# Is it always necessary to perform an axillary lymph node dissection on patients undergoing neoadjuvant therapy? Outcomes of a retrospective study



Ann. Ital. Chir., 2019 90, 4: 292-296 pii: S0003469X19030458

Benedetto Neola, Battistino Puppio, Graziella Marino, Giuseppe La Torre

Breast Surgery Unit, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy

# Is it always necessary to perform an axillary lymph node dissection on patients undergoing neoadjuvant therapy? Outcomes of a retrospective study

BACKGROUND: Some Trials have demonstrated that the rate of false negative results of a sentinel lymph node biopsy in patients undergoing neoadjuvant chemotherapy is >10%. The aim of this study is to identify the predictive factors of a pathologic complete response in the axilla in order to make a better choice between the performance of an axillary lymphadenectomy or the performance of a sentinel lymph node biopsy.

METHODS: All patients diagnosed with positive axillary lymph nodes and achieving a clinical complete response after a neoadjuvant therapy were the object of our study. Radiologic, clinical and histopathological data were collected before and after the neoadjuvant therapy. Data regarding surgery, post-operative period and follow-up were also collected. RESULTS: Clinically negative lymph nodes were reported in 26 patients after they had received a neoadjuvant therapy

RESULTS: Clinically negative lymph nodes were reported in 26 patients after they had received a neoadjuvant therapy (59.09%, 26/44). 57.69% of patients, who were clinically cN0 after neoadjuvant therapy, were reported to have a nodal disease on histological examination (pN+). Patients with a pathologic complete response in the axilla are more likely to be Her2-positive (58.33% vs 3.13%, p<0.05) whereas a Luminal B phenotype is more frequently reported in those patients with an incomplete response (62.5% vs 16.67%, p<0.05).

CONCLUSIONS: The possibility to detect patients with a lower risk of nodal disease before surgery may reduce the rate of false negative results of sentinel lymph node biopsy in patients receiving a neoadjuvant therapy.

KEY WORDS: Axilla, Breast cancer, Lymphnodes, Lymphonodes sentinel

#### Introduction

The state of axillary lymph nodes in patients suffering from breast cancer is a highly important prognostic factor and it considerably influences the line of conduct in therapy. At present, many patients affected by breast neoplasia spread to axillary lymph nodes receive a neoadjuvant chemotherapy.

40%-75% of patients diagnosed with lymph node neoplasm may achieve a complete remission at the end of the neoadjuvant therapy <sup>1,2</sup>. In such cases, the most common clinical practice provides that an axillary lymphadenectomy is to be performed anyway. Yet, over the last years more and more Authors have been performing a sentinel lymph node biopsy first and, just in case of a positive result, the axillary lymphadenectomy<sup>3,4</sup>.

The advantages of a sentinel lymph node biopsy are evident. In fact, complications linked to axillary lymphadenectomy can be disabling and lasting. There are, however, some Trials which have demonstrated that the rate of false negative results of a sentinel lymph node biopsy in patients undergoing neoadjuvant chemotherapy is  $>10\%^{-1}$ . A reason for these data lies in either the possibility of a lymphatic pattern altered by chemotherapy or the possibility that, while the sentinel lymph node has achieved a complete pathologic response, other axillary lymph nodes turn out to be still affected.

In order to reduce the rate of false negative results of a

Pervenuto in Redazione Febbraio 2019. Accettato per la pubblicazione Marzo 2019

Correspondence to: Benedetto Neola, IRCCS CROB – Dipartimento di Chirurgia Oncologica, Via Padre Pio 1, 85028 Rionero in Vulture (PZ), Italy (e-mail: dottbneola@gmail.com)

sentinel lymph node biopsy, some Authors have made some changes in the standard technique: it is possible to use at the same time more than one modality of identification of this lymph node; moreover, it is possible to mark with anatomical landmarks the pathological lymph node under biopsy so as to remove it during surgery even if it is not a sentinel lymph node <sup>5</sup>.

The aim of this study is to identify the predictive factors of a pathologic complete response in the axilla in order to make a better choice between the performance of an axillary lymphadenectomy or the performance of a sentinel lymph node biopsy in patients undergoing neoadjuvant chemotherapy.

# Methods

A retrospective study has been carried out on patients undergoing surgery at the IRCCS Hospital "Centro di Riferimento Oncologico della Basilicata" (Centre of Oncological Reference in Basilicata), a clinical and research centre devoted to oncology. All patients affected by breast carcinoma who had undergone surgery after a neoadjuvant therapy from January 2010 and December 2015 were enrolled. The patients diagnosed with positive axillary lymph nodes (cN+) and achieving a clinical complete response after a neoadjuvant therapy were the object of our study. Inclusion criteria are shown in Table I.

