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Original research

Breast cancer subtypes can be determinant in the decision making process to avoid surgical axillary staging: A retrospective cohort study

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HIGHLIGHTS

- Axillary dissection is actually not indicated for positive sentinel lymph node (SLN) in selected breast cancer patients.
- This study is to assess probability to have a positive lymph-node in a low risk subgroup of early breast cancer patients.
- Results suggest that SLN biopsy could be avoided in triple negative subtypes and in absence of vascular/lymphatic invasions.

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ABSTRACT

Introduction: The need for performing axillary lymph-node dissection in early breast cancer when the sentinel lymph node (SLN) is positive has been questioned in recent years. The purpose of this study was to identify a low-risk subgroup of early breast cancer patients in whom surgical axillary staging could be avoided, and to assess the probability of having a positive lymph-node (LN).
Methods: We evaluated the cohort of 612 consecutive women affected by early breast cancer. We considered age, tumor size, histological grade, vascular invasion, lymphatic invasion and cancer subtype (Luminal A, Luminal B HER-2+, Luminal B HER-2−, HER-2+, and Triple Negative) as variables for univariate and multivariate analyses to assess probability of there being a positive SLN o nonsentinel lymph node (NSLN). Chi-square, Fisher's Exact test and Student's t tests were used to investigate the relationship between variables; whereas logit models were used to estimate and quantify the strength of the relationship among some covariates and SLN or the number of metastases.
Results: A significant positive effect of vascular invasion and lymphatic invasion (odds ratios are 4 and 6), and a negative effect of TN (odds ratios is 10) were noted. With respect to positive NSLN, size alone has a significant (positive) effect on tumor presence, but focusing on the number of metastases, also age has a (negative) significant effect.
Conclusion: This work shows correlation between subtypes and the probability of having positive SLN. Patients not expressing vascular invasion, lymphatic invasion and, moreover, a triple-negative tumor subtype may be good candidates for breast conservative surgery without axillary surgical staging.

1. Introduction

In recent years, the axillary management of early breast cancer patients has changed. Patients with a clinically-negative axillae are offered sentinel lymph node (SLN) biopsy and axillary lymph node dissection (ALND) only in the presence of positive SLN.

The need for performing ALND when the SLN is positive and the patient is receiving concurrent adjuvant treatment including radiotherapy, chemotherapy and/or hormonal therapy has been questioned in recent years.

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The IBCSG 23-01 trial [1] clearly stated that in the presence of micrometastasis in the SLN (tumor clusters range between 0.2 and 2 mm), axillary dissection can be avoided, thus eliminating complications of axillary surgery with no effect on survival.

Data from the ACOSOG Z0011 trial suggest that ALND may be omitted in selected patients with one or two positive SLNs. This obviates the complications related to ALND and provides adequate surgical staging and comparable loco-regional control and survival [2,3]. Critics of Z0011 have focused on issues of case selection arguing that estrogen receptor (ER) negative tumors were underrepresented [4]. They highlight the major dilemma of targeted management of breast cancer surgical treatment. The worldwide response to Z0011 cautioned that a policy of no-ALND for SLN-positive patients should adhere strictly to the Z0011 selection criteria [4] but without considering biology of the tumor, warning that the criteria do not take into consideration the biology of the tumor.

The purpose of this study was to identify a low risk subgroup of early breast cancer patients in whom surgical axillary staging could be avoided, and assess the probability of having a positive lymph-node (LN).

2. Material and methods

Experimental protocol was approved by the institutional review committee and meet the guidelines of responsible governmental agency.

Between January 2006 and December 2012, we retrospectively evaluated 612 consecutive women affected by early breast cancer. All patients underwent breast conservative surgery, sentinel lymph-node biopsy and, in cases of positive sentinel node, axillary dissection.

A total of 397 patients had SLN localization by radio colloid, 183 by blue dye and 32 by combined techniques as previously reported by the authors [5–7].

Complete axillary dissection was performed when the sentinel nodes contained metastases.

All patients were treated with breast conservative surgery followed by external-beam radiation therapy on the whole breast through two tangential fields (50 plus 10 Gy as a boost to the tumor bed) with a linear accelerator.

