

Metastatic sentinel node and axillary lymphadenectomy revisited

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Complete axillary lymph node dissection (ALND) is an integral part of the surgical treatment for breast carcinoma in spite of carrying a high morbidity and frequent secondary side effects.

The benefit of ALND begins to be questioned in the second half of the 20th century when Fisher demonstrates, through the NSABP B-32 trial, that it only offers staging value and prevention of axillary recurrence (AR) but has no impact on overall survival (OS) (1). Since this trial showed that ALND provides no additional benefit to cN0 patients then the indication for ALND is restricted only to patients with axillary metastases.

In the 90's, the progressive and rapid acceptance of sentinel node (SN) as the regional staging method sets forth the conservative surgical axillary approach. The exhaustiveness of the study of SN also leads to an increase in the detection of small-volume metastases (micrometastases and isolated tumor cells) and arouses the interest to investigate its correlation with metastasis on non-sentinel lymph nodes (LN) in the ALND specimen.

When a SN is metastatic, the positivity rate in the ALND ranges between 40 and 70% depending, as in the case of SN, of the thoroughness of the pathological study applied (2). The application of molecular protocols (such as OSNA) to study the ALND specimen diagnoses metastasis in more than 80% of lymph nodes, and surprisingly, 36% of them are macrometastasis (3,4). This findings correlate with the negative impact observed in OS when either ITC or micrometastases are detected in the SN (5).

Recently the ACOSOG Z-0011 trial (6) justified the omission of ALND in a selected group of patients randomized to ALND *vs.* no-ALND after finding similar rates of local recurrence and OS at 5 years. However, patients enrolled in the trial had low risk tumors (T1

and hormone receptors positive) and all of them received systemic therapy and tangential breast radiotherapy that included low axillary region, so these results should not to be extrapolated to patients with high risk tumors. Anyhow, the low rates of axillary recurrence described raise the possibility that the omission of ALND is a safe procedure in some cases with metastatic SN (5).

In this scenario it seems clear that the prognostic regional stratification of TNM staging system may be insufficient to predict further axillary involvement and to identify the individual risk of each patient is urgently needed in order to plan the best axillary approach, whether be it medical or surgical.

Trying to build such tools it has been shown, by validated studies, that logistic regression models such as nomograms are useful to discuss a tailored treatment with the patient. Most of these nomograms have false negative rates (FNR) that range from 14% to 30% (7). The FNR is lower in cases of micrometastasis than in cases of macrometastasis and all models overestimate the probability of ALND metastasis in high risk cases and underestimate this probability in low-risk cases. Therefore, their predictive values (PV) are still insufficient for the assessment of risk for each individual patient (7).

Several nomograms exist but the most accurate ones are the MSKCC one, whose AUC ranges from 0.63 to 0.70 and the Stanford one, whose AUC ranges from 0.57 to 0.63 (7). Interestingly, Mittendorf *et al.*, entering the measure of the metastasis size, have improved the predictive value of their nomogram, with an AUC of 0.80 in spite of being an imprecise and not standardized measurement (8).

One step beyond could be to include in the nomogram the SN tumor burden measured as the number of copies of mARN of CK19 and as a continuous variable.

In summary, to add sentinel node metastasis size as a continuous variable improves nomograms actually in use. Since new molecular tools allow the possibility to accurately measure the tumour load it would be interesting to work in this direction.

Also, the search of new variables with prognostic and predictive importance should be the goal of all specialties related to diagnosis and treatment of breast cancer.

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