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JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 3.2017 — November 10, 2017

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Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale

Donald L Weaver[1,2,3]

[1]*Department of Pathology, University of Vermont College of Medicine, Burlington, VT, USA;* [2]*Vermont Cancer Center, Burlington, VT, USA and* [3]*Fletcher Allen Health Care, Burlington, VT, USA*

Protocol IOCN

Macroscopie:

Ganglion santinela

<6 lgl

Inspectie pentru macrometastaze

Sectiuni de 2mm

Fiecare sectiune intr-o caseta separata

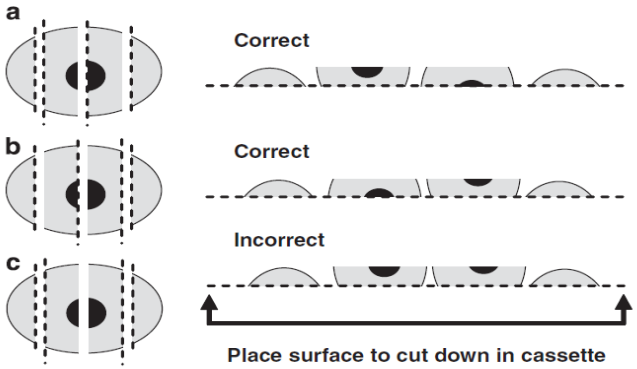

Figure 1 Gross sectioning and embedding of sentinel nodes. The primary objective of the gross management of sentinel nodes is assuring that all macrometastases larger than 2.0 mm are identified microscopically by assuring no slice is thicker than 2.0 mm before embedding in paraffin. When nodes are serially sectioned, special care must be taken to place the sections into the embedding cassette in a manner that eliminates more than 2.0 mm of unexamined tissue. Histology technicians are taught to embed and cut the surface that is placed down in the tissue-processing cassette. Dashed lines represent the surface placed down in the cassette. (**a** and **b**) Central serial sections are placed in the cassette so that nonopposing surfaces are examined microscopically. One of the end sections will be an opposing surface. (**c**) This shows incorrect grossing and embedding preparation. The central serial sections were placed in the cassette so that neither surface containing the micrometastasis was evaluated microscopically.

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Protocol IOCN

Prelucrare preanalitica

prima sectiune

150µm panglica

A doua sectiune

150µm panglica

A treia sectiune

Examinare microscopica

Macrometastaze≥2mm

Micrometastaza0,2 mm-2mm sau ≥200 celule izolate

ITC < 0,2 mm,<200celule

IHC probare metastaze sau HE negativ

Rates of occult metastases deeper in SLN paraffin blocks

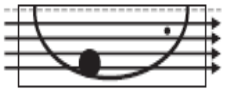
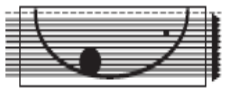
Evaluation Protocol		Micromet (%)	ITC (%)	Total (%)
a		Reference (all initial sections negative)		
b		0.6	3.9	4.5
c		0.6	5.7	6.3
d		1.7	6.3	8.0
e		2.9	8.5	11.4

Figure 3 Performance of various microscopic sectioning protocols for detecting occult micrometastases. (**a–e**) All SLNs were grossly sectioned at close to 2.0 mm thick sections. (**a**) The reference protocol examined one section from the top of the block. All cases with negative initial sections were evaluated with protocol (**e**); protocols (**b–d**) were simulated by examining only specific sections from protocol (**e**). Detection rates for micrometastases >0.2 mm and no larger than 2.0 mm (Micromet) and ITCs no larger than 0.2 mm (ITC) were calculated for each protocol. (**b**) Two additional sections separated by 0.18 mm. (**c**) Two additional sections separated by 0.5 mm. (**d**) Four additional sections separated by 0.5 mm. (**e**) Multiple additional sections separated by 0.18 mm completely through the block (median 11 sections per block). Only protocol (**e**) can reliably detect all micrometastases present but will still miss ITCs. The maximum size of missed metastases is dependent on the thickness of tissue not examined between each section or remaining in the block. Protocols (**c**) and (**d**) are compromise protocols that perform better than protocol (**b**) and do not perform as well as protocol (**e**) but are less expensive and less time consuming than protocol (**e**). (Data adapted from Ref. 12).