In this analysis, according to the TNM classification, LN with micrometastasis were considered as positive, LN with isolated tumor cells were considered as negative.

Estrogen receptor, progesterone receptor (PgR) and proliferation index (KI-67,%) status were determined on the basis of immunohistochemistry (IHC) staining. Tumors were considered HER-2 positive only if they were either scored as 3 + by IHC or if they were 2 + by IHC and also HER-2 amplified (ratio >2.0) on the basis of fluorescence in situ hybridization (FISH) [8,9].

According to different combinations of ER, PgR, KI 67 and HER2 status, all patients were categorized into five subgroups [10] as follows: Luminal A-like (ER+/PgR+/Ki67 < 14%/HER2-), luminal B HER2 positive-like (ER+/PgR+/Ki67 > 14%/HER2+), Luminal B HER2 negative-like (ER+/PgR+/Ki67 > 14%/HER2-), HER2 positive-like (ER-/PgR-/HER2+), and Triple negative like (ER-/PgR-/HER2-).

3. Statistical analysis

We considered age, tumor size (mm), histological grade (1–3), vascular invasion, lymphatic invasion and cancer subtype (Luminal A, Luminal B HER-2+, Luminal B HER-2−, HER-2+, and Triple Negative) as variables for univariate and multivariate analyses to assess probability of there being a positive LN. The univariate analysis is used to study the distributions of the variables and their association with positive or negative SLN and NSLN: The Chi-square or Fisher's Exact tests [11], and the Student's t-test [12] were used for categorical variables and for continuous variables, respectively. The multivariate analysis concerns just those variables that are significantly associated with positive or negative SLN and NSLN in the univariate analyses. A multiple logistic model on NSLN, just to estimate and quantify the strength of the relationship, and a multinomial logistic model [13] on the number of metastases (considered in three classes) were taken into account.

For this study, a p-value <0.05 was considered as statistically significant. The analyses were performed using R software (http://cran.r-project.org).

4. Results

The median age was 57 (range 29–86 years). Patients characteristics are summarized in Table 1. With respect to all the 612 patients, complete data from 590 patients were available for the molecular subtype classification: 180 patients were luminal A-like (34.45%), 272 patients were Luminal B HER2 negative-like (46.02%), 46 patients were Luminal B HER2 positive-like (7.78%), 33 patients was HER2 positive-like (5.58%) and 59 patients were triple negative-like (TN) (9.98%).

The SLN identification rate was 100% irrespective of different techniques. 391 patients (63.72%) had negative SLN, 35 had isolated cancer cells, 221 had metastasis (36.28%), of these micrometastases were detected in 59 patients. Complete ALND was performed in 220 patients, and the median number of dissected Non-Sentinel Lymph Nodes (NSLN) was 19 (range 9–43). Among these 220 patients, 89 (40.45%) had at least one positive NSLN.

At univariate analysis (Table 1) tumor size, presence of lymphatic and vascular invasion and molecular subtype were significantly associated with positivity of SLN ($p < 0.0001$). Age ($p = 0.124$) and grading ($p = 0.370$) did not show significant association with positive SLN.

Among molecular subtypes, triple negative showed the higher rate of SLN negativity than other groups (91.53% vs 8.47%, $p < 0.0001$).

The strength of the relationship between the significant variables of Table 1 and SLN was evaluated through a multivariate logistic regression model.

Baseline characteristics are: no vascular invasion, no lymphatic invasion, mean tumor Size, and Luminal A Subtype.

Results are reported in Table 2 and Table 3. In Table 2, it is possible to notice the significant effect of all the covariates with the exception of three subtypes (Luminal B HER-2+, Luminal B HER-2−, and HER-2+).

Modeling without subtypes was also performed, but the comparison with the previous modeling suggests that subtype be kept as a covariate (p-value = 0.00015).

A more suitable interpretation of the parameter estimations is given by their transformation into odds ratios (Table 2). The main effects are due to lymphatic invasion, vascular invasion, and triple negative subtype (TN): the odds of positive SN for those who have lymphatic invasion is 6 times the odds for those who do not, and for those having vascular invasion it is 4 times the odds for those who do not. Moreover, having TN seems to reduce the odds of positive SN (the odds of positive SN for those not having TN is 10 times the odds for those having it), whereas tumor size seems to increase the odds of positive SN by 8%.

