Reporting of Surgically Removed Lymph Nodes for Breast Tumors

Recommendations From the International Collaboration on Cancer Reporting

Gábor Cserni, MD, PhD, DSc; Edi Brogi, MD, PhD; Hiram S. Cody III, MD; Rahul Deb, MD, FEBP, FRCPath; Gelareh Farshid, MBBS, MD, MPh, FRCPA; Sandra O'Toole, MB BS (HONS), BSC MED (HONS), PHD, FRCPA; Elena Provenzano, MB BS, PhD; Cecily M. Quinn, MB (HONS), MD, FRCPI, FRCPath; Aysegul A. Sahin, MD; Fernando Schmitt, MD, PhD; Donald L. Weaver, MD; Rin Yamaguchi, MD, PhD; Fleur Webster, MSc, MPH; Puay Hoon Tan, MBBS, FRCPA

Accepted for publication April 11, 2022.

From the Department of Pathology, Albert Szent-Györgyi Medical Center, University of Szeged, Szeged, Hungary (Cserni); the Department of Pathology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary (Cserni); the Department of Pathology (Brogi) and The Breast Service, Department of Surgery (Cody III), Memorial Sloan Kettering Cancer Center, New York, New York; the Department of Pathology, Royal Derby Hospital, University Hospitals of Derby and Burton, Derby, United Kingdom (Deb); the Department of Anatomical Pathology, SA Pathology, Royal Adelaide Hospital, Adelaide, South Australia, Australia (Farshid); School of Medicine, Adelaide University, Adelaide, South Australia, Australia (Farshid); the Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia (O'Toole); Sydney Medical School, University New South Wales, Sydney, New South Wales, Australia (O'Toole); Cambridge Experimental Cancer Medicine Centre (ECMR), NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom (Provenzano); the Department of Histopathology, Addenbrookes Hospital, Cambridge, United Kingdom (Provenzano); the Department of Histopathology, BreastCheck, Irish National Breast Screening Programme & St. Vincent's University Hospital, Dublin, Ireland (Quinn); University College Dublin, School of Medicine, Dublin, Ireland (Quinn); Division of Pathology and Laboratory Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas (Sahin); the Department of Pathology, Medical Faculty of Porto University, and Molecular Unit, Institute of Pathology and Immunology of Porto University, Porto, Portugal (Schmitt); RISE (Health Research Network) @ CINTESIS (Center for Health Technology and Services Research), Porto, Portugal (Schmitt); the Department of Pathology, University of Vermont Larner College of Medicine, Burlington (Weaver); the Department of Pathology and Laboratory Medicine, Kurume University Medical Center, Fukuoka, Japan (Yamaguchi); International Collaboration on Cancer Reporting, Sydney, NSW, Australia, and ICCR Project Manager, Surry Hills, Australia (Webster); and the Division of Pathology, Singapore General Hospital, Academia, Singapore (Tan).

The authors have no relevant financial interest in the products or companies described in this article.

Brogi and Cody III were supported in part by a Cancer Center Support Grant of the National Institutes of Health/National Cancer Institute (grant No. P30CA008748). We acknowledge the support of the International Society of Breast Pathology (ISBP) and Singapore General Hospital (SGH) - Breast Pathology Course toward the production of this data set.

Corresponding author: Gábor Cserni, MD, PhD, DSc, Bács-Kiskun County Teaching Hospital, Department of Pathology, Nyíri út 38, Kecskemét, n.a. H6000, Hungary (email: cserni@freemail.hu).

• ***Context.***—**The International Collaboration on Cancer Reporting (ICCR), supported by major pathology and cancer organizations, aims at the standardization of evidence-based pathology reporting of different types of cancers, with the inclusion of all parameters deemed to be relevant for best patient care and future data collection. Lymph node metastasis is one of the most important prognostic factors in breast cancer.**

Objective.—**To produce a histopathology reporting guide by a panel of recognized experts from the fields of pathology and surgery with elements deemed to be core (required) and noncore (recommended) to report when assessing regional lymph nodes of patients with breast cancer.**

Data Sources.—**Published literature, previous guidelines/recommendations, and current cancer staging principles were the basis of the data set drafted by the expert panel. This was discussed in a series of teleconferences and email communications. The draft data set was then made available for public consultation through the ICCR Web site. After this consultation and ICCR ratification, the data set was finalized.**

Conclusions.—**The ICCR has published a data set for the reporting of surgically removed lymph nodes (including sentinel lymph node biopsy, axillary lymph node dissection, targeted axillary surgery, and lymph node sampling specimens) for breast tumors. This is part of a series of 4 ICCR breast cancer–related data sets. It includes 10 core elements along with 2 noncore elements. This should allow for synoptic reporting, which is more precise, uniform, and complete than nonsynoptic reporting, and leads to improved patient outcomes.**

