Original Study

Sentinel Lymph Node Biopsy and Isolated Tumor Cells in Invasive Lobular Versus Ductal Breast Cancer

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Abstract

Sentinel lymph node biopsy is the standard of care for axillary staging in invasive breast cancer. With the introduction of sentinel lymph node biopsy and the renewed 2002 TNM classification, patients with invasive lobular carcinoma have been more frequently diagnosed with isolated tumor cells than have patients with invasive ductal carcinoma.

Background: Sentinel lymph node (SLN) biopsy is the standard of care for axillary staging in invasive breast cancer. The introduction of SLN biopsy with an extensive pathology examination, in addition to the introduction of the 2002 TNM classification, led to different axillary classification outcomes. We evaluated the effect of axillary staging procedures and subsequent axillary nodal status in patients with invasive lobular carcinoma (ILC) versus invasive ductal carcinoma (IDC) from 1998 to 2013. **Materials and Methods:** The use of SLN biopsy and the nodal status distribution were analyzed in patients with stage T1-T2 ILC and IDC. Logistic regression analysis was performed to determine the independent effect of histologic type on the probability of the presence of isolated tumor cells (ITCs), micrometastases, and macrometastases. **Results:** A total of 89,971 women were diagnosed, 10,146 with ILC (11%) and 79,825 with IDC (89%). The patients who had undergone SLN biopsy were more frequently diagnosed with ITCs than were those who had undergone axillary lymph node dissection only (odds ratio, 8.8; 95% confidence interval, 7.0-11.2). In 2013, the proportion of patients with ITCs in the axillary nodes was 8% in those with ILC and 4.4% in those with IDC. Patients with ILC were significantly more likely to have ITCs in their axillary lymph nodes than were patients with IDC (odds ratio, 1.8; 95% confidence interval, 1.6-2.0). **Conclusion:** With the introduction of SLN biopsy and the renewed 2002 TNM classification, patients with ILC have been more frequently diagnosed with ITCs than have patients with IDC. The clinical consequence of this finding must be established from further research.

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Introduction

Axillary lymph node status remains the single most important prognostic factor in invasive breast cancer.[1,2] The introduction of the sentinel lymph node (SLN) biopsy as an axillary staging procedure has led to a marked reduction in the usage of axillary lymph node dissection (ALND).[3] The main advantage of the SLN biopsy is the reduced risk of treatment-related morbidity in the arm and shoulder compared with ALND but with similar staging capacity.[4,5] Recent studies have indicated that ALND can even be avoided in selected patients with SLN-positive breast cancer.[6]

The implementation of the SLN biopsy has resulted in an increasing proportion of patients diagnosed with tumor-positive axillary lymph nodes. Various studies have reported an overall

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increase of up to 10% since the introduction of the SLN procedure, which seemed to be almost solely attributed to the increased detection of isolated tumor cells (ITCs) and micrometastases in the SLN.[7,8] However, these reports referred to the period before the revised TNM classification in 2002. After the introduction of the revised version, ITCs were distinguished from micrometastases and coded as pN0(i+).[9] Thus, no stage migration could be observed, because ITCs were considered to indicate node-negative disease.[10]

Currently, with the SLN biopsy considered the standard of care for axillary staging in patients with clinically node-negative breast cancer has enabled the pathologist to perform a detailed examination of the SLN, including serial sectioning, hematoxylin and eosin (H&E) staining, and immunohistochemistry.[11] From pathologic studies of invasive lobular carcinoma (ILC), it is known that the nodal metastases of ILC can be difficult to detect on standard histologic sections using H&E, because they are composed of noncohesive cells of similar size to benign lymphocytes and histiocytes.[12,13] Therefore, we hypothesized that with the introduction of the SLN procedure, including serial sectioning and immunohistochemistry (IHC), relatively more ITCs would be diagnosed in ILC than in invasive ductal carcinoma (IDC).

