# Can we define a role for perisentinel lymph-nodes on breast cancer disease?



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## Can we define a role for perisentinel lymph-nodes on breast cancer disease?

BACKGROUND: The development of sentinel lymph node biopsy in breast cancer disease and the increasing of using adjuvant systemic therapy provide a rational reduction of axillary dissection in patients with Sentinel Lymph Nodes free from breast cancer cells. The aim of our study was to assess the state of the perisentinel lymph nodes removed and how these nodes can provide further information about the status of the axillary lymph nodes.

MATERIALS AND METHODS: We have analysed data about 319 patients undergoing surgery for benign and malignant breast disease from January 2007 to July 2010; 134 cases were subjected to the sentinel lymph node biopsy; 29 cases of these patients had the presence of perisentinel lymph nodes at histological examination. Before the intervention, we have used colloidal albumin marked with 99mtc to select the sentinel lymph node; during the intervention, we identified by probe the ipercaptant lymph node, consequently we removed and sent it to histological extemporaneous definitive examination.

RESULTS: In 134 Sentinel Lymph Nodes examined, 15 resulted positive for breast cancer cells at extemporaneous examination. In these cases, we decided to proceed with an axillary dissection in the same operative session, with the discovery of axillary lymph nodes metastases in 3 cases on 15 (20%). The positive predictive value of sentinel lymph node in case of positivity was 0.2. 8 cases (6,7% of the lymph nodes sentinel biopsy made) were negative to extemporaneous examination and positive to definitive histological examination for presence of micrometastasis. In 8 axillary dissection, 3 patients were positive for the presence of metastasis. We have analysed with the test "t-student" these data divided on age and the value of Ki-67. Then we calculated the

We have analysed with the test "t-student" these data divided on age and the value of Ki-67. Then we calculated the predictive positive and negative value (patients with negative sentinel lymph node: Mean age  $(\pm sd) = 61.93\pm13$ . 8 years, ki-67=10. 87±5. 78; patients with positive sentinel lymph node: Age mean  $(\pm sd) = 64 \pm 12$  36 years, ki-67=14. 08  $\pm$  8.005). The study showed no statistically significant differences between the positive and negative sentinel lymphnodes about the age (p=0.58) and the Ki-67 (p=0.184). In the 29 cases in which the sentinel lymph node was negative at extemporaneous histological examination and in which were removed the perisentinel lymph nodes, resulted negative at definitive histological examination, the negative predictive value was equal to 1.

CONCLUSIONS: The method of sentinel lymph node has demonstrated to be a reproducible, reliable and safe technique. The positivity of sentinel lymph node at final examination (micrometastasis, cells isolated) in case of extemporaneous examination negative for breast cancer cells, determines specifical considerations on surgical indication to axillary dissection. We think that in selected cases (age, biological characteristic of cancer) in which perisentinel lymph nodes were removed and free from breast cancer cells, may not be indicated in case of sentinel node positivity, the axillary dissection.

KEY WORDS: Axillary echography, Breast cancer, Breast surgery, Perisentinel lymphnodes, Sentinel biopsy.

## Introduction

Axillary dissection has represented for a long time, the standard therapy for patients with breast cancer. The state of the axillary lymph nodes is the more important

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prognostic factor and the axillary status permits a good regional control of disease <sup>1</sup>.

The sentinel lymph node biopsy is a procedure with low morbidity and high negative predictive value and today it is the gold standard for axillary staging <sup>2-10</sup>.

In patients with positive sentinel lymph node, the axillary dissection is the standard treatment. However, sentinel node biopsy positive identifies patients with higher risk of metastases to the axillary nodes but the rate of patients negative for metastases after axillary dissection is high. These patients were exposed to surgical risk without therapeutic advantages.

On these findings, we have analyzed the role of perisentinel nodes removed during the sentinel biopsy. The objective of our study was to determine if the surgical treatment of breast cancer can use the histological examination of perisentinel nodes as criterion to stage axilla status together with the age of patients and the Ki 67 values.

