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Archives of Cancer Biology and Therapy Commentary

Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy for Breast Cancer

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Breast cancer is the second most common cancer worldwide, affecting nearly one in eight women [1]. Accurate cancer staging is essential for determining the patient's prognosis and for choosing the appropriate treatment. The staging system most often used is the American Joint Committee on Cancer (AJCC) TNM system, where T refers to the size of the tumor, N refers to spread of the primary cancer to nearby lymph nodes, and M refers to the spread of metastasis to distant sites in the body [2]. While the prognosis of patients with breast cancer is known to depend on many factors, one of the most important prognostic indicators is the extent of axillary lymph nodal involvement [3]; metastasis to these lymph nodes has been shown to decrease the 5-year survival rate by 28-40% [4]. Therefore, determining lymph node involvement is of great importance, as it is one of the main factors that guides local, regional, and systemic treatment decisions [5].

Axillary management for patients with breast cancer has significantly evolved over the past decade. Recent trends have shifted from axillary lymph node dissection (ALND) to a less invasive sentinel lymph node biopsy (SLNB) in patients presenting with clinically node-negative disease (cN0) [6]. SLNB can accurately spare node-negative patients an operation from which they cannot benefit. While patients with node positive disease may undergo ALND, it is preferable for those with clinically node negative disease to undergo SLNB. SLNB lessens the complications that often follow ALND, such as upper extremity lymphedema and paresthesia [7-9]. Sentinel lymph node surgery allows the surgeon to identify the first lymph node(s) into which the primary tumor drains. Thus, if there are no metastases in the sentinel lymph node(s), it is predictive of non-sentinel axillary lymph node status [10].

During a sentinel lymph node biopsy, single or dual tracer (radiolabeled colloid and blue dye) is injected into the breast either peri-tumorally or periaereolar and taken up by the breast lymphatics. Lymph nodes that are blue, radioactive, or palpably abnormal are resected and undergo further pathological analysis. Blue dye was first used to identify the SLN in melanoma in 1992. Soon after, Krag et al. and Giuliano et al. were the first to use radioisotope and blue dye tracers, respectively, to locate the SLN in patients with breast cancer [11,12]. In 1996, Albertini was the first to report the technique of combining the two methods [13]. Despite success with each method individually, we support the use of combined tracer. Combination dye and isotype technique has been shown to best identify the SLN with the lowest false negative rate (FNR) when compared to either tracer alone [14]. The median number of SLNs in the non-neoadjuvant setting is two. Histological examination of lymph nodes is the most accurate way to identify metastasis in the lymph nodes [15].

The relevance of metastases in the SLN has been questioned over recent decades with regard to predicted risk for non-sentinel node metastases. Various groups set out to determine which patients with SLN metastases would actually benefit from additional ALND (i.e., which patients were likely to have non-sentinel metastases). In 2014, Koca et al. validated 14 existing models for prediction of non-sentinel node metastases, and they found that tumor size, presence of lymphovascular invasion, extranodal extension of SLN, large size of metastatic SLN, number of negative SLNs, and multifocality were independent predictive factors for non-SLN metastases [16]. These findings may be used to guide decisions regarding adjuvant therapy and need for further axillary surgery.

Though it is well-established that SLNB predicts axillary nodal status with high accuracy, it has recently come into question whether SLNB following neoadjuvant chemotherapy (NAC) is as reliable. In the 1970s,

neoadjuvant chemotherapy was first introduced for the treatment of patients with locally advanced breast cancer [17]. Neoadjuvant chemotherapy not only allows tumor response to be assessed *in situ*, but it also downstages tumor burden in the breast or axilla. The latter is particularly beneficial as it allows for less extensive surgery, i.e., ALND [15]. SLNB after chemotherapy provides information about residual nodal disease in order to guide regional therapy. It is important to determine whether there is residual tumor in the axillary lymph nodes after preoperative chemotherapy in patients with breast cancer so that they can be removed to improve local control and because the finding of residual disease is an independent prognostic factor [18].

One potential downfall of chemotherapy is that it leads to shrinkage and fibrosis, while also inducing emboli and debris to deposit in lymphatic channels [19]. As a result, lymphatic drainage routes may be altered, thus decreasing identification rates of the SLN following preoperative chemotherapy. The sentinel node concept is most reliable when primary organ lymphatic channels are free from malignant obstruction. Further, there is concern that chemotherapy may cause histological changes of metastases and lymph nodes, thereby interfering with the accuracy of N staging via SLNB [20]. As the reliability and accuracy of SLNB following chemotherapy was challenged, many groups sought to assess the FNR of SLNB following NAC. False-negatives occur when metastases are not identified in the SLN but are found in non-sentinel axillary lymph nodes. False negative rates have varied historically across the board, ranging from 0 [21] to 19.4% [22]. In studies on SLNB in clinically node-negative patients who underwent surgery without any prior chemotherapy, FNRs < 10% have been deemed oncologically acceptable [23].

