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Prognosis and Treatment of Micrometastatic Breast Cancer Sentinel Lymph Node: A Population-Based Study

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Background and Objectives: Major concern of sentinel lymph node (SLN) biopsy (SLNB) regards the prognosis of micrometastasis (Nmic) in SLN. The purpose of this study is to determine the adequate surgical treatment and prognosis of Nmic in a population-based series of breast cancer patients.
Methods: All non-metastatic breast cancer patients registered by the Modena Cancer Registry (MCR), from January 2000 to December 2008, were evaluated for SLNB. Information on patients' characteristics, treatment and follow-up was collected.
Results: Among 2,078 patients treated with SLNB, 28.5% (590) showed a positive SLN, subdivided in N0i+ 6.3% (31), Nmic 28.8% (176), N1 64.1% (378), and N2 0.8% (5). Of 176 Nmic, 80% (142) received an axillary lymph node dissection (ALND). Only three patients had ≥4 SLN involved. No axillary recurrence occurred in Nmic patients. The overall and disease-free survival rates were N0 99.2% and 97.7%, N0i+ 100% and 100%, Nmic 96% and 93.2%, N+ (N1 + N2) 96.1% and 92.4%, respectively (N0 vs. Nmic $P < 0.001$).
Conclusions: This study suggests that patients with Nmic have a similar prognosis to N+ (N1 + N2) patients, and a low risk of local recurrence, questioning the necessity of ALND for Nmic SLN.
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KEY WORDS: **breast cancer; sentinel lymph node; micrometastasis; prognosis**

INTRODUCTION

Breast cancer is by far the most frequent tumor in women, and is currently being diagnosed in younger women than in the past. The multidisciplinary diagnostic-therapeutic approach has led to significant improvements both in 10-year overall survival (OS) rates and in quality of life measurements [1]. The improvement of new diagnostic techniques enabling the exclusion of increased ipsilateral and/or contralateral breast cancer development risk, by sequencing *BRCA1* and *BRCA2* genes, or major radiosensitivity, together with improved female self-awareness, have led to possibility of conservative surgery in most cases [2–4]. Breast cancer aggressiveness today is considered to be more closely related to the neoplasm biological characteristics rather than tumor size [5,6]. However, the tumor burden, histology, and morphological characteristics of the involved organ and/or loco-regional structure still play an important role in the surgical decision making process between conservative or radical surgery [7].

Following the consolidated success of the quadrantectomy plus radiotherapy (QUART) [8,9] the development of new conservative surgery techniques has became fundamental, especially in the treatment of the axilla. During the past decade, partial or a total axillary lymph node dissection (ALND) has been debated because ALND may result in complications, such as sensitive and motor diseases, shoulder pain, and lymphedema [10] in association with a noted high morbidity of ALND procedure [11–14].

Management decisions regarding local and/or adjuvant therapy is influenced by the most important prognostic factor in patients with operable breast cancer: the lymph nodes status. After its first application in 1993 [15,16], the sentinel lymph node biopsy (SLNB) technique has been widely adopted. SLNB is not routinely necessary for patients with ductal carcinoma in situ (DCIS), although it has been offered to individuals undergoing mastectomy or those with large, palpable, high-grade, or recurrent lesions, in view of the risk of accompanying invasive disease [17]. In parallel with SLNB, pathologic analysis has become more and more detailed, increasing the accuracy of staging and reducing the proportion of false-negative. The sentinel lymph node (SLN) has been defined as "the first lymph node to receive lymphatic drainage from a primary tumor" [18]. Although current guidelines recommend ALND for women whose SLNB contains macrometastasis [19], data from the ACOSOG-Z0011 randomized trial, show no differences between positive SNLB patients treated with or without ALND in terms of local recurrence [20]. Additionally, the 2011 St. Gallen Conference Consensus defined that isolated tumor cells, and even metastases up to 2 mm (micrometastases) in the SLN, should not constitute an indication for axillary dissection regardless of the type of breast surgery carried out [21].

