General information

The number of lymph nodes with metastatic carcinoma and the extent of metastatic involvement (macrometastases or micrometastases) carry specific clinical, treatment and prognostic implications.

Prospective randomised trials have proven that 1) sentinel node biopsy is not inferior to axillary lymph node dissection; 2) patients with micrometastases or even macrometastases in one or two sentinel lymph nodes do no worse than patients without metastases if appropriate adjuvant therapy is also given to them; and 3) radiotherapy might be an alternative treatment modality to surgical axillary clearance.[1-7] Accordingly, at present, sentinel lymph node biopsy is the preferred surgical procedure for axillary staging.[8]

Based on the results of the aforementioned studies, the number of sentinel lymph nodes with metastatic carcinoma and the extent of carcinoma present in the sentinel lymph nodes need to be precisely quantified to determine whether axillary dissection is warranted or it might be safely omitted.[2-8]

Carcinoma in lymph nodes is quantified according to its largest size as macrometastatic, micrometastatic or consisting of isolated tumour cells (ITCs) (see specific sections). Invasive lobular carcinomas typically metastasize with single cells spanning a given area of the lymph nodes with or without desmoplastic stromal reaction and counting tumour cells may be needed. At the lower end, the 200 cell limit distinguishes between ITCs and micrometastasis. When the cancer cell burden is well above 200 cells, measuring the largest span of the area involved is the most pragmatic approach to classify the metastasis as micrometastasis or macrometastasis. If there is any doubt about precise classification, the lower category should be chosen.[9-11]

Pathological classification of lymph node status (pN) is used for excision or sentinel lymph node biopsy *only* in conjunction with a pathological T assignment. In the absence of assignment of a pT category, excisional biopsy of a lymph node or biopsy of a sentinel node, is classified as a clinical N (e.g., cN1 or cN1(sn)).[9,11]

The pathologic assessment of regional lymph nodes (pN) ideally requires resection of a minimum number of lymph nodes to assure that sampling was sufficient to identify positive nodes if present. The Union for International Cancer Control (UICC) 8th Edition Staging System suggests that *at least six axillary lymph nodes be examined* to assess pN status (equivalent of axillary level I lymph nodes).[11] This guideline does not apply if sentinel lymph node biopsy is performed (see discussion below). If, for any reason, at least one but less than six lymph nodes are examined (i.e., the six-node-requirement is not met), the pN category should still be determined, and the pNx category should not be used.

<u>Sentinel lymph node biopsy</u>

Classification of lymph node status based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for 'sentinel node,' (e.g., pN0(sn)).

In cases where sentinel node biopsy has been accepted as accurate for defining regional node involvement and a sentinel node procedure has been performed, the recommended number of at least six axillary lymph nodes (level I) does not apply.

If sentinel lymph node biopsy was performed before the patient received adjuvant systemic treatment, histologic examination of at least one sentinel lymph node is required for pathologic N classification.

For accurate histologic evaluation of sentinel lymph nodes, it is recommended that the lymph node(s) be sectioned into 2 millimetre (mm) thick slices. If more than one lymph node is placed in the same tissue cassette it is recommended to ink differentially each lymph node so that the number of the sentinel lymph nodes with metastatic carcinoma and the total number of sentinel lymph nodes can be accurately assessed.

The use of cytokeratin immunohistochemical stains to evaluate lymph nodes with no evidence of carcinoma in haematoxylin-eosin (H&E) stained sections is not routinely undertaken. Immunohistochemical staining for cytokeratins can be used to evaluate uncertain findings in H&E-stained sections (see also **ANCILLARY STUDIES**).

Evaluation and reporting of lymph nodes obtained post neoadjuvant treatment

Neoadjuvant systemic therapy is administered before definitive surgery, often with the intent to reduce tumour burden (reduce T, downstage) or temporarily control the disease.

Sentinel lymph node biopsy may be used to assess axillary lymph node status post neoadjuvant treatment in patients with cT1-T2 cN0 or cN1 disease at initial diagnosis who appear to be free of disease clinically and by imaging studies after completion of systemic therapy (i.e., converting to ycN0).

The number of lymph nodes with residual carcinoma post-neoadjuvant treatment and the extent of residual lymph node involvement are quantified and reported according to the same guidelines as for treatment-naïve lymph nodes. In the post-neoadjuvant setting, the guidelines for measuring the size of residual carcinoma in the lymph node(s) vary depending on the practices endorsed by different societies.[12]

According to the College of American Pathologists guidelines, “the largest contiguous focus of residual tumour in the lymph nodes, if present, is used to determine ypN category.[13] Treatment-related fibrosis adjacent to residual nodal deposits or between foci of residual metastatic disease is not included in determining ypN dimension”.[9,13,14]

In other parts of the world, including the United Kingdom, Ireland, and Australasian and South-East Asian countries, the size of the residual metastatic deposit post-neoadjuvant treatment includes foci of residual viable carcinoma with intervening treatment-induced stromal fibrosis. As stated by Provenzano et al (2015),[12] “The size of the largest metastatic deposit should be measured microscopically. Post-neoadjuvant systemic therapy tumour cells are often present as scattered single cells within an area of reactive stromal changes or lymphoid tissue. When measuring the size of the metastasis in this context, the size of the area that is even partly involved by metastatic tumour should be measured, and not just the size of the largest tumour cluster. Clearly separate smaller foci in a node are not included in the maximum size measurement.” This measurement is also used in the calculation of the Residual Cancer Burden Class.[15]

Given these different approaches and the limited data available regarding the clinical significance of ITCs versus micrometastases in the lymph nodes of patients status post-neoadjuvant treatment, further investigation is required to assess the most appropriate way to measure and report limited involvement of post-neoadjuvant lymph nodes. Local guidance is recommended with respect to providing pathologic information for clinical prognostic calculations.