In lieu of randomized trials to guide practice, Xing *et al.* conducted a meta-analysis in 2006 to assess the use of SLNB after NAC [24]. The authors concluded that SLNB following preoperative chemotherapy appears to be an accurate and reliable technique for determining the need for axillary treatment in patients who are clinically node-negative. This group estimated the sensitivity of SLNB after preoperative chemotherapy to be 88% with a false negative rate of 12%. Thus, it was demonstrated that SLNB is a reliable technique for identifying or ruling out lymph node metastases in patients who underwent neoadjuvant chemotherapy.

More recently, in 2016, Geng *et al.* published a systematic review and meta-analysis on the accuracy of SLNB after NAC for initially clinically node-negative breast cancer [25]. They included 16 studies that were published from 2000 to 2015. In 2019, Shirzadi *et al.* published a meta-analysis that assessed SLNB after NAC in two cohorts: patients who were initially node negative (n=23 studies) and patients who were initially node positive and converted to node negative (n=13 studies) [19]. Geng *et al.* calculated a pooled FNR of 6%, with a 95% confidence interval (CI) of 3-8%. Similarly, Shirzadi *et al.* calculated a pooled FNR of 7% in the cohort that was initially node negative, and a pooled FNR of 13% in the cohort that was node-positive converted to node-negative.

How many lymph nodes should be sampled to increase the identification rate (IR) and decrease the FNR in patients who undergo SLNB after NAC? Most studies argue identification of 2-3 SLNs is preferred over one SLN. The SENTINA and Alliance trials put forward that in order to achieve a FNR < 10%, at least 3 SLNs should be harvested [5,26]. Similarly, the SN-FNAC study, as well as the meta-analysis by Shirzadi *et al.*, state that ≥ 2 sentinel lymph nodes should be harvested [14,23]. Wong *et al.* assessed FNRs in a cohort in which only 1 SLN was biopsied compared vs. 2 or more, and they found a much higher FNR rate in the former group (14.3% vs. 4.3%) [27].

Various studies also looked at whether the type of tracer mapping agent used during the procedure impacts the IR and FNR. While the meta-analysis by Geng *et al.* did not find any difference in outcomes amongst the different types of tracer, most studies concluded that using either radioisotope alone or a combination of two tracers was beneficial, as it increased the IR and decreased the FNR [5,23,26,27]. Moreover, a recent study from Japan discussed the use of a novel triple tracer technique that resulted in an IR of 100% and a FNR of 0% [28]. With respect to these studies, dual or triple tracer seem to be the better choices.

Over the past few decades, an increasing number of studies have assessed the accuracy and efficacy of SLNB after NAC in patients being treated for breast cancer. Two recent meta-analyses reported pooled FNRs of < 10% for patients who were initially clinically node-negative, concluding that SLNB following NAC is acceptable for this group of patients. Therefore, these patients may avoid ALND and the morbidities that often follow. Although, less is known regarding FNRs in patients who were initially node-positive and then converted to node-negative. Based on the ACOSOG 1071 study, it is reasonable to consider SLNB in patients with a cN1 or cN2 disease at presentation and good clinical response to neoadjuvant chemotherapy [5]. SLNB should be performed with dual tracer and effort made to remove any positive lymph nodes and all sentinel nodes. At least two, and ideally three SLNs should be removed as the FNR is lower and reliably predicts axillary status. When residual disease is identified in the SLN following neoadjuvant treatment, the current standard of care is to perform a completion ALND given the high risk of additional disease in non-sentinel nodes. The goal of

axillary staging is to avoid a false-negative biopsy in which a patient would be understaged and perhaps undertreated.

In regards to sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer, the current standard of care for management of viable tumor cells, including micrometastatic disease in the SLN in this group of pretreated patients is ALND [29]. Axillary radiotherapy could although yield comparable outcomes to completion ALND with fewer adverse side effects [30]. Nonetheless, in patients with cN1 disease, SLNB is accurate with an acceptable FNR using dual tracer mapping and removal of > 2 sentinel nodes.

References

1. How Common is Breast Cancer? https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html. Accessed October 18, 2020.

2. Breast Cancer Stages. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html. Accessed October 18, 2020. Gherghe M, Bordea C, Blidaru A. Sentinel lymph node biopsy (SLNB) vs. axillary lymph node dissection (ALND) in the current surgical treatment of early stage breast cancer. Journal of medicine and life. 2015 Apr;8(2):176.

3. Gherghe M, Bordea C, Blidaru A. Sentinel lymph node biopsy (SLNB) vs. axillary lymph node dissection (ALND) in the current surgical treatment of early stage breast cancer. Journal of medicine and life. 2015 Apr;8(2):176-180.

4. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989 Jan 1;63(1):181-7.