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In 2009, we are still debating and trying to understand the clinical significance of micrometastases in breast SLNs. In the context of studies using pre-2003 data, micrometastases include all metastases $\leqslant$2.0 mm in greatest dimension. A recent analysis of population-based data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) national cancer database showed that the presence of micrometastases no larger than 2.0 mm in lymph nodes is associated with an overall decrease in survival at 10 years of 1, 6, and 2% for T1 (no larger than 2.0 cm), T2 (larger than 2.0 cm but no larger than 5.0 cm), and T3 (larger than 5.0 cm) tumors, respectively, compared to patients with no nodal metastases detected.[3] This SEER analysis included years prior and subsequent to the widespread use of SLN biopsy. Thus, for the usual sentinel node patient with a mammographically detected tumor $<$2.0 cm, this study suggests there is little expected detrimental impact associated with the presence of micrometastases. However, the study does suggest that for larger tumors, detection of micrometastases may be more important. As this is a population-based study, we have no idea how the nodes were sampled leaving open the possibility that micrometastases in larger tumors are a marker of aggressive intrinsic biology or a marker of undetected macrometastases deeper in paraffin blocks. In

T1 1%

T2 6%

T3 2%

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Recommendations

Recommendation 1. Clinicians should not recommend axillary lymph node dissection (ALND) for women with early-stage breast cancer who do not have nodal metastases (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong).

Recommendation 2.1. Clinicians should not recommend ALND for women with early-stage breast cancer who have one or two sentinel lymph node metastases and will receive breast-conserving surgery with conventionally fractionated whole-breast radiotherapy (Type: evidence based; benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong).

Recommendation 2.2. Clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found in SNB specimens who will receive mastectomy (Type: evidence based; benefits outweigh harms. Evidence quality: low. Strength of recommendation: weak).

Recommendation 3. Clinicians may offer SNB for women who have operable breast cancer who have the following circumstances:

3.1. Multicentric tumors (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate).

3.2. Ductal carcinoma in situ when mastectomy is performed. (Type: informal consensus; benefits outweigh harms. Evidence quality: insufficient. Strength of recommendation: weak).

3.3. Prior breast and/or axillary surgery (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: strong).

3.4. Preoperative/neoadjuvant systemic therapy (Type: evidence based; benefits outweigh harms. Evidence quality: intermediate. Strength of recommendation: moderate).

Recommendation 4. There are insufficient data to change the 2005 recommendation that clinicians should not perform SNB for women who have early-stage breast cancer and are in the following circumstances:

4.1. Large or locally advanced invasive breast cancers (tumor size T3/T4) (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).

4.2. Inflammatory breast cancer (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).

4.3. Ductal carcinoma in situ when breast-conserving surgery is planned (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong).

4.4. Pregnancy (Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak).

(continued on following page)

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Sampling SLNs

A single hematoxylin-eosin (HE) –stained full-face section from each submitted SLN paraffin block can identify macrometastases and a high proportion of micrometastases (Weaver DL: Mod Pathol 23:S26-S32, 2010; Weaver DL et al: Am J Surg Pathol 33:1583-1589, 2009). Outcomes from large clinical trial cohorts have not shown any benefit from identifying micrometastases or ITCs (Giuliano AE et al: JAMA 306:385-393, 2011).[7,16] Widely spaced step sections from the block (top level plus one or two sections cut at 500-micron intervals into the block) enhance detection of micrometastases and may compensate for SLNs cut thicker than 2.0 mm (Weaver DL et al: Am J Surg Pathol 33:1583-1589, 2009). Superficial serial sections limit sampling to the upper levels of the block. If the SLN has been grossly sectioned as recommended, a single section will detect virtually all macrometastases ($>$ 2.0 mm) and most cases of micrometastases ($>$ 0.2 to 2.0 mm; Turner RR: Semin Breast Dis 5:35-40, 2002; Viale G et al: Cancer 85:2433-2438, 1999; Weaver DL et al: Cancer 88:1099-1107, 2000). This sectioning technique will also detect ITCs and clusters ($\leq$ 0.2 mm) in some patients, particularly if immunohistochemical analysis is used.