The aim of this study was to evaluate the prognosis of micrometastatic SLN in a population-based study and to define the optimal surgical approach in this subgroup of patients, analyzing the OS, disease free survival (DFS), and any breast cancer-related event.

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PATIENTS AND METHODS

The Modena Cancer Registry (MCR) collects data of all malignant tumor cases in an Italian province, with a population of 644,289 inhabitants. All cases were coded according to the International Classification of Diseases for Oncology [22]. Information concerning diagnosis, staging, surgery, chemotherapy, radiotherapy, and follow-up status were obtained from patients files and computerized departmental and hospital service archives. Follow-up was updated to December 2008, and survival data were recovered through cross matching with the local sanitary registry office. Due to the sensitivity of the data, the database is installed on a limited access server, reserved for authorized operators only.

Sentinel Node Biopsy Procedure

Since January 2000, radioactive SLNB has been performed at our Breast Unit as previously described by Veronesi et al. [23].

During the study period, sentinel node pathologic examination was carried out as follows: the SLN was completely frozen and sectioned at 200-μm intervals or alternatively four sections at 200-μm intervals. In case of a negative result, further sections for immunocytochemical analysis were performed. Hematoxylin–eosin staining was carried out on all sections.

Lymph node involvement was defined by The American Joint Committee on Cancer (AJCC) [24] as follows: macrometastasis "greater than 2.0 mm", micrometastasis "greater than 0.2 mm but not larger than 2.0 mm", and isolated tumor cell clusters (ITC) "no larger than 0.2 mm".

Treatment of the Primary Carcinoma

Routinely patients with N0 SLN did not receive further ALND, except for some 145 cases, studied in the period 2000–2003, which underwent ALND contemporary to SLNB, since surgeons need to monitor the accuracy of the new procedure.

The vast majority of patients treated with conservative breast surgery underwent conventional external beam radiotherapy on the entire ipsilateral breast through tangential fields (50 + 10 Gy as a boost on the tumor bed). No radiotherapy was performed to the axilla. Systemic adjuvant treatment was prescribed according to tumor biological and stage characteristics.

Statistical Analysis

The chi-square test was used to determine differences in clinicopathological features between positive and negative SLN. The purpose of the study was to review the data on the development of axillary recurrence, any breast cancer-related event and OS. DFS was calculated from the date of surgery to the date of the event or last follow-up visit. OS was calculated from the date of surgery to the date of death or last follow-up visit. OS and DFS were calculated using the Kaplan–Meier method, including the log-rank test group comparison. Univariate and multivariate analyses of DFS were conducted using a proportional hazards Cox regression model. All statistical analyses were done with SPSS, version 12.0 (SPSS Inc, Chicago, IL).

RESULTS

Patients' Characteristics

Between January 2000 and December 2008, 46.4% (2,078/4,477) of women diagnosed with invasive breast cancer (median age 62 years old) in an Italian province underwent SLNB. During the study period, the number of patients treated with this procedure increased exponentially; from 10.8% in 2000 to 68% in 2008. Between 2000 and 2003 a learning curve to monitor the accuracy of the procedure was introduced, in which axillary clearance on all patients was performed. Each of the three surgeons performed 80 cases each, a total of 240 cases. A portable gamma probe for intraoperative determination of SLN location was routinely available from 2005; before that date only a small number of cases could be evaluated for SLNB.

Eligibility for SLNB included patients with T1–T2 invasive breast cancers and clinically negative (N0–N1) axillary nodes. Exclusion criteria included patients with palpable lymph nodes in axilla and/or inflammatory breast cancer. Other exclusion criteria for SLNB were pregnancy, feeding and neo-adjuvant treatments, since preoperative chemotherapy could modify the lymphatic flow and reduce the sensitivity of SLNB. Furthermore, multifocal or multicentric breast cancer were initially excluded from the SLNB but were more recently considered eligible. Finally patients with suspect imaging of axilla, by ultrasound or breast MRI, or with a positive fine needle aspiration prior to surgical intervention underwent immediately ALND.