(*Arch Pathol Lab Med.* 2022;146:1308–1318; doi: 10.5858/arpa.2022-0060-RA)

The International Collaboration on Cancer Reporting (ICCR) stems from an unprecedented effort to provide standards for evidence-based reporting of the pathologic diagnosis of different types of cancers, including all parameters deemed to be relevant for best patient care and future data collection. The ICCR is supported by a global network of major pathology and cancer organizations, including the College of American Pathologists; the

European Society of Pathology; the Royal College of Pathologists of Australasia; the Royal College of Pathologists, United Kingdom; the International Agency for Research on Cancer/World Health Organization; and many others.[1,2]

The ICCR guidelines on breast cancer are organized in 4 separate data sets focused on reporting of (1) in situ carcinomas, (2) invasive carcinomas, (3) carcinoma in the postneoadjuvant setting, and (4) lymph nodes in patients with breast cancer. All data sets were initially drafted by an appointed international expert panel. Following multiple discussions, the final draft of each data set was posted publicly for an open period during which international and national organizations and medical personnel involved in the care of patients with breast cancer were invited to comment and contribute suggestions, which were then incorporated and addressed in the final data sets. Periodic revisions of the data sets are also planned to allow their maintenance and adaptation of new developments.

The data sets include core and noncore elements. All core elements of a data set need to be reported for accurate lymph node staging. Reporting of the noncore elements is not required for staging, but it is recommended for optimal data collection. Core elements will either have evidentiary support at level III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence). In rare circumstances, where level III-2 evidence is not available, an element may be designated as a core element when there is unanimous agreement in the expert committee. An appropriate staging system, for example, pathologic TNM staging, would normally be included as a core element. The summation of all core elements is considered to be the minimum reporting standard for a specific cancer.[3] Noncore elements are those which, by unanimous agreement, should be included in the data set 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, which is fundamental to the histologic diagnosis and conclusion, for example, macroscopic tumor details, may be included as either core or noncore elements according to the consensus of the Dataset Authoring Committee.

The data set for Surgically Removed Lymph Nodes for Breast Tumors (developed with support from the International Society of Breast Pathology and the Singapore General Hospital, Breast Pathology Course) was published online in May 2021.[4] This article provides an overview of the data set and its background.

Lymph node status is one of the most important prognostic factors of breast cancer,[5] but the interpretation and reporting of nodal involvement can differ significantly. For example, the protocols used for sentinel lymph node evaluation vary greatly in different countries (as reflected in the guidelines set forth by various national societies) and even between pathology departments in the same country (as reflected by differences in individual practices).[5] In this context, establishing uniformity in reporting and data collection of the lymph node status of breast cancer is imperative.

Although, in some cases, lymph node status can be assessed preoperatively, this data set is limited to surgically removed ipsilateral lymph nodes in patients with invasive breast carcinoma, including sentinel lymph node biopsy, axillary lymph node dissection, targeted axillary surgery, and lymph node sampling specimens. The reporting of invasive breast carcinoma and in situ disease (ductal carcinoma in situ, pleomorphic and florid lobular carcinoma in situ, encapsulated papillary carcinoma, and solid papillary carcinoma in situ) is dealt with in separate ICCR data sets, which may be used as appropriate, in conjunction with the lymph node data set.

The ICCR generally follows the Union for International Cancer Control (UICC) recommendations for staging. One thoroughly discussed exception from this rule occurs in this data set, and relates to the N classification of larger-volume metastatic involvement detected by molecular methods without the possibility of histologic size measurement.

The ICCR lymph node reporting data set has an introductory General Information section summarizing rules and parameters relevant to lymph node staging in patients with invasive breast carcinoma. For clarity and completeness, the General Information section is reproduced herein.

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 randomized trials have proven that (1) sentinel node biopsy is not inferior to axillary lymph node dissection; (2) patients with cT1-T2 cN0 breast cancer and micrometastases or even macrometastases in 1 or 2 sentinel lymph nodes do not do 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.[6–12] Accordingly, at present sentinel lymph node biopsy is the preferred surgical procedure for axillary staging.[13]

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.

