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Surgically Removed Lymph Nodes for Breast Tumours Histopathology Reporting Guide

ICCR

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION[a] (select all that apply) (Note 1)

◯ Information not provided

Clinical and/or imaging findings that prompted current lymph node evaluation

◯ Information not provided
☐ Ipsilateral breast carcinoma
☐ Enlarged/palpable axillary lymph node(s) in a patient with prior history of breast carcinoma
☐ Axillary lymph node(s) suspicious on imaging
  ☐ Imaging findings, *specify if available*
  ☐ Prior biopsy of the suspicious lymph node(s)
    ☐ Prior fine needle aspiration (FNA)
    ☐ Prior core needle biopsy (CNB)
    ☐ Prior CNB/FNA diagnosis
      ◯ Positive for carcinoma
      ◯ Negative for carcinoma
      ◯ Atypical cells present/suspicious for malignancy
      ◯ Non-diagnostic specimen
☐ Other relevant clinical/imaging findings, *specify*

Prior neoadjuvant treatment

◯ Information not provided ◯ No
◯ Yes (*a separate dataset is to be used in the setting of neoadjuvant therapy*)
  ☐ Neoadjuvant chemotherapy
  ☐ Neoadjuvant hormonal therapy

Other clinical information, *specify*

[a] *This is a core element if ONLY a sentinel lymph node and/or axillary lymph nodes are obtained. If the lymph nodes are obtained together with a breast specimen this element will be non-core.*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

☐ Sentinel lymph node biopsy
☐ Non-sentinel lymph node biopsy
☐ Axillary lymph node dissection
  ◯ Level I
  ◯ Levels I and II
  ◯ Levels I to III
☐ Axillary lymph node level III, excision
☐ Other regional lymph node(s) biopsy
  ☐ Internal mammary
  ☐ Infraclavicular (subclavicular)
  ☐ Supraclavicular
☐ Other, *specify*

SPECIMEN LATERALITY (Note 3)

◯ Left
◯ Right
◯ Not specified

NUMBER OF LYMPH NODES EXAMINED (Note 4)

(These values may be reported in the corresponding cells in Table 1A)

Total number of sentinel lymph nodes examined[b]

Total number of non-sentinel lymph nodes examined[c]

Total number of lymph nodes examined

[b] *This is a core element only if sentinel lymph nodes are submitted by the surgeon.*

[c] *Non-sentinel lymph nodes include:*
1. *any lymph node submitted by the surgeon as 'non-sentinel lymph node' at the time of sentinel lymph node biopsy; and*
2. *axillary lymph nodes from an axillary lymph node dissection.*

Version 1.2 Published May 2021 ISBN: 978-1-922324-11-5

NUMBER OF LYMPH NODES WITH METASTATIC CARCINOMA[d] (Note 5)

(This value may be reported in the corresponding cell in Table 1A)

[d] *This value includes the number of lymph nodes with macrometastatic (>2 mm) and micrometastatic carcinoma (>0.2 mm to 2 mm and/or ≥200 cells).*

NUMBER OF LYMPH NODES WITH MACROMETASTASES[e]

(These values may be reported in the corresponding cells in Table 1B)

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[e] *A macrometastasis is any tumour deposit spanning >2 mm microscopically.*

NUMBER OF LYMPH NODES WITH MICROMETASTASES[f] (Note 6)

(These values may be reported in the corresponding cells in Table 1B)

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[f] *A micrometastasis is any tumour deposit spanning >0.2 mm to 2 mm microscopically and/or consisting of more than 200 cells in one lymph node section but not exceeding 2 mm in extent.*

LYMPH NODES CONTAIN ONLY ISOLATED TUMOUR CELLS (ITCs)[g] (Note 7)

(These responses may be reported in the corresponding cells in Tables 1A and 1B)

- ◯ No
- ◯ Yes

Number of lymph nodes with ITCs when ONLY ITC involvement is present[h]

Sentinel lymph nodes	
Non-sentinel lymph nodes	
Total lymph nodes	

[g] *≤0.2 mm and ≤200 cells.*

[h] *This is a core element ONLY if macro- or micrometastatic carcinoma is NOT present in any lymph nodes. If metastatic (macro- or micrometastatic) carcinoma is identified in lymph nodes the number of lymph nodes with ONLY ITCs is a non-core element.*

SIZE OF LARGEST METASTASIS[i] (Note 8)

(This value may be reported in the corresponding cell in Table 1A)

- ◯ Not assessable[j]
- ◯ Size of largest metastatic deposit[k] mm
- ◯ At least[l] mm