Radiologic, clinical and histopathological data were collected before and after the neoadjuvant therapy. Patients were selected according to our inclusion criteria and data regarding surgery, post-operative period and follow-up were also collected.

The clinical response to neoadjuvant therapy was evaluated by comparing per- and post- therapy MR Imaging. The pathologic response was classified as partial or complete response; in case of partial response, the component of fibrosis and residual neoplasia was indicated. The histopathological study of biopsic samples indicated the histological type, the expression of estrogen receptors (ER), progesterone receptors (PR), Ki-67 and HER2, the presence of micro or macro residual disease, the number of recessed lymph nodes.

Categorical data were presented as frequencies and percentages and were analyzed by the Chi-squared test or by the Fisher exact test. Continuous variables were pre-

TABLE I - Inclusion criteria

Breast cancer
No distant metastasis (M0) Positive axillary lymph nodes (cN+) Neoadjuvant therapy Potentially curative breast surgery Complete follow-up

sented as mean  $\pm$  SD and were compared using Student t-test or the Mann-Whitney test, as appropriate. All tests were two-sided and differences were considered to be significant for p < 0.05. Statistical analysis was performed using SPSS (IBM<sup>®</sup> SPSS<sup>®</sup> Statistics v20.0; IBM, Armonk, NY).

The study protocol was approved by the institutional ethics committee which hold it unnecessary to have further informed consent except for the one already signed by patients before surgery, since it dealt with a retrospective study.

# Results

During the study period, 112 patients with breast neoplasia spreading to axillary lymph nodes were observed. Among them, 44 patients respected our inclusion criteria and were subjected to surgery after a neoadjuvant therapy.

The demographic and clinical characteristics of patients at the time of diagnosis are shown in Table II. 4/44 patients (9.09%) had T1 tumour; 40/44 patients (90.91%) had >T1 tumour. Following our inclusion criteria, all patients were reported to have a disease spread to lymph nodes (N+) without distant metastases. They all had completed the neoadjuvant chemotherapy suggested by the Department of Oncology.

A complete axillary lymphadenectomy, together with a mastectomy (81.82%, 36/44) or partial resection (18.18%, 8/44), was performed on all patients. The histological features of neoplasia, the type of surgery and the clinical outcomes are summarized in Table III. Clinically negative lymph nodes were reported in 26 patients after they had received a neoadjuvant therapy with a clinical response rate of 59.09% (26/44). A pathologic complete response with impossibility to identify neoplasia on histological examination was observed in 2 patients.

Then, we analysed the data considering the state of axillary lymph nodes (pN0/pN+) on the histological examination of the specimen. Patients with clinically nega-

TABLE II - Patient characteristics at diagnosis

Patients [F/M]	44 [44/0]		
Age	57.3y (range 38-82)		
ASA score > $2$	6/44 (13.64%)		
Performance status > 2	5/44 (11.36%)		
cT status	T1: 4/44 (9.09%) T2: 19/44 (43.18%) T3: 11/44 (25%) T4: 10/44 (22.73%)		
cN0/cN+	0/44		
cM0/cM+	44/0		

#### TABLE III - Outcomes

	All Patients	pN0	pN+	p-value
N° of Patients	44	12/44 (27.27%)	32/44 (72.73%)	
pT status	pT0: 2/44 (4.55%) pT1: 16/44 (36.36%) pT2: 20/44 (45.45%) pT3: 4/44 (9.09%) pT4: 2/44 (4.55%)	pT0: 2/12 (16.67%) pT1: 6/12 (50.00%) pT2: 4/12 (33.33%) pT3: 0/12 (0.00%) pT4: 0/12 (0.00%)	pT0: 0/32 (0.00%) pT1: 10/32 (31.25%) pT2: 16/32 (50.00%) pT3: 4/32 (12.50%) pT4: 2/32 (6.25%)	0.07 0.30 0.50 0.56 1.00
cN status after neoadjuvant therapy	cN0: 26/44 (59.09%) cN+: 18/44 (40.91%)	cN0: 11/12 (91.67%) cN+: 1/12(8.33%)	cN0: 15/32 (46.88%) cN+: 17/32 (53.12%)	0.01
Histotype Ductal Others	37/44 (84.09%) 7/44 (15.91%)	11/12 (91.67%) 1/12 (8.33%)	26/32 (81.25%) 6/32 (18.75%)	0.65
Prognostic factors Luminal A Luminal B HER 2-positive Basal-like	10/44 (22.73%) 22/44 (50%) 8/44 (18.18%) 4/44 (9.09%)	2/12 (16.67%) 2/12 (16.67%) 7/12 (58.33%) 1/12 (8.33%)	8/32 (25%) 20/32 (62.5%) 1/32 (3.13%) 3/32 (9,37%)	0.70 0.01 <0.01 1.00
Surgery Quadrantectomia Partial resection	8/44 (18.18%) 36/44 (81.82%)	4/12 (33.33%) 8/12 (66.67%)	4/32 (12.5%) 28/32 (87.5%)	0.18
Radical resection R0 R>0	41/44 (93.18%) 3/44 (6.82%)	12/12 (100%) 0/12 (0.00%)	29/32 (90.63%) 3/32 (9.37%)	0.55
Complete pathologic response	2/44 (4.55%)	2/12 (16.67%)	0/32 (0.00%)	0.07
N° of lymph nodes	26.32 ± 9.32	27.40 ± 7.20	25.97 ± 11.97	0.72