Carcinoma in lymph nodes is quantified according to its largest size as macrometastatic, micrometastatic, or consisting of isolated tumor cells (ITCs) (Figure 1).[14–18] Invasive lobular carcinomas typically metastasize with single cells spanning a given area of the lymph nodes with or without desmoplastic stromal reaction, and counting tumor 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.[14–17]

Pathologic classification of lymph node status (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic 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 (eg, cN1 or cN1[sn]).[14,17]

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 UICC 8th edition staging

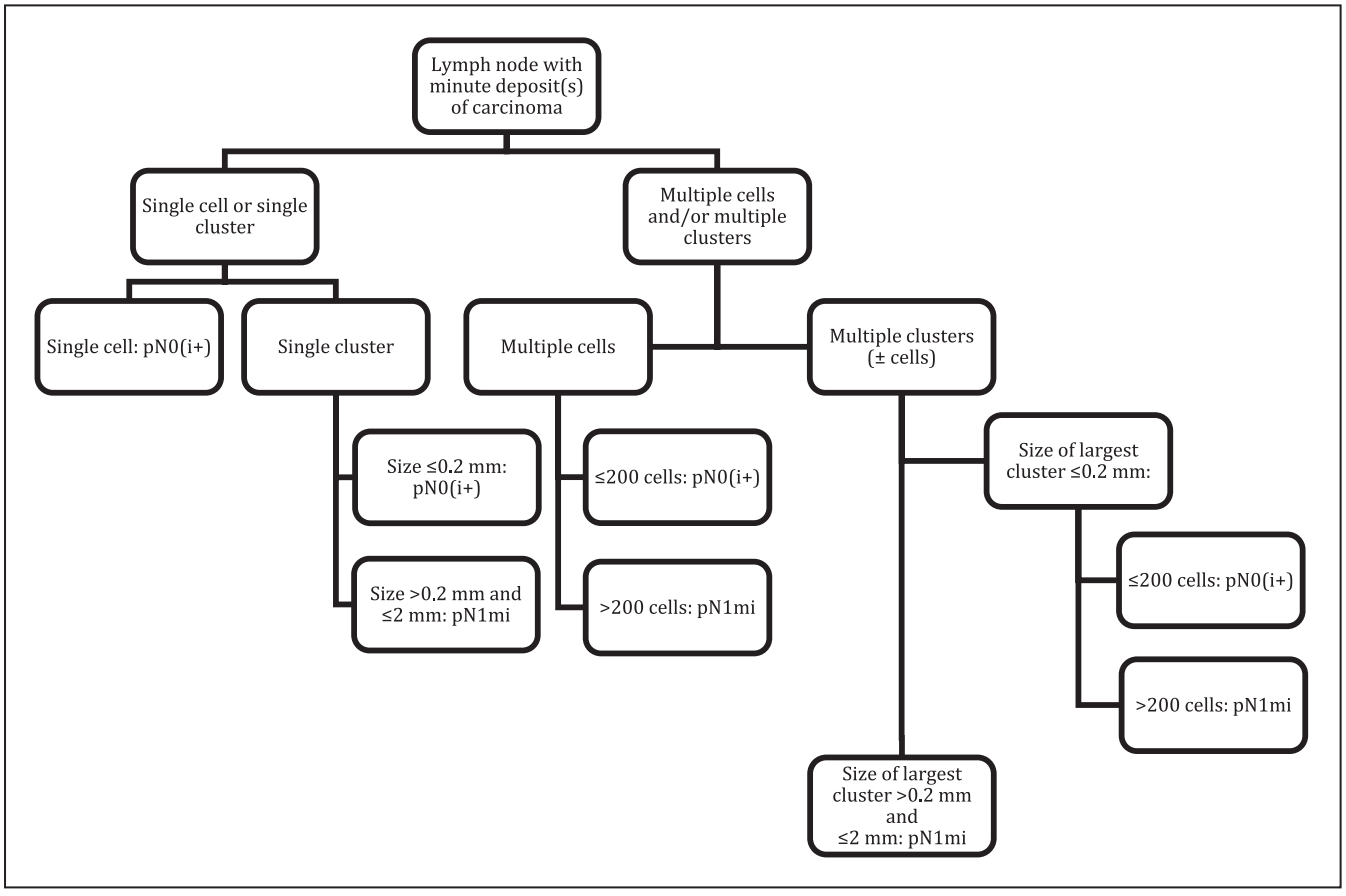

Figure 1. *Flow chart outlining the steps involved in deciding whether minute tumor deposits of carcinoma in a lymph node constitute a micrometastasis (pN1) or isolated tumor cells (pN0). Modified from Cserni et al.*[18] *Distinction of isolated tumour cells and micrometastasis in lymph nodes of breast cancer patients according to the new Tumour Node Metastasis (TNM) definitions.* Eur J Cancer. *2011;47(6):887-894, with permission from Elsevier.*

system suggests that at least 6 axillary lymph nodes be examined to assess pN status (equivalent of axillary level I lymph nodes).[17] To avoid confusion, this recommendation reflects the reliability of staging when lymph nodes are not removed on the basis of their qualitative features (eg, taking up tracers during lymphatic mapping), that is, this guideline does not apply if sentinel lymph node biopsy is performed. If, for any reason, at least 1 but less than 6 lymph nodes are examined (ie, the 6-node requirement is not met), the pN category should still be determined, and the pNX category should not be used.