[i] *Required only if macro- or micrometastatic carcinoma is present.*

[j] *Only to be used for cases investigated by one-step nucleic acid amplification.*

[k] *Denotes the largest span of metastatic carcinoma and is used to further stage pN involvement (micrometastatic carcinoma versus macrometastatic carcinoma).*

[l] *Refers to the minimum value of the size of the metastasis when the metastasis appears to be larger, but a more precise measurement is not possible (e.g., the lymph node is fragmented, the largest size of the metastasis is in the third dimension).*

EXTRANODAL EXTENSION[m] (Note 9)

(This response may be reported in the corresponding cell in Table 1A)

- ◯ Not identified
- ◯ Present
- ◯ Cannot be determined

[m] *This is a core element only if macro- or micrometastases are present.*

TREATMENT EFFECT[n] (Note 10)

- ◯ Not identified
- ◯ Present
- ◯ Cannot be determined

[n] *Combined reporting of the presence of residual metastatic carcinoma and/or treatment-induced fibrosis as summarised in Table 1C is strongly recommended.*

ANCILLARY STUDIES (Note 11)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry[o], *specify test(s) and result(s)*
  - ☐ One-step nucleic acid amplification[o], *record results*
  - ☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

[o] *This response may be reported in the corresponding cell in Table 1B.*

ISBN: 978-1-922324-11-5

REGIONAL LYMPH NODE CATEGORISATION (Note 12) **(UICC TNM 8th edition)**[p]

TNM Descriptors (only if applicable) (select all that apply)

- ☐ r - recurrent
- ☐ y - post-therapy
- ☐ p - histopathologic examination was performed; and the primary tumour was removed – the latter being a requisite for "p" classification
- ☐ c - based on clinical or imaging studies, no histopathologic examination was performed – or lymph node assessment was done without the primary breast tumour being removed

Regional lymph nodes (pN)

(This value may be reported in the corresponding cell in Table 1A)

- ◯ NX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathological study)
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Micrometastasis; or metastasis in 1 to 3 axillary ipsilateral lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected[q]
  - ◯ N1mi Micrometastasis (larger than 0.2 mm and/or more than 200 cells, but none larger than 2.0 mm)
  - ◯ N1mi(mol+) Using molecular methods[r]
  - ◯ N1a Metastasis in 1–3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
  - ◯ N1a(mol+) Using molecular methods[r]
  - ◯ N1b Metastasis in internal mammary lymph nodes not clinically detected[q]
  - ◯ N1c Metastasis in 1–3 axillary lymph nodes and internal mammary lymph nodes not clinically detected[q]
- ◯ N2 Metastasis in 4–9 ipsilateral axillary lymph nodes, or in clinically detected[q] ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
  - ◯ N2a Metastasis in 4–9 axillary lymph nodes, including at least one that is larger than 2 mm
  - ◯ N2b Metastasis in clinically detected internal mammary lymph node(s), in the absence of axillary lymph node metastasis
- ◯ N3 Metastasis as described below:[s]
  - ◯ N3a Metastasis in 10 or more ipsilateral axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes/level III lymph nodes
  - ◯ N3b Metastasis in clinically detected[q] internal ipsilateral mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic or macroscopic metastasis detected by sentinel lymph node biopsy but not clinically detected
  - ◯ N3c Metastasis in ipsilateral supraclavicular lymph node(s)

[p] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[q] *Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on FNA biopsy with cytological examination. Confirmation of clinically detected metastatic disease by FNA without excision biopsy is designated with a (f) suffix, e.g., cN3a(f). Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.*

[r] *Not included in UICC TNM 8th Edition.*

[s] *Definition of N3 not included in UICC TNM 8th Edition.*

The following tables are provided for reference, and may be used as needed.

Core elements are summarised in Table 1A. Although all core elements need to be reported for accurate staging of lymph node status, reporting in table format is not required, and the same information may be provided as indicated in the reporting guide. The same applies to the non-core elements summarised in Tables 1B and 1C.