Immunohistochemistry

Immunohistochemistry may facilitate scanning of nodal sections and also enhances identification of micrometastases and ITCs. However, detection of micrometastases and ITCs does not predict recurrence or improve survival (Giuliano AE et al: JAMA 306:385-393, 2011).[7,16] Thus, although micrometastases and ITCs have differing prognostic significance, strategies to enhance their detection are not necessary or required. Immunohistochemistry using anticytokeratin antibodies may be useful for confirming or excluding suspicious findings on HE stains.

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Pathology Reporting of SLNs

Pathologists should provide sufficient information in their pathology reports to facilitate accurate cancer staging using the criteria of the current AJCC/UICC system (Edge SB et al: AJCC Cancer Staging Manual [ed 7]. New York, NY, Springer, 2010). This includes documentation of nodal tumor burden. If any nodal metastasis is larger than 2.0 mm, total number of metastatic nodes determines N category. Special rules apply if internal mammary, supraclavicular, or infraclavicular nodes contain tumor. Micrometastases have an upper and lower size limit and are individual tumor deposits larger than 0.2 mm but no larger than 2.0 mm. The lower size limit accommodates the frequency of small tumor deposit identification in SLN. When the largest confluent focus of nodal tumor is no larger than 0.2 mm, deposits are classified as ITC clusters . When more than 200 single cells are identified in a single cross-section of a SLN, a pathologist may classify the node as a micrometastasis. Micrometastases are coded as pN1mi. ITCs or cell clusters are coded as pN0 (i+). Examples of this format follow:

Example 1 (level one and two axillary dissection):

"One of 12 lymph nodes positive for metastatic tumor (1/12; AJCC: pN1a); largest metastasis measures 4.5 mm."

Example 2 (sentinel node biopsy):

"One of three lymph nodes positive for micrometastatic tumor (1/3; AJCC: pN1mi [sn]); largest metastasis measures 1.5 mm."

Example 3 (sentinel node biopsy):

"Two of three lymph nodes positive for isolated tumor cell clusters (2/3; AJCC: pN0 [i+; sn]); largest metastasis measures 0.1 mm."

The (i+) notation indicates that a node contains ITC clusters, whereas pN0 indicates prognosis is similar to that of patients with tumor-free nodes. Careful attention should be given to accurately reporting the correct number of metastatic nodes. Bisected, trisected, or serially sectioned metastatic SLNs may be over-recorded absent coordination between the dissector of the gross specimen and the attending pathologist. This underscores the need to separately identify SLNs and carefully document the manner in which they are sectioned before microscopic examination.

Table 1 (continued)

Regional Lymph Nodes (N)

Clinical

NX		Regional lymph nodes cannot be assessed (e.g., previously removed)
N0		No regional lymph node metastasis
N1		Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2		Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
	N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3		Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
	N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
	N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

**Note: 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 pathologic macrometastasis based on fine needle aspiration.

Pathologic (pN)*

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

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Breast Cancer Staging

Table 1 (continued)

Pathologic (pN) *(continued)*

pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes;
pN3a	Metastases in ten or more axillary lymp tumor deposit greater than 2.0 mm); or infraclavicular (level III axillary lymph)
pN3b	Metastases in clinically detected**** ips lymph nodes in the *presence* of one or lymph nodes; or in more than three axi in internal mammary lymph nodes with macrometastases detected by sentinel not clinically detected***
pN3c	Metastasis in ipsilateral supraclavicular