5. Boughey 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. 2013 Oct 9;310(14):1455-61.

6. Zahoor S, Haji A, Battoo A, Qurieshi M, Mir W, Shah M. Sentinel lymph node biopsy in breast cancer: a clinical review and update. Journal of Breast Cancer. 2017 Sep 1;20(3):217-27.

7. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. New England Journal of Medicine. 2003 Aug 7;349(6):546-53.

8. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. The lancet Oncology. 2006 Dec 1;7(12):983-90.

9. Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node–negative breast cancer. Journal of Clinical Oncology. 2000 Jul 1;18(13):2553-9.

10. Bell Z, Cameron I, Dace JS. Imprint cytology predicts axillary node status in sentinel lymph node biopsy. The Ulster Medical Journal. 2010 Sep;79(3):119-122.

11. Krag DN, Weaver DL, Alex JC, Fairbank JE. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surgical Oncology. 1993 Dec 1;2(6):335-40.

12. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Annals of Surgery. 1994 Sep;220(3):391-401.

13. Albertini JJ, Lyman GH, Cox C, Yeatman T, Balducci L, Ku N, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. Jama. 1996 Dec 11;276(22):1818-22.

14. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. Journal of Clinical Oncology. 2015 Jan 20;33(3):258-64.

15. Overview of sentinel lymph node biopsy in breast cancer - UpToDate. https://www.uptodate.com/contents/overview-of-sentinel-lymph-node-biopsy-in-breast-cancer?topicRef=805&source=see_link. Accessed October 18, 2020.

16. Koca B, Kuru B, Ozen N, Yoruker S, Bek Y. A breast cancer nomogram for prediction of non-sentinel node metastasis-validation of fourteen existing models. Asian Pac J Cancer Prev. 2014 Jan 1;15(3):1481-8.

17. Koyama H, Wada T, Takahashi Y, Iwanaga T, Aoki Y, Wada A, et al. Intra-arterial infusion chemotherapy as a preoperative treatment of locally advanced breast cancer. Cancer. 1975 Nov;36(5):1603-12.

18. Kuerer HM, Sahin AA, Hunt KK, Newman LA, Breslin TM, Ames FC, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant

chemotherapy. Annals of Surgery. 1999 Jul;230(1):72-78.

19. Shirzadi A, Mahmoodzadeh H, Qorbani M. Assessment of sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer in two subgroups: Initially node negative and node positive converted to node negative–A systemic review and meta-analysis. Journal of Research in Medical Sciences: the official journal of Isfahan University of Medical Sciences. 2019;24(1):18.

20. Shimazu K, Tamaki Y, Taguchi T, Tsukamoto F, Kasugai T, Noguchi S. Intraoperative frozen section analysis of sentinel lymph node in breast cancer patients treated with neoadjuvant chemotherapy. Annals of Surgical Oncology. 2008 Jun 1;15(6):1717-1722.

21. Tafra L, Verbanac KM, Lannin DR. Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. The American Journal of Surgery. 2001 Oct 1;182(4):312-5.

22. Vigario A, Sapienza MT, Sampaio AP, Piato JR, Barros N, Barros A, et al. Primary chemotherapy effect in sentinel node detection in breast cancer. Clinical Nuclear Medicine. 2003 Jul 1;28(7):553-7.

23. Shirzadi A, Mahmoodzadeh H, Qorbani M. Assessment of sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer in two subgroups: Initially node negative and node positive converted to node negative–A systemic review and meta-analysis. Journal of Research in Medical Sciences: the official journal of Isfahan University of Medical Sciences. 2019;24.

24. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. British Journal of Surgery. 2006 May 1;93(5):539-46.

25. Geng C, Chen X, Pan X, Li J. The feasibility and accuracy of sentinel lymph node biopsy in initially clinically node-negative breast cancer after neoadjuvant chemotherapy: a systematic review and meta-analysis. PloS one. 2016 Sep 8;11(9): e0162605.

26. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. The lancet Oncology. 2013 Jun 1;14(7):609-18.

27. Wong SL, Edwards MJ, Chao C, Tuttle TM, Noyes RD, Carlson DJ, et al. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. Journal of the American College of Surgeons. 2001 Jun 1;192(6):684-9.

28. Takao Y, Toh U, Sakurai S, Saku S, Takenaka M, Akashi M, Sugihara R, et al. Triple-Tracer Technique of Sentinel Lymph Node Biopsy Using Blue Dye plus Radioisotope Combined with Real-Time Indocyanine Green (ICG) Fluorescence Imaging Procedures for Patients with Breast Cancer Treated with Neoadjuvant Chemotherapy. Gan to Kagaku ryoho. Cancer & Chemotherapy. 2020 Aug 1;47(8):1225-7.

29. Clinical practice guidelines oncology - breast cancer (version 2.2017). https://www.nccn.org/professionals/physician_gla/pdf/breast.pdf.

30. Boughey J, Haffty B, Buchholz T, Symmans WF, Hunt K, Armer J, et al. Alliance A011202: A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (CT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Receiving Neoadjuvant Chemotherapy.