Table 1A: Regional lymph node status – core elements

Type of lymph nodes	Number of lymph nodes	Status post-neoadjuvant treatment[c]	Total lymph nodes with metastatic carcinoma (size >0.2 mm)	Size of largest metastasis (mm)[d]	Only ITCs present (Yes/No)	Total lymph nodes with ITCs when ONLY ITC involvement is present[e,f]	pN status[g] (UICC TNM8)	Extranodal extension (ENE)
SLNs[a]								
Non-SLNs[a]								
Total lymph nodes[b]								

SLNs: sentinel lymph nodes
ITCs: isolated tumour cells
ENE: extranodal extension

Status post-neoadjuvant treatment: Information not provided; No neoadjuvant treatment given; Residual disease not identified; Residual disease present

ENE: Not identified; Present; Cannot be determined

[a] *Core elements only if SLN biopsy was performed; if no SLN biopsy was performed report only total number of lymph nodes (LNs).*

[b] *The total number of LNs removed includes the number of SLNs (if SLN biopsy was performed) + number of non-SLNs. Non-SLNs are all the LNs that are not submitted as SLNs by the surgeon. If an axillary lymph node dissection has been performed without a SLN biopsy, only the total number of LNs needs to be given.*

[c] *If the LNs were obtained post-neoadjuvant treatment, it is strongly suggested to provide the non-core information summarized in Table 1C.*

[d] *If the size cannot be measured (e.g., LN removed in several pieces and multiple pieces involved by the metastatic process) the largest measurable size should be given as "at least" size. If one-step nucleic acid amplification was used for nodal staging the size will be not assessable; the CK19 mRNA copy numbers can be given alternatively as a quantitative value. (Macrometastasis: one-step nucleic acid amplification assay result with >5000 CK19 mRNA copy number/µL lisate; Micrometastasis: one-step nucleic acid amplification assay result with CK19 mRNA copy number between 250 and 5000/µL lisate)*

[e] *ITCs are tumour deposits spanning ≤0.2 mm and ≤200 cells in a single LN profile. LNs with ITCs are not counted as metastatic LNs.*

[f] *This is a core element ONLY if macro- or micrometastatic carcinoma is NOT present in any lymph nodes. If metastatic (macro- or micrometastatic) carcinoma is identified in lymph nodes the number of lymph nodes with ONLY ITCs is a non-core element.*

[g] *If SLN biopsy was performed the minimum number of LNs required for staging purposes is one (sentinel) LN. If no SLN biopsy was performed, non-SLNs usually are obtained by axillary LN dissection (level I + level II +/- level III axillary LNs, depending on regional practices).*

Table 1B: Regional lymph node status – non-core elements

Type of lymph nodes	Number of lymph nodes with macrometastasis (size >2 mm)	Number of lymph nodes with micrometastasis (size >0.2 mm to ≤2 mm or >200 cells)	Total lymph nodes with ITCs when ONLY ITC involvement is present[a,b]	Immunohistochemistry[c] (Yes/No)	One-step nucleic acid amplification[c] (Yes/No)
SLNs					
Non-SLNs					
Total lymph nodes					

[a] *ITCs are tumour deposits spanning ≤0.2 mm and ≤200 cells in a single LN profile. LNs with ITCs are not counted as metastatic LNs.*

[b] *This is a core element ONLY if macro- or micrometastatic carcinoma is NOT present in any lymph nodes. If metastatic (macro- or micrometastatic) carcinoma is identified in lymph nodes the number of lymph nodes with ONLY ITCs is a non-core element.*

[c] *The elements summarised in Table 1B are non-core elements (optional reporting). However, if immunohistochemical evaluation or one-step nucleic acid amplification was performed and the results are used for LN staging purpose, the information pertaining to immunohistochemistry or one-step nucleic acid amplification needs to be reported.*

Table 1C: Regional lymph node status post-neoadjuvant treatment – non-core elements

Tumour regression	Number of lymph nodes WITH residual carcinoma	Number of lymph nodes WITHOUT residual carcinoma	Total number of lymph nodes
Not identified			
Present			
Cannot be determined			
Total lymph nodes examined			

ISBN: 978-1-922324-11-5

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) recommends that some ancillary testing in ICCR Datasets is included as core elements. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

⬆ Back

Scope

This dataset has been developed for the reporting of surgically removed ipsilateral lymph nodes (including lymph node dissection, targeted axillary surgery, nodal sampling and sentinel node biopsy specimens) for breast tumours. It is not intended for use in reporting core biopsy or fine needle aspiration (FNA) of lymph nodes. The assessment of ipsilateral lymph nodes is part of nodal staging of breast cancer, whereas the rare contralateral lymph node involvement is currently interpreted as distant metastasis and is not part of the dataset.

The reporting of invasive breast cancer and in situ disease (ductal carcinoma in situ (DCIS), pleomorphic and florid lobular carcinoma in situ (LCIS), encapsulated papillary carcinoma and solid papillary carcinoma in situ) are dealt with in separate ICCR datasets which may be used, as appropriate, in conjunction with this dataset.