Materials and Methods

The method, results, and discussion of the present study were reported according to the reporting recommendations for tumor marker prognostic studies (REMARK) criteria on the reporting of tumor marker studies.[14] The patient data were derived from the population-based Netherlands Cancer Registry (NCR), covering the data for all newly diagnosed in situ and invasive tumors. The NCR has been deemed complete since 1989. Notification is mainly obtained from the automated pathology archive. Other sources were the National Registry of Hospital Discharge Diagnoses and radiotherapy departments. Specially trained registration clerks collect the data about the patient-, tumor-, and treatment-related characteristics from the patient hospital records. Because of the thorough registrar training, computerized consistency checks, and regular national quality checks, the quality of the data has been considered high.[15]

According to the NCR, 109,451 women were diagnosed with invasive breast cancer and underwent surgery in the Netherlands from 1998 to 2013. From this group, we excluded patients with metastatic disease at diagnosis and selected those patients with stage T1 or T2 breast cancer. The size of the primary tumor was defined as < 20 mm for stage T1 tumors and 20 to 50 mm for stage T2 tumors. Patients with histologic subtypes other than ILC or IDC, including mixed-type lobular cancer, were also excluded from the present study, leaving 89,971 patients with ILC or IDC. Surgical treatment was defined as breast-conserving surgery or mastectomy.

For the present study, data on individual axillary lymph node status were collected from the NCR, including the axillary staging procedure and nodal status. The tumors were staged using the TNM system of the Union for International Cancer Control.[9] The nodal status was defined as negative if no metastases or only ITCs were present. ITCs, which are staged as pN0(i+), were defined as deposits of ≤ 0.2 mm. Micrometastases were staged as pN1(mi) and defined as deposits > 0.2 to ≤ 2.0 mm. Macrometastases (pN1) were classified as metastases > 2.0 mm. Positive nodal status was defined as the presence of micro- or macrometastases. ITCs were recorded in the NCR from 2003 onward.

The use of SLN biopsy and the distribution of nodal status from 1998 to 2013 were analyzed according to the year of diagnosis. Four periods were defined to study the time trends. Period 1 included 1998 to 2001 and was considered the period when SLN biopsy was introduced in most hospitals. Period 2 included 2002 to 2005, during which the SLN biopsy was used on a larger scale, and periods 3 and 4 (2006-2009 and 2010-2013, respectively) covered the era with full implementation of the SLN biopsy. According to the Dutch breast cancer treatment guidelines, most SLN biopsies were examined with H&E and IHC during the diagnostic process.

Differences in the disease and treatment characteristics between the patients with ILC and IDC were calculated using the χ^2 test. Logistic regression analysis was performed to determine the independent effect of histologic type (ILC and IDC) on the probability of the presence of ITCs, micrometastases, or macrometastases. In the multivariate analysis, we adjusted for the method of staging (SLN biopsy or ALND), period of diagnosis (1998-2001, 2002-2005, 2006-2009, and 2010-2013), age at diagnosis (< 40, 40-49, 50-59, 60-69, and ≥ 70 years), pathologic tumor size (pT1 and pT2), and tumor grade (1, 2, 3, and unknown). Statistical analyses were performed using SAS, version 9.2, for Windows (SAS Institute Inc., Cary, NC).

Results

Characteristics

From 1998 to 2013, 89,971 patients were treated for ILC or IDC in the Netherlands. Their characteristics are listed in Table 1, stratified according to the tumor histologic type. The study group consisted of 10,146 patients with ILC (11%) and 79,825 patients with IDC (89%). The age distribution and period of diagnosis did not differ significantly, although patients with ILC seemed to be somewhat older at diagnosis than the patients with IDC. The patients with ILC had larger tumors than did those with IDC (46% with stage T2 in ILC vs. 34% with stage T2 in IDC; $P < .0001$). In contrast, patients with IDC were more likely to have poorly differentiated (grade 3) tumors ($P < .0001$). Of the patients with T1 or T2 ILC, 43% underwent breast-conserving surgery compared with 57% of the patients with IDC. No differences were observed in the type of axillary surgery or final nodal status between patients with stage T1 or T2 ILC and IDC when considering the complete inclusion period.

Trends in SLN Biopsy and Axillary Nodal Status

The percentage of patients who underwent staging with SLN biopsy (with or without completion ALND) gradually and significantly increased from 7.5% in 1998 to 87% in 2013. No significant difference was observed between those with ILC and IDC (Figure 1).