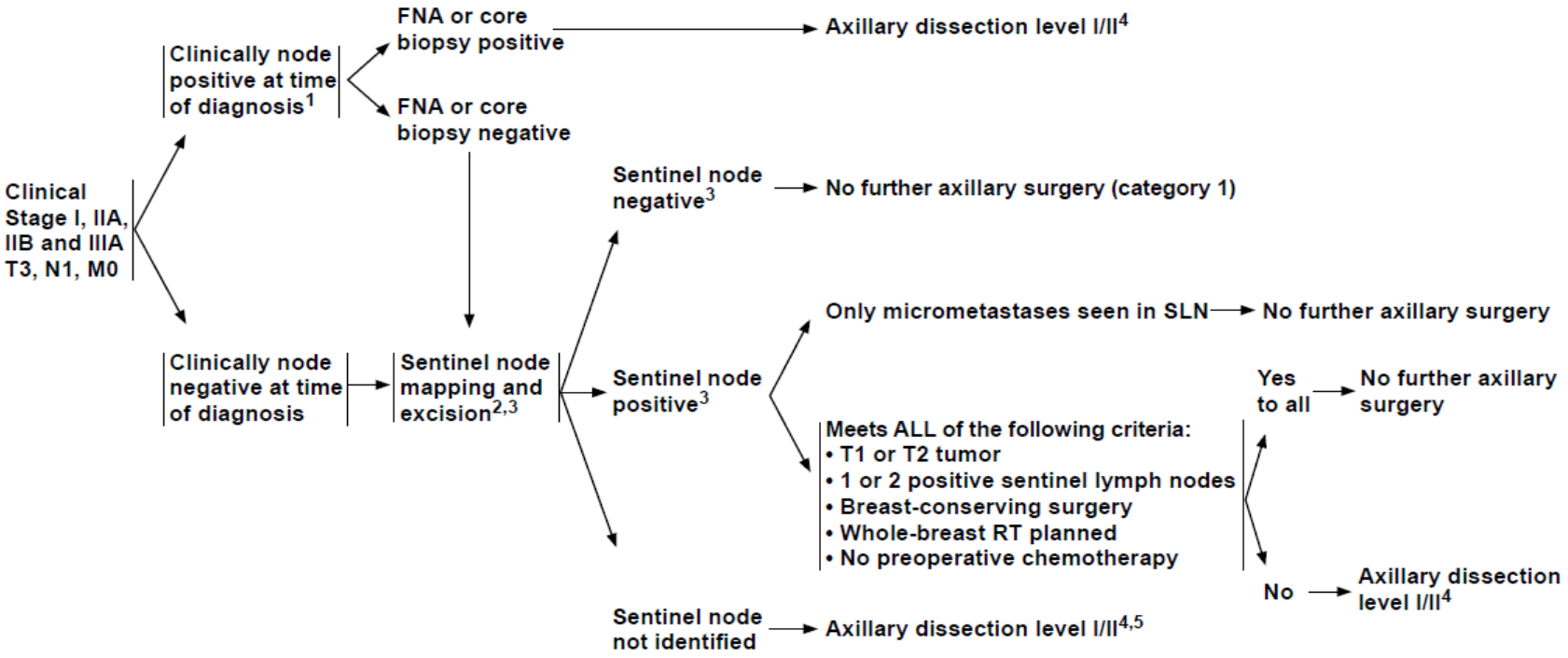
*** "Not clinically detected" is defined as not detected (excluding lymphoscintigraphy) or not detected by

**** "Clinically detected" is defined as detected by imag lymphoscintigraphy) or by clinical examination and highly suspicious for malignancy or a presumed pa based on fine needle aspiration biopsy with cytolog

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant
cM0(I+)	No clinical or radiographic evidence of distant of molecularly or microscopically detected tu blood, bone marrow, or other nonregional noc than 0.2 mm in a patient without symptoms o
M1	Distant detectable metastases as determined radiographic means and/or histologically prov

SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



[1]Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.

[2]Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.