For **General information** related to this dataset, please click here.

The authors of this dataset can be accessed here.

⬆ Back

Note 1 – Clinical information (Core)

Information on the clinical presentation and/or imaging findings that prompted examination of the lymph nodes may be useful in the interpretation of the histologic findings. It may also help guide the choice of an appropriate panel of markers for immunohistochemical work-up, if needed.

Knowledge of the histologic diagnosis of any synchronous, or prior, ipsilateral or contralateral mammary carcinoma (invasive or in situ) is also important. Similarly, information on prior treatment is essential for the adequate reporting and classification of the lymph node status.

Back

Note 2 – Operative procedure (Core)

The metastatic involvement of the axillary lymph nodes has specific clinical, treatment and prognostic implications. Accurate staging requires that all submitted lymph nodes be accurately designated by the surgeon.

Currently, in some countries (e.g., United States, Canada, Singapore) an axillary lymph node dissection does not routinely include level III lymph nodes.

Back

Note 3 – Specimen laterality (Core)

Staging of the axillary lymph node status differs substantially depending on whether carcinoma is present in the ipsilateral or contralateral axillary lymph nodes.

Lymph node(s) laterality is also an essential element for correlation with clinical presentation and prior history. Some patients may have synchronous or metachronous bilateral breast carcinoma. The assessment of ipsilateral lymph nodes is part of nodal staging of breast cancer, whereas the rare contralateral lymph node involvement is currently interpreted as distant metastasis and is not part of the dataset. Bilateral breast cancer is considered two diseases and requires two separate datasets, one for each side.

Back

Note 4 – Number of lymph nodes examined (Core)

Note: The total number of lymph nodes examined (C) is the sum of the number of all sentinel lymph nodes (A) and the number of all non-sentinel lymph nodes (B) examined. The “sn” modifier is used when the number of sentinel and non-sentinel level I/II nodes combined is less than six nodes (provided there is at least one sentinel node included in the specimen). Intramammary nodes are included in the level I lymph node count. Similarly, carcinoma foci in the axillary fat (without structural elements of a lymph node) also qualify as axillary lymph node metastases and should therefore be included in both the total and the metastatic lymph node count. Rarely, metastatic lymph nodes with massive involvement become fixed to each other and form a conglomerate with bosselated contours. In such cases, gross (and microscopic) examination may sometimes estimate the number of fused nodes, but on other occasions this is not

assessable. As the presence of conglomerates does not influence staging anymore, it is advised to give the best estimate of the number of examined and involved nodes in such cases, keeping in mind the general rule favouring the lower categories in case of uncertainty; i.e., the number of lymph nodes examined and found to have metastatic disease in such a conglomerate may be one (if the mass does not show any distinct suggestion for more than one lymph node) or more (if the mass contours suggest two or more fused lymph nodes).

In patients deemed to be clinically node negative (cN0), sentinel lymph node biopsy has been proven as non-inferior to axillary dissection.[2] Accordingly, sentinel lymph node biopsy is currently the preferred surgical procedure for axillary staging.[9] Based on the results of the IBCSG 23-01 prospective randomised clinical trial in patients with cT1-T2 cN0 breast carcinoma found to have micrometastatic carcinoma (pN1mi; carcinoma >0.2 mm to 2 mm in size), patients with micrometastases in only one or more sentinel lymph nodes do not benefit from axillary lymph node dissection.[3,4] Based on the results of the prospective randomised ACOSOG Z0011 clinical trial, patients with cT1-T2 cN0 carcinoma undergoing lumpectomy and whole breast irradiation do not benefit from axillary lymph node dissection if metastatic carcinoma (including micrometastases and macrometastases) is present in only one or two sentinel lymph nodes.[5,6] Therefore, in patients undergoing sentinel lymph node biopsy, the number of sentinel lymph nodes with metastatic carcinoma needs to be precisely assessed, as it will determine whether complete axillary lymph node dissection is required (if metastatic carcinoma is present in three or more sentinel lymph nodes) or not (no evidence of metastatic carcinoma, or metastases in one or two sentinel lymph nodes).[3-6]

In patients undergoing sentinel lymph node biopsy, usually the sentinel lymph node(s) is/are the lymph node(s) containing carcinoma. If carcinoma is found *only* in non-sentinel lymph nodes the sentinel lymph node is a false negative sentinel lymph node. A possible explanation of this scenario includes complete or nearly complete replacement of the true sentinel lymph node by metastatic carcinoma and consequent reversal or deviation of lymph flow from this node (which results in the true sentinel lymph node not draining the radioactive tracer or dye, and not being identified as “sentinel”). Metastatic carcinoma may be present in non-sentinel lymph nodes despite negative sentinel lymph nodes also due to unusual lymphatic drainage (i.e., secondary to local fibrosis following prior surgery), or if there is failure of the technique used to identify sentinel lymph nodes.