The trend in the distribution of axillary nodal status is shown in Figure 2. The percentage of patients with ITCs or micrometastases increased significantly, and the proportion of patients with macrometastases decreased during the study period. No significant change over time was observed in the percentage of patients with negative axillary nodal status [ie, the combination of pN0(i−) and pN0(i+)].

Table 1 General Patient Characteristics

Characteristic	ILC (n = 10,146)	IDC (N = 79,825)
Age at diagnosis (year)		
<40	226 (2)	5013 (6)
40-49	1704 (17)	15,431 (19)
50-59	2627 (26)	21,922 (28)
60-69	2733 (27)	19,622 (25)
≥70	2856 (28)	17,837 (22)
Period of diagnosis		
1998-2001	2339 (23)	17,212 (22)
2002-2005	2446 (24)	19,391 (24)
2006-2009	2631 (26)	20,938 (26)
2010-2013	2730 (27)	22,284 (28)
Pathologic tumor size		
pT1	5483 (54)	52,304 (66)
pT2	4663 (46)	27,521 (34)
Final nodal status		
pN0	5666 (56)	46,419 (58)
pN0(i+)	457 (4)	2009 (2)
pN1(mi)	572 (6)	4728 (6)
pN1-pN3	3201 (32)	24,395 (31)
Unknown	250 (2)	2274 (3)
Tumor grade		
1	1840 (18)	16,567 (21)
2	5325 (52)	31,176 (39)
3	873 (9)	24,629 (31)
Unknown	2108 (21)	7453 (9)
Surgical treatment		
BCS	4388 (43)	45,716 (57)
Mastectomy	5755 (57)	34,082 (43)
Unknown	3 (0)	27 (0)
Axillary surgery		
SLN biopsy alone	4537 (45)	38,001 (48)
SLN biopsy + ALND	2366 (23)	15,854 (20)
ALND alone	3061 (30)	24,224 (30)
None	94 (1)	1033 (1)
Axillary surgery, NOS	88 (1)	713 (1)

Data presented as n (%).
Abbreviations: ALND = axillary lymph node dissection; BCS = breast-conserving surgery; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; pN0(i+) = isolated tumor cells; pN1(mi) = micrometastases; NOS = not otherwise specified; SLN = sentinel lymph node.

The results of the multivariate logistic regression analyses are presented in Table 2. After adjustment for the period of diagnosis, age at diagnosis, tumor size, and tumor grade, patients undergoing SLN biopsy (with or without completion ALND) had a greater frequency of ITC detection compared with those who had undergone ALND alone (odds ratio [OR], 8.8; 95% confidence interval [CI], 7.0-11.2) and also a greater frequency of micrometastasis detection in ≥ 1 axillary lymph nodes compared with those who had undergone ALND alone (OR, 4.7; 95% CI, 4.27-5.20).

Trends in Axillary Nodal Status From SLN Biopsy Stratified by Histologic Type

From 2002, since the introduction of the revised TNM classification, to 2013, the incidence of ITCs in the SLN increased from 4.4% to 8% in ILC cases and from 2.2% to 4.4% in IDC cases (Figure 3A). The percentage of patients with micrometastases increased from 1.3% in 1998 to 5.8% in 2013 for patients with ILC and from 1.9% in 1998 to 7.9% in 2013 for patients with IDC (Figure 3B).

On multivariate analysis (Table 2), patients with T1-T2 ILC were slightly less likely to have positive axillary lymph nodes than were patients with IDC (OR, 0.95; 95% CI, 0.90-0.99). On multivariate analysis, a small, but statistically significant, difference was observed between patients with ILC and IDC in the risk of having micrometastases (OR, 0.91; 95% CI, 0.83-0.99). In contrast, the multivariate analysis showed that women with ILC were significantly more likely to be diagnosed with ITCs in their SLNs than were patients with IDC (OR, 1.81; 95% CI, 1.62-2.02).