# Materials and methods

From January 2007 to July 2010, at the Unit of General Surgery and Organ transplantation of University Hospital of Parma we examined retrospectively data relating to patients undergoing surgery for breast cancer and treated with sentinel-node biopsy.All cases were previously examined by axillary echographic evaluation <sup>11</sup>.

#### The inclusion criteria were:

- diagnosis of Ductal Infiltrating Carcinoma at biopsy(B5), or by cytologic examination (C5) or with definitive histological report if already treated with tumorectomy or quadrantectomy;

- diagnosis of invasive carcinoma suspected at FNAC (C4) with instrumental picture suggestive for invasive carcinoma (U5, R5);

- diagnosis of carcinoma in situ in cases where the suspicion of microinvasivity is high;

- multicentric mammary lesions with maximum size of 3 cm;

- No inflammatory carcinoma;

- No positive FNAC of axillary nodes (C5).

The patients were informed about the procedures concerning the method of sentinel lymph node biopsy by a consensus paper.

The day before surgery, patients were marked with injection of colloidal albumin to identify the sentinel lymph node.

Colloidal albumin had size between 20 and 80 nanometers (nanocoll), marked with 99mtc. The solution containing the radioactive tracer (0.2 MCI to 99mtc in a volume of 0.2-0.4 ml, followed by 0.2 ml of physiological saline or air) was inoculated by nuclear specialist. In obese patients is increased the dose to 0.3-0.4 MCI. The injection was performed in subskin near the breast lesion previously identified on ultrasonographic or mammographic guide. After one hour was performed a lymphoscintigraphy to verify the procedure.

The day after, we have performed the surgical procedure with sentinel lymphnode biopsy as reported in previous work.

After the biopsy, if the probe signed a minimal radioactivity we have removed others perisentinel nodes.

The sentinel node was analyzed with extemporaneous histological examination. The lymph node was frozen, dissected at intervals of 150 µm and stained with haematoxylin and eosin, to obtain 3-4 sections for slice. According to the last "TNM" classification, we defined macrometastasis those lesions exceeding 2 mm in maximum diameter and micrometastasis those lesions size of less than 2 mm but higher than 0.2 mm, while cancer cells isolated (ITC) are defined as cells isolated or in aggregate of diameter of less than 0.2 mm, usually identified using anti-citocheratine antibodies. The result was given to the surgeon that, in presence of metastatic node, proceeded with axillary lymph node dissection.

The perisentinel lymphnodes were examined again together with the breast gland for the definitive histological report. We proceeded, in case of "false negative" at extemporaneous examination of sentinel-node or of positivity at "definitive" examination of peri-sentinel nodes, to a second look with an axillary dissection. In this case suction drainage was applied for a time ranging from 2 to 13 days.

All these data were collected in data base divided for histological results, age, Ki 67 values.

The age data and Ki 67 were verified by statistical analysis with the test "t-student"; we have calculated the positive and negative predictive value; p values lower than 0. 05 were considered statistically significant.

## Results

On 319 consecutive patients surgically treated for benign or malignant breast disease, we have examined 134 cases with sentinel node biopsy.

TABLE I - Histological type of breast cancer surgical treated

Туре	%	
Ductal infiltrating carcinoma	31	
Lobular infiltrating carcinoma	6	
Mixed infiltrating carcinoma	8	
Tubular carcinoma	3	
Carcinoma in situ	23	
Mucoid Carcinoma	2	
Intraductal carcinoma	15	
Intralobular carcinoma	4	
Others	8	

The histological results for neoplastic lesions examined (in cases of sentinel-node biopsy), are summarized in Table I.

The mean age ( $\pm$  sd) of patients with negative sentinel lymph node was 61.93  $\pm$  13.8 years, while the mean age of patients with positive sentinel lymph node was 64  $\pm$ 12.36 years.

The statistical analysis of age in positive sentinel group and negative sentinel group was no significant (p=0.58); also the statistical analysis of Ki-67 has shown no significant differences with p = 0,184 (patients with sentinel lymph node negative: Ki-67 = 10.87 ± 5.78, patients with sentinel lymph node positive: Ki-67 = 14.08 ± 8,005) (Table II).