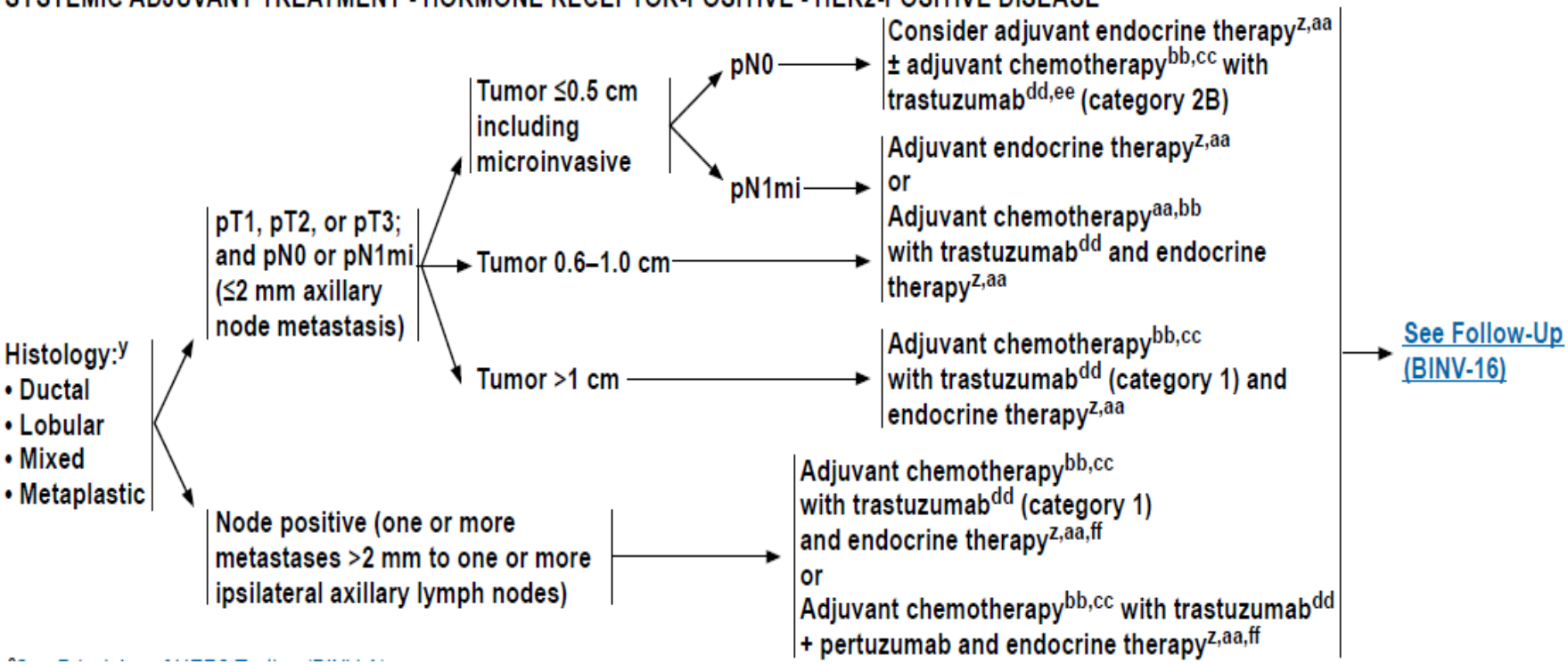
[3]Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.

[4]See Axillary Lymph Node Staging (BINV-E).