Sentinel Lymph Node Biopsy

Classification of lymph node status based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," (eg, 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 6 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 1 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-mm-thick slices. If more than 1 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 (CK) immunohistochemical stains to evaluate lymph nodes with no evidence of carcinoma in hematoxylin-eosin (H&E)–stained sections is not routinely undertaken, a practice which is supported by the evidence from the NSABP-B32 and ACOSOG Z0010 studies.[19,20] Immunohistochemical staining for CKs can be used to evaluate uncertain findings in H&E-stained sections.

Evaluation and Reporting of Lymph Nodes Obtained Post Neoadjuvant Treatment

Neoadjuvant systemic therapy is administered before definitive surgery, often with the intent to reduce tumor 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 (ie, 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-naive lymph nodes. In the postneoadjuvant setting, the guidelines for measuring the size of residual carcinoma in the lymph node(s) vary depending on the practices endorsed by different societies.[21]

According to the College of American Pathologists' guideline,[22] "the largest contiguous focus of residual tumor in the lymph nodes, if present, is used to determine ypN category. Treatment-related fibrosis adjacent to residual nodal deposits or between foci of residual metastatic disease is not included in determining ypN dimension."[14,15,22]

In other parts of the world, including the United Kingdom, Ireland, and Australasian and Southeast 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,[21] "The size of the largest metastatic deposit should be measured microscopically. Post-neoadjuvant systemic therapy, tumor 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 tumor should be measured, and not just the size of the largest tumor 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.[23]

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

At present, the use of CK 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 CKs may be used to evaluate uncertain findings in H&E-stained sections.

Postneoadjuvant 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-naive patients. Posttreatment "ypN" should be evaluated as for clinical (pretreatment) "N" methods. ypN categories are the same as those used for pN, but the clinical significance differs.

For patients after neoadjuvant systemic treatment, the modifier "sn" is used if only a sentinel lymph node evaluation was performed after neoadjuvant treatment (eg, ypN0[sn]). 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 posttreatment sentinel lymph node biopsy or axillary dissection was performed. In this situation, the clinical N status is used for overall stage determination (eg, ycN0 or ycN1).

Treatment effect is defined as areas of scarring, hyalinization, necrosis, mucoid or myxoid change, a collection of foamy histiocytes in the lymph node (akin to tumor 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 tumor 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 2 summarizes the core and Figures 3 and 4 the noncore elements of the Surgically Removed Lymph Nodes for Breast Tumors data set.

REQUIRED (CORE) ELEMENTS OF THE DATA SET

Clinical Information

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 workup, 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 sampling or treatment is essential for the adequate reporting and classification of the lymph node status.

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 noncore.

Operative Procedure

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 (eg, United States, Canada, Singapore, most countries in continental Europe) an axillary lymph node dissection does not routinely include level III lymph nodes.

Specimen Laterality

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 data set. Bilateral breast cancer is considered 2 diseases and requires 2 separate data sets, 1 for each side.

Number of Lymph Nodes Examined

The total number of lymph nodes examined is the sum of the number of all sentinel lymph nodes and the number of all nonsentinel lymph nodes examined. The "sn" modifier is used when the number of sentinel and nonsentinel level I/II nodes combined is fewer than 6 nodes (provided there is at least 1 sentinel node included in the specimen). Intramam-

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)[e]	Total lymph nodes with ITCs when ONLY ITC involvement is present[e,f]	pN status[g] ([17]UICC TNM8)	Extranodal extension (ENE)[h]
SLNs[a]								
Non-SLNs[a]								
Total lymph nodes[b]								

Figure 2. *Regional LN status—core elements. Although all core elements need to be reported for accurate staging of LN 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 noncore elements summarized in Figures 3 and 4.* [a]*Core elements only if SLN biopsy was performed; if no SLN biopsy was performed, report only total number of 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 LN dissection has been performed without an 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 noncore information summarized in Figure 4. Possible entries include the following: Information not provided/No neoadjuvant treatment given/Residual disease not identified/Residual disease present.* [d]*If the size cannot be measured (eg, 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 not be 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 lysate; micrometastasis: one-step nucleic acid amplification assay result with CK19 mRNA copy number between 250 and 5000/μL lysate).* [e]*ITCs are tumor deposits spanning up to 0.2 mm, with up to 200 cells in a single LN profile. LNs with ITCs are not counted as metastatic LNs.* [f]*This is a core element only if macrometastatic or micrometastatic carcinoma is not present in any LNs. If metastatic (macrometastatic or micrometastatic) carcinoma is identified in LNs, the number of LNs with only ITCs is a noncore element.* [g]*If SLN biopsy was performed the minimum number of LNs required for staging purposes is 1 (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).* [h]*For ENE, possible entries include the following: Not identified/Present/Cannot be determined. Abbreviations: CK, cytokeratin; ENE, extranodal extension; ITCs, isolated tumor cells; LNs, lymph nodes; SLNs, sentinel lymph nodes; UICC, Union for International Cancer Control.*