We have analyzed the positive predictive value of sentinel node biopsy in patients treated with axillary dissection and in patients with perisentinel nodes dissection.

In 29 patients with perisentinel nodes dissection, the sentinel node biopsy was negative; the mean number of nodes dissected was 4.13 (range 2-8). All these nodes were free from metastasis.

In 15/134 sentinel nodes analysed we have performed a contestual axillary dissection for positivity to extemporaneous histological examination. In 3 cases on 15 (20%) the axillary nodes were positive for metastasis. In our experience these data has allowed us to define the positive predictive value of sentinel lymph node positive equal to 0.2 (capacity to predict the positive axillary status) and the negative predictive value equal to 1 (capacity to predict the negative axillary status).

In 8 cases (6.7%) of sentinel node negative at extemporaneous examination we showed, at definitive histological report, the presence of micrometastasis or isolated cancer cells. The axillary dissection was positive in 3 cases.

In patients "positive" at extemporaneous histological examination of sentinel lymph node, we didn't highlight

TABLE II - Statistical results between SNB (+) and SNB (–) about age and Ki67.

	negative	positive	Р
Age (years) Ki67	61.93±13.8	64±12.36	0.58

TABLE III - Statistical results between Axillary positive dissection and Axillary negative dissection about age and Ki67.

	Axillary nodes negative	Axillary nodes positive	р
Age (years)	68.56±10.83	58±5.29	0.245
Ki67	8.667±4.153	1.67±7.638	0.393

the age as a factor statistically significant to predict the positivity metastatic stage of axilla after axillary dissection (axillary nodes negative:  $68.56 \pm 10$ . 83 years vs. axillary nodes positive:  $58 \pm 5.29$  years; p=0,245).

In the same group the statistical analysis of Ki 67 value was negative (negative axillary status Ki-67 =  $8.667 \pm 4,153$ , positive axillary status Ki-67 =  $1.67 \pm 7.638$ ; p= 0.393) (Table III).

# Discussion

The axillary lymph nodes status is still today a very important prognostic factor in breast cancer.

In the past, the axillary dissection was the traditional surgical treatment of the breast cancer. The benefits in terms of prognosis and treatment were associated to a significant morbidity (chronic lymphedema) consequent to the dissection of lymphatic drainage of the arm. Furthermore, it was found that many patients had a negative axillary status.

These conditions developed minimally invasive diagnostic procedures that provided an accuracy of axillary status similar to axillary dissection, identifying the subgroup of patients at risk for axillary nodes metastasis.

So, several surgeons especially in the USA, have adopted the dissection limited to I and II Berg's level as an alternative to complete dissection; unfortunately this technique has proved less advantageous in terms of radicalism, in terms of no correct staging with more problems in case of new surgical axillary dissection.

The use of axillary ultrasonography is useful in all cases which will be submitted to sentinel node biopsy to identify the suspected lymphoadenopathy before the surgical treatment, in fact, a preoperative ultrasound examination associated to a FNAC, may identify the metastatic nodes <sup>11</sup>.

We know that the possibility of skip lesions has an incidence of 2% but in higher rate of cases the breast cancer metastasis goes from I° to III° level <sup>12</sup>.

These characteristics of dissemination have allowed to use a minimally invasive surgical technique with lower rate of complications: the sentinel lymph node biopsy.

The sentinel lymph node is the first lymph node that drains the breast cancer region. Normally this is an axillary lymph node, more often is a lymph node of the central level, but may be in II° and III° levels or at internal mammary level.

In our study the analysis of the perisentinel lymph nodes has proved that the method of sentinel lymph node biopsy is safe, without discrepance at the definitive histology, with exclusion of skip lesions.

In the selection of patients candidates to sentinel node biopsy, the inclusion criteria are no more limited by multifocality of neoplasia because as demonstred, the lymphatic drainage follows, even in these cases, the way of axillary lymphatic ways. The sentinel lymph node predictivity at histological examination was validated in different studies as 95% <sup>13</sup>. There is a variable rate of false negative (negative sentinel lymph node in the presence of other metastatic lymphnodes) whose impact on prognosis, today it's not clear because we haven't the results of controlled trials at long time.