For the purpose of axillary staging, at least one sentinel node is required in patients who did not receive neoadjuvant treatment.

In the setting of neoadjuvant systemic therapy in patients with cT1-T2 cN0 and in patients with cT1-T2 cN1 disease with clinical and imaging resolution of lymph node positivity after completion of neoadjuvant treatment, sentinel lymph node biopsy is performed at the time of definitive surgery. In this context, based on the results of three separate clinical trials,[18-20] evaluation of at least three sentinel lymph nodes identified with dual tracer technique is associated with a false negative sentinel lymph node rate of less than 10%. In patients with biopsy-proven lymph node metastasis documented before neoadjuvant chemotherapy, placement of a marker in the positive lymph node at the time of biopsy followed by surgical removal of the lymph node containing the marker at the time of definitive surgery (targeted axillary surgery) has been found to reduce the false negative rate of sentinel lymph node biopsy after neoadjuvant treatment.[21]

Type of lymph nodes:

Sentinel lymph nodes are identified intraoperatively by the surgeon by uptake of radiotracer or dye or both. The surgeon may also submit as sentinel lymph nodes, adjacent palpable lymph nodes that they deem suspicious intraoperatively. Rarely, intramammary nodes may be sentinel lymph nodes. Specimens which appear to be a single sentinel lymph node in the operating room and are submitted as such may be found by the pathologist to contain more than one node. All identified lymph nodes should be considered as sentinel lymph nodes.

Non-sentinel lymph nodes are any lymph node(s) *not* designated as sentinel lymph node by the surgeon. Non-sentinel lymph nodes include any of the lymph nodes specified below.

- **Lymph nodes adjacent to sentinel lymph nodes.** These lymph nodes may be identified and excised by the surgeon intraoperatively during sentinel lymph node biopsy but not deemed suspicious, as they do not appear enlarged, are not firm by palpation, do not show uptake of a tracer. In terms of lymph node count, non-sentinel lymph nodes should *not* be grouped with "sentinel" lymph nodes. For staging classification such non-sentinel lymph nodes are coded as axillary lymph nodes level I.

- **Intramammary nodes.** Intramammary nodes are lymph nodes present within breast tissue. They are usually found in the upper outer quadrant and/ or axillary tail of the breast. Most intramammary lymph nodes are non-sentinel lymph nodes. Rarely an intramammary lymph node may be identified intraoperatively as a sentinel lymph node. Unless specifically designated by the surgeon as "sentinel", intramammary lymph nodes are coded as axillary lymph nodes level I for staging classification purpose.

- **Axillary lymph nodes.** Axillary lymph nodes are divided into levels:
    - **Level I (low-axilla):** Lymph nodes lateral to the lateral border of the pectoralis minor muscle. (If present, intramammary lymph nodes are coded as level I lymph nodes.)
    - **Level II (mid-axilla):** Lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter) lymph nodes.
    - **Level III (apical axilla):** Apical lymph nodes and lymph nodes medial to the medial margin of the pectoralis minor muscle, excluding lymph nodes inferior to the clavicle.

      In some countries level III lymph nodes are routinely included in an axillary lymph node dissection. Typically, this yields a total of approximately 15 lymph nodes across the three levels (this number is intended as a practical reference, not as an absolute requirement). In other countries, level III lymph nodes are not part of a routine axillary lymph node dissection and they are excised only if they are proven to contain metastatic carcinoma, or they are suspicious for metastatic carcinoma clinically or by imaging studies. Level I and II lymph nodes combined usually consist of at least 10 lymph nodes in total (again this number is intended as a practical reference, not as an absolute requirement). The surgeon usually submits level III lymph nodes separately from level I and II lymph nodes. Specific N staging applies if carcinoma is present in level III lymph nodes

      There is no requirement to report separately the number of level I and II lymph nodes examined and/or the number of lymph nodes with macro/micrometastatic carcinoma in each axillary lymph node level.

- **Other non-sentinel lymph nodes.** These include:
    - **Internal mammary (ipsilateral)** lymph nodes: Lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.
    - **Infraclavicular (subclavicular)** ipsilateral lymph nodes.
    - **Supraclavicular (ipsilateral)** lymph nodes.