Moreover, we focused on patients with positive SLN and ALND. In the univariate analysis of NLSN (Table 3), just age and size seem to be associated with NSLN metastasis, while no relationship with other variables seems to be significant.

If a logistic model is performed on NSLN with age and size, the

Table 1
Clinical and pathologic features of the sentinel node negative and positive tumors.

	SLN (612)		TOT	p-value
	Negative 391 (63.72%)	Positive 221 (36.28%)		
Age (years)	58.25 (13.22)	56.59 (11.95)	57.65 (12.790)	0.124
Size (mm)	15.89 (7.24)	20.19 (8.53)	17.45 (8.00)	<0.0001
Grade				
1	98 (65.33%)	52 (34.67%)	150 (25.29%)	0.370
2	128 (59.26%)	88 (40.74%)	216 (36.43%)	
3	148 (65.2%)	79 (34.80%)	227 (38.28%)	
Vascular invasion				
0	359 (67.99%)	169 (32.01%)	528 (86.42%)	<0.0001
1	30 (36.14%)	53 (63.86%)	83 (13.58%)	
Lymphatic invasion				
0 (no)	380 (66.09%)	195 (33.91%)	575 (94.11%)	<0.0001
1 (yes)	9 (25.00%)	27 (75.00%)	36 (5.89%)	
Subtype				
Luminal A	117 (65.04)	63 (35.%)	180 (30.54%)	<0.0001
Luminal B HER-2+	29 (63.04%)	17(36.95%)	46 (7.79%)	
Luminal B HER-2-	159 (58.45%)	112 (41.17%)	272 (46.10%)	
HER-2+	18 (54.54%)	15 (45.45%)	33 (5.59.00%)	
Triple negative	54 (91.53%)	5 (8.47%)	59 (10.00%)	

For Age and Size, marginal and conditional means and standard errors (in parentheses) are reported.
For other variables, marginal and conditional counts and percentage (in parentheses and by row) are reported.
The analysis does not account for missing data.

Table 2
Multivariate logistic regression model to predict the probability of SLN metastases.

Coefficients	Estimate	Std. Error	OR (95% C.I.)	p-value
(Intercept)	−2.14669	0.28488	0.1169	<0.0001
Vascular invasion	1.38190	0.27218	3.9825	<0.0001
Size	0.08172	0.01384	1.0851	<0.0001
Lymph invasion	1.81500	0.43035	6.1411	<0.0001
Luminal B HER-2+	−0.29937	0.37604	0.7413	0.426
Luminal B HER-2-	−0.02662	0.22032	0.9737	0.904
HER-2+	0.20266	0.43444	1.2247	0.641
Triple negative	−2.31401	0.53092	0.0989	<0.0001

results (Table 4) show the significant effect of both variables. With respect to the baseline (Negative NSLN patients, with mean age of 58.15 and mean tumor size of 18.29), the effect of the variables is different in sign: the higher the age, the lower the odds of having a NSLN metastasis (having a metastasis is 3% more likely among those are younger), whereas the greater the size of tumor, the higher the odds of having a NSLN metastasis (more than 7%).

Table 4
Coefficients estimation and their significance for the logit model on NSLN.

Coefficients	Estimate	Std. Error	OR (95% C.I.)	p-value
Intercept	−0.2591	0.7999	0.7717	0.7460
Age	−0.0290	0.0126	0.9714	0.0210
Size	0.0748	0.0199	1.0777	0.000176

Finally, if the number of metastases is categorized into three classes (0, 1|-|3, >3), a multinomial logit model on positive NLSN can be considered with age and size. Results in Table 5 confirm the previous results, stressing the same effect of age and size on the odds of having 1|-|3 or >3 metastases with respect to having none:

Table 3
Clinical and pathologic features of the nonsentinel node negative and positive tumors.