tive axillary lymph nodes (pN0) show also a more frequent pathologic response (16.67% vs 0.00%, p=0.07) in the breast and they incur partial breast resection more frequently (33.33% vs 12.55%, p=0.18), even if it is not statistically significant. Moreover, the rate of radical surgery indicated as proportion of cases RO is tendentially greater as well (100% vs 90.63%, p=0.55).

According to our data, patients with clinically negative lymph nodes (pN0) are precisely identified with the preoperative staging examinations: as a matter of fact, 91.67% of patients pN0 were also reported as clinically cN0 before surgery. However, the predictive value of the test is 42.31%, that is 57.69% of patients, who were clinically cN0 after neoadjuvant therapy, were reported to have a nodal disease on histological examination (pN+). In our experience patients with a pathologic complete response in the axilla are more likely to be Her2-positive (58.33% vs 3.13%) whereas a Luminal B phenotype is more frequently reported in those patients with an incomplete response (62.5% vs 16.67%). Both differences are statistically significant with p<0.05.

## Discussion

According to our data, 59.09% (26/44) of patients diagnosed with a nodal neoplasia (cN+) show clinically negative lymph nodes after neoadjuvant therapy (cN0)

but only 27.27% of patients (12/44) have a pathologic complete response in the lymph nodes (pN0). These patients are precisely identified with the preoperative staging. As a result, 91.67% of patients pN0 was also cN0. However, the preoperative radiological staging is characterized by 57.69% of false negative results and consequently it is not an adequate test for the identification of patients with pathologic complete response in the axilla. Our data demonstrate how patients with a pathologic complete response in the axilla are more likely to be Her2-positive (58.33% vs 3.13%, p<0.05) whereas a Luminal B phenotype is more frequently reported in those patients with an incomplete response (62.5% vs 16.67%, p<0.05).

Over the years the surgical treatment of patients suffering from breast carcinoma has been characterized by a lower invasiveness and an increasing attention to functional and aesthetic outcomes. Extremely demolitive surgeries, such as Halsted's mastectomy, which were performed in the past, have been abandoned; more and more often surgeons employ techniques preserving skin, nipple-areola complex and providing for immediate breast reconstruction.

The increasing use of neoadjuvant therapy is part of this path, reducing the amount of breast parenchyma which is necessary to remove in order to obtain a radical surgical resection (R0) of breast neoplasia. Moreover, the neoadju-

vant therapy can also have effect on the axillary lymph node disease. Similarly to breast resections, many Authors perform a more limited axillary surgery in case of nodal downstaging due to neoadjuvant chemotherapy <sup>3</sup>.

As a consequence, the question under debate is the necessity to perform a complete axillary lymphadenectomy on a patient showing clinically unharmed lymph nodes after neoadjuvant chemotherapy, even if neoplasia had already spread to axillary lymph nodes since the beginning. Yet, it is still necessary to do a reliable test in order to identify patients with a pathologic complete response in the axilla.

Some Trials have evaluated the reliability of the sentinel lymph node biopsy within this subgroup of patients and have demonstrated that the rate of false negative results is 12,6% <sup>1,5</sup>. Although this value is little higher than the cut-off (10%) chosen by the Authors to reject the hypothesis of the study, the validity of the technique of the sentinel lymph node biopsy in patients undergoing neoadjuvant therapy has never been clearly called into question. A thorough analysis of the data in Literature, including the histological type of neoplasia, has demonstrated that the rate of false negative results in the sentinel lymph node is respectively 8% for HER2positive tumours, 15% for triple-negative and 45% for ER-PR positive/HER2-negative <sup>6</sup>. Other studies confirm the link between the histological and hormonal features of neoplasia and the possibility to achieve a pathologic response in the axilla<sup>9-14</sup>.