In our 134 cases treated with sentinel node biopsy, 15 patients have undergone axillary dissection after extemporaneous histological examination; 20% of these patients presented metastases in others lymph nodes after histological examination of the axilla. Only in 8 cases the extemporaneous examination was negative and the definitive examination was positive for metastases, highlighted with the use of anticitocheratine antibodies.

All these cases were retreated with axillary dissection and in 3/8 cases, we found others metastatic lymphnodes.

This real clinical problem could be solved by the dissection of only perisentinel lymphnodes (in our 29 cases selected retrospectively, these perisentinel nodes were a correct indicator of the axilla state). Selected cases for age and biological characteristics of breast cancer could not be subjected to a second surgical procedure of complete axilla dissection. We can determine, in association with biological cancer parameters, the probability that other metastases could be in others axillary lymph nodes as highlighted by the models of Rivers, Chagpar and Katz in the study of Mayo Clinic <sup>14</sup>.

In our experience the false-negative patients at extemporaneous examination represent the 6.7%; this result is lower than in other studies (Geertsema).It remains controversial establish if we must proceed to axillary dissection after diagnosis of micrometastasis or isolated cancer cells in sentinel lymph node (Fig. 1). Results of several studies showed that in cases diagnosed as pN1mic and pN0i+ the rate of axilla limph node metastasis after dissection is low <sup>15</sup>.



Fig. 1: Micrometastasis in axillary lymphnode.

## Riassunto

BACKGROUND: Lo sviluppo dell'utilizzo della metodica del linfonodo sentinella nel trattamento chirurgico del carcinoma mammario e l'aumento di terapia adiuvante ha determinato una riduzione della dissezione ascellare con linfonodi sentinella liberi da malattia. Lo scopo dello studio è stato di chiarire lo stato dei linfonodi perisentinella rimossi e come questi possano fornire ulteriori informazioni sullo stato dei linfonodi ascellari.

MATERIALI E METODI: Abbiamo analizzato 319 casi sottoposti a chirurgia per malattia benigna e maligna mammaria da Gennaio 2007 a Luglio 2010. 134 casi erano stati sottoposti a biopsia del linfonodo sentinella; 29 casi/134 presentavano linfonodi perisentinella all'esame istologico. Prima dell'intervento abbiamo utilizzato albumina colloidale marcata con 99 mtc per selezionare il linfonodo sentinella;durante l'intervento abbiamo identificato con la sonda il linfonodo captante conseguentemente rimosso e inviato all'esame istologico estemporaneo e definitivo.

RISULTATI: In 134 casi i linfonodi sentinella esaminati sono risultati positivi, per 15 casi, all'esame estemporaneo al congelatore. In questi casi abbiamo proceduto con dissezione ascellare nella stessa sessione operatoria con il riscontro di metastasi ascellari in 3 casi su 15 (20%).

Il valore predittivo positivo del linfonodo sentinella in caso di positività era 0,2

8 casi (6,7%) erano negativi all'esame estemporaneo al congelatore e positivi al definitivo per la presenza di micrometastasi. In 8 dissezioni ascellari, 3 pazienti risultarono positivi per la presenza di micrometastasi.

Abbiamo analizzato con esame t-student questi dati dividendoli in base all'età ed al valore di ki 67. Abbiamo calcolato il valore predittivo positivo e negativo (pazienti con sentinella negativo:età media pari a 61.93±13.8 anni, ki 67 pari a 10.87±5.78:pazienti con sentinella positivo. Età media pari a 64±12.36 anni, ki67 pari a 14.08±8.0005). Lo studio non ha evidenziato differenza statisticamente significative tra la positività e non del linfonodo sentinella in base all'età ed al ki 67. In 29 casi nei quali il linfonodo sentinella era negativo all'esame estemporaneo al congelatore e nei quali erano stati rimossi i linfonodi perisentinella, risultati negativi all'esame istologico definitivo, il valore predittivo risultò pari a 1.