mary 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 favoring the lower categories in case of uncertainty; that is, the number of lymph nodes examined and found to have metastatic disease in such a conglomerate may be 1 (if the mass does not show any distinct suggestion for more than 1 lymph node) or more (if the mass contours suggest 2 or more fused lymph nodes).

In patients deemed to be clinically node negative (cN0), sentinel lymph node biopsy has been proved noninferior to

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					

Figure 3. *Regional LN status—noncore elements.* [a]*ITCs are tumor deposits spanning up to 0.2 mm, with up to 200 cells in a single LN profile. LNs with ITCs are not counted as metastatic LNs.* [b]*This is a core element only if macrometastatic or micrometastatic carcinoma is not present in any LNs. If metastatic (macrometastatic or micrometastatic) carcinoma is identified in LNs, the number of LNs with only ITCs is a noncore element.* [c]*The elements summarized in this figure are noncore elements (optional reporting). However, if immunohistochemical evaluation or one-step nucleic acid amplification was performed and the results are used for LN staging purposes, the information pertaining to immunohistochemistry or one-step nucleic acid amplification needs to be reported. Abbreviations: ITCs, isolated tumor cells; LN, lymph node; SLNs, sentinel lymph nodes.*

Tumor 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			

Figure 4. *Regional lymph node status post neoadjuvant treatment—noncore elements.*

axillary dissection.[6] Accordingly, sentinel lymph node biopsy is currently the preferred surgical procedure for axillary staging.[13] Based on the results of the IBCSG 23-01 prospective randomized 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 1 or more sentinel lymph nodes do not benefit from axillary lymph node dissection.[7,8] Based on the results of the prospective randomized ACOSOG Z0011 clinical trial, patients with cT1-T2 cN0 carcinoma who undergo lumpectomy and whole breast irradiation do not benefit from axillary lymph node dissection if metastatic carcinoma (including micrometastases and macrometastases) is present in only 1 or 2 sentinel lymph nodes.[9,10] 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 3 or more sentinel lymph nodes) or not (no evidence of metastatic carcinoma, or metastases in 1 or 2 sentinel lymph nodes).[7–10]

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 nonsentinel 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 nonsentinel lymph nodes despite negative sentinel lymph nodes, also owing to unusual lymphatic drainage (ie, secondary to local fibrosis following prior surgery), or if there is failure of the technique used to identify sentinel lymph nodes.

For axillary staging purposes, at least 1 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 3 separate clinical trials,[24–26] evaluation of at least 3 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.[27]

Type of Lymph Nodes

Lymph nodes are generally classified as sentinel or nonsentinel.

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 that 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 1 node. All identified lymph nodes should be considered as sentinel lymph nodes.

Nonsentinel lymph nodes are any lymph node(s) not designated as a sentinel lymph node by the surgeon. Nonsentinel 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, and do not show uptake of a tracer. In terms of lymph node count, nonsentinel lymph nodes should not be grouped with "sentinel" lymph nodes. For staging classification such nonsentinel 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 nonsentinel 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) includes lymph nodes lateral to the lateral border of the pectoralis minor muscle and intramammary lymph nodes, if present. Level II (mid-axilla) includes lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter) lymph nodes, whereas level III (apical axilla) includes 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 3 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 suggestive of 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 macrometastatic/micrometastatic carcinoma in each axillary lymph node level.

Other Nonsentinel 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; and 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.

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

Number of Lymph Nodes With Metastatic Carcinoma

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

Lymph Nodes Contain Only ITCs

ITCs are single tumor cells or small clusters of carcinoma spanning up to 0.2 mm in greatest dimension or adding to at most 200 cells in a single histologic cross section (Figure 1). There are 2 limits for defining ITC: cluster size of 0.2 mm or less, and presence of up to 200 cells (in a single cut surface); the latter is mainly but not exclusively for lobular carcinoma involvement. There are cases where the 2 limits are dichotomous, one being in favor of ITC, and the other in favor of micrometastasis. The algorithm in Figure 1 makes a hierarchy—that is, cell count does not matter if the largest cluster size is greater than 0.2 mm; this is micrometastasis even if 200 cells or fewer are present. Cell counts may make a difference only for smaller largest clusters. ITCs can be detected by routine H&E stains or immunohistochemistry (IHC) but should be verified in H&E-stained slides.