In order to minimize the rate of false negative results, some Authors suggest removing not only the sentinel lymph node but also the lymph nodes affected by the disease before the neoadjuvant therapy. It is possible to mark these lymph nodes before performing the neoadjuvant chemotherapy so as to be able to identify and remove them during surgery. Such technique would allow to reduce the rate of false negative results to 2-4% <sup>7</sup>. As a matter of fact, in case of partial pathologic response, it is not possible to predict the lymph nodes that are still affected by residual disease <sup>8</sup>.

In our opinion, a thorough preoperative study may contribute to achieving better clinical outcomes in the employment of the sentinel lymph node technique. In fact, by identifying the predictive factors of a pathologic complete response in the axilla to the neoadjuvant therapy, it is possible to perform a sentinel lymph node biopsy on patients with a lower "a priori" risk of nodal disease in order to reduce the rate of false negative results. In our experience, MR Imaging in the preoperative staging, with its 57.69% of false negative results, has proven to be an inadequate test. On the contrary, it has been demonstrated that patients with a pathologic complete response in the axilla are more likely to be Her2-positive (58.33% vs 3.13%, p<0.05) whereas patients with an incomplete response are more likely to report a Luminal B phenotype (62.5% vs 16.67%, p<0.05).

Our study has several limitations: it is a retrospective

work based on the data of one single Centre so it was not possible to carry out a study about numerousness. In addition, our protocols do not provide for the performance of a lymph node biopsy before neoadjuvant therapy. In our opinion, further high-quality studies are absolutely necessary to identify new predictive factors of pathologic response in the axilla and to test the ones we already have on a higher number of patients.

# Conclusion

The possibility to detect patients with a lower risk of nodal disease before surgery may reduce the rate of false negative results of sentinel lymph node biopsy in patients receiving a neoadjuvant therapy. Therefore, the identification of predictive factors of nodal pathologic response may allow the use of the sentinel lymph node biopsy to a larger extent for these patients, taking into account the unquestionable benefits of this technique.

## Riassunto

Lo stato dei linfonodi ascellari nei pazienti affetti da tumore della mammella è un importante fattore prognostico ed influenza notevolmente la condotta terapeutica. Il 40-75% dei pazienti che presentano alla diagnosi linfonodi affetti da neoplasia possono andare incontro ad una completa remissione clinica della malattia linfonodale una volta completata la terapia neoadiuvante. In questi casi la pratica clinica più diffusa prevede di eseguire comunque la linfadenectomia ascellare. Tuttavia negli ultimi anni stanno aumentando gli Autori che eseguono la biopsia del linfonodo sentinella e, solo in caso di positività di quest'ultima, la linfadenectomia ascellare. Esistono però alcuni Trial che hanno dimostrato che il tasso di falsi negativi della biopsia del linfonodo sentinella nei Pazienti sottoposti a chemioterapia neoadiuvante è > del 10%. Obiettivo di questo studio è cercare di individuare i fattori predittivi di una risposta patologica completa ascellare così da poter meglio indirizzare la scelta tra l'esecuzione della linfadenectomia ascellare o della biopsia del linfonodo sentinella nei Pazienti sottoposti a chemioterapia neoadiuvante.

Sono stati considerati per l'arruolamento tutti i Pazienti affetti da carcinoma mammario sottoposti ad intervento chirurgico dopo terapia neoadiuvante fra Gennaio 2010 e Dicembre 2015. Oggetto del nostro studio erano i Pazienti con positività clinica dei linfonodi ascellari al momento della diagnosi (cN+) e che dopo terapia neoadiuvante presentavano una risposta clinica completa a livello ascellare. Nel periodo di studio, 112 Pazienti giunti alla nostra osservazione presentavano una neoplasia mammaria con coinvolgimento dei linfonodi ascellari. Tra questi Pazienti, 44 rispettavano i nostri criteri di inclusione e sono stati sottoposti ad intervento chirurgico dopo terapia neoadiuvante. In tutti i Pazienti è stata eseguita una linfadenectomia ascellare completa, associata ad una mastectomia (81.82% 36/44) o ad una resezione mammaria parziale (18.18% 8/44). Secondo i nostri dati, il 59.09% (26/44) dei Pazienti che alla diagnosi presenta una neoplasia con coinvolgimento linfonodale (cN+) mostra una negativizzazione clinica di questi linfonodi dopo la terapia neoadiuvante (cN0) ma solo il 27.27% dei Pazienti (12/44) ha una risposta patologica linfonodale completa (pN0). Questi Pazienti sono individuati correttamente dalla stadiazione preoperatoria, infatti il 91.67% dei Pazienti pN0 era anche cN0. Tuttavia la stadiazione radiologica preoperatoria è caratterizzata dal 57.69% di falsi negativi e non è pertanto un test adeguato per individuare i Pazienti con risposta patologica completa a livello ascellare. I nostri dati dimostrano come i Pazienti con una risposta patologica ascellare completa sono più probabilmente Her2-positive (58.33% vs 3.13%, p<0.05) mentre quelli con una risposta incompleta presentano più frequentemente un fenotipo Luminal B (62.5% vs 16.67%, p<0.05).

