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IMPACT OF MICROMETASTASIS AND ISOLATED TUMOR CELLS FOUND ON SENTINEL LYMPH NODES IN EARLY BREAST CANCER

Impacto do encontro de micrometástase e células tumorais isoladas nos linfonodos sentinela no câncer de mama precoce

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ABSTRACT

The presence of axillary lymph node metastases is one of the most important prognostic factors in breast cancer and it is often used to guide locoregional and systemic therapy decisions. The question of whether axillary dissection (AD) can be safely omitted in patients with early breast cancer when isolated tumor cells (ITC) or micrometastasis is found in the sentinel node remains a controversial issue in the literature. On the basis of current evidence, AD could probably be safely omitted when micrometastasis or ITC are found. On making this decision, as micrometastasis and ITC are a sign of a biologically different disease, adjuvant radiotherapy and the adjuvant systemic treatment need to be considered.

KEYWORDS: Sentinel Lymph Node Biopsy; Radiotherapy; Breast Cancer; Micrometastasis.

RESUMO

A presença de metástases linfonodais axilares é um dos fatores prognósticos mais importantes no câncer de mama e é freqüentemente utilizada para guiar as decisões da necessidade de terapias locorregional e/ou sistêmica adicionais. A questão se a dissecção axilar (AD) pode ser omitida com segurança em pacientes com câncer de mama precoce, quando células tumorais isoladas ou micrometástases são encontradas no linfonodo sentinela, permanece um assunto controverso na literatura. Com base nas evidências atuais, a AD poderia ser omitida quando micrometástases ou CTI são encontradas. Ao tomar essa decisão, deve-se levar em conta que a presença de micrometástases e CTI são sinais de uma doença biologicamente diferente, em que a radioterapia adjuvante e o tratamento sistêmico adjuvante precisam ser considerados.

PALAVRAS-CHAVE: Biópsia de Linfonodo Sentinela; Radioterapia; Câncer de Mama; Micrometástase.

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Numerous studies have shown that the status of the sentinel lymph node is an accurate predictor of the status of axillary nodes in breast cancer, thus avoiding total axillary dissection (AD) in selected cases. For patients who had surgical intervention in the axilla, long-term sequels may include sensory neuropathy, lymphedema, and/or motor neuropathy.

The first randomized trial to validate sentinel-node biopsy (SNB) in breast cancer was published in 2003. The sample consisted of 516 patients with primary breast cancer, whose tumor was less than or equal to 2 cm in diameter assigned to either SNB and AD or to SNB followed by AD only if the sentinel lymph node contained metastasis. As a result, they noted that the sentinel lymph node was positive in 83 of the 257 patients in the AD group (32.3%), and in 92 of the 259 patients in the SNB group (35.5%). It was also observed that the overall accuracy of the sentinel-node status in the AD group was 96.9%, the sensitivity 91.2%, and the specificity 100%, concluding that SNB is a safe and accurate method of screening the axillary nodes for metastasis in women with small breast cancer[1]. SNB became an integral part of the conservative treatment of breast cancer since it allowed for the avoidance of AD in a large proportion of patients with early breast cancer, while still providing information to guide adjuvant treatment. More recent data also confirmed the value of SNB. The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC)[2] and the NSABP B32[3] recruited 954 and 5,611 women, respectively, and identified the value of SNB procedures in invasive breast cancer patients with clinically negative axilla.

There are three options if a tumor sentinel lymph node is positive:

- proceed to AD;
- irradiate the axilla;
- observe.

The standard approach for these patients has been to carry out an AD, once it is supposed to be a therapeutic treatment and can provide the additional information needed to direct adjuvant treatments.

The advantages of SNB include an enhanced pathological examination of a small number of sentinel lymph nodes. In the era of SNB, the sentinel lymph node is serial sectioned and all sections examined, conversely to the era before SNB, where about three sections per axillary lymph node were typically examined[4]. When sentinel lymph nodes are sliced at 2.0 mm intervals and totally embedded, the probability of identifying all metastases with more than 2.0 mm is high. Staging guidelines have established a lower limit for micrometastases and defined metastases no larger than 0.2 mm as isolated tumor cells (ITC)[5]. An increased number of micrometastases or ITC have been described and the question of whether AD can be safely omitted in patients with early breast cancer when micrometastases or ITC are found in the sentinel lymph node remains a controversial issue[6].

At the same time, however, SNB raises two new concerns: does the involvement by micrometastasis or ITC significantly impact on survival and should patients with such minimal involvement undergo further AD? The consequences of increased detection of micrometastasis has not been fully explored.

Micrometastatic disease from breast cancer is a major concern both for clinicians and pathologists. They can be defined as potentially invasive microfoci of tumoral cancer cells. Micrometastatic disease is mainly looked for in bone marrow and lymph nodes specimens. Their diagnosis is currently easier due to immunohistochemistry[7].

The further management of micrometastatic disease in the era of SNB has been evolving. Gradually, guidelines are shifting away from clearing the axilla if micrometastases are found during sentinel lymph node biopsy[8,9].

The MIRROR study showed that patients with micrometastasis and ITC who didn't receive systemic treatment had a higher event rate than those who did[10]. A recent study by Youssef et al., despite the limitations of a retrospective study and small number of patients (n=95), found a 7.01% difference in overall survival (OS) favoring the AD over the SNB group (p=0.004)[11].

In contrast, prospective early outcome data in SNB suggest no adverse outcome for patients with metastases no larger than 2.0 mm, a finding aligned with the current definition of micrometastasis[5]. The IBCSG 23–01 was a two-group, multicentered, randomized, non-inferiority, phase 3 trial comparing no-AD with AD in patients with breast cancer and micrometastases in the sentinel lymph node. Patients were recruited from 27 institutions and considered eligible if they had clinically non-palpable axillary lymph node(s), a primary tumor of 5 cm or less and who, after SNB, had one or more micrometastatic (≤mm) sentinel lymph node(s) with no extracapsular extension. Between April, 2001 and February, 2010, 465 patients were randomly assigned to AD and 469 to no-AD. The results showed no difference of outcomes in terms of disease free survival or overall survival when the axillary treatment was omitted for micrometastasis in SNB[12].

On the basis of current evidence, AD could probably be safely omitted after SNB when micrometastases or ITC are found, given the higher rate of lymphoedema and the little staging information it further adds[13]. On making this decision, as micrometastases and ITC found in the SNB are a sign of a biologically different disease, the field of adjuvant radiotherapy and the adjuvant systemic treatment need to be considered. The results of prospective large trials on going, among them the *Sentinelle Envahi et Randomisation du Curage* (SERC) study[14], may provide further evidence on this matter.

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