      Internal mammary nodes, supraclavicular nodes, and infraclavicular nodes are rarely removed for breast cancer staging. Specific stage categories apply if carcinoma is present in these lymph nodes (see **Note 12 REGIONAL LYMPH NODE CATEGORISATION**).

Any other lymph node metastasis (including metastases to the contralateral axillary lymph nodes) is coded as distant metastasis (M1).

⬆ **Back**

Note 5 – Number of lymph nodes with metastatic carcinoma (Core)

The number of lymph nodes with metastatic carcinoma is used for pN classification.

Back

Note 6 – Number of lymph nodes with micrometastases (Non-core)

The number of micrometastatic lymph nodes is added to the number of macrometastatic lymph nodes, provided that there is at least one lymph node with macrometastasis to derive the pN category.

If no macrometastasis is present, the number of micrometastastic lymph nodes (provided there is at least one) does not alter the pN1mi category, but may still reflect prognostic information.

Back

Note 7 – Lymph nodes contain only isolated tumour cells (Core and Non-core)

Isolated tumour cell clusters (ITCs) are single tumour cells or small clusters of carcinoma spanning less than or equal to 0.2 mm in greatest dimension or adding to less than or equal to 200 cells in a single histological cross section. ITCs can be detected by routine haematoxylin and eosin (H&E) stains or immunohistochemistry (IHC) but should be verified in H&E-stained slides.

If no macro- and/or micrometastatic carcinoma is identified in lymph nodes, the number of lymph nodes containing only ITCs needs to be reported.

Currently ITCs are not classified as metastatic deposits for the purposes of staging. If only ITCs are identified in lymph nodes, the pN classification is pN0(i+).

If macrometastatic or micrometastatic carcinoma is present in lymph nodes, the number of lymph nodes containing ITCs should not be added to the number of lymph nodes with metastatic carcinoma for staging purposes, but should be included in the total number of nodes evaluated, and reporting the number of lymph nodes with *only* ITCs becomes optional. (The American Joint Committee on Cancer (AJCC) Cancer Staging Manual recommends that the number of lymph nodes involved by ITC only should be noted in the report.[10])

In the post neoadjuvant setting, the presence of ITCs (ypN0(i+) category) excludes pCR.

Back

Note 8 – Size of largest metastasis (Core)

The size of the largest focus of metastatic carcinoma does not influence the pN classification provided that the 2 mm inclusive cut-off for micrometastasis distinction from macrometastasis is considered.

Nonetheless, the size of the largest metastasis in a sentinel lymph node reflects the risk of spread to additional lymph nodes akin to the size of the primary tumour reflecting the risk of spreading to lymph nodes or distant sites.[22-26]

Even though the largest metastatic focus is usually identified in a sentinel lymph node, there are cases in which the largest metastasis is found in a non-sentinel lymph node. The size of the largest lymph node metastasis should be reported regardless of the type of lymph node (sentinel or non-sentinel) that contains it.

If sentinel and non-sentinel lymph nodes are excised, one could report separately the size of the largest focus of metastatic carcinoma identified in sentinel lymph nodes and in non-sentinel lymph nodes, but such detailed reporting is not required.

In the post neoadjuvant therapy setting, the size of the largest lymph node metastasis is a variable required to calculate the Residual Cancer Burden.[16]

The measurement of residual carcinoma in the post neoadjuvant therapy setting is a subject of debate and varies in different classification systems. According to the AJCC 8th edition Staging System, only the size of the largest contiguous focus of residual carcinoma present in the lymph nodes is used for lymph node classification.[10] Treatment-induced fibrosis between adjacent foci of residual carcinoma is not included in the size measurement.[10,14,15] In other regions such as the United Kingdom, Ireland, Australasian and South-East Asian countries, the size includes foci of residual viable carcinoma with intervening treatment-induced stromal fibrosis.

Back

Note 9 – Extranodal extension (Core)

Extranodal extension (ENE) may be grossly visible (matted lymph nodes) but is most often a microscopic finding. In studies which looked at the effect of ENE on prognosis and overall nodal burden when ENE was present only in sentinel lymph nodes, ENE was only included as a qualitative variable i.e., present or absent.[24-27] There is no firm evidence to recommend further quantifying ENE at this stage.

Back

Note 10 – Treatment effect (Core)

Treatment effect is defined as areas of scarring, hyalinisation, necrosis, mucoid or myxoid change; 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. Reporting of treatment effect in lymph nodes is *strongly* encouraged, as it constitutes an index of the extent of lymph node involvement before neoadjuvant treatment, and of the tumour response to treatment.