	NSLN (220)		TOT	p-value
	Negative 131 (59.54%)	Positive 89 (40.45%)		
Age (years)	58.15 (12.05)	54.38 (11.15)	56.61 (11.81)	0.0201
Size (mm)	18.29 (6.45)	23.01 (10.20)	20.22 (8.49)	<0.0001
Grade				
1	31 (59.62%)	21 (40.38%)	52 (24.19%)	0.09276
2	58 (67.44%)	28 (32.56%)	86 (40.00%)	
3	39 (50.65%)	39 (49.35%)	77 (35.81%)	
Vascular invasion				
Negative	102 (61.45%)	64 (38.55%)	166 (76.15%)	0.2903
Positive	27 (51.92%)	25 (48.08%)	52 (23.85%)	
Lymphatic Invasion				
Negative	116 (60.73%)	75 (39.27%)	191 (87.61%)	0.3001
Positive	13 (48.15%)	14 (51.85%)	27 (12.39%)	
Subtype				
Luminal A	40 (61.53%)	25 (38.46%)	65 (30.37%)	0.4362
Luminal B HER-2+	7 (36.84%)	12 (63.15%)	19 (8.87%)	
Luminal B HER-2-	70 (63.66%)	40 (36.36%)	110 (51.40%)	
HER-2+	6 (40.00%)	9 (60.00%))	15 (7.01%)	
Triple negative	3 (60.00%)	2 (40.00%)	5 (2.33%)	

For Age and Size, marginal and conditional means and standard errors (in parentheses) are reported.
For other variables, marginal and conditional counts and percentage (in parentheses and by row) are reported.
The analysis does not account for missing data.

Table 5
Multinomial logistic model to predict the probability of NSLN number of metastases.

NSLN positive	Intercept (OR 95% C.I.)	Age (OR 95% C.I.)	Size (OR 95% C.I.)
1|-|3	−0.1749 (0.8385)*	−0.0262 (0.9741)	0.0310 (1.0315)
>3	−1.8212 (0.1618)	−0.0311 (0.9694)	0.1168 (1.1239)

Note: '*' is not significant.

in this case, greater the size of the tumor, the higher the odds of having >3 metastases with respect to having none (12% more likely).

In summary, the analyses highlight the non-significant effect of age and grade on SLN, a significant positive effect of vascular invasion and lymphatic invasion, and a negative effect of TN. With respect to positive NSLN, only size has a significant (positive) effect on tumor presence, but if we focus on the number of metastases, also age has a (negative) significant effect.

5. Discussion

This work shows the correlation between subtypes and probability of having positive SLN.

Considering results of the present study, patients with early breast cancer without expression of vascular invasion, lymphatic invasion and, moreover, triple negative tumor subtype could be good candidates for breast conservative surgery without axillary surgical staging.

Recent clinical trials suggest that there is no difference in outcome between patients with positive SLN if they are treated with ALND or given no further axillary surgery [2,3,14].

These studies raise doubts concerning the role of SLN biopsy. A new trial on this topic comparing SLN biopsy with the assessment of whether an axillary ultrasound is negative in patients with small breast cancer is actually running [15] so, considering that metastasis is observed in approximately 30% of SLN biopsies [16], it is important to predict the axillary node status before SLN biopsy.

Agresti et al. [17], recently published a randomized clinical trial performed in patients with T1N0 breast cancer to test the hypothesis of the non-inferiority of breast conservative surgery without axillary dissection compared with breast conservative surgery and complete axillary lymph node dissection, using overall survival as the primary endpoint. He states an alternative pattern of adjuvant treatment decision making exclusively based on a set of pathologic and biological characteristics of the primary tumor. Additional information regarding axillary lymph node involvement at the time of breast surgery would not have changed the decision concerning adjuvant treatment. It is worth noting that this study was designed before sentinel lymph node biopsy was introduced into routine clinical practice (1998). Thus, the intriguing question is what would happen if Agresti et al. reanalyzed the patient data bank on the basis of the new molecularly defined subentities of breast cancer (luminal A, luminal B, basal-like, or triple-negative) determined by ER, progesterone receptor, Ki-67, human epidermal growth factor receptor 2 (HER2) status. Consequently, the authors could analyze how the adjuvant strategy might have been changed and what the resulting impact on OS and DFS was. Based on current knowledge, there is an urgent need to redefine lymph node significance in the treatment of patients with breast cancer and there is the need to select which patients may have the risk of downstaging which may affect the choice of adjuvant treatments and therefore prognosis.

