Advances in Breast Cancer Research, 2014, 3, 124-130
Published Online October 2014 in SciRes. http://www.scirp.org/journal/abcr
http://dx.doi.org/10.4236/abcr.2014.34019

Non-Axillary Sentinel Node in Breast Cancer. Are we Staging Correctly? A Multicenter Study

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Received 22 August 2014; revised 20 September 2014; accepted 14 October 2014

Abstract

Purpose: The study of the sentinel lymph node is the best technique to stage, have a prognosis and decide the adequate treatment in breast cancer. The usual technique implies studding the axillary lymph node. Our work tries to identify affected nodes in other regions apart from the axilla and its possible impact in staging and treatment. Methods: The sentinel lymph node technique was performed on 1660 patients included in an observational and multicentric study designed to observe the presence of metastatic cells in axillary and non-axillary lymph nodes. Results: In 19% of the patients the sentinel lymph node was detected in non-axillary regions. In these cases metastatic cells were more frequent which could suppose a change in the stage and/or treatment. As protective factor against non-axillary nodes involvement we found the localization of the cancer in external quadrants while youth and injecting the tracer inside the tumor were found to be risk factors. Conclusions: Detecting and studding non-axillary lymph nodes in breast cancer leads to a more precise staging of the disease which could imply a change in the optimal treatment.

Keywords

Breast Neoplasms, Sentinel Lymph Node Biopsy, Neoplasm Staging

1. Introduction

Sentinel lymph node (SLN) assessment is the gold standard method to achieve a correct breast cancer staging [1]

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How to cite this paper: Méndez, J.E., Ibáñez, J.F.J., Pérez, M.C., Navinés, J., Schulte-Eversum, J.V., López-Amor, M.F. and Carrasco, M.A. (2014) Non-Axillary Sentinel Node in Breast Cancer. Are we Staging Correctly? A Multicenter Study. *Advances in Breast Cancer Research*, **3**, 124-130. http://dx.doi.org/10.4236/abcr.2014.34019

and, subsequently, decide its optimal treatment. Moreover, it is known to be one of the main prognostic factors in this disease [2].

It is remarkable that its use has usually been focused on the axillary lymph nodes, undervaluing hypothetic positive nodes in other areas and its possible consequences [3].

Nevertheless, traditional interpretation of SLN biopsy (SLNB) results is recently being questioned. As almost 70% of positive axillary SLN patients do not have metastasis performing an axillary lymph node dissection (ALND) seems to be overtreatment [4]. Selected patients with specific tumor characteristic, even with a positive axillary SLN, may benefit from a conservative attitude, thus eliminating complications of axillary surgery with no adverse effect on survival [5] [6].

Currently not many trials have been done to confirm this hypothesis so more research in this field is needed.

However, despite the decisions taken after this possible new interpretation, the SLN technique remains the main staging test in breast cancer.

That is why it is relevant to identify and examine sentinel lymph nodes located in other areas than the axilla to reach a more precise staging [7] [8] of the disease, changing its treatment if necessary.

2. Material and Methods

A prospective, multicenter cohort study was undertaken in 9 different hospitals in Catalonia (Spain) from January 2000 to February 2008.

All patients diagnosed of breast cancer who underwent a sentinel lymph node assessment and accomplished the selection criteria (**Table 1**, **Table 2**) were enrolled.

The sample size was calculated using the ENE program and fixed to 1660 patients. As reference we took an estimated prevalence of 20% of positive non-axillary nodes (CI 95% and accuracy +/−2%).

We focused our study on nodal identification, whether axillary or non-axillary.

As secondary variables, and related to the breast cancer, we assessed the patients age, preoperative diagnostic, radiological diagnostic, margin status, palpable nodes, presence of micrometastasis, single or multiple nodal involvement, location, histological type, vascular or lymphatic infiltration, tumor size, positive hormone receptors and/or Erb2 and type of treatment.

Related to the SLN biopsy we studied the injection method, the number of nodes identified in the lymphoscintigraphy, the number of nodes identified in the dissection and the number of nodal metastasis.

To carry out the study all the institutions followed the same protocol.

Table 1. Inclusion criteria.

Inclusion Criteria
Infiltrative carcinomas, less than 3 cm wide, with clinically negative axillary nodes
Multifocal tumor in the same breast quadrant
Large intraductal *in situ* carcinoma (>3 cm, high grade and/or comedo)
Male patients with breast cancer and the same characteristics

Table 2. Exclusion criteria.

Exclusion Criteria
Patients with no nodal involvement after SLNB
Pregnancy
Multicentric tumors
Patients with advanced disease who require preoperative chemotherapy or those who present metastatic axillary nodes after FNA
Inflammatory breast carcinoma
Previous axillary radiotherapy
Previous axillary surgery

The day before surgery patients were visited and, after and axillary sonography to rule out suspicious unpalpable lymph nodes, 0.3 ml of tracer (99 m-Tc labeled human albumin) was injected either inside of the tumor, peritumorally, subdermally or subareorarly. No colorant was used.