Discussion

In the present nationwide study of data from the NCR, we compared patients with ILC to those with IDC with respect to the effect of the introduction of SLN biopsy on the risk of finding ITCs, micrometastases, or macrometastases. Several population-based studies have reported on stage migration after the introduction of SLN biopsy; however, in those studies, no comparisons were made between different histologic entities.[7,8,16–19] Furthermore, most studies did not account for the revision of the TNM classification of 2002.[9] To our knowledge, the present study is the first to investigate the axillary nodal involvement in ILC versus IDC in the era since the separate notification of ITCs.

We have demonstrated that after its introduction in the late 1990s, the SLN biopsy was implemented within a 5-year period in our country and is currently applied in approximately 85% of patients with T1-T2 ILC and IDC. With the introduction of the SLN biopsy, almost a fivefold increase in the likelihood of finding micrometastases was observed, reaching a plateau in the years afterward to approximately 7%. The incidence of ITCs increased to 8% in patients with ILC but, in contrast, to only 4% in patients with IDC. Therefore, the risk of finding ITCs was about twofold greater in patients with ILC than in those with IDC. However, patients with ILC were slightly less likely to have macrometastases in their axillary lymph nodes than were patients with IDC.

The introduction of the SLN biopsy resulted in a significant increase in the detection of micrometastases. Also, the detection rate of micrometastases increased from 1999 to 2002 but remained stable thereafter; however, the number of SLN biopsies increased further from 60% to approximately 85% from 2002 to 2013. This observation might suggest that from 1999 to 2002, pathologists became increasingly aware of the greater numbers of small metastases. Thus, the quality of daily practice N-classification might have improved by using the existing separate category for micrometastases in the fifth TNM version (published in 1997).[20] However, in the fifth TNM edition, the micrometastasis category also included "isolated tumor cells." The separate documentation of ITCs in the revised 2002 6th edition of the TNM classification, in

Figure 1 Performance of Sentinel Lymph Node Biopsy for Stage T1-T2 Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC) in the Netherlands From 1998 to 2013