Patients' characteristics are summarized in Table I. The majority of patients (87.5%) were diagnosed with a tumor size of <2 cm, with only 12.5% being ≥ 2 cm. Invasive ductal carcinoma was diagnosed in 89.9% of patients (1,867). The mean numbers of SLNs found per patients were 1.8 (range 1–12).

Conservative surgery was performed in 85% of cases (1,756), and radiotherapy was performed on the operated mammary gland in 76.3% (1,586).

Among all 2,078 patients, 89.9% (1,847) received a systemic therapy. Totally, hormonal therapy was prescribed for 1,644 patients. The most frequent hormonal treatment was Tamoxifen (64%), followed by aromatase inhibitors (36%). Seven hundred and fifty-two patients received chemotherapy regimens. The most adopted chemotherapy regimen was anthracycline based (56%), followed by CMF scheme (39%) and finally the taxane containing regimens (5%; data not shown).

Sentinel Lymph Node Biopsy Results

Results of SLNB are reported in Table II. Positive SLN was found in 28.5% (590) which was proven statistically related to grading 3, and high proliferative activity ($\geq$20%). Among the 590 women with positive SLN, 5.3% (31) were N0i+, 29.8% (176) were Nmic, 64.1% (378) were N1 and 0.8% (5) were N2. ALND was performed in 86% of positive SLN (511/590): 25.8% N0i+ (8/31), 80% Nmic (142/176), 95.6% N1 (356/378), and 100% N2 (5/5).

Furthermore, 145 patients without positive SLN, received ALND contemporary to SLNB during the learning period 2000–2003. Therefore, the total number of ALND was equal to 656 compared with 1,422 patients who did not undergo ALND.

Differences in systemic treatment between patients with and without ALND is shown in Table III. As expected, 36% of patients which underwent ALND received hormonal treatment compared with 68.5% in the group without ALND ($P < 0.001$). Otherwise, chemotherapy and combination with chemotherapy plus hormonal treatment was more offered to patients who received ALND (16% and 45.1%, respectively) than to patients without ALND (9.7% and 8.7%, respectively). In both cases the differences were statistically significant ($P < 0.001$).

The distribution of lymph node positivity at ALND in the various categories is shown in Table IV. Of interest, two patients with N0i+ SLN showed more lymph nodes involved at the ALND. Furthermore, among the 176 patients with Nmic SLN 80.7% (142) underwent ALND; negative ALND was evidenced in 80.3% (114), 11.3% (16)

TABLE I. Descriptive Characteristics by Different Breast Cancer Subtypes (n = 2,078)

Characteristics	No. of patients	(%)
Age (years)		
Median (range)	62 (24–99)	
T		
T1X	2	(0.1)
Tis	4	(0.2)
T1mic	65	(3.1)
T1a	153	(7.4)
T1b	584	(28.1)
T1c	1,010	(48.6)
T2	248	(12.0)
T3	5	(0.2)
T4	7	(0.3)
Hystology		
Ductal	1,867	(89.9)
Lobular	140	(6.8)
Mucinous	21	(1.0)
Ductal/lobular	21	(1.0)
Tubular	0	0
Papillary	0	0
Medullary	0	0
Others[a]	29	(1.4)
Grading		
1	276	(13.3)
2	1,008	(48.5)
3	739	(35.6)
Unknown	55	(2.6)
Estrogen receptor status		
0	187	(9.0)
1–10	48	(2.3)
>10	1,802	(86.7)
Unknown	41	(2.0)
Progesteron receptor status		
0	361	(17.4)
1–10	212	(10.2)
>10	1,461	(70.3)
Unknown	44	(2.1)
Proliferative rate		
<20	1,277	(61.4)
≥20	716	(34.4)
Unknown	85	(4.1)
Surgery		
Conservative	1,765	(85)
Mastectomy	313	(15)
No. of excised sentinel node		
Mean (range)	1.8	(1–12)
1	1,139	(54.8)
2	555	(26.7)
3	193	(9.3)
>3	191	(9.2)
Postoperative radiotherapy		
Yes	1,586	(76.3)
No	411	(19.8)
Unknown	81	(3.9)
Adjuvant treatments		
Hormonal therapy	1,095	(52.7)
Chemotherapy	203	(9.8)
Both	549	(26.4)
None	231	(11.1)

