Intra-operative molecular diagnosis of sentinel lymph node and prediction of non-sentinel lymph node metastasis in breast cancer patients

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To the Editor: Sentinel lymph node biopsy has become a universal procedure performed in node-negative breast cancer patients. The accurate intra-operative assessment of the sentinel lymph node (SLN) is prominent in enabling axillary lymph node dissection (ALND) synchronously performed during the breast surgery, in case of the morbidity, inconvenience, and extra cost resulting from a second operation. One-step nucleic acid amplification (OSNA) assay (Sysmex, Kobe, Japan) is a moderately sensitive molecular technique combining node tissue homogenization and subsequent reverse-transcription loop-mediated isothermal amplification of cytokeratin-19 (CK-19) mRNA in a single reaction. The assay could accurately discern nodal metastases of over 0.2 mm intra-operatively.

We performed two studies to validate the intraoperative OSNA assay (Clinical trial registry Nos. CBCSG-001c and NCT03937414). One trial (hereinafter referred to as “trial 1”) consisting of five centers (n = 552) has confirmed the good performance of OSNA assay with the accuracy of 91.4% and the sensitivity of 83.7% in 2010.¹ Another trial (trial 2) consisting of three centers (n = 1090) has been conducted from June 2015 to May 2017, the results have demonstrated that the sensitivity, specificity, and accuracy of the OSNA assay in SLN-positive breast cancer patients are 88.72% (173/195), 91.28% (817/895), and 90.83% (990/1090), respectively.

Results from two large randomized trials have facilitated the clinical practice in breast cancer patients with SLN metastases. ACOSOG Z0011 trial² has demonstrated that the patients with T1-2 tumors who received breast-conserving treatment can be exempt from ALND and axillary radiotherapy when the number of metastatic SLN is merely 1–2. The AMAROS trial³ suggests that if axillary treatment is necessary for SLN-positive patients, axillary radiotherapy instead of ALND will be preferable, as axillary radiotherapy provides similar local control and less morbidity. Thus, for these patients who fail to meet the criteria of the Z0011 and AMAROS trials, ALND is the standard treatment. In addition, for SLN-positive patients who undergo mastectomy and meet the criteria of the AMAROS trial, ALND is one of the alternatives. However, it has also been reported that 20% to 60% patients with positive SLNs have not developed to non-sentinel lymph node (NSLN) metastasis and ALND seems to be an over-treatment for these patients.⁴ Therefore, the predictive nomogram model available to distinguish SLN-positive patients who have no need of ALND is of very remarkable clinical significance. Surgeons have called for a great demand for the predictive model regarded as an indispensable model for guiding the subsequent surgical treatment.

In trial 1, data of 103 patients receiving ALND as a result of positive SLNs were collected to construct the nomogram. Variables selected from the traditional predictive models such as Memorial Sloan-Kettering Cancer Center (MSKCC), MD Anderson (MDA), Mayo, Tenon, Cambridge, Stanford, Helsinki, and total tumor load (TTL, the sum of the CK-19 mRNA copy number/μL of all positive lymph nodes) were adopted as clinicopathological indicators to construct the model. Logistic multivariate regression analysis was performed on the statistically significant variables, and then a novel nomo-
gram model for predicting NSLN metastasis was established by using TTL, clinical primary tumor size, and number of positive and negative SLNs [Figure 1]. As a result, the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis of the model in trial 1 was 0.814. In trial 2, all data of 159 patients undergoing ALND as a result of positive SLNs were utilized to validate the nomogram. The AUC of the ROC analysis of the model in trial 2 was 0.842. The sensitivity and specificity were 81.48% and 79.41%. A comparative analysis of the model with the traditional predictive models (represented by MDA and Tenon models) was conducted on the data of trial 2. The AUCs of MDA and Tenon were 0.745 and 0.623, respectively. It was evident that the AUCs of our nomogram was statistically superior to the MDA and Tenon ones ($P = 0.0449; \ P = 0.0156$).