If no macrometastatic and/or micrometastatic carcinoma is identified in lymph nodes, the number of lymph nodes containing only ITCs becomes a core element and 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+). The (i+) qualifier refers to the presence of ITCs, whereas in the pN0(i–) category, the (i–) refers to the use of IHC (for CKs, for example) and the lack of any positive findings with this method.

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 *AJCC Cancer Staging Manual* recommends that the number of lymph nodes involved by ITC only should be noted in the report).[14,15]

In the postneoadjuvant setting, the presence of ITCs (ypN0[i+] category) excludes pathologic complete response (pCR). These also contribute to the "total number of positive nodes" in the MD Anderson Residual Cancer Burden calculator.[23]

Size of Largest Metastasis

The size of the largest focus of metastatic carcinoma does not influence the pN classification provided that the 2-mm inclusive cutoff 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 tumor reflecting the risk of spreading to lymph nodes or distant sites.[28–32]

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 nonsentinel lymph node. The size of the largest lymph node metastasis should be reported regardless of the type of lymph node (sentinel or nonsentinel) that contains it.

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

In the postneoadjuvant therapy setting, the size of the largest lymph node metastasis is a variable required to calculate the Residual Cancer Burden.[23]

The measurement of residual carcinoma in the postneoadjuvant 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.[14,15] Treatment-induced fibrosis between adjacent foci of residual carcinoma is not included in the size measurement.[22] In other countries such as the United Kingdom, Ireland, Japan, and Australasian and Southeast Asian countries, the size includes foci of residual viable carcinoma with intervening treatment-induced stromal fibrosis.

Extranodal Extension

Extranodal extension (ENE) may be grossly visible (matted lymph nodes) but is most often a microscopic finding. In studies that 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, that is, present or absent.[30–33] There is no firm evidence to recommend further quantifying ENE at this stage.

Treatment Effect

Treatment effect is defined as areas of scarring, hyalinization, necrosis, mucoid or myxoid change; collection of foamy histiocytes in the lymph node (akin to tumor 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 tumor 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 posttreatment fibrosis and no residual viable carcinoma. The number of nodes with fibrosis but no residual viable carcinoma should be given as a reflection of pretreatment 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. For example, post biopsy tissue reaction cannot always be distinguished with certainty from posttreatment fibrosis.

In some cases, scattered residual carcinoma cells may resemble histiocytes, and collections of histiocytes may also be present in areas of tumor regression. Immunohistochemical stains can be used to resolve uncertain cases, as carcinoma cells usually retain expression of broad-spectrum CKs, 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.

Regional Lymph Node Categorization

In the UICC TNM staging system,[16] breast cancer staging can be done for primary untreated disease, breast cancer treated with primary systemic therapies, or in the recurrence setting. To distinguish between these, the symbols of categorization 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 2 are given, this is synonymous with c). For example: postneoadjuvant therapy (y) with histopathologic examination (p) of the lymph nodes (N) (and the primary tumor was removed) = ypN…; T2 = cT2.

The UICC TNM classification 8th edition does not include a provision for lymph node staging using quantitative molecular techniques, such as one-step nucleic acid amplification.[16] The quantity of protein (CK19)–specific mRNA disclosed by loop-mediated isothermal amplification (LAMP)–based methods is proportional to the number of nonlymphoid 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.[16] The only categories mentioned in the classification are pN0(mol+), corresponding to low-volume involvement of the isolated tumor 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 cutoffs for nodal involvement in the micrometastatic range, and therefore anything with more than 5000 copies would be consistent with macrometastatic involvement. This type of nodal positivity cannot be perfectly reflected by the UICC TNM classification–defined pathologic nodal categories[16]; 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.[34] Owing to the restrictive usage of molecular staging methods in the intraoperative examination of grossly negative lymph nodes, pN categories other than pN1mi and pN1a are very unlikely to require the (mol+) qualifier.

Accordingly, the TNM nodal categories were complemented as follows:

- 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 (not included in UICC TNM classification 8th edition)
- N1a: Metastasis in 1 to 3 axillary lymph node(s), including at least 1 larger than 2 mm in greatest dimension
- N1a(mol+): Using molecular methods (not included in UICC TNM classification 8th edition)

OPTIONAL (NONCORE) ELEMENTS OF THE DATA SET

As mentioned previously, some of the core elements are conditionally core or noncore; for example, clinical information becomes a noncore element if surgically removed lymph nodes are submitted along with the breast tumor specimen, where the clinical information has already been given.

Number of Lymph Nodes With Micrometastases

The number of micrometastatic lymph nodes is added to the number of macrometastatic lymph nodes provided that there is at least 1 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 1) does not alter the pN1mi category, but may still reflect prognostic information.