Various clinicopathological factors have been identified as independent predictors of axillary LN metastasis in early stage breast cancer, lymphatic and vascular involvement, tumor grade, hormone receptor (HR) status, age, molecular subtype classification and tumor size [18–32].

Predicting the NSLN status is important because the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [2] indicated that ALND should be avoided if SLN metastases detected in only one or two nodes showing that SLN biopsy alone without ALND results in extremely low locoregional recurrence and excellent overall survival comparable to that in patients undergoing ALND if SLN metastasis is present.

To predict the association between NSLN metastasis and clinicopathological factors, particularly in the case of SLN metastasis in two or fewer nodes in breast cancer, is still a matter of debate and it is so important when making decisions regarding additional ALND in the case of positive SLN metastasis.

Hasegawa M et al. [33] reported that SLN metastasis was associated with younger age, large tumor size and prominent lymphovascular involvement; however, NSLN metastasis was hard to predict using clinicopathological factors.

Previous studies have reported that younger age, higher pT stage, or lymphovascular involvement are independent predictors of SLN metastasis [19–25]. With regard to the prediction of NSLN metastases, younger age, large tumor size or lympho-vascular involvement have been reported as useful markers. One of the most important studies is reported by Toshikawa C. et al. [14] that show that invasive tumor size and lymphatic involvement are significantly associated with NSLN metastasis in the case of SLN metastasis in two or fewer nodes.

Our findings show furthermore that age is correlated to NSLN metastasis but not with SLN metastasis. Tvedskov TF. et al. [34] identified increased proportion of NSLN metastasis in patients with isolated tumor cells into SN in younger age at diagnosiss, thus that was not confirmed in case of micrometastatic or metastatic SN.

The independent association of age with NSLN metastases and, in other studies, with poor prognosis has not been explained by the association of age with other prognostic variables. These results suggest that surgeons and pathologists should be diligent and thorough in searching for lymph node metastases in young patients with large tumors or lymphatic invasion.

In a meta-analysis conducted by Lowery AJ et al. [35], locoregional recurrence rate varied between different subtypes. In particular, RR is 0.49 for any luminal subtypes versus TN regarding breast conservative surgery and of 0.66 regarding mastectomy.

The subtypes may be predictive of loco-regional recurrence and survival also after post-mastectomy radiotherapy [36], and after neo-adjuvant chemotherapy [37,38].

Although there is a paucity of data on associations between presence or extent of nodal diseases across all breast cancer subtypes, conflicting results on the relationship between the TN subtype and nodal disease have been reported [37,38]. Several publications suggest that the TN subtype may predict a lower risk of nodal involvement [18,28,29,31,39] despite Jones T et al. [40] reporting no association between TN subtype and nodal involvement, presumably because HER-2 2 + tumors were considered positive without the FISH test. Possibly this altered the real number of TN.

Although axillary surgery maintains its role in local disease control in patients with clinically evident lymph node involvement, biological characteristics of the primary tumor are important for guiding therapeutic decisions regarding nodal management. Our results thus provide useful information on the risk factors for renmant NSLN metastasis under the condition of SLN contributing to decision-making with regard to the addition of ALND or the kind of adjuvant therapies in the case of SLN metastasis.

Ethical approval

Experimental protocol was approved by the institutional review

committee and meet the guidelines of responsible governmental agency.

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Nill.

Author contribution

Antonio Marrazzo for the study design and writing.
Antonio Marrazzo Giovanni Boscaino for data analysis.
Antonio Marrazzo, Pietra Taormina and Emilia Marrazzo for data collections.
Antonio Toesca to write with the first author.
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Conflict of interest statement

The authors have no conflict of interest to declare.

Guarantors

Antonio Marrazzo, Pietra Taormina, Giovanni Boscaino, Emilia Marrazzo, Antonio Toesca.

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