[a]Others: cancer not otherwise specified and metaplastic.

had two positive lymph nodes, 4.9% (7) had three positive lymph nodes, 1.4% (2) had four positive lymph nodes and the remaining 2.1% (3) had six or more positive lymph nodes. Among 356 N1 SLN treated with ALND, 53% (185) had a negative ALND, 22% (80) had two positive nodes, 7% (23) had three positive nodes, 5% (17) had four positive lymph nodes, and 13% (51) had five or more positive lymph nodes. Among five N2 positive SLN, all patients resulted with five or more positive lymph nodes.

The SLN median size was statistically different between those diagnosed as negative (13.23 mm) compared with positive SLN (14.12 mm), respectively ($P = 0.03$).

TABLE II. Different Characteristics Expression Between Positive and Negative SLN (n = 2,078)

	Positive SLN (%)	Negative SLN (%)	*P*-value
No. Total	590	1,488	
Grading			
1	38 (6.4)	247 (16.6)	<0.001
2	289 (48.9)	747 (50.2)	
3	263 (44.7)	494 (33.2)	
Ki67			
0–19	156 (26.5)	516 (34.7)	0.03
≥20	434 (73.5)	972 (65.3)	
ER			
Negative	48 (8.1)	187 (12.6)	NS
Positive	535 (90.7)	1,267 (85.1)	
Unknown	7 (1.2)	34 (2.3)	
PgR			
Negative	129 (21.9)	444 (29.8)	NS
Positive	453(76.8)	1,008 (67.7)	
Unknown	8 (1.3)	38 (2.5)	
ALND			
Yes	511 (86)	145 (9.7)	<0.001
No	79 (14)	1,343 (90.3)	

TABLE III. Differences in Systemic Treatment Between ALND and No ALND

	All (%)	ALND (%)	No ALND (%)	*P*-value
Hormonal treatment	1,211 (58.3)	237 (36.1)	974 (68.5)	<0.001
Chemotherapy	229 (11.0)	105 (16.0)	138 (9.7)	<0.001
Both	420 (20.2)	296 (45.1)	124 (8.7)	<0.001
None	218 (10.5)	18 (2.8)	200 (13.1)	<0.001
Total	2,078 (100)	656 (100)	1,422 (100)	<0.001

TABLE IV. Overall Positive Lymph Nodes Among 511 ALND

	N0 (i+) (%)	Nmic (%)	N1 (%)	N2 (%)
1	6 (75)	114 (80)	185 (53)	0 (0)
2	1 (12.5)	16 (11)	80 (22)	0 (0)
3	0 (0)	7 (5)	23 (7)	0 (0)
4	0 (0)	2 (1)	17 (5)	0 (0)
5	0 (0)	0 (0)	8 (2)	1 (20)
6	0 (0)	1 (1)	8 (2)	0 (0)
7	1 (12.5)	0 (0)	5 (1)	1 (20)
8	0 (0)	1 (1)	5 (1)	1 (20)
9	0 (0)	0 (0)	5 (1)	0 (0)
10	0 (0)	0 (0)	6 (2)	0 (0)
>10	0 (0)	1 (1)	14 (4)	2 (40)
Total	8 (100)	142 (100)	356 (100)	5 (100)