Ancillary Studies

Immunohistochemistry.—It is important to document the immunohistochemical antibody(ies) 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.[19,20] The pathologist may use IHC to evaluate cells that are suggestive of but not diagnostic of carcinoma in routine H&E-stained sections, especially for lymph nodes obtained post neoadjuvant therapies. IHC for broad-spectrum 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 (eg, 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 nonepithelial cells (such as dendritic reticulum cells or lymphoid cells) may show nonspecific 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 workup demonstrates axillary lymph node metastases from an extramammary primary site (eg, 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 human epidermal growth factor receptor-2 (HER2) 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 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 suggestive of 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.[35] 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 in August 2013.[36] Analysis of the whole lymph node, using the RD-100i OSNA system, may be used for detecting sentinel lymph node metastases in patients with clinically node-negative disease 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 analyzed. 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/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 owing to the nonmicroscopic 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 Tumors)[16] 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 nonmicroscopic 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, owing 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.

DISCUSSION

Axillary lymph node surgery has radically changed during the past 2½ decades. Although the metastatic status of regional lymph nodes is still a very important prognostic factor of breast cancer, considerable de-escalation has occurred in the surgical approach to staging. Its theoretical background in early breast cancer has moved from a Halstedian therapeutic intervention to a Fisherian staging procedure aiming to obtain maximum information with minimum morbidity.[37] With the advent of lymphatic mapping and recognition of the functional hierarchical arrangement of the lymph nodes in the regional basin, sentinel lymph node biopsy has allowed the selective removal of the most likely sites of nodal metastasis, allowing for the sparing of the axilla from further surgery if the sentinel nodes are free of metastasis[6] or have limited nodal involvement in the form of micrometastasis.[7,8] In many countries, axillary sparing also extends to patients with macrometastasis in not more than 2 lymph nodes,[9,10] whereas in some countries the presence of macrometastatic lymph node involvement prompts further axillary treatment (radiotherapy or surgery) based on multidisciplinary team discussion. The de-escalation of lymph node surgery has facilitated more thorough and detailed sampling of sentinel lymph nodes and the introduction of more sensitive methods of nodal metastasis detection such as IHC or molecular methods.[38,39] This has resulted in a considerable

variety of different protocols for the examination of sentinel lymph nodes.[5,40,41] Although this data set cannot make the assessment of lymph nodes, especially sentinel lymph nodes, uniform—a topic which is discussed in other publications[13,42]—it aims to promote and achieve uniformity in reporting of the microscopic lymph node findings.

Many reporting guidelines at the national or international level have been formulated. The ICCR data set has amalgamated and updated some of these as required. In the present form, it provides a good framework for the reporting of lymph node findings irrespective of the evaluation methods used. The template allows for synoptic reporting, which is more precise, uniform, and complete than nonsynoptic reporting. This is to be used in conjunction with the data sets for in situ breast carcinomas (including some low-grade lesions, ie, encapsulated papillary carcinoma and solid papillary carcinoma),[43] for invasive breast carcinoma,[44] and for the postneoadjuvant setting.[45]

References

1. International Collaboration on Cancer Reporting. www.iccr-cancer.org. Accessed March 12, 2022.

2. Srigley JR, Judge M, Helliwell T, Birdsong GG, Ellis DW. The International Collaboration on Cancer Reporting (ICCR): a decade of progress towards global pathology standardisation and data interoperability. *Histopathology*. 2021;79:897–901.

3. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol*. 2009;9:34. doi:10.1186/1471-2288-9-34

4. Cserni G, Brogi E, Cody HS III, et al. *Surgically Removed Lymph Nodes for Breast Tumours Histopathology Reporting Guide*. Sydney, Australia: International Collaboration on Cancer Reporting; 2021.

5. Cserni G, Maguire A, Bianchi S, Ryska A, Kovács A. Sentinel lymph node assessment in breast cancer-an update on current recommendations. *Virchows Arch*. 2022;480(1):95–107.

6. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927–933.

7. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14(4):297–305.

8. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(10):1385–1393.

9. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305(6):569–575.

10. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA*. 2017;318(10):918–926.

11. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303–1310.

12. Sávolt Á, Péley G, Polgár C, et al. Eight-year follow up result of the OTOASOR trial: the Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol*. 2017;43(4):672–679.

13. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32(13):1365–1383.

14. Amin MB, Edge S, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

15. American Joint Committee on Cancer. Updated breast chapter for 8th edition of *AJCC Cancer Staging Manual*. https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%20Breast%20Cancer%20Staging%20System.pdf. Accessed March 31, 2021.

