World Journal of Clinical Oncology

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DOI: 10.5306/wjco.v6.i6.202

World J Clin Oncol 2015 December 10; 6(6): 202-206
ISSN 2218-4333 (online)

EDITORIAL

Sentinel lymph node metastasis after neoadjuvant treatment in breast cancer: Any size matters?

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Author contributions: Rubio IT had contributed to all parts of the manuscript.

Conflict-of-interest statement: No conflict of interest to disclose.

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Received: May 25, 2015
Peer-review started: May 27, 2015
First decision: August 4, 2015
Revised: August 9, 2015
Accepted: September 25, 2015
Article in press: September 28, 2015
Published online: December 10, 2015

Abstract

One of the advantages of neoadjuvant chemotherapy (NAC) treatments is its ability to convert patients who need a mastectomy in breast conservative surgery. NAC has also increased the conversion of node positive patients into node negative in around 40% allowing the use of sentinel node biopsy (SLN) in this setting. Timing of SLN biopsy after NAC has been a subject of debate. In patients with clinically node negative before NAC, rates of success and false negative rates of SLN after NAC are similar to those in the adjuvant setting, so SLN after NAC in previous negative axilla has been incorporated in the staging of the axilla. More controversial is its use in patients with positive axillary nodes before NAC who convert to node negative after NAC. Several randomized studies have reported the identification rates and the false negative rates of the SLN after NAC, concordant in the importance of surgical technique. As there is an agreement in the abandon of the immunohistochemistry (IHC) for SLN in the adjuvant setting as SLN IHC detected metastasis appear to have no impact on overall survival, in patients with SLN after NAC the inclusion of isolated tumor cell (ITC) as positive nodes lowers the false negative rates of the technique, suggesting the importance of assessing the SLN by IHC after NAC and considering it as residual disease. Longer follow up is needed to determine the prognostic implications of ITC in the SLN after NAC.

Key words: Sentinel node; Metastasis; Neoadjuvant treatment; Breast cancer

Core tip: One of the advantages of neoadjuvant chemotherapy treatment in breast cancer is to downstage positive axillary nodes to negative. Postneoadjuvant sentinel lymph node (SLN) has been increasingly used and randomized studies in patients with positive axillary nodes who convert to node negative have shown that false negative rates are highly influenced by the surgical technique. Information from these studies has shown that isolated tumor cells in the SLN, when considered as positive nodes, lower false negative rates. Whether any residual disease in the SLNs may have prognostic implications warrants further research.

treatment in breast cancer: Any size matters? *World J Clin Oncol* 2015; 6(6): 202-206 Available from: URL: http://www.wjgnet.com/2218-4333/full/v6/i6/202.htm DOI: http://dx.doi.org/10.5306/wjco.v6.i6.202

RATIONALE FOR NEOADJUVANT TREATMENT IN BREAST CANCER

Neoadjuvant chemotherapy (NAC) is an accepted treatment for locally advanced and early stage breast cancer as it has shown many advantages. It allows *in vivo* determination of an individual tumor's chemosensitivity, it reduces micrometastatic disease and it can downstage tumors, allowing for breast conserving surgery in previously ineligible patients for conserving surgery[1]. Randomized studies have reported rates of downstaging after NAC between 49%-94% and 20%-40% of patients achieve a complete pathologic response[2-6].

There is clear evidence that NAC downstages positive axillary nodes in a proportion of patients. Early studies have shown that NAC can completely clear axillary metastases in approximately 23% of patients with locally advanced breast cancer[6], rates that have increased to 40%-60% with the use of targeted therapies[7]. Axillary complete downstaging after NAC has been correlated with better prognosis and assessment of residual disease after NAC is important not only in determining the prognostic information but also in selecting candidates for further systemic and radiation therapy treatment[7,8].