TABLE V. Relapses and Deaths in SLNB

	No. of patients (%)
Local recurrence	
Breast only	18 (0.8)
Axilla only	4 (0.2)
Breast and axilla	1 (0.1)
Total	23 (1.1)
Distant relapse	
Distant only	48 (2.3)
Distant and breast	5 (0.2)
Distant and axilla	2 (0.1)
Total	55 (2.6)
Second primary tumor	
Contralateral breast cancer	37 (1.8)
Other primary cancer	62 (3.0)
Total	99 (4.8)
Deaths	
Death from breast cancer	34 (1.6)
Death from other causes	49 (2.4)
Total	83 (4.0)
Total events	261 (12.6)

Survival Analysis

At a median follow-up of 48.6 months (range 1–120 months), unfavourable events occurred in 8.5% (177) and mortality was reported in 4% of patients (83; Table V).

Axillary recurrences in patients with SLNB occurred in 0.3% of cases (7): four were isolated recurrences, two had distant and axillary relapse and one had axillary and breast recurrence. Distribution of axillary recurrence according to SLN status was the following: four were N0 (0.3%), one was N0i+ (3.2%) and arose among 23 patients without ALND, two were N1 (0.5%; one in a patient without ALND and one in a patient who received ALND). No axillary recurrence was reported among both the 142 Nmic patients who underwent ALND or the 34 patients which did not receive ALND. Eighteen patients had a local breast recurrence (0.8%), including five cases with distant and in-breast relapse.

Overall, 2.6% (55) patients developed distant metastases and 4.7% (99) a new primary cancer (37 contralateral breast cancer and 62 cancers other than breast). The median time to relapse was 46 months (range 1–120).

Of the 83 deaths which occurred during the study period, 41% (34) were breast cancer related while the remaining 59% (49) were related to other causes.

Differences between women with (656) and without (1,422) ALND in OS (93% vs. 94%) and DFS (90% vs. 95%) are shown in Figure 1A,B, respectively. OS and DFS were also evaluated according to SLN status, presented in Figure 2A,B. The OS and DFS rates, respectively, were 99.2% and 97.7% for N0, 100% and 100% for N0i + , 96% and 93.2% for Nmic and 96.1% and 92.4% for N+ (N0 vs. Nmic, $P < 0.001$). Among 142 Nmic positive SLN who received ALND, no differences in OS were seen between patients who had only one positive node (114) and patients who had additional positive nodes (28) (Fig. 3).

Univariate and Multivariate Survival Analysis According to Prognostic Factors

Of the 2,078 patients, 2,030 were evaluated in univariate and multivariate analyses for DFS, which included grading, Ki67 activity, ER status, PgR status, HER2 status, SLN size. In the univariate analysis grading 3, Ki67 activity $\geq$20, ER negative, PgR negative and HER2 positive status represented a significant factor for decreased DFS, whereas SLN size $\geq$14 mm did not influence the DFS. In a multivariate analysis only grading 3 (HR = 2.40: $P = 0.016$), ER negative (HR = 4.64; $P < 0.001$), and PgR negative (HR = 3.33; $P < 0.001$) remained as independent significant factors for poorer DFS. Detailed results for multivariate analysis are shown in Table VI.