16. Wittekind C, Brierley JD, Lee A, van Eycken E, eds. *TNM Supplement: A Commentary on Uniform Use*. 5th ed. Hoboken, NJ: Wiley; 2019.

17. Brierley JD, Gospodarowicz MK, Wittekind C, eds. *Union for International Cancer Control. TNM Classification of Malignant Tumours*. 8th ed. Hoboken, NJ: Wiley; 2016.

18. Cserni G, Amendoeira I, Bianchi S, 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. *Eur J Cancer*. 2011;47(6):887–894.

19. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011;364(5):412–421.

20. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA*. 2011;306(4):385–393.

21. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol*. 2015;28(9):1185–1201.

22. College of American Pathologists. *Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast, Version 4.4.0.0*. February 2020. https://documents.cap.org/protocols/cp-breast-invasive-resection-20-4400.pdf. Accessed September 22, 2020.

23. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. 2007;25(28):4414–4422.

24. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609–618.

25. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol*. 2015;33(3):258–264.

26. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455–1461.

27. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). *Ann Surg*. 2016;263(4):802–807.

28. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol*. 2003;10(10):1140–1151.

29. van la Parra RF, Ernst MF, Bevilacqua JL, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. *Ann Surg Oncol*. 2009;16(5):1128–1135.

30. van la Parra RF, Peer PG, Ernst MF, Bosscha K. Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN. *Eur J Surg Oncol*. 2011;37(4):290–299.

31. Cserni G. Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN. *Breast Diseases: A Year Book Quarterly*. 2011;22(4):390–391.

32. Cserni G. Sentinel node biopsy and nodal staging. In: Kahan Z, Tot T, eds. *Breast Cancer, A Heterogeneous Disease Entity: The Very Early Stages*. Dordrecht-Heidelberg-London-New York: Springer Science+Business Media; 2011:149–184.

33. Nottegar A, Veronese N, Senthil M, et al. Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: a systematic review and an exploratory meta-analysis. *Eur J Surg Oncol*. 2016;42(7):919–925.

34. Wells CA, Amendoeira I, Bellocq JP, et al. S2: pathology update—quality assurance guidelines for pathology. In: Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L, eds. *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*. 4th ed (supplements). Luxembourg: European Commission, Office for Official Publications of the European Union; 2013.

35. Cserni G. Intraoperative analysis of sentinel lymph nodes in breast cancer by one-step nucleic acid amplification. *J Clin Pathol*. 2012;65(3):193–199.

36. National Institute for Health and Care Excellence. Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer. 2013. https://www.nice.org.uk/guidance/dg8/chapter/1-Recommendations. Accessed June 1, 2020.

37. Halsted CP, Benson JR, Jatoi I. A historical account of breast cancer surgery: beware of local recurrence but be not radical. *Future Oncol*. 2014;10(9):1649–1657.

38. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg*. 1995;222(3):394–401.

39. Cserni G, Amendoeira I, Apostolikas N, et al. Pathological work-up of sentinel lymph nodes in breast cancer: review of current data to be considered for the formulation of guidelines. *Eur J Cancer*. 2003;39(12):1654–1667.

40. Cserni G, Amendoeira I, Apostolikas N, et al. Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer: results of a questionnaire based survey by the European Working Group for Breast Screening Pathology. *J Clin Pathol*. 2004;57(7):695–701.

41. Asirvatham JR, Jorns JM. How do pathologists in academic institutions across the United States and Canada evaluate sentinel lymph nodes in breast cancer: a practice survey. *Am J Clin Pathol*. 2021;156(6):980–988.

42. Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. *Mod Pathol*. 2010;23(suppl 2):S26–S32.

43. Fox S, Chen CJ, Chua B, et al (2021). *Ductal Carcinoma In Situ, Variants of Lobular Carcinoma In Situ and Low Grade Lesions Histopathology Reporting Guide*. Sydney, Australia: International Collaboration on Cancer Reporting; 2021. http://www.iccr-cancer.org/datasets/published-datasets/breast/dcis-variants-of-lcis-and-low-grade-lesions. Accessed January 18, 2022.

44. Ellis I, Allison KH, Dang C, et al. *Invasive Carcinoma of the Breast Histopathology Reporting Guide*. Sydney, Australia: International Collaboration on Cancer Reporting; 2021. http://www.iccr-cancer.org/datasets/published-datasets/breast/invasive-carcinoma-of-the-breast. Accessed January 18, 2022.

45. Bossuyt V, Provenzano E, Symmans WF, et al. *Invasive Carcinoma of the Breast in the Setting of Neoadjuvant Therapy Histopathology Reporting Guide*. Sydney, Australia: International Collaboration on Cancer Reporting; 2022. http://www.iccr-cancer.org/datasets/published-datasets/breast. Forthcoming June/July 2022.