SENTINEL LYMPH NODE AFTER NEOADJUVANT TREATMENT

Timing of sentinel lymph node (SLN) in breast cancer patients undergoing NAC has been subject of continuous debate. An advantage of performing SLN after NAC is a single surgery and that patients with downstaging axillary nodes after NAC may potentially spared an axillary lymph node dissection (ALND). Most authors have taken the position to do it after NAC[9-14], and results from meta-analysis and prospective studies have reported a success rate of SLN identification after NAC of 90% and rates of false negative around 10.5%[9,10]. In patients with clinically negative axilla, rates of success and false negative rates are similar to those in the adjuvant setting, so SLN after NAC in previous negative axilla has been incorporated in the staging of the axilla[15]. Recently, in a population-based study of SLN before (980 patients) or after NAC (203 patients) in clinically node negative patients of the Netherlands Cancer Registry, the SNL identification rate was higher in the SLN pre NAC group *vs* after NAC (98% *vs* 95%; P = 0.032). Significantly, a lower proportion of patients had a negative SNB pre NAC compared to after NAC. In 67% of patients with SNB after NAC no axillary treatment was given, compared to 55% of the patients with SNB before NAC. The authors conclude that SNL after NAC appears to lower surgical procedures and can benefit patients with downstaging of the axilla from less axillary treatment[16].

In those patients with clinically positive axilla previous to NAC, three recently published prospective studies, ACOSOG Z1071, SENTINA and SN FNAC have shown that SLN false negative rates are directly related to the technique, the number of SLNs excised and the size of the SLN metastases after NAC[17-19]. In the ACOSOG Z0071, in 525 women who met the eligibility criteria, the SLN identification rate was 92.5%. The use of dual technique (radioisotope and blue dye) and the excision of ≥ 2 SLNs lower the false negative rates to 10.8% and 12.8% respectively. Because the FN rate was higher than the pre-established 10%, additional analysis of factors that influences the FN rates should be assessed[17]. The SENTINA trial, a four arm prospective multicenter cohort study, included patients with SLN before NAC and after NAC. In 592 patients with clinically positive axillary nodes before NAC who downstaged to node negative after NAC underwent SLN biopsy plus ALND. In this group, FN rates dropped to 9.6% when ≥ 2 SLNs were removed and to 8.6% when the dual technique (blue + radioisotope) was used[18]. The third study, the SN FNAC study included 153 patients with biopsy proven positive axillary nodes before NAC. Rates of FN were 9.6% with an identification rate of 87.6%. Similarly to the other studies, when 2 or more SLNs were removed the FN dropped to 4.9% that improves significantly the FN rates compared to the previous studies. Interestingly, this study analyses the FN rates related to the inclusion or not of isolated tumor cell (ITC) in the SLN as positive or negative staging. In those patients where ypN0(i+) were considered negative nodes, the FN increased to 13.3%, indicating the importance of including any residual tumor burden in the SLN as a positive node[19].

MINIMAL SLN INVOLVEMENT IN THE SLN (ISOLATED TUMOR CELLS)

Since the introduction of the SLN, we have learnt that the more thoroughly examination of the SLNs has increased the detection of minimal metastasis in the SLNs. Traditionally, routine hematoxiline-eosine (H and E) staining has been used to identify lymph node metastasis, and with the introduction of immunohistochemistry (IHC) staining the detection of ITC has come into the scenario. Recent studies showed a 10% increased in detection of micrometastasis in the SLN when using more extensive examination[20]. The outcome of histopathological analysis has implications in the surgical and adjuvant treatment of breast cancer patients. Staging breast cancer relies heavily on the status of the lymph nodes and the 6th edition incorporated the ITCs and micrometastasis

Table 1 False negative rates in the randomized trials of sentinel lymph node after neoadjuvant chemotherapy in patients with axillary metastasis before neoadjuvant chemotherapy

	ACOSOG Z1071	SENTINA	FN SNAC
No. of patients	756	592	153
FNR with 1 SLN	31.5%	24.3%	18.2%
FNR with > 2 SLNs	12.6%	9.6%	4.9%
FNR with single tracer	20.3%	16%	16%
FNR with dual tracer	10.8%	8.6%	5.2%
FNR with N0(i+) as positive	8.7%	-	8.4%

FNR: False negative rates; SLN: Sentinel lymph node.

into their classification. As the size of SLN metastasis increases, the rate of non-SLN metastasis size also increased from around 4% in the ITC, to 5%-19% in the micrometastasis and around 50%-60% in the macrometastasis[20-22].