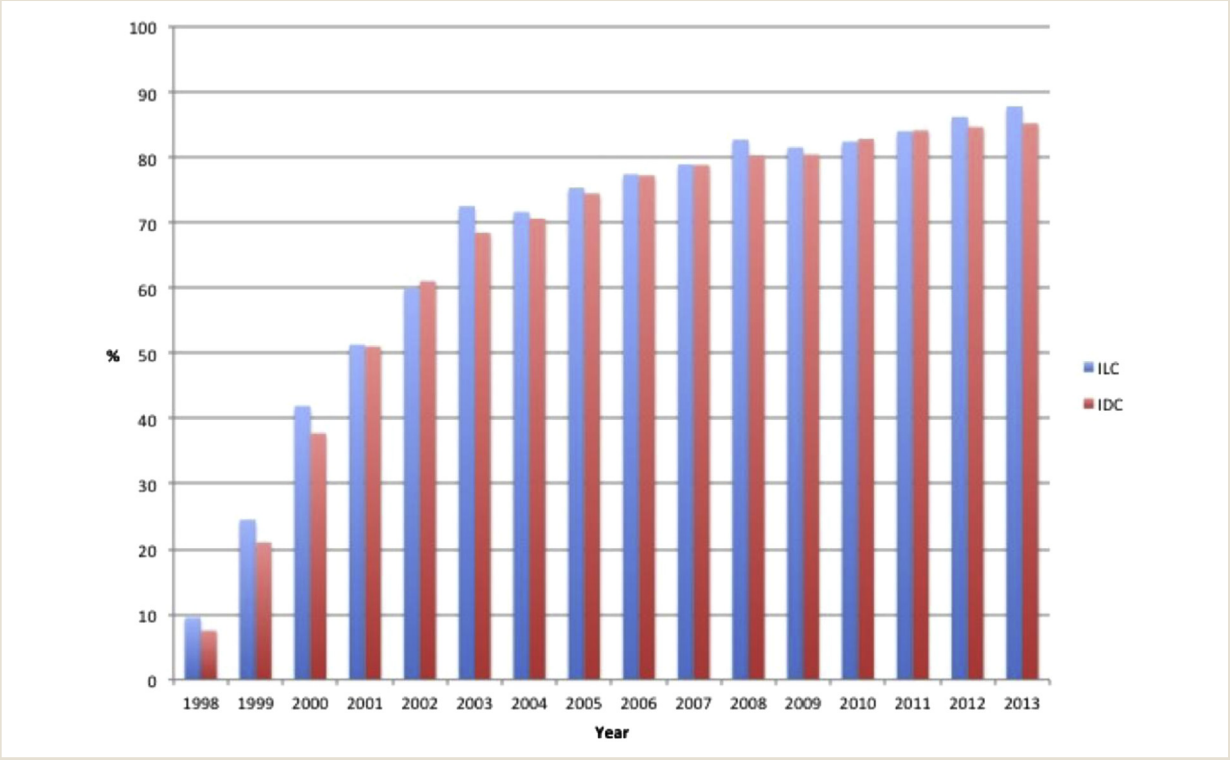


Figure 2 Distribution of Nodal Status in Stage T1-T2 Breast Cancer in the Netherlands From 1998 to 2013. Isolated Tumor Cells Were Recorded From 2003 Onward After the Introduction of the Revised TNM 2002 Classification

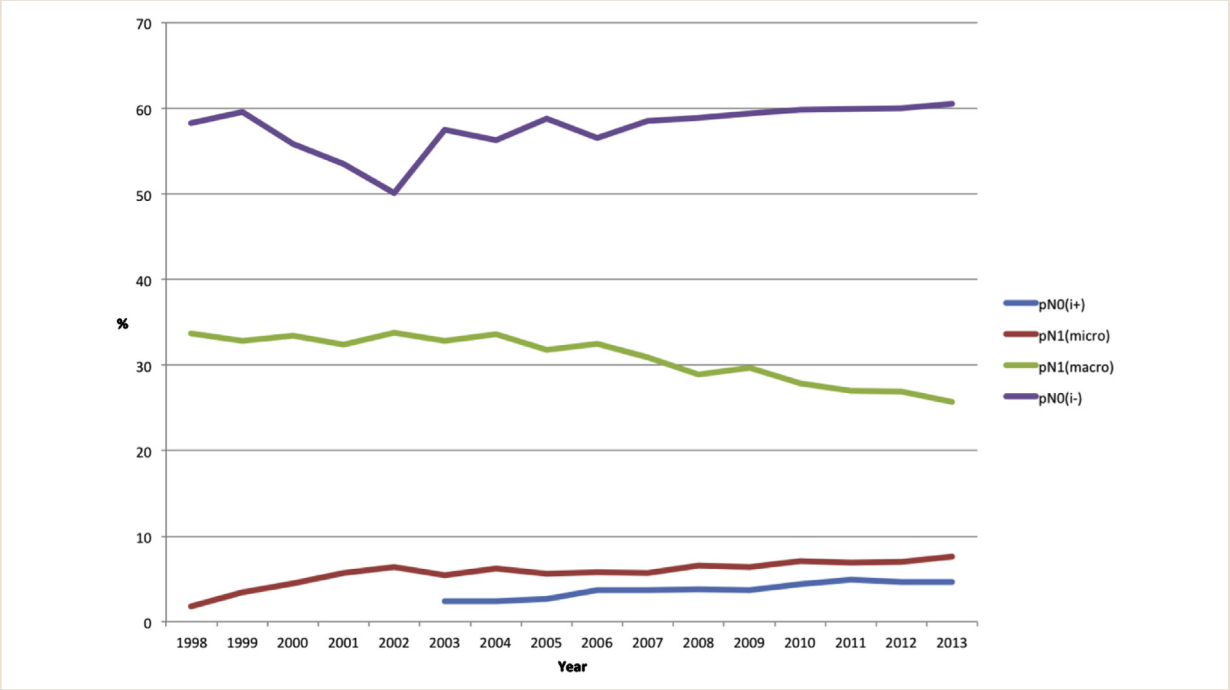


Table 2 Multivariate Analysis of Probability of Diagnosis of ITCs, Micrometastases, or Macrometastases at Final Axillary (Including Sentinel) Nodal Examination

