1.27, $p = 0.13$) (Table II). Tumor size and proportion of positive sentinel nodes were not significantly associated with non-sentinel node metastases in the multivariate analysis, but again with estimates in accordance with previous results [11].

Discussion

In this nationwide study on the significance of method of detection on the risk of lymphatic spread beyond the sentinel node, we could not show an increased risk of non-sentinel node metastases in symptomatic cancers compared to screen-detected breast cancers.

The strength of this study is that it was made on a large and nationwide dataset that allowed adjustments for several other risk factors for non-sentinel node metastases. Due to the reduced number of patients included in this study compared to the previous study on risk factors for non-sentinel node metastases, not all previously identified risk factors became significant in the multivariate analysis. Only tumor size and proportion of positive sentinel nodes were significantly associated to the risk of non-sentinel node metastases, underlining the importance of a sufficiently large sample size to show weak associations. Screen-detected cancers are a selected group of cancers and adjustment for covariates is essential to rule out confounders.

This study is a retrospective register study based on two different registries; The DBCG database and the Danish Quality Database of Mammography Screening. Data from the DBCG database have been prospectively collected from all Danish women with breast cancer and registered on standardized forms. Substantial validation and search for missing data using original patient files have been performed for the patients included in this study. Patients not registered in the Danish Quality Database of Mammography Screening as having screen-detected cancers were considered as having symptomatic cancers. It is possible that some of these cancers were diagnosed due to other reasons than clinically evident symptoms, i.e. by mammography of other indications than screening. These patients were included in the group of symptomatic cancers and could potentially bias the results.

Only 181 patients were included in the analysis of the risk of non-sentinel node metastases in patients with ITC in the sentinel node, of which only 19 patients had non-sentinel node metastases, and the results regarding ITC should be taken with caution.

It is well known that screen-detected breast cancers have the prognostic advantage of smaller tumor size and a lower risk of lymph node metastases compared to symptomatic cancers because they are diagnosed at an earlier stage [12,13]. In addition, some studies have shown that screen-detected cancers tend to be less aggressive with a lower malignancy grade, lower mitotic score [13], and more often estrogen receptor positive and HER2 negative [14]. Several of these less aggressive characteristics are confirmed in our study, where patients with screen-detected cancers had smaller tumor size, lower risk of lymphovascular invasion and were more often hormone receptor positive. The slow growing characteristics could result in a lower risk of further metastatic spread beyond the sentinel node in sentinel node positive patients, which could advocate for a less aggressive axillary treatment of these patients.

Surprisingly, we found that patients with screen-detected cancers had a higher proportion of positive sentinel nodes. This was probably due to the fact that a larger proportion of patients with screen-detected cancers had only one sentinel node removed. The sentinel node procedure does not differ between patients with screen-detected and symptomatic cancers. Thus, there was no evident explanation for the difference in the number of sentinel nodes removed.

To our knowledge, only three previous studies have examined the risk of non-sentinel node metastases in patients with screen-detected breast cancers. These studies are small and only limited adjustments for confounders were made [6,15,16]. A study by Barry et al. included 110 patients with screen-detected breast cancer and macrometastases in the sentinel node. There was no control group with symptomatic cancers and the risk of non-sentinel node metastases was 55% [16]. Another study by Farshid et al. included 82 patients, of which some had screen-detected cancers. A decreased risk of non-sentinel node metastases was found in the screen-detected group, but method of detection was not significant in a multivariate analysis of the risk of non-sentinel node metastases [15]. Finally, Grabau et al. included 140 patients with micrometastases in the sentinel node and a subsequent ALND [6]. They found a five times higher risk of non-sentinel node metastases in patients with symptomatic cancers compared to patients with screen-detected breast cancers. This is in contrast to the results from our study where no difference was found. The Swedish patients were included over a longer period minimizing the effect from lead time bias in the first round of screening. Still, in our study there was no significant difference in the risk of non-sentinel node metastases when looking at each year separately. In addition, local screening programs were conducted in some areas in Denmark before the national screening program was implemented during 2007. Screen-detected cancers included in our study from these areas were not from the first round of screening. In the Swedish study patients between the age of 30 and 88 at diagnosis were included in the group with symptomatic cancers, and no adjustment for age, but only adjustments for tumor size and malignancy grade, were done in the multivariate analysis. It is well known that tumor characteristics vary by age, and young age at diagnosis is associated with poor prognosis [17]. For that reason we included only patients in the age span of the screening population in both groups. Screen-detected breast cancers are a selective group of cancers and accordingly, the Swedish results could be explained by residual confounding in addition to small sample size.

Our results are in line with the results from a large review on the characteristics of screen-detected and symptomatic cancers, where no difference in the relation between tumor size and lymph node metastases was found [12]. The authors concluded that the biological difference between screen-detected and symptomatic cancers, if present, is small. In this study we only included patients with micrometastases or ITC in the sentinel node, but we do not see any biological explanation for a different result in patients with macrometastases.

In conclusion, despite the more aggressive nature of symptomatic breast cancers we did not find an increased risk of non-sentinel node metastases in these patients compared to patients with screen-detected cancers. Our results do not support a differentiated treatment of the axilla between patients with symptomatic and screen-detected cancers based on the examination of the sentinel node.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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