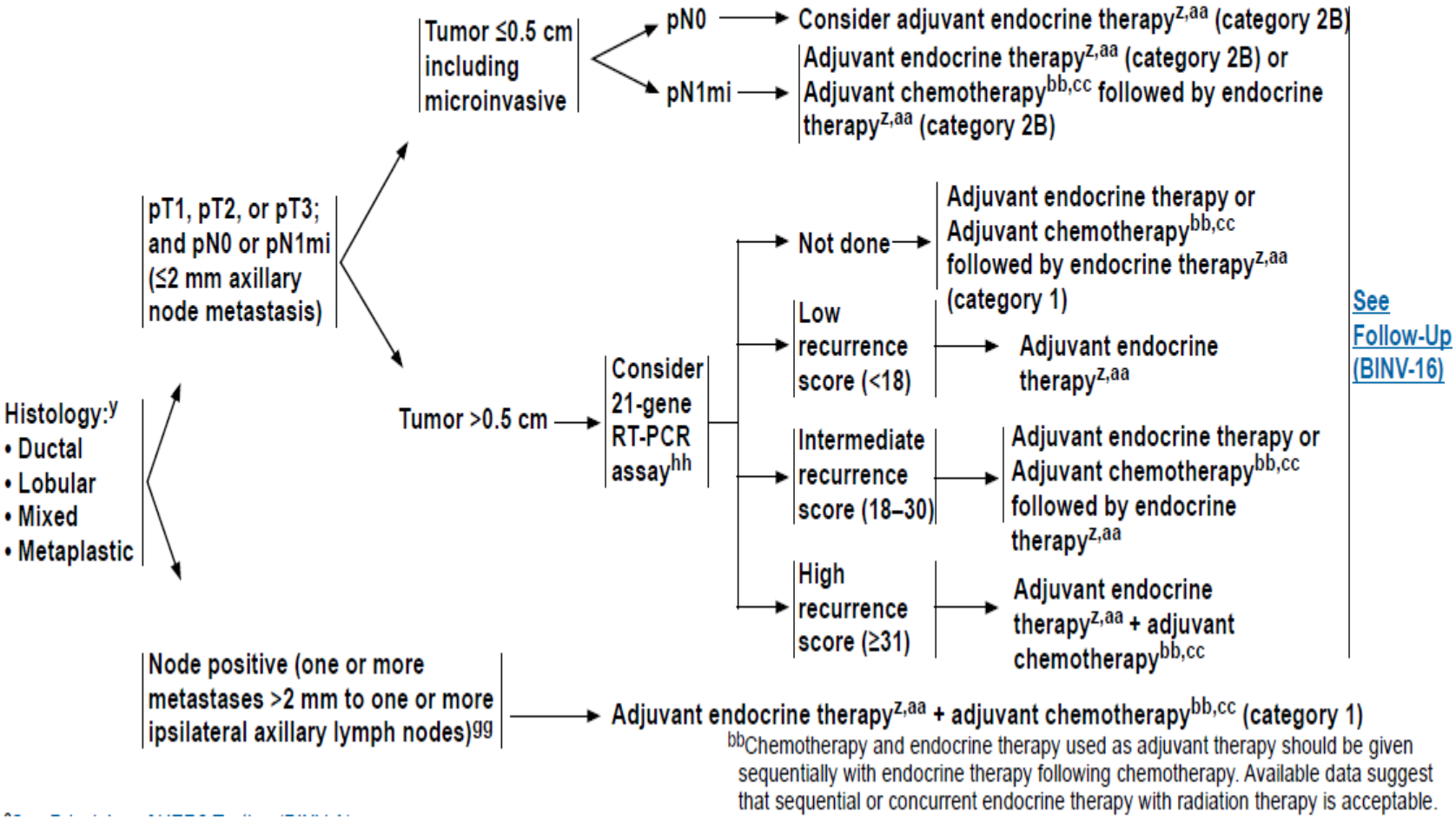
[5]For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[c]