	Final Axillary Nodal Status					
	pN0(i+)		pN1(mi)[a]		pN1-pN3	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Axillary staging method						
SLN biopsy vs. ALND alone	8.8	7.0-11.2	4.7	4.27-5.20	NA	NA
Period of diagnosis						
2002-2005 vs. 1998-2001	NA	NA	0.86	0.78-0.95	0.99	0.95-1.04
2006-2009 vs. 1998-2001	NA	NA	0.79	0.71-0.86	0.89	0.85-0.93
2010-2013 vs. 1998-2001	NA	NA	0.90	0.82-0.98	0.78	0.74-0.81
2006-2009 vs. 2003-2005	1.40	1.25-1.58	NA	NA	NA	NA
2010-2013 vs. 2003-2005	1.71	1.53-1.92	NA	NA	NA	NA
Age at diagnosis (year)						
<40 vs. 40-49	1.23	1.02-1.48	0.96	0.85-1.10	1.02	0.95-1.09
50-59 vs. 40-49	0.93	0.83-1.05	0.90	0.83-0.98	0.80	0.77-0.84
60-69 vs. 40-49	0.89	0.79-1.01	0.76	0.70-0.83	0.63	0.61-0.66
>70 vs. 40-49	0.75	0.66-0.85	0.71	0.65-0.78	0.63	0.60-0.66
Pathologic tumor size						
pT2 vs. pT1	1.28	1.17-1.40	1.18	1.11-1.28	3.13	3.03-3.23
Tumor grade						
2 vs. 1	1.24	1.11-1.38	1.06	0.99-1.14	1.49	1.43-1.56
3 vs. 1	1.13	1.00-1.28	0.89	0.82-0.97	1.67	1.59-1.75
X vs. 1	1.24	1.03-1.49	1.01	0.90-1.14	1.71	1.62-1.82
Histologic type						
Lobular vs. ductal	1.81	1.62-2.02	0.91	0.83-0.99	0.95	0.90-0.99

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; ITCs = isolated tumor cells; NA = not applicable; OR = odds ratio; pN+ = positive nodal status; pN1(mi) = micrometastases; pN0(i+) = isolated tumor cells; SLN = sentinel lymph node.
[a]Stage pN1(mi) included patients with pN0(i+) for year of diagnosis before 2003.

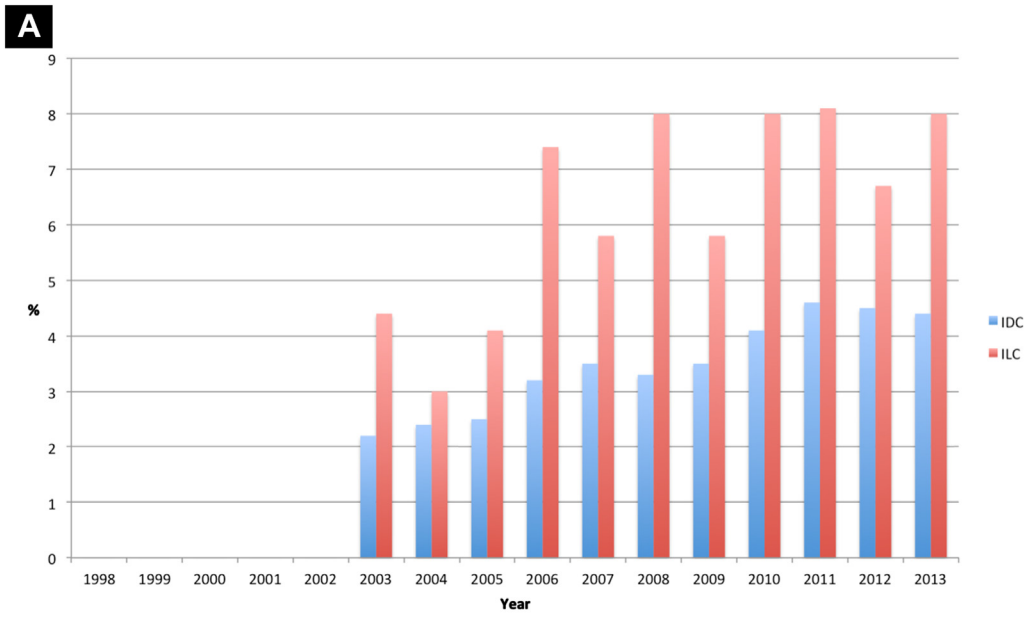
which ITCs (≤ 0.2 mm) were categorized as lymph node-negative disease, actually prevented stage migration.[10] Thus, any further increase in the number of micrometastases detected because of the increasing number of SLN biopsies was counterbalanced by the introduction of pN0(i+) as a separate category. The changed pN classification combined with the more appropriate use of the existing pN classifications largely explains the observed time trends, including the slightly lower number of macrometastases, the rapid increase in the number of micrometastases during the initial years of SLN introduction, and the increase in ITCs in more recent years.