The prognostic implications of minimal lymph node involvement (*i.e.*, isolated tumor cells, micrometastasis) in early breast cancer have been long debated. The impact of finding this minimal metastasis in the SLN in the adjuvant setting has been reported extensively with different outcomes due to the great variability in patient population, tumor characteristics, histology assessment and so on[22,23]. Even more, the significance of micrometastasis in patients with ALND seems to be worst than in patients with SLN, making more difficult to establish its real significance[24]. It is important to consider that the studies that reported improved disease free survival in patients with SLN micrometastasis or ITCs are the ones where the majority of patients receive systemic treatments, and in this can also influence how to manage the axilla surgically[22].

To shed light to this subject, the ACOSOG Z10 trial with 5184 patients, showed that IHC detected metastasis in neither the SLN (P = 0.66) nor bone marrow (P = 0.08) were independent predictors of overall survival, although bone marrow status showed a strong trend on multivariate analysis. SLN IHC detected metastasis appear to have no impact on overall survival[25], because in the Z0010 trial treatment decisions were not based in the IHC results, the significance of ITCs may be better determined. Since the report of this trial, in many centers IHC has been abandoned for the assessment of SLN in the adjuvant setting.

Despite the knowledge of the prognosis of minimal involvement of SLNs in the adjuvant setting, this cannot be extrapolate to the neoadjuvant setting and actually, there is no such studies in the NAC setting. Rates of positivity of non sentinel nodes with a micrometastasis in the SLN in patients with NAC have been reported to be between 12% to 50%[13-15] and the SLN is the only positive node in around 50% of cases, rates lower than the adjuvant setting[15].

It is likely that micrometastasis in the SLN in patients after NAC has a different meaning than micrometastasis in the SLN in adjuvant therapy. Micrometastasis or ITC in the SLN in NAC patients could represent the presence of minimal nodal disease pretreatment which did not respond to therapy or the remnants of macroscopic nodal disease which has had a partial response to the treatment and in this way it has been addressed in the 7th edition of the AJCC[26], where ypN0(i+) is considered residual disease in the SLN. Maybe, the classification of ITC after NAC under N0 should be revised although follow up on these patients is required to assess the real prognostic value of the ITC after NAC.

The number of residual metastastic axillary nodes after NAC has been established as an important prognostic factor for disease free survival[6]. Axillary response after NAC is a better prognostic factor than response of the primary tumor[6,8,27].

Because most of these studies included patients with ALND, ITC in the axillary nodes are not reported. But one of the most important finding of the SN FNAC trial is that metastasis in the SLN after NAC of any size influences the rate of FN results, so ITC in the SLN after NAC should be considered positive[19]. In the ACOSOG Z0071, SLNs were not examined by IHC and positive SLNs were defined as those with metastasis higher than 0.2 mm, so ITC when reported were considered as node negative[17]. Data from the trial presented at the San Antonio Breast cancer Conference suggested that FN rate could be improved when ITC were included in the analysis as positive nodes, in these cases, FN rates decreased to 8.7% (Table 1). Also, our group presented data at the Society of Surgical Oncology assessing the overall survival (OS) of patients depending on the response to NAC treatment. A SLN biopsy was performed in 118 patients (32.5%). Eleven (9.3%) patients had residual ITCs in the SLN. When analyzing OS by axillary response, patients with ypN0(i+) who had a clinically negative axilla at diagnosis (cN0) had similar OS than those with pathologic complete response in the axilla, while those with ypN0(i+) who had a clinically positive axilla before NAC treatment (cN+) had a worse OS. This results suggest the importance of the ITCs in the SLN after a proven axillary metastasis before NAC, although these results need to be regarded with caution as the number of patients with ypN0(i+) were low in our study[27].

In conclusion, SLN after NAC in patients with biopsy proven positive axillary nodes before NAC is feasible and accurate when surgical technique is improved by excising 2 or more SLNs, and by using a dual technique. False negative rates can be lowered when considering ITCs as positive nodes, suggesting that any size of metastasis in the SLN after NAC is important. Further follow up on this group of patients is needed to know the prognostic implications of the ITCs in the SLN after NAC.

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P- Reviewer: Furka A **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

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