Treatment effect is best reported separately for lymph nodes with residual metastatic carcinoma and for lymph nodes without residual metastatic carcinoma.

Some lymph nodes show residual viable carcinoma admixed with areas of fibrosis, indicating metastasis with evidence of some treatment response. The total number of lymph nodes with residual viable carcinoma should be reported.

Some lymph nodes show only post treatment fibrosis and no residual viable carcinoma. The number of nodes with fibrosis but no residual viable carcinoma should be given as a reflection of pre-treatment nodal burden.

In some cases, it may be difficult to determine with certainty whether a (small) focus of fibrosis is secondary to the resolution of a metastatic deposit or not. For example, post biopsy tissue reaction cannot always be distinguished with certainty from post treatment fibrosis.

In some cases, scattered residual carcinoma cells may resemble histiocytes and collections of histiocytes may also be present in areas of tumour regression. Immunohistochemical stains can be used to resolve uncertain cases, as carcinoma cells usually retain expression of broad-spectrum cytokeratins, whereas macrophages will express CD68.

In patients with biopsy-proven lymph node metastasis documented before neoadjuvant chemotherapy, for which a marker was placed during biopsy, histologic evidence of the marker site in the lymph node should also be documented in the final pathology report.

⬆ **Back**

Note 11 – Ancillary studies (Non-core)

Immunohistochemistry (IHC)

It is important to document the immunohistochemical antibody(s) used for assessment and the result(s) of IHC stains in the report. The routine application of IHC to assess the presence of carcinoma in lymph nodes is not recommended. The pathologist may use IHC to evaluate cells that are suspicious but not diagnostic of carcinoma in routine H&E-stained sections, especially for lymph nodes obtained post neoadjuvant therapies. IHC for broad spectrum cytokeratins (CKs), such as AE1/AE3, as well as other CKs (CK7, pancytokeratin, OSCAR, CK19) are suitable. The pattern of CK reactivity of the primary invasive carcinoma (e.g., CK7-negative but CK20-positive primary mammary carcinoma with apocrine morphology) may guide the choice of the IHC panel most suitable to evaluate suspicious cells in lymph nodes.

Some non-epithelial cells (such as dendritic reticulum cells or lymphoid cells) may show non-specific uptake of CKs. Keratin debris including anucleate keratin squames may also yield staining that is specific for keratin but should not be interpreted as carcinoma cells. Diagnostic interpretation mandates careful correlation of morphologic and IHC findings. In problematic cases, comparison with the morphology and IHC profile of the primary invasive carcinoma is advised, whenever possible.

When the IHC work-up demonstrates axillary lymph node metastases from an extramammary primary site (e.g., müllerian carcinoma, melanoma), this finding needs to be clearly stated in the report and the pN classification for breast carcinoma does not apply.

Although it is standard practice to assess estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor status of the primary invasive carcinoma in the breast, occasionally it might be necessary to assess receptor status of nodal metastatic carcinoma. In such cases, the same guidelines for interpretation and reporting of ER, PR and HER2 status of primary invasive carcinoma should be used.

Molecular techniques

All lymph node macrometastases must be identified histologically. The use of loop-mediated isothermal amplification (LAMP), as a quantitative mRNA amplification technique, is approved as an alternative method only for the evaluation of lymph nodes that are negative by gross examination. This test requires that the entire lymph node tissue (or nearly the entire lymph node tissue) be submitted for LAMP analysis, preventing histologic examination. Consequently, any lymph node suspicious for metastatic carcinoma at gross examination should *not* be submitted for quantitative molecular metastasis analysis.

It is important to specify the results of one-step nucleic acid amplification in the report. One-step nucleic acid amplification is a commercially available LAMP-based assay for the detection of mRNA (*CK19*) associated with breast carcinoma. It is used to deduce the presence of epithelial cells in the lymph node and estimate the volume of disease.[28] The RD-100i OSNA system, a one-step nucleic acid amplification-based test for the detection and quantification of *CK19* mRNA, was formally approved by the United Kingdom's National Institute for Health and Cancer Excellence (NICE) in August 2013.[29] Analysis of the whole lymph node using the RD-100i OSNA system may be used for detecting sentinel lymph node metastases in clinically node-negative patients with early (T1-T2) invasive breast carcinoma who undergo sentinel lymph node biopsy and are candidates for axillary lymph node dissection. Histologic examination has high specificity but may miss minute deposits of carcinoma, while the one-step nucleic acid amplification assay eliminates tissue sampling bias as the whole node is analysed. The one-step nucleic acid amplification assay has a rapid turnaround time and is less resource intensive than histology. When compared to alternate slice histology, the RD-100i OSNA has a 96% agreement. Quantification of *CK19* mRNA using one-step nucleic acid amplification correlates with the extent of carcinoma in the lymph nodes.