However, an explanation is needed for the reason ITCs were more frequently diagnosed in the SLN biopsy of patients with ILC. Previous studies investigating lymph node metastases in patients with ILC concluded that they were difficult to detect with routine H&E, because they are composed of noncohesive cells of similar size to lymphocytes.[12,13] Neoplastic cells from ILC are often "benign-looking" and tend to fill the sinuses, mimicking sinus histiocytosis, or invade into the lymphoreticular tissue in a lymphoma-like pattern difficult to detect on standard H&E-stained sections. The introduction of IHC for analyzing SLN biopsy led to increased detection of metastatic activity in SLN biopsy. A number of studies revealed occult metastatic foci in ILC with IHC, originally classified as negative using H&E (ie, ≤ 89% more ITCs in patient with ILC).[21,22]

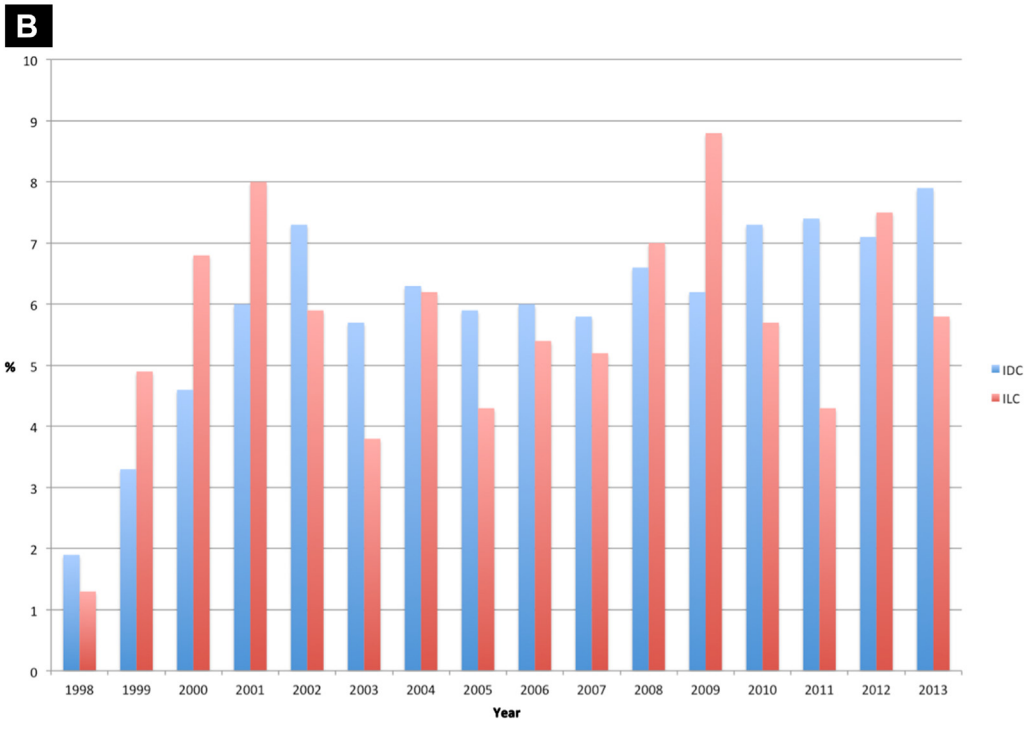
Also, previous studies concluded different metastatic behavior for ILC compared with IDC. For instance, Ashton et al[12] showed that metastases of ILC presented in body cavity fluids as a population of primarily single cells, with a ratio of 13 single cells to each tissue fragment, compared with an admixture of single cells and tissue fragments at a ratio of 0.86:1 in metastatic ductal carcinoma. Thus, the ILC cells metastasize to the lymph nodes and elsewhere in a scattered fashion, making their recognition difficult, with recognition even more difficult because of their lack of severe cytologic atypia.[12,13]