In case of positive sonography fine needle aspiration (FNA) cytology was performed.

Sentinel nodes (SNs) were initially identified with lymphoscintigraphy to ease surgical location and dissection. Surgery took place the day after the lymphoscintigraphic study and a hand-held γ-probe was used to identify SNs following the 10% rule.

Cytology was carried out perioperatively when axillary SNs were located, proceeding to perform an axillary lymph node dissection (ALND) if positive. On the other hand, when internal mammary SNs were located its study was completed postoperatively as results would not modify the surgical procedure.

Next, all SNs were studied with immunohistochemical analysis to detect unseen metastasis in the cytology.

In case of positive results our therapeutic approach varied depending on the size and location:

- More than 2 mm: We performed a complete ALND;
- Between 0.2 and 2 mm (micrometastasis): Patients joined a clinical trial where ALND and routine controls were compared [9];
- Less than 0.2 mm: Were considered as isolated tumor cells (ITC) so no ALND was carried out;
- If located in the internal mammary radiotherapy was indicated.

Once all data was collected we carried out descriptive, bivariate and multivariate analysis with the statistical softwares SPSS and G-Stat with a P value < 0.05.

3. Results

A middle age woman, with a single palpable tumor located in the upper outer quadrants was the most common presentation. Infiltrative ductal carcinoma with hormone receptor expression represented the typical histology. The most frequent nodal location was axillary followed by simultaneous axillary and non-axillary drainage.

Lymph node metastasis varied depending on its location. Thus, patients with drainage to axillary and non-axillary nodes, without involvement of internal mammary ones, were the group of patients who presented a higher rate of metastasis. Afterwards, we found those who had involvement of non-axillary nodes with exception of internal mammary ones, followed by those who presented simultaneous axillary and internal mammary nodes. It is not until the fourth group that we found patients with only axillary drainage and, finally, patients with only involvement of internal mammary nodes.

Patients, tumor and drainage characteristics are presented in **Table 3**.

4. Bivariate Statistical Analysis

Patients that presented non-axillary drainage were statistically younger, with an average age of 52 yo, in comparison with those who had axillary drainage ($p < 0.001$) (**Table 4**). Similarly, younger patients presented a greater proportion of non-axillary drainage.

Regarding the injection technique, intratumoral and peritumoral injection also showed a greater tendency towards non-axillary nodes [10] [11] than subdermal or subareolar injection ($p = 0.009$) (**Table 5**).

It's also remarkable that the number of sentinel nodes detected was statistically larger when non-axillary drainage was present ($p < 0.001$) and the incidence of metastatic nodes was higher too in this scenario ($p < 0.001$).

Tumor location, as described in the literature, is clearly related to lymph drainage. Accordingly, in our study, tumors in outer quadrants tended to have a lymphatic drain towards axillary nodes (53% vs 39%; $p < 0.001$) while those in inner quadrants presented opposite results (47% vs 61%; $p < 0.001$).

Patients with non-axillary nodes affected had more aggressive tumors. Mastectomies were more frequent in these cases than tumorectomies (18 vs 13%; $p = 0.014$) and vascular and lymphatic infiltration were more prevalent (33% vs 18%) although the difference was not statistically significant ($p = 0.064$).

There were no apparent differences in tumor size, presence of free margins after surgery, micrometastasis, hormone receptors, HER 2 expression, histologic type and grade of cancer.

5. Multivariate Statistical Analysis

A logistic regression was carried out to identify important dependent variables related with axillary and non-

axillary lymph draining.

As dependent variables we included the tumor location, the number of nodes dissected, the number of metastatic nodes, the age and the tracer injection method. The model was statistically significant with $p < 0.001$.

Results showed that being less than 50 yo (OR = 2.21) and intratumoral and peritumoral tracer injection (OR = 1.52) were risk factors to present non-axillary lymph nodes involvement (**Table 6**).

Table 3. Patient, tumor and drainage characteristics.

Number of Patients	1660 Women
Mean Age	57 years old
Major Incidence Range	50 to 63 years old
Palpable Tumor	53% of cases
Single Tumor	89% of cases
Location	34.96% upper outer quadrant
	16.20% upper quadrant union
	11.44% upper inner quadrant
	10.38% outer quadrant union
	9.19% inner quadrant union
	8.38% areolar
	5.13% lower outer quadrant
	4.32% lower inner quadrant
Histology	70.4% infiltrative ducal carcinoma
	11.87% intraductal *in situ* carcinoma
	5.86% infiltrative intraductal carcinoma
	5.73% lobulillar carcinoma
	8.14% others
Size	1.82 cm (SD 0.98; range 0.2 - 8.1 cm)
Vascular or Linfatic Infiltration	28% of cases
Positive Hormone Receptors	83% of cases
Positive Erb2	30% of cases
Tracer Injection	59.81% intratumoral
	31.57% intratumoral + subdermal
	6.44% peritumoral
	2.19% subareolar
Number of Nodes Biopsied	1.44 (SD 0.69)
Number of Metastatic Sentinel Nodes	0.3 (SD 0.56)
Nodal Location	1.364 axillary (82.2%)
	267 axillary and non-axillary (16.1%)
	29 extra-axillary (1.7%)
Surgical Treatment	86.45% tumorectomy
	13.55% mastectomy
Axillary Lymph Node Dissection	24% of cases
Metastatic Nodes	0.87 (SD 2.15; range 0 - 21)

Table 4. Quantitative variables comparing axillary vs non-axillary drainage.