RD-100i one-step nucleic acid amplification is calibrated so that it may ignore ITCs (defined as *CK19* mRNA copy numbers between 100 and 250/microlitre (μL)) but can detect micrometastases (translated to *CK19* mRNA copy numbers between 250 and 5000/μL) and it may also detect macrometastases (interpreted as such if *CK19* mRNA copy numbers exceed 5000/μL). As the copy numbers are proportional to the number of cells expressing CK19 and therefore to the volume of nodal involvement, greater copy numbers reflect greater volume, and although these are not measurable in metric units due to the non-microscopic nature of the assay, results are extrapolated as micrometastases or macrometastases. Therefore, the coding of such results as pN0(mol+) (the category defined in the UICC TNM Classification of malignant tumours[12]) would be inaccurate; pN1mi(mol+) and pN1(mol+), although not defined in the UICC TNM Classification, would be the most appropriate labels for such types of nodal involvement as they refer both to the extrapolated size and the non-microscopic detection. One-step nucleic acid amplification finds application in some countries (such as Spain, France, Italy, Japan and Australia) especially in settings when rapid intraoperative assessment of lymph node status is required to expedite patient care.

False positive and false negative results may occur with quantitative molecular tests. In rare cases, a positive result may be "false positive", biologically speaking, because it is secondary to the presence of benign mammary epithelium in a lymph node, due to displacement during prior procedure(s), ectopic intranodal benign mammary glands or skin adnexa, or endosalpingiosis/benign müllerian inclusions within the lymph nodes. Rarely, secondary involvement of an axillary lymph node by a CK19-positive carcinoma that is primary at an extramammary site might also possibly yield a false-positive result. At present, the clinical significance and management implications of a positive quantitative molecular result in the setting of a histologically negative lymph node are unknown.

⬆ **Back**

Note 12 – Regional lymph node categorisation (Core)

In the UICC TNM Staging System,[12] breast cancer staging can be done for primary untreated disease, breast cancer treated with primary systemic therapies or in the recurrent setting. To distinguish between these, the symbols of categorisation are added before the nodal category. For uniform use, the order of these categories is advised to be y – r – p or c (if none of these latter two are given, this is synonymous with c). For example: post neoadjuvant therapy (y) with histopathologic examination (p) of the lymph nodes (N) (and the primary tumour was removed) = ypN…; T2 = cT2.

The UICC TNM 8th edition does not include a provision for lymph node staging using quantitative molecular techniques, such as one-step nucleic acid amplification.[12] The quantity of protein (CK19) specific messenger RNA (mRNA) disclosed by LAMP based methods is proportional to the number of non-lymphoid cells expressing this protein, and therefore with the volume of the metastasis in the lymph node. Although the acknowledged use of these techniques is in the intraoperative assessment of grossly negative lymph nodes, it may happen that the test results are reflecting metastases in the micrometastatic or the macrometastatic range. This scenario cannot be perfectly reflected with the categories defined by the UICC TNM Classification.[12] The only categories mentioned in the classification are pN0(mol+), corresponding to low volume involvement of the isolated tumour cell range disclosed by molecular methods, and pN0(mol-), to reflect a node-negative status after molecular testing of the lymph node(s). Quantitative molecular nodal staging methods clearly have the potential to disclose larger volume metastatic involvement that would impact differently on staging. One-step nucleic acid amplification uses 250 and 5000 copies of *CK19* mRNA/µL as lower and upper cut-offs for nodal involvement in the micrometastatic range, and therefore anything with >5000 copies would be consistent with macrometastatic involvement. This type of nodal positivity cannot be perfectly reflected by the UICC TNM Classification[12] defined pathological nodal categories. pN0(mol+) is clearly inadequate, as these results are reflecting a node-positive status. Categories like pN1mi or pN1a are more suitable with a note that these are not size defined but mRNA copy number based staging categories. However, categories like pN1mi(mol+) or pN1a(mol+) are the optimal reflection of such a staging situation and should be reported if possible.[30] Owing to the restrictive usage of molecular staging methods in the intraoperative examination of grossly negative lymph nodes, other pN categories than pN1mi and pN1a are very unlikely to require the (mol+) qualifier.

Back

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