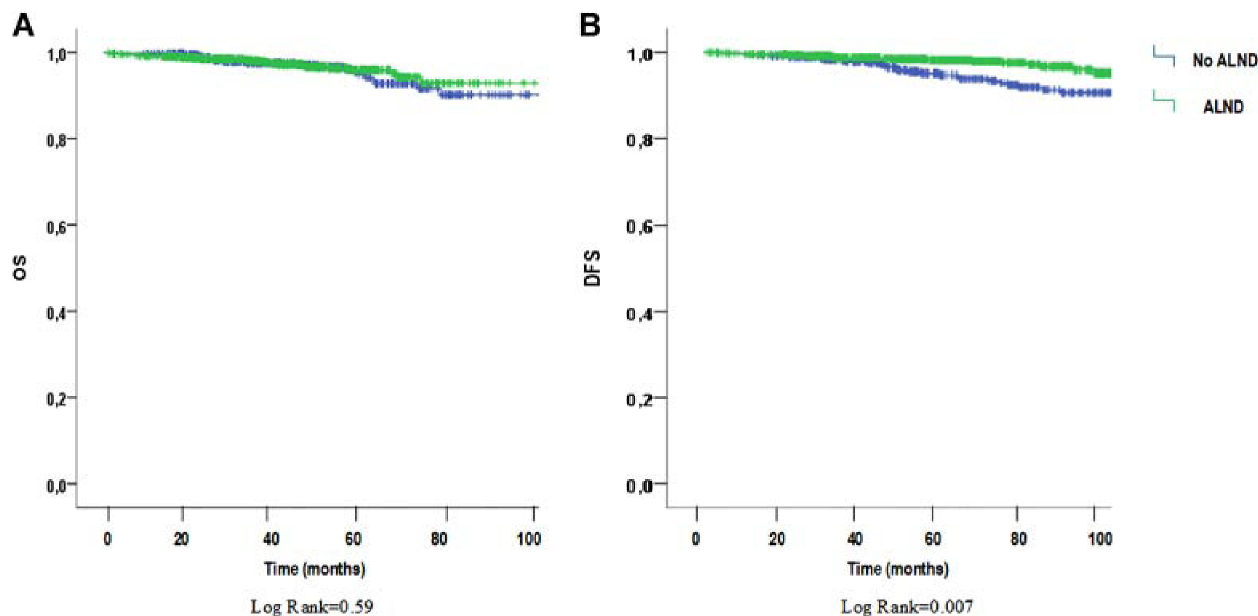

Fig. 1. Overall survival (**A**) and disease-free survival (**B**) according to ALND performance. The OS and DFS at 5-year for patients without or with ALND were 94% and 95% ($P = 0.59$), 93% and 90% ($P = 0.007$), respectively.

