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# A risk score model predictive of the presence of additional disease in the axilla in early-breast cancer patients with one or two metastatic sentinel lymph nodes

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**Abstract**

*Background*: Axillary lymph node dissection (ALND) in early-breast cancer patients with positive sentinel node (SLN+) may not always be necessary.
*Aims*: To predict the finding of ≥1 metastatic axillary node in addition to SLN+(s); to discriminate between patients who would or not benefit from ALND.
*Methods*: Records of 397 consecutive patients with 1-2 SLN+s receiving ALND were reviewed. Clinico-pathological features were used in univariate and multivariate analyses to develop a logistic regression model predictive of the risk of ≥1 additional axillary node involved. The discrimination power of the model was quantified by the area under the receiver operating characteristic curve (AUC) and validated using an independent set of 83 patients.
*Results*: In univariate analyses, the risk of ≥1 additional node involved was correlated with tumor size, grade, HER-2 and Ki-67 over-expression, number of SLN+s. All factors, but Ki-67, retained in multivariate regressions were used to generate a predictive model with good discriminating power on both the training and the validation sets (AUC 0.73 and 0.75, respectively). Three patient groups were defined based on their risk to present additional axillary burden.
*Conclusions*: The model identifies SLN+-patients at low risk (≤15%) who could reasonably be spared ALND and those at high risk (>75%) who should receive ALND. For patients at intermediate risk, ALND appropriateness could be individually evaluated based on other clinico-pathological parameters.
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*Keywords:* Axillary lymph node dissection; Metastatic sentinel lymph node; Breast cancer; Axillary metastasis risk; Predictive model

## Introduction

Axillary lymph node dissection (ALND) has long been the standard procedure for disease staging and loco-regional control in early-breast cancer patients. This procedure is now replaced by the sentinel lymph node biopsy (SLNB). Due to its acceptable negative predictive value, SLNB is nowadays recommended by International Clinical Guidelines for axillary status assessment in patients with T1-2 tumors and clinically negative nodes (N0).[1] Randomized studies consistently showed that ALND can be safely omitted when the sentinel lymph node (SLN) is histologically negative, without jeopardizing overall survival (OS) or local disease control but sparing those patients the known morbidities and reduced quality of life often associated with axillary clearance.[2–6]

However, due to its prognostic and therapeutic implications, ALND has remained the standard of care for patients with positive SLNs. Still, axillary metastases are present

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in only 35%–65% of patients and only ≈50% of them have additional metastases in non-sentinel lymph nodes (NSLN).[7] The other 50% with disease-free nodes will have no benefit from ALND but may unnecessarily face morbidities associated with that procedure.

Hence, the need of ALND in presence of metastatic SLNs has been questioned, especially when nodal involvement is limited (low number of positive SLNs and/or micrometastasis). Three randomized trials, IBCSG-23-01, ASCOG-Z0011 and EORTC-AMAROS, are addressing this issue, assessing the consequences of omitting ALND in terms of survival in patients with metastatic SLNs. The first study involving patients with only micrometastatic SLNs recently showed that disease-free survival in the arm not receiving ALND was not inferior as compared to the arm undergoing ALND.[8] However, these results should be taken cautiously because of possible biais in patient selection; median age was over 50 years; most patients had a <2 cm-tumor (≈70% of the cases), positive-estrogen receptor (≈90%) and presented SLN with ≤1 mm-micrometastases (≈70%).

Interim analyses of the ASCOG-Z0011 study also indicated that, in patients with 1–2 macrometastatic SLNs, omitting ALND did not result in inferior OS or DFS as compared to performing ALND.[9]

The EORTC-AMAROS study that compares axillary radiotherapy to ALND in positive-SLN patients is still in follow-up.

Nevertheless, in devising a possible modulation of the use of ALND in the context of positive SLNs, there is a real need to first re-evaluate the criteria accurately predicting the presence of a clinically significant axillary disease burden (e.g. 3 or more positive nodes). Indeed, the finding of metastatic nodes and their number have major prognostic value and guide the choice of the most appropriate adjuvant therapy.[10] Consequently, avoiding ALND and leaving behind undetected involved nodes might lead to unacceptable under-treatment. In addition, although a correlation between extent of axillary node involvement and prognosis worsening is known since long[11], this concept has been emphasized in the context of cancer molecular signatures: using the multigene prognostic Oncotype DX assay to score the recurrence risk in postmenopausal women under hormonal therapy, the TransATAC study showed that, among patients with an equal score, the probability of distal recurrence progressively increased with the number of axillary nodes involved, being higher in patients with 4 or more positive nodes as compared to patients diagnosed N0 or presenting only 1–3 metastatic nodes.[12]

With the intent to better define the individual therapeutic approach, taking into account not only the SLN status but also other clinico-pathological factors, we have developed and here report on a risk score predictive of the probability of a patient with 1–2 metastatic SLNs to have further axillary disease. This score allows dividing the patients into 3 groups according to the benefit they may derive from ALND, benefit that could be null, quite substantial or questionable.

## Patients and methods

### *Patient population*

This retrospective study includes 397 consecutive patients with invasive breast carcinoma and 1–2 positive SLNs who underwent surgery at the IRCSS-AOU-San Martino-IST of Genoa, Italy, between January 2004 and December 2010. To comply with the selection criteria used in the ASCOG-Z0011 study,[9] positive SLNs could present micro- (>0.2 mm but ≤2.0 mm) and/or macrometastasis (>2.0 mm). Patients with only isolated tumor cells (ITCs, ≤0.2 mm) were considered disease-free and were thus excluded. Given that we intended to include human epidermal growth factor receptor-2 (HER-2) overexpression as prognostic factor in our analyses, patients treated before 2004 were excluded because assessing HER-2 amplification by fluorescence in situ hybridization was not routinely performed in case of dubious or 2 + scored immunohistochemical evaluations. All patients underwent diagnostic imaging including mammography, ultrasound and/or nuclear magnetic resonance. All patients were clinically node negative. None of them received neo-adjuvant chemotherapy. They all underwent level I and II axillary node dissection and either conservative breast surgery or mastectomy. For each patient, data regarding the clinico-pathological features of the primary tumor, the total number of SLNs and NSLNs retrieved, and the number of positive ones were collected. Medical records reviewing had been approved by the Institutional Review Board.

### *Sentinel lymph node identification and evaluation*

The SLN was identified by lymphoscintigraphy. The day before surgery, a subdermal injection of 0.2 mCi of $^{99m}$Technetium (Nanocol, Amersham-Sorin Biomedica, Saluggia, Italy) was performed at the tumor site. At the time of surgery, a small axillary incision was performed, and the radioactive SLN was localized with a γ-ray detecting probe. The SLN was retrieved, bisected along its major axis, examined intraoperatively with hematoxylin–eosin on frozen sections, fixed in formalin for 24 h and embedded in paraffin. In each half, 10 sections, each 4-μm thick, were cut every 50 μm (first 5) and every 150 μm (next 5). All sections, but the second and the ninth, were stained with hematoxylin–eosin. If the histological evaluation resulted negative or ambiguous, the second and the ninth sections were tested by immunohistochemistry for the presence of cytokeratins (EPOS method with cytokeratin MNF116 monoclonal antibody and horseradish peroxidase, Dako).

Non-sentinel lymph nodes were bisected along their major axis, fixed in formalin and embedded in paraffin. In each half, 3 consecutive sections, each 4-μm thick, were stained with hematoxylin–eosin.

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