Multiple studies have concluded that omitting ALND in patients with ITCs in the SLN will not lead to a clinical relevant increase in the risk of regional recurrence.[23–25] However, the risk of non-SLN involvement and regional recurrence is dependent, not only on the SLN metastatic size, but also on other risk factors such as primary tumor size, tumor grade, vessel invasion, hormonal receptor status, and, thus, perhaps, the histologic features.[26,27] In contrast to regional recurrence, debate still exists regarding the effect of ITCs and micrometastases on the clinical outcome. Multiple studies of the prognostic value of occult metastases in the SLN biopsy were hampered by the small sample size, short follow-up period, or the lack of multivariate analysis.[28,29] Larger studies have shown a negative prognostic effect of the presence of ITCs and micrometastases on disease-free survival in patients with early-stage breast

Figure 3 (A) Detection Frequency of Isolated Tumor Cells in the Sentinel Lymph Node Biopsy in the Netherlands From 1998 to 2013, Stratified by the Histologic Type. Isolated Tumor Cells Were Recorded From 2003 Onward After the Introduction of the Revised TNM 2002 Classification. (B) Detection Frequency of Micrometastases in Sentinel Lymph Node Biopsy in the Netherlands From 1998 to 2013 Stratified by the Histologic Type



* Isolated tumor cells are recorded from 2003 onwards since the introduction of the revised TNM 2002 classification



Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

cancer.[30,31] However, the negative effect of occult metastases on overall survival has been rather small, and the unfavorable outcome can be attenuated by the use of local radiation therapy and adjuvant systemic therapy.[32]

To the best of our knowledge, no studies have questioned whether the prognostic relevance of ITCs from ILC is different from the prognostic relevance of ITCs from IDC. A worse long-term prognosis for patients with ILC could be of relevance for deciding whether to use adjuvant systemic therapy for these different histologic entities. Further investigation on this subject, which is one of our future goals, should elucidate this question.

The present study had some potential limitations. First, no central pathology review was performed of the included data. From previous studies, we know that a central pathology review will alter the N classification for 24% of patients, resulting mainly in upstaging with potential clinical relevance.[33] Also, from studies of the nodal staging classification, we know that measurement of SLN metastases, especially in ILC, is very complex. van Deurzen et al[34] showed that different interpretations of the pTNM classification will led to a change in the pN classification in 19% of the patients with lobular histologic features. This outcome was partly based on differences in the Union for International Cancer Control TNM classification of malignant tumors and the sixth edition of the American Joint Committee on Cancer staging manual, both of which used different interpretations of the definitions. For example, no definition for a cluster has been generally accepted, complicating the size measurement in the case of multiple clusters and/or cells.[34] With the introduction of the seventh edition of the TNM classification of malignant tumors, ITCs include a single cluster of < 200 cells in a single histologic cross-section but also still refer to single tumor cells or small clusters of cells measuring ≤ 0.2 mm in greatest extent.[35] Therefore, with the constant updates of the TNM classification and changing pathologic insights, we should reconsider the prognostic and therapeutic effects of the presence of ITCs in daily clinical practice.

Conclusion

Patients with ILC will be more frequently diagnosed with ITCs in the axillary (sentinel) lymph nodes than will patients with IDC. Future studies are needed to evaluate the prognostic relevance of ITCs in ILC versus IDC, because this could have different adjuvant systemic therapeutic implications.

Clinical Practice Points

- SLN biopsy is the standard of care for axillary staging in invasive breast cancer.
- The introduction of SLN biopsy with an extensive pathologic examination, in addition to the introduction of the 2002 TNM classification, led to different axillary classification outcomes.
- ILC is a different clinical and biologic entity compared with IDC.
- With the introduction of the SLN biopsy, patients with ILC are significantly more likely to have ITCs in their axillary lymph nodes than are patients with IDC.
- Future research should determine the clinical relevance of these differences in SLN biopsy findings between ILC and IDC.

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Disclosure

The authors declare that they have no competing interests.

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