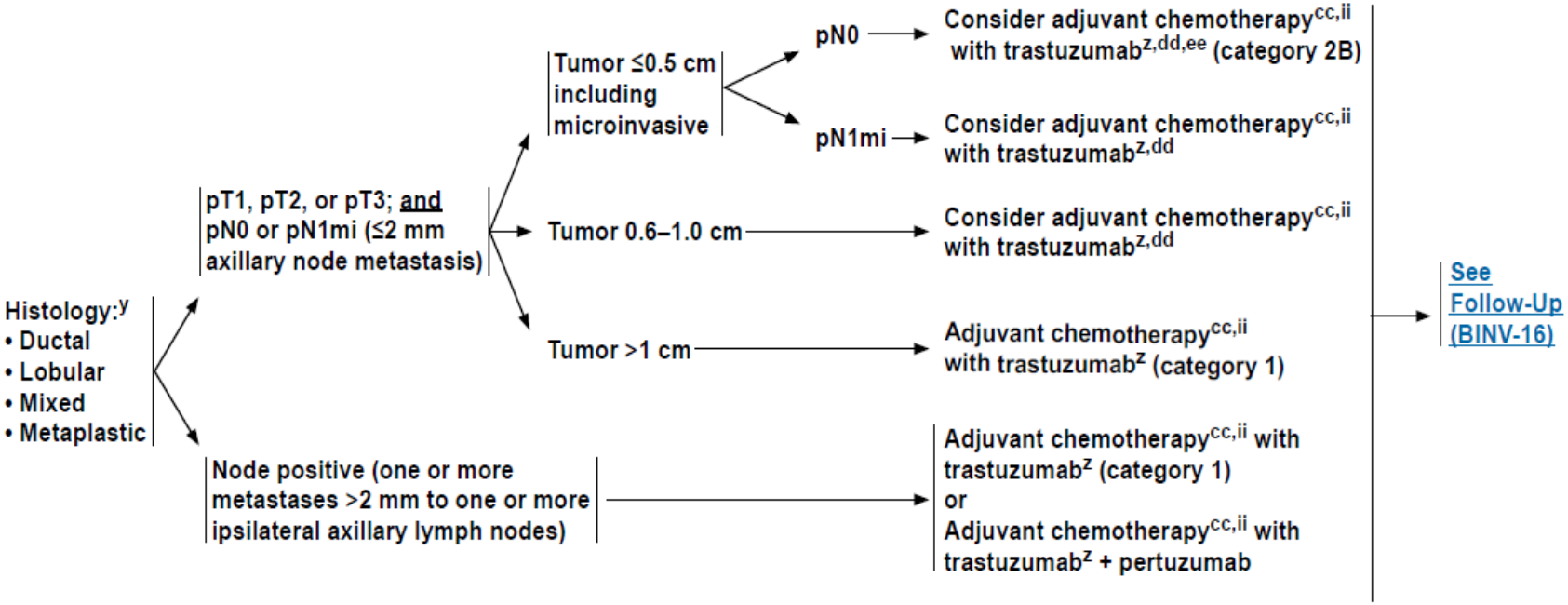


SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[c]



[bb]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[c]



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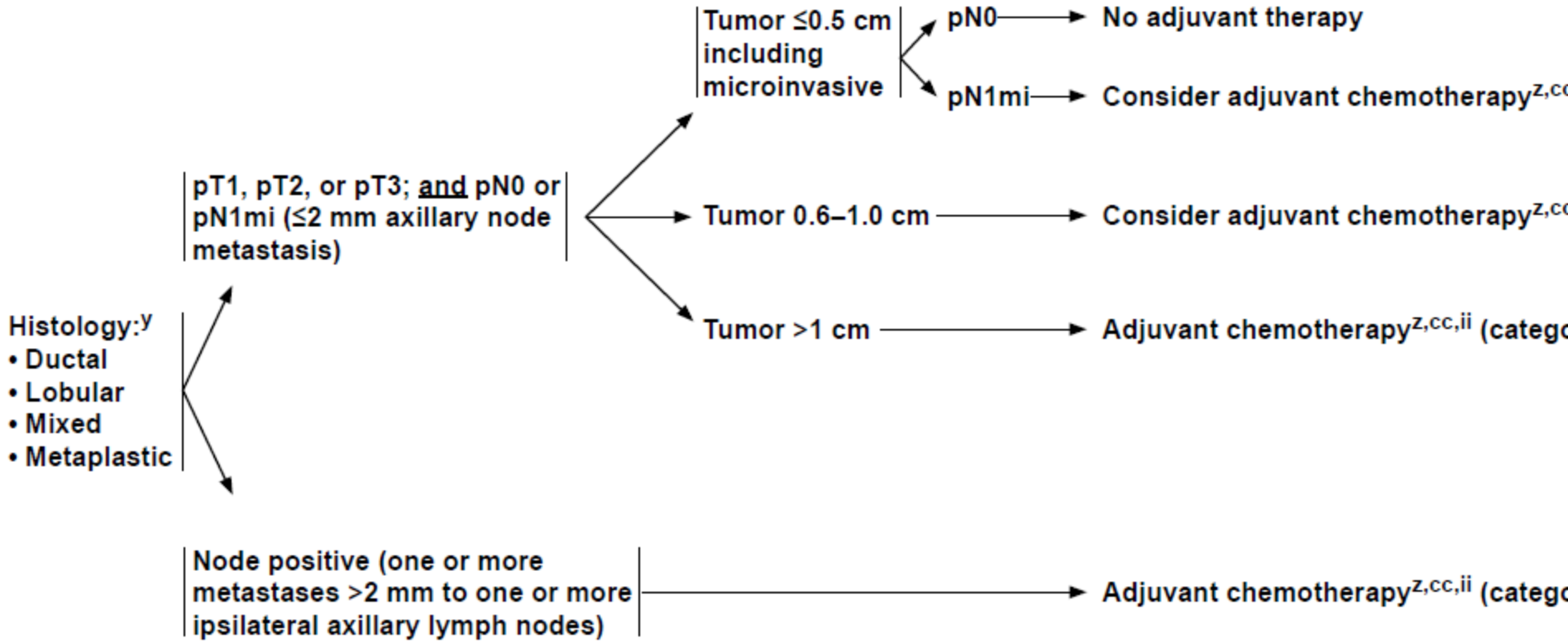
