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Gianluca Franceschini, Alba Di Leone, Alejandro Martin Sanchez, Sabatino D'Archi, Daniela Terribile, Stefano Magno, Lorenzo Scardina, Riccardo Masetti.

Division of Breast Surgery, Department of Woman, Child and Public Health, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Update on sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer patient.

Today, sentinel lymph node biopsy (SLNB) is considered the gold standard for axillary staging in early breast cancer patients with clinically negative lymph nodes (cN0). SLNB allows to determine the axillary lymph node status sparing the axillary dissection (AD) and its potential complications (seroma formation, loss of sensation, shoulder dysfunction and lymphedema)
On the other hand, SLNB for nodal staging in breast cancer patients with clinically negative lymph nodes after neoadjuvant chemotherapy (ycN0) is a highly debated topic due to different reported success rates. In order to optimize oncological results, high identification rate (> 90%) and false negative rate as low as possible (< 10%) should always be obtained when performing SLNB after neoadjuvant chemotherapy. The success rates of SLNB after neoadjuvant chemotherapy (NAC) mainly depend on the clinical lymph node status pre-NAC.
In patients with pre-NAC clinically negative nodes (cN0) and at restaging with post-NAC clinically negative nodes (ycN0), SLNB after chemotherapy should be performed because it is an accurate and safe procedure.
In patients with pre-NAC clinically positive nodes (cN+) and at restaging with post-NAC clinically negative nodes (ycN0), SLNB after chemotherapy might be considered thanks to the high lymph nodal pathologic complete response rate; however, in this last setting, individual ability, technical skills and repetitive performance of specific tasks must always be followed to improve the identification rate and false negative rate.
AD may be avoided only if sentinel lymph node is negative [ypN0(sn)]; instead, to date, patients with metastatic sentinel lymph node after neoadjuvant chemotherapy, even with only isolated tumor cells, [ypN+(sn) including ypN0i+(sn) and ypN1mic(sn)] should always be treated with AD.
However, NAC significantly increases the difficulties and complexity of axillary surgical management. A personalized multidisciplinary path in specialized breast centers should ensure an accurate clinical counselling and refined patient selection for SLNB post-NAC.

KEY WORDS: Axillary treatment, Breast cancer, Neoadjuvant chemotherapy, Sentinel lymph node biopsy

Introduction

Over the past decade, there was been an important change in surgical management of axillary nodes in breast cancer. Today, sentinel lymph node biopsy (SLNB) is considered the gold standard for axillary staging in early breast cancer patients with clinically negative lymph nodes (cN0). Crossref, PubMed, Scopus (226) Google ScholarSee all Referencescomparing SLNB versus axillary dissection (AD), have shown that SLNB provides appropriate staging information without decreasing survival and without increasing the risk of local-regional recurrence. SLNB allows to determine the axillary lymph node status with a less invasive procedure sparing the AD and its potential complications (seroma formation, loss of sensation, shoulder dysfunction and lymphedema) [1].

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Correspondence to: Prof. Gianluca Franceschini, Division of Breast Surgery, Department of Woman, Child and Public Health,Fondazione Policlinico Universitario Agostino Gemelli – IRCCS,Università Cattolica del Sacro Cuore, Largo Agostino Gemelli, 8 - 00168, Rome, Italy (e-mail: gianlucafranceschini70@gmail.com)

On the other hand, SLNB for nodal staging in breast cancer patients with clinically negative lymph nodes after neoadjuvant chemotherapy (ycN0) is a highly debated topic due to different reported success rates [2].
In order to optimize oncological results, high identification rate (IR) (> 90%) and false negative rate (FNR) as low as possible (< 10%) should always be obtained when performing SLNB after neoadjuvant chemotherapy (NAC) [3,4].
However, the success rates of SLNB after neoadjuvant chemotherapy mainly depend on the clinical lymph node staging pre-NAC [2].

Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with cN0 disease

In patients with pre-NAC clinically negative nodes (cN0) and at restaging with post-NAC clinically negative nodes (ycN0), SLNB after chemotherapy should be performed because it is an accurate and safe procedure for axillary staging.
Studies examining the accuracy of SLNB after NAC in cN0 patients showed adequate IR and FNR similar to those seen in patients undergoing primary surgery [(2,3)].
In GANEA 1 prospective trial, among 130 cN0 patients, IR was 94,6% and FNR was 9,4% after NAD [5].
A retrospective study of cN0 patients from MD Anderson Cancer (including 575 patients who had SLNB following NAC) reported similar results with IR of 97,4% and FNR of 5,9% post-NAC .[6]
Some meta-analyses including more than 5000 patients treated with SLNB after NAC reported IR of 90-94% and FNR of 7-12% in patients with pre-NAC clinically negative nodes [6].
Besides, in the GANEA 2 trial, a large prospective multi-institutional study, among the 419 patients from the cN0 group treated after NAC with SLNB, only one axillary recurrence occurred after a median follow-up of 3 years [7].
In a retrospective mono-institutional series of 183 patients with an initially negative axilla, treated with SLNB alone after NAC for T0–T3 breast cancer, no patients showed axillary relapse after a median follow-up of 51.1 months [8].

Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with cN+ disease

In patients with pre-NAC clinically positive nodes (cN+) and at restaging with post-NAC clinically negative nodes (ycN0), SLNB might be considered thanks to the high lymph nodal pathologic complete response (pCR) rates. Recent studies showed pCR rates in lymph nodes of approximately 40% for patients presenting with clinically positive nodes (cN+) and treated with current NAC regimens [3,9-11]. Even these patients could be spared the AD and its potential complications by staging nodes with a less invasive SLNB.
However, despite the proven axillary downstaging occurring after NAC, there is still some degree of reluctance in applying SLNB in patients with pre-treatment node-positive. Some concerns regard the reliability of SLNB in terms of IR, FNR and oncologic safety in this setting.
The success rates of SLNB in terms of detection and accuracy could be less favorable in patients with pre-treatment node-positive due to alterations of the lymphatic drainage by chemotherapy [3,4,9]. Some studies showed that for patients with initially pathologic nodes, the IR of the SLNB after NAC might be between 60% to 99.0% and FNR between 6% to 52%.
In a recent meta-analysis the pooled estimate of the IR was 91% and that of the FNR was 13% (3,9). False-negative SLNB with consequent residual nodal disease could lead to understaging of the disease, with possible omission of appropriate adjuvant radiotherapy and chemotherapy increasing the risk of locoregional and systemic recurrence.
So, the repetitive performance of specific tasks should always be considered to refine detection and minimize FNR of SLNB post-NAC in patients with pathologically proven pre-treatment node-positive [4]:
– A careful axillary staging before NAC with clinical examination, ultrasonography, magnetic resonance and PET- TAC should be performed.
– All abnormal lymph nodes at the time of needle biopsy pre-NAC should be marked with clips.
– An accurate clinical restaging of the axillary disease at the completion of NAC should be performed.
Nomograms developed to select patients with more likelihood of pCR to consider for SLNB should be used in multidisciplinary discussion. Kantor developed a model based on 19,115 node-positive patients undergoing NAC to contribute even more to the reduction of SLNB failures after NAC. Young age, tumor histology, grading, subtype, clinical node staging, and tumor response were predictive for nodal pCR [12].
Dual agent mapping techniques to identify sentinel nodes should be used. In the SENTINA and ACOSOGZ1071 trial, the dual tracer method combining blue dye and radiocolloid was superior to radiocolloid alone regarding IR and FNR in initially cN+ patients converting to ycN0; in the SENTINA study using dual tracer method IR was 87.8 and and FNR was 8,6%. In the ACOSOG Z1071 trial the IR was 92.7% and FNR was 10,8% [2,5].
A removal of three or more sentinel nodes should be performed. ACOSOGZ1071, SENTINA, and the "Swedish Prospective Multicenter Trial" showed clearly improved FNRs with an increasing number of identified sentinel nodes; FNRs in the case of at least 3 sentinel nodes removed were as low as 7% and 9%, respectively, and 4% in the case of at least 2 sentinel nodes in the Swedish study [2,5].

A "Target Axillary Dissection" (TAD) should be performed with removal of SLNs and also including all target lymph nodes clipped prior to NAC. This technique is based on the concept of marking positive lymph nodes before the start of NAC and then locating and removing those marked nodes in a targeted procedure at surgery post-NAC. In a prospective trial, TAD improved the feasibility and reliability of SLNB with a FNR of 2%x[32] Boughey, J.C., Ballman, K.V., Le-Petross, H.T., McCall, L.M., Mittendorf, E.A., Ahrendt, G.M. et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). *Ann Surg.* 2016; 263: 802–807[13]. Crossref, PubMed, Scopus (99), Google ScholarSee all References [32].
Intraoperative radiological evaluation of removed lymph nodes to verify the correct and complete removal of all clipped nodes.
Intraoperative clinical and ultrasound evaluation of axillary cavity to verify the absence of others suspicious nodes.
Accurate pathological assessment of lymph nodes using examination of additional levels of hematoxylin and eosin staining and keratin staining to identify patients at SLNB post-NAC [ypN+(sn) including ypN0i+(sn) and ypN1mic(sn)] mandating AD.

