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Prognostic impact of macrometastasis linear size in sentinel node biopsy for breast carcinoma

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Abstract

Aim: The aim of the present study was to evaluate the risk of axillary non-sentinel lymph-node metastases (ALN) in breast cancer patients presenting macrometastasis (Mac-m) in the sentinel lymph node (SN).
Materials and methods: A retrospective series of 1464 breast cancers from patients who underwent ALN dissection following the diagnosis of Mac-m in the sentinel node (SN) was studied. In all the cases the MAC-m linear size was evaluated and correlated with presence or absence of non-SN ALN metastases.
Results: Non-SN metastases were detected in 644\1464 cases (43.98%). The risk of further axillary metastases ranged from 20.2% (37/183) in cases with Mac-m between 2 and 2.9 mm, to 65.3% (262/401) in cases with Mac-m measuring > 10 mm. The risk of non-SN ALN metastases showed a 3% increase, parallel to each mm increment in SN metastasis size. The data evaluated with the receiver operating characteristic (ROC) curve showed that the Mac-m could be subdivided according to a new cut-off of 7 mm. pT1 tumours, with Mac-m < 7 mm had a risk of non-SN ALN metastases of <30%. Furthermore 109/127 of these (85.8%) had 3 or less non-SN ALN -metastases.
Conclusions: The present data give a detailed description on the risk of non-SN ALN involvement, that may be useful in the evaluation of breast cancer patients. It is suggested that a Mac-m size of <7 mm is related to a low residual axillary disease burden in breast cancer patients with small (pT1) tumours.

Keywords: Sentinel node; Macrometastasis; Breast cancer; Axillary dissection; Axillary metastasis; Staging

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Introduction

In patients with breast cancer, the wide application of SN biopsy (SNB) has led to a reduction of side effects occurring after axillary lymph node dissection (ALND).

SNs free of metastatic deposits, can reliably predict the absence of further metastases in the axilla.[6] It is similarly clear that the presence or absence of metastatic deposits in the SN(s) cannot be the only feature to be evaluated, to predict further axillary node (ALN) involvement.[1,2]

The size of the metastatic deposits has been one of the most important and most studied parameters in this respect.[5–7] It has been evident that small volume metastatic deposits in the SN were related to a low risk of further axillary metastases. Therefore, the SN metastatic deposits were arbitrarily classified into three size categories: isolated tumour cells (ITC) when not greater than 0.2 mm; micrometastasis (Mic-m) when between 0.2 and 2 mm and macrometastasis (Mac-m) when larger than 2 mm.These definitions, with some refinements, are currently applied in SN evaluation.[8]

Despite the diagnostic problems and pitfalls,[9–12] it is evident that small volume metastatic deposits correspond to a low risk of further axillary involvement.[13] Accordingly, the presence of ITCs, even if related to a small increase in the risk of axillary metastases[14] was not considered enough to perform ALDN, which at that time was limited to patients with Mic-m and Mac-m.

In 2011, Giuliano et al.[15] demonstrated that selected patients with metastatic disease, including Mic-m and limited Mac-m, can safely avoid ALND, when breast conserving surgery is combined with whole breast irradiation (RT) and patients receive adjuvant systemic treatment (mostly chemotherapy, CHT) as well. The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial published by Giuliano et al.,[15] even if subject to criticisms,[16] have significantly changed the practice of axillary treatment in breast cancer, and have initiated a large scale validation study, the POSNOC (POsitive Sentinel NOde-adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) trial which aims to overcome the criticized aspects of the ACOSOG Z0011 trial.[17] Two other randomized trials also support the omission of ALND in cases of SN Mic-m.[18,19] Therefore, recently published guidelines, accept that ALND can be avoided in patients with early stage breast cancer and Mic-m, when matching the selection criteria of the Z0011 trial.[1,2]

Avoiding ALND in appropriately selected patients is expected to harbour no or very limited tumour burden in the axilla and greatly reduces the risk of local complications, leading to a better quality of life for patients without increasing the risk of disease recurrence.

In daily practice, it is evident that even patients with Mac-m in the SN who undergo ALND, are frequently free of further metastatic deposits, and in retrospect, receive unnecessary surgery with the potential risk of local complications.

On the other side, the arbitrary cut-off size to separate Mic-m from Mac-m, currently established at 2 mm based on a historical work by Huvos and colleagues introducing the term Mic-m,[20] has been proposed without being validated in large series.

Recently Illyes et al.,[21] proposed that the 2 mm cut-off, could be modified to 6 mm, allowing the avoidance of completion ALND in a larger proportion of patients.

In addition, numerous papers demonstrated that the size of the metastatic deposit in the SN is not the only parameter to consider the risk evaluation of further axillary involvement. Indeed, size and grade of the primary tumour, multifocality, presence of lympho-vascular invasion (LVI), extra capsular extension (ECE), are important parameters predicting the risk of further axillary involvement.[3,4,22–24]

Therefore, the aim of the present study was to retrospectively evaluate a large multi-institutional series of MAC-m in the SN with patients who underwent ALND, and to correlate the presence of further lymph-node metastatic involvement with the Mac-m linear size and primary tumour features. The final goal of the study was to provide data useful to evaluate the real risk of further axillary involvement in each breast cancer patient, in order to better tailor therapeutic planning.

Materials and methods

Cases were collected retrospectively from 13 European centres, all of which are involved in the diagnosis and treatment of screen detected breast cancer patients. All centres, but one (Imola, Bologna), are associated with the European Working Group for Breast Screening Pathology (EWGBSP), and therefore follow similar diagnostic protocols. The Imola centre, due to its geographical location very close to Bologna, shares the same diagnostic protocols with the Bologna Bellaria centre, and consequently the two centres were considered together.

Cases were included when they met the following criteria: a) SNB was performed at primary surgery for staging purposes; b) at least one SN contained a Mac-m; c) ALND with the removal of at least 10 axillary lymph nodes was performed in addition to the SNB; d) data on the primary tumour were available; e) no neo-adjuvant chemo- or hormonal therapy had been administered. According to the inclusion criteria above, cases without metastatic deposits, or with either Mic-m or ITC in the SN, as well as male breast cancers were excluded. The cases therefore represent a consecutive series meeting the inclusion criteria from each centre.

In each case, the following parameters were evaluated: 1) largest linear size of the Mac-m, in millimetres (mm); 2) the number of SN involved by MAC-m; 3) presence of extra capsular extension (ECE). In addition, the following parameters were evaluated in the primary tumour: histotype, grade, size, presence of LVI and multifocality.

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