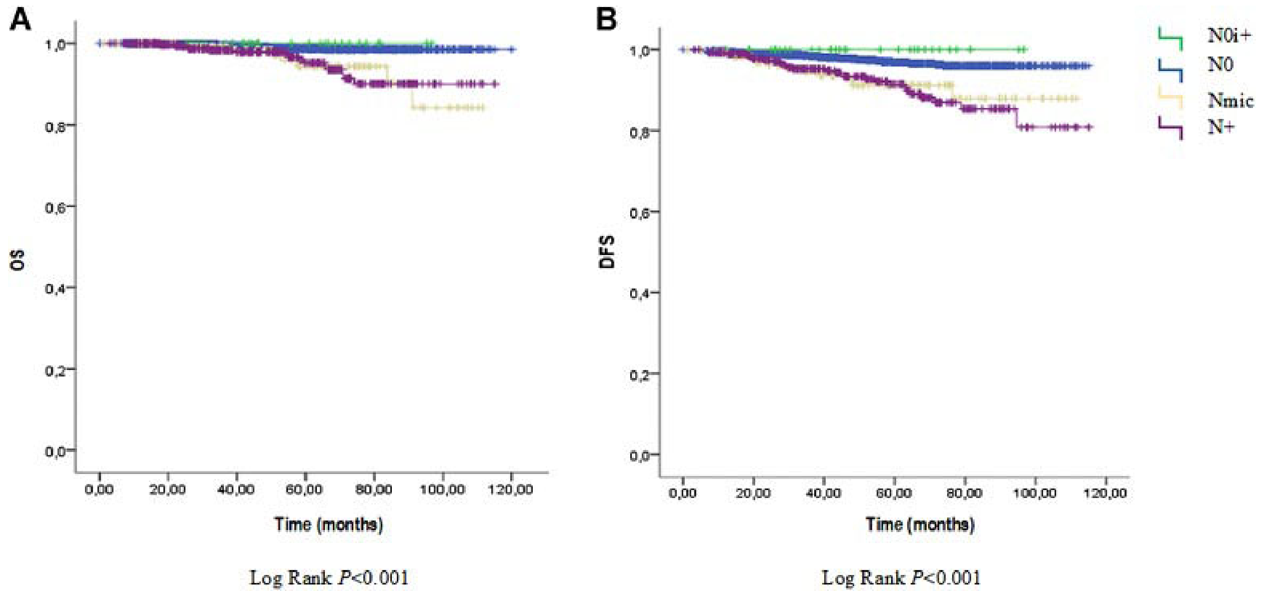

Fig. 2. Overall survival (**A**) and disease-free survival (**B**) according to SLNB results. The OS and DFS at 5 years for patients with N0, N0i+, Nmic, N+ were 99.2% and 97.7%, 100%, and 100%, 96% and 93.2%, 96.1% and 92.4%, respectively.

DISCUSSION

SLNB in early breast cancer aims at identifying axillary lymph node-negative patients in order to spare them unnecessary ALND [25] and its related morbidity [26]. Although the procedure has proven to be accurate and safe, a rate of false-negative SLN of 3–5% has been reported [27,28].

Data analysis surveying the rate of axillary recurrence after a negative SLNB without adjuvant ALND highlights this issue. A recent large randomized trial [29] showed that OS, DFS, and regional control were statistically equivalent between groups with and without ALND. Hence, with clinically negative SLN, ALND is not required and this strategy has been proven to be an appropriate, safe, and effective therapy.

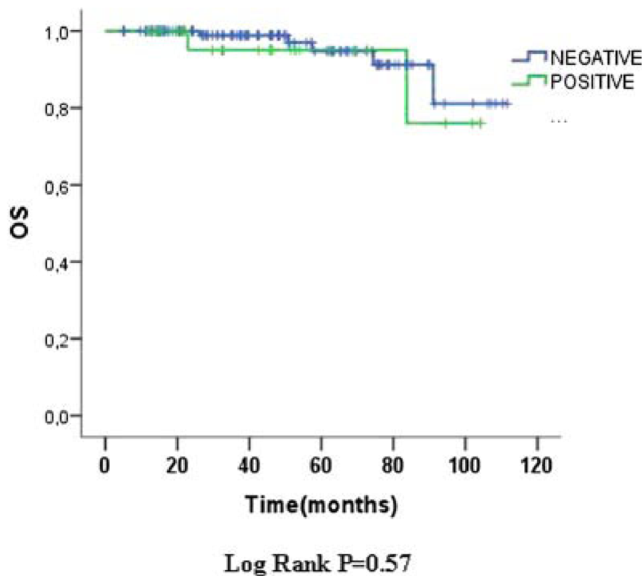

Fig. 3. Overall Survival of Nmic patients who received ALND according to positive or negative axilla. The OS at 5 years is 96% for both arms.

ALND has become a widespread therapy and is now routinely used worldwide, even in small centers. Thanks to the MCR data we can monitor the safety and the learning curve of this procedure.

This large population-based series supports previously published results originating from single referral institutions and multicenter experiences, with axillary recurrence rates ranging from 0% to 1% (median 0.6%) [30–33]. At a median follow-up of 48.6 months, in a series of 2,078 patients treated with SLNB, only seven cases of recurrence were reported; four (0.2%) isolated axillary, one (0.05%) axillary and breast recurrences and two (0.1%) axillary and distant metastasis. All seven patients with axillary recurrence received total ALND with further systemic adjuvant therapies. Of these seven patients, mortality was reported in a single patient only, who underwent concomitant axillary and distant metastasis.

TABLE VI. Univariate and Multivariate Analysis of Disease-Free Survival

	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Grading 1	1.00[a]	—	1.00	—
Grading 3	3.21 (2.69–9.44)	0.04	2.40 (1.23–8.35)	0.016
Ki67 <20	1.00[a]	—	1.00	—
Ki67 >20	4.79 (3.29–17.1)	<0.001	3.41 (0.77–15.04)	0.105
ER positive	1.00[a]	—	1.00	—
ER negative	1.78 (1.11–4.19)	<0.001	4.64 (1.11–5.72)	<0.001
PgR positive	1.00[a]	—	1.00	—
PgR negative	1.67 (0.18–6.46)	<0.001	3.33 (1.86–6.46)	<0.001
HER2 negative	1.00[a]	—	1.00	—
HER2 positive	2.51 (1.24–5.77)	0.012	1.57 (0.78–8.64)	0.118

[a]Reference category.