	Non-Axillary (mean)	Axillary (mean)	p-Value
Age	52	58	<0.001
Nodes Identified	2.05	1.29	<0.001
Mestatatic Nodes	0.46	0.26	<0.001
Tumoral Size (cm)	1.87	1.81	0.299

Table 5. Qualitative variables comparing axillary vs non-axillary drainage.

	Non-Axillary N (%)	Axillary N (%)	p-Value
Age			<0.001
<50 yo	155 (49.4)	379 (28.6)	
>50 yo	159 (50.6)	945 (71.4)	
Injection Method			0.009
Intratumoral	204 (65.2)	781 (58.5)	
Peritumoral	24 (7.7)	82 (6.1)	
Subdermal	84 (26.8)	436 (31.6)	
Subareolar	1 (0.3)	35 (2.6)	
Treatment			0.014
Tumorectomy	261 (82.1)	1162 (87.5)	
Mastectomy	57 (17.9)	166 (12.5)	
Tumor Location			<0.001
Outer Quadrants	122 (39.2)	685 (53.2)	
Inner Quadrants	189 (60.8)	603 (46.8)	
Vascular/Lymphatic Infiltration			
Yes	54 (33.5)	375 (26.3)	0.064
No	107 (66.5)	522 (73.7)	
Number of Nodes			
1 or more	101 (31.8)	328 (24.4)	0.007
0	217 (68.2)	1014 (75.6)	
Free Margins			0.501
Cytology			0.169
Micrometastasis			0.843
Single/Multiple			0.346
Histology			0.130
Hormone Receptors			0.222
Erb2			0.184

Table 6. Multivariate analysis.

	p-Value	OR	CI 95%
Age	<0.001	2.21	1.64 - 2.98
Number of nodes	<0.001	0.22	0.18 - 0.28
Metastasic nodes	0.579		
Location	<0.001	0.49	0.36 - 0.67
Injection method	<0.001	1.52	1.10 - 2.10

On the contrary, outer quadrants location of the tumor seemed to be a protective factor (OR = 0.49).

The number of nodes detected remained higher when non-axillary drainage was detected but the number of metastatic nodes was not statistically different when analyzed simultaneously with the number of nodes detected ($p = 0.579$).

6. Discussion

Breast cancer is a very prevalent illness and implies important clinical and aesthetic consequences, mainly in women. Nevertheless, thanks to the evolution of diagnostics and treatments, almost 80% of patients get cured.

But not only rates of cure must be taken into account. To avoid consequences of surgical treatment the SLNB technique was developed, saving lots of unnecessary axillary dissections.

Nowadays this question is more up-to-date than ever given that, even with a positive axillary SLN, the necessity of performing an ALND is being questioned in the literature [4]-[6] [12]. Essentially, this implies that to improve our treatments and adapt them to each patient needs, an accurate staging must previously be carried out.

Consequently, although axillary draining is the most common and its implications have been well studied, non-axillary drainage is often underestimated. Current research shows draining towards internal mammary nodes in a range between 2.4% and 23.3% [7] [13] [14]. Obviously, this proportion gets higher when Rotter, intramammary or intercostal nodes are also included. This fact may lead to suppose that an incorrect staging is sometimes performed, meaning that a suboptimal treatment could be given.

It is important to highlight that almost 20% of breast neoplasm present lymphatic draining to non-axillary nodes, the vast majority with concomitant draining to axillary ones, being more frequently metastatic.

The presence of metastatic nodes in non-axillary regions would imply a change in the illness stage in case of negative axillary ones. Moreover, those patients presenting both axillary and non-axillary metastatic nodes would remain in the same illness stage but optimal treatment would require addition of radiotherapy, at least in internal mammary nodal chain [14].

Another interesting consequence is that, traditionally, it has been proposed that the presence of nodal metastasis could imply a lymphatic block that could lead to alternative drainage pathways. This may be the reason why there seems to be more metastatic nodes when simultaneous drainage to axillary and non-axillary regions is present [10]. However, more studies need to be done to confirm this hypothesis.

If that was the case, the attitude in patients with positive preoperative axillary nodes should be reconsidered as, currently, the SLNB is dismissed and an ALND is directly performed. Consequently, we fail to know if there is simultaneous draining towards non-axillary nodes which would be an indication of postoperative radiotherapy.

Unfortunately, given the usual difficulty to reach non-axillary nodes, its dissection is hardly ever performed.

In conclusion, we consider that doing a biopsy of non-axillary nodes is an important factor to carry out an accurate staging of the disease, and therefore, decide the optimal treatment in each patient [8]. Moreover, traditional staging should also be reconsidered given that atypical nodal location is not considered.

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