CONCLUSIONI: Il metodo del linfonodo sentinella è stato dimostrato essere riproducibile, affidabile e sicuro. La positività del sentinella all'esame istologico definitivo (micrometastasi e cellule isolate) in caso di congelatore negativo per cellule mammarie, determina specifiche considerazioni sulle indicazioni chirurgiche alla dissezione ascellare. Pensiamo che in casi selezionati (età, caratteristiche biologiche del carcinoma) nei quali i linfonodi perisentinella rimossi risultino liberi da cellule da carcinoma mammario, possa non essere indicata in caso di sentinella positivo la dissezione ascellare.

# References

1) Carter CL, Allen C, Henson DE: *Relation of tumor size, lympho-node status and survival in 24740 breast cancer cases.* Cancer, 1998; 63:181-87.

2) Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, Costa A, de Cicco G Gerahty JG, Luini A, Sacchini V., Veronesi P: *Sentinel node biopsy to avoid axillary dissection in breast cancer with clinically negative lymphnodes*. Lancet, 1997; 349: 1864-867.

3) Giuliano AE, Haight PI, Brennan MB, et al.: *Prospective obser*vational study of sentinel lymphadenectomu without further axillary dissection in patient with sentinel node-negative breast cancer. J Clin Oncol, 2000; 13:2553-559.

4) Krag DN, Ashikaga T, et al.: *The sentinel node in breast cancer- aq multicenter validation study.* N Engl J Med, 1998; 339:941-46.

5) Nieweg OE, Rutgers EJ, Jansen L, et al.: *Is lymphatic msapping in breast cancer adequate and safe?* World J Surg, 2001; 25:780-88.

6) Reisamer R, Peintinger F, Prokop E, et al.: 200 sentinel lymph node biopsy whitout axillary lymph node dissetcion -no axillary recurrences after a 3-year follow-up. Br J Cancer, 2004; 90:1551-564.

7) Veronesi U. Paganelli G, Viale G, et al.: A randomized comparison of sentinel node biopsy with routine axillary dissection in breast cancer. N Engl J Med, 2003; 349:546-53.

8) Noguchi M: Axillary reverse mapping for breast cancer. Breasr Cancer Res Treat, 2010; 119:529-35.

9) Macellari G, Pluchinotto A, Terribile D: Senologia pratica. Torino: Edizioni Minerva Medica, 2007; 114-59.

10) Ruco L, Scarpa A: *Anatomia Patologica. Le basi.* Torino: UTET Scienze Mediche, 2007; 359-69.

11) Sianesi M, Ceci G, Ghirarduzzi A, Del Rio P, Guazzi M, Pisanelli B, Martella E, Ardizzoni A, Di Biasio B, Arcuri MF: Use of axillary ultrasonography in breast cancer :A useful tool to reduce sentinel node procedures. Ann Ital Chir, 2009; 80(4):315-18.

12) Msya CA Hortueit F: *Skip lesions in the axilla in breast cancer and their association with micrometastases.* Breast Cancer Res treat, 1991, 19(3):277-81.

13) Galimberti V, Intra M, Mauri G, Mazzaroli G, De Cicco C, Luini A: La biopsia del linfonodo sentinella nel carcinoma mammario:tecnica ed indicazioni. In: EMC Techniche chirurgiche. Chirurgia generale. Paris: Elsevier.

14) Zendejas B, Hoskin TL, Degnim AC, Reynolds CA, Farley DR,Boughey JC: *Predicting four or more metastatic axillary lymph nodes in patients with sentinel node-positive breast cancer: Assessment of existent risk scores.* Ann Surg Oncol, 2010 April 26 (Epub ahead of print).

15) Geertsema D, Gobardhan PD, Madsn EV, Albregts M, van Gorp J, de Hooge P, van Dalen T: Discordance of intraoperative frozen section analysis with definitive histology of sentinel lymph node dissection is irrelevant for subsequent systemic therapy. Ann Surg Oncol, 2010 April 27. Epub ahead of print.