The 2016 breast cancer National Comprehensive Cancer Network guideline has recommended irradiation of the internal mammary for patients with more than 4 positive axillary lymph nodes (category 1), and strongly considered the internal mammary radiation for patients with 1 to 3 positive axillary lymph nodes (category 2A). For this reason, radiotherapists have also been concentrating on the value of the predictive models. Because the local regional treatment of patients with axillary lymph node status (pN) of pN1 and ≥pN2 are distinct, the predictive model may help radiotherapists delineate the radiotherapy target more accurately. To explore the predictive power of the nomogram in patients with 1 to 3 metastases and ≥4 metastases in axillary lymph nodes, a combination data of 262 patients from trial 1 and trial 2, including 193 with pN1 and 69 with ≥pN2 were involved in our study. The cut-off value of our new model which was sensitive to discern the patients with pN1 and ≥pN2 was 0.454 and the AUC was 0.861 ($P < 0.0001$).

Researchers around the world endeavor to develop models for predicting the latent risks of NSLN metastasis. The existing models contain MSKCC, MDA, Mayo, Tenon, Cambridge, Stanford, Helsinki, and so on, some of which have already been applied in clinical practice. However, defects can be found in traditional predictive models. In general, first, though histological evaluations of SLNs are prevalently used in all models, no unified standard has been confirmed by various institutions to minimize the discrepancy. Second, it is difficult to precisely measure the maximum size of a complex three-dimensional metastasis in SLNs merely by the conventional histological evaluation of two-dimensional sections. Third, information for the construction of traditional models can be only achieved after the surgery histologically, including tumor grade, multi-focus, and vascular invasion, and so on, which means that it is impossible to adopt a traditional model ahead of and even to guide an axillary operation. In other words, the status of axillary lymph nodes can only be evaluated according to the post-operative information. These defects extremely constrain the clinical application of traditional predictive models. Compared with the conventional ones, our model established on the basis of the intraoperative molecular diagnostics is objective and standardized. Information on primary clinical tumor size, TTL, and the number of positive and negative SLNs can be obtained pre-operatively and intra-operatively. Unlike the conventional ones that can only predict based on post-operative information, our model has made rapid intra-operative prediction to guide subsequent axillary treatment timely. Moreover, the new model can synchronously distinguish the risk of lymph node metastasis in breast cancer patients with pN1 and ≥pN2, which is helpful to pinpoint the target area of radiotherapy in clinical practice.
In summary, the OSNA assay is an accurate intraoperative assessment for breast SLNs. The nomogram for predicting NSLN metastasis based on TTL, primary clinical tumor size, and the number of positive and negative SLNs presents superior over other predictive models. The novel model will help to guide the axillary management and precisely confirm the target region of radiotherapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

References

1. Wang YS, Ou-Yang T, Wu J, Liu YH, Cao XC, Sun X, et al. Comparative study of one-step nucleic acid amplification assay, frozen section, and touch imprint cytology for intraoperative assessment of breast sentinel lymph node in Chinese patients. Cancer Sci 2012;103:1989–1993. doi: 10.1111/cas.12001.

2. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACONOG Z0011 (Alliance) randomized clinical trial. JAMA 2017;318:918–926. doi: 10.1001/jama.2017.11470.

3. Donker M, van Tienhoven G, Straver ME, Moijn P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303–1310. doi: 10.1016/S1470-2045(14)70460-7.

4. Hwang RF, Krishnamurthy S, Hunt KK, Mirza N, Ames FC, Feig B, et al. Clinicopathologic factors predicting involvement of non-sentinel axillary nodes in women with breast cancer. Ann Surg Oncol 2003;10:248–254. doi: 10.1245/ASO.2003.05.020.

5. Hessman CJ, Naik AM, Kearney NM, Jensen AJ, Diggs BS, Troxell ML, et al. Comparative validation of online nomograms for predicting nonsentinel lymph node status in sentinel lymph node-positive breast cancer. Arch Surg 2011;146:35–40. doi: 10.1001/archsurg.2011.201.

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