Surgical management of the axilla in patient with metastatic sentinel lymph node [ypN+(sn)] after neoadjuvant chemotherapy

Sentinel lymph node metastases are categorized as isolated tumor cells [small clusters of cells not greater than 0.2 mm – ypN0(i+)(sn)] or micrometastases [tumor foci > 0.2 mm and no greater than 2.0 mm – ypN1mic(sn)] or macrometastases [tumor foci >2 mm – ypN1(sn)], depending upon the size of the largest tumor deposit in the sentinel node.
AD may be avoided only if sentinel lymph node is negative [ypN0(sn)]; instead, to date, patients with metastatic sentinel lymph node after NAC [ypN+(sn) including ypN0i+(sn) and ypN1mic(sn)] should always be treated with AD.
According to the "8th Edition of the American Joint Committee on Cancer (AJCC) staging System" patients post-NAD who have isolated tumor cells in sentinel node [ypN0i+(sn)] should also be treated with AD; to date, there are still no trials that have shown that AD can be avoided in these patients without compromising locoregional disease control, disease-free survival and overall survival.
However, new prospective randomized trials are being designed to assess the replacement of AD by RT in selected cases and obtain a further de-escalation of axillary surgical management in patients ypN+(sn).

Conclusions

In breast cancer patients with clinically negative lymph nodes at restaging after neoadjuvant chemotherapy (ycN0), SLNB should be considered as an effective and safe axillary treatment option thanks to the high lymph nodal pCR rate.
However, NAC significantly increases the difficulties and complexity of axillary surgical management. A personalized multidisciplinary path in specialized breast centers should ensure an accurate clinical counselling and refined patient selection for SLNB post-NAC.
Individual ability, technical skills and repetitive performance of specific tasks are able to improve the IR and FNR making SLNB post-NAC a valid alternative to AD also in patients with pre-treatment node-positive.

Riassunto

La biopsia del linfonodo sentinella (BLS) è considerata lo standard per la stadiazione ascellare nelle pazienti con carcinoma mammario in fase iniziale e con linfonodi clinicamente negativi (cN0).
La BLS consente di determinare lo stato dei linfonodi ascellari evitando la dissezione ascellare e le sue potenziali complicanze (formazione di sieroma, perdita di sensibilità, disfunzione della spalla e linfedema).
D'altra parte, la BLS nelle pazienti con carcinoma mammario e linfonodi ascellari clinicamente negativi (ycN0) dopo chemioterapia neoadiuvante (NAC) è un argomento molto dibattuto a causa delle diverse percentuali di successo riportate.
Quando si esegue la BLS dopo chemioterapia, al fine di ottimizzare i risultati oncologici, è necessario ottenere sempre un tasso di identificazione elevato (> 90%) e un tasso di falsi negativi il più basso possibile (<10%). Le percentuali di successo della BLS dopo chemioterapia neoadiuvante dipendono principalmente dalla stadiazione clinica dei linfonodi ascellari prima di eseguire la NAC.
Nelle pazienti con linfonodi clinicamente negativi pre-NAC (cN0) e confermati clinicamente negativi post-NAC (ycN0), la BLS dopo il trattamento chemioterapico può essere eseguita in sicurezza poiché diversi studi hanno confermato che è una procedura accurata ed affidabile per la stadiazione ascellare.
Anche, nelle pazienti con linfonodi clinicamente positivi pre-NAC (cN+) e ristadiati con linfonodi clinicamente negativi post-NAC (ycN0), la BLS dopo chemioterapia può essere presa in considerazione grazie all'elevato tasso di risposta patologica completa linfonodale; tuttavia in quest'ultimo caso è sempre necessario porre attenzione ad eseguire alcuni specifici compiti per migliorare i tassi di identificazione e i tassi di falsi negativi.
La dissezione ascellare può essere evitata solo se il linfonodo sentinella è negativo [ypN0(sn)] all'esame istologi-

co definitivo; viceversa, le pazienti con linfonodo sentinella metastatico dopo chemioterapia neoadiuvante, anche quelle con isolate cellule tumorali [ypN+(sn) compresi ypN0i+(sn) e ypN1mic(sn)] dovrebbero sempre eseguire una dissezione ascellare.
Comunque, la NAC aumenta significativamente le difficoltà e la complessità della gestione chirurgica ascellare. Un percorso multidisciplinare personalizzato in Centri senologici specializzati può garantire un'adeguata consulenza clinica e un'accurata selezione delle pazienti candidate a BLS dopo trattamento chemioterapico.

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