This very low rate of axillary recurrence supports the hypothesis that SLNB without ALND can be safely offered to SLN-negative breast cancer patients.

Furthermore, this study confirms recent results from the ACOSOG Z0011 trial [20] in which SLNB with hematoxylin–eosin-detected metastasis without ALND was found to offer excellent regional control and is proposed as a reasonable management therapy for selected patients with early-stage breast cancer treated with breast-conserving therapy, whole breast irradiation and adjuvant systemic therapy.

Among the 896 patients with metastatic SLN in this study, 33.6% (301) had lymph node involvement >0.2 mm, ≤2.0 mm (micrometastasis). Of the patients with micrometastasis, 10% had additional involved nodes removed by ALND. A similar percentage of Nmic was found (28.8%). The rate of additional involved nodes was 20%, in line with the range of 24–35%, as reported by McCready et al. [34]. No axillary recurrence was evidenced in patients treated either with or without ALND treatment in the Nmic group. This data compare well with a previous report by Yegiyants et al. [35] where only one of the 33 patients (3%) with micrometastases developed an axillary recurrence, yielding a 97% recurrence-free rate. Furthermore, local control does not seem to influence OS in Nmic patients, as reported in Figure 3 where no differences were seen between patients with negative and positive ALND.

We hypothesize that it would therefore be likely that Nmic patients have worse outcomes in terms of local or distant recurrence than N0 patients, requiring conservative axillary treatment but a more aggressive systemic therapy, such as in the case of N+ patients. In fact, in the cases of Nmic and N+ SLN cases who underwent ALND, a very high proportion of patients also received adjuvant treatment (97%) and postoperative radiotherapy (96%). Maybe, the low rate of axillary recurrence could be attributable to the very high rate of radiotherapy, that could include, in the whole breast irradiation, the SLN region (I and II axillary levels), as proposed by Schlembach et al. [36]. As already shown in other studies there were no differences in OS and DFS between N0 and N0i+ patients, despite a very low number of cases with isolated cells (31). Conversely, a statistically significant difference was seen for Nmic and N+ patients, underlying that a lymph node microinvasion is prognostically unfavourable in terms of OS and DFS, even in the absence of local recurrence.

Finally our findings show a very high rate of 5-years OS and DFS in early breast cancer with a 96.1% and 92.4%, respectively for N+ patients, according to the ACOSOG Z0011 trial. Since the vast majority of cases (about 80%) falls in the luminal A group (ER+/PgR+/HER2−), we think that a longer follow-up period will confirm the good prognosis of our patients, as shown by the MCR data. In fact (data not published), after 66 months of follow-up, women classified as having a luminal A phenotype, registered in a population-based study by the MCR, have on the whole a 88% of OS, regardless the stage. These data confirm the meaning of biological factors which are going to substitute the classical parameters, such as tumor size and node involvement.

The weakness of our study is the lack of a perspective randomization of patients to ALND versus observation, since data are collected in a retrospective way by a population-based cancer registry.

We are trying to propose, in collaboration with other institutions, a new perspective study in which only T1a-b tumor will be randomized to receive SLNB or nil in axilla.

To our knowledge, this is the largest series available in literature of a population-based cancer registry which investigates the prognosis of patients treated with and without SLNB. As other studies confirm, prognosis of N0 and N0i+ seem to be improved compared with patients with Nmic and N+ SLN.

This study suggests that patients with Nmic have a similar prognosis to N+ (N1 + N2) patients, and a low risk of local recurrence, questioning the necessity of ALND for Nmic SLN.

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