La possibilità di riconoscere prima dell'intervento i Pazienti con un minore rischio di malattia linfonodale potrebbe ridurre il tasso di falsi negativi della biopsia del linfonodo sentinella nei Pazienti sottoposti a terapia neoadiuvante. Pertanto l'individuazione dei fattori predittivi di risposta patologica linfonodale potrebbe consentire di adottare più estesamente la biopsia del linfonodo sentinella in questi Pazienti con gli indubbi vantaggi clinici che questa tecnica comporta.

#### References

1. RwerencesBoughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al.: Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: The ACOSOG Z1071 (Alliance) clinical trial: JAMA J Am Med Assoc, 2013; 310(14):1455-461.

2. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al.: *Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy.* J Clin Oncol, 2005; 23:9304-311.

3. Nguyen TT, Hoskin TL, Day CN, et al.: *Decreasing use of axillary dissection in node-positive*. Breast Cancer, Patients Treated with Neoadjuvant Chemotherapy, Ann Surg Oncol, 2018; 25:2596. 4. Corso G, Grana CM, Gilardi L, Baio SM, De Lorenzo D, Maisonneuve P, et al.: *Feasibility of lymphoscintigraphy for sentinel node identification after neo-adjuvant therapy.* Ann Ital Chir, 2017; 88:201-05.

5. Layeequr Rahman R, Crawford SL, Siwawa P: *Management of axilla in breast cancer. The saga continues.* Breast, 2015; 24(4):343-53.

6. Layeequr Rahman R, Marshall AJ: *Evidence basis for sentinel node biopsy post neoadjuvant chemotherapy. Bias is a 4-letter word.* Eur J Surg Oncol, 2018; 44(4):541-42.

7. Caudle AS, Yang WT, Krishnamurthy S, et al.: Improved axillary evaluation following neoadjuvant therapy for patients with nodepositive breast cancer using selective evaluation of clipped nodes: Implementation of targeted axillary dissection. J Clin Oncol 2016; 34(10):1072-1078.

8. Green M, Neamonitou F, Vidya R: Conservative management of positive axilla after neoadjuvant systemic therapy-The need for, and review of techniques used for lymph node localization. Clin Breast Cancer, 2018; pii: S1526-8209(18)30165-4. doi: 10.1016/j.clbc. 2018.06.001. [Epub ahead of print]

9. Mamtani A, Barrio AV, King TA, et al.: *How often does neoadju*vant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastases? results of a Prospective Study. Ann Surg Oncol, 2016; 23(11):3467-474.

10. Barrio AV, Mamtani A, Edelweiss M, et al.: *How often is treatment effect identified in axillary nodes with a pathologic complete response after neoadjuvant chemotherapy?* Ann Surg Oncol, 2016; 23(11):3475-480.

11. Galimberti V, Ribeiro Fontana SK, Maisonneuve P, et al.: Sentinel node biopsy after neoadjuvant treatment in breast cancer: Fiveyear follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol, 2016; 42(3):361-68.

12. Kuehn T, Bauerfeind I, Fehm T, et al.: Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol, 2013; 14(7):609-18.

13. Caldana M, Pellini F, Lombardi D, Mirandola S, Invento A, Pollini GP: *Breast cancer and neoadjuvant chemotherapy: indications for and limits of breast-conserving surgery.* Ann Ital Chir, 2018; 89:392-97.

14. Franceschini G, Di Leone A, Natale M, Sanchez MA, Masett R: *Conservative surgery after neoadjuvant chemotherapy in patients with operable breast cancer.* Ann Ital Chir, 2018; 89:290.