At present, the use of cytokeratin immunohistochemical stains to evaluate lymph nodes obtained post-neoadjuvant treatment with no evidence of carcinoma in H&E-stained sections is not recommended as routine practice, but immunohistochemical staining for cytokeratins may be used to evaluate uncertain findings in H&E-stained sections (see also **ANCILLARY STUDIES**).

Post-neoadjuvant status is designated by using the "y" prefix when reporting N classification. The presence of residual disease in the lymph nodes obtained post-neoadjuvant treatment carries greater adverse clinical and prognostic significance than the same extent of disease in treatment-naïve patients. Post-treatment 'ypN' should be evaluated as for clinical (pre-treatment) 'N' methods. ypN categories are the same as those used for pN, but the clinical significance differs.

In patients who are status-post neoadjuvant systemic treatment, the modifier 'sn' is used if only a sentinel lymph node evaluation was performed *after neoadjuvant treatment*. If no postscript is attached, it is assumed the axillary nodal evaluation was by axillary node dissection.

The X classification will be used (ypNX) if no post-treatment sentinel lymph node biopsy or axillary dissection was performed. In this situation, the clinical N status is utilised for overall stage determination (e.g., ycN0 or ycN1).

Treatment effect is defined as areas of scarring, hyalinisation, necrosis, mucoid or myxoid change, a collection of foamy histiocytes in the lymph node (akin to tumour bed in the breast specimen), and/or the presence of cellular alterations in the residual carcinoma attributable to the neoadjuvant treatment.

Direct extension of primary carcinoma into a regional node is classified as a positive node. A tumour nodule with a smooth contour in a regional node area is classified as a positive node. The size of the metastasis, not the size of the node, is used for the criterion for the pN category.

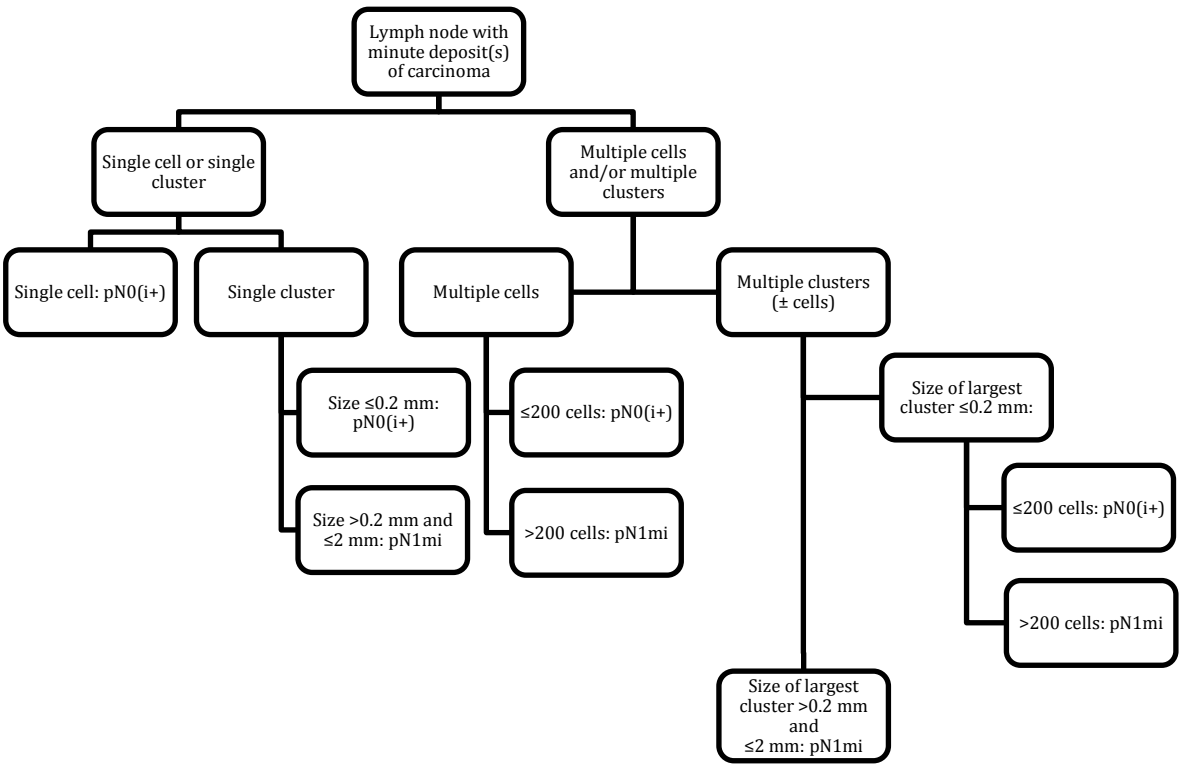

Figure 1: Flow chart outlining the steps involved in deciding whether minute tumour deposits of carcinoma in a lymph node constitute a micrometastasis (pN1) or isolated tumour cells (pN0). Modifed version reprinted from Eur J Cancer, 47(6), Cserni et al, Distinction of isolated tumour cells and micrometastasis in lymph nodes of breast cancer patients according to the new Tumour Node Metastasis (TNM) definitions, Pages 887-94 (2011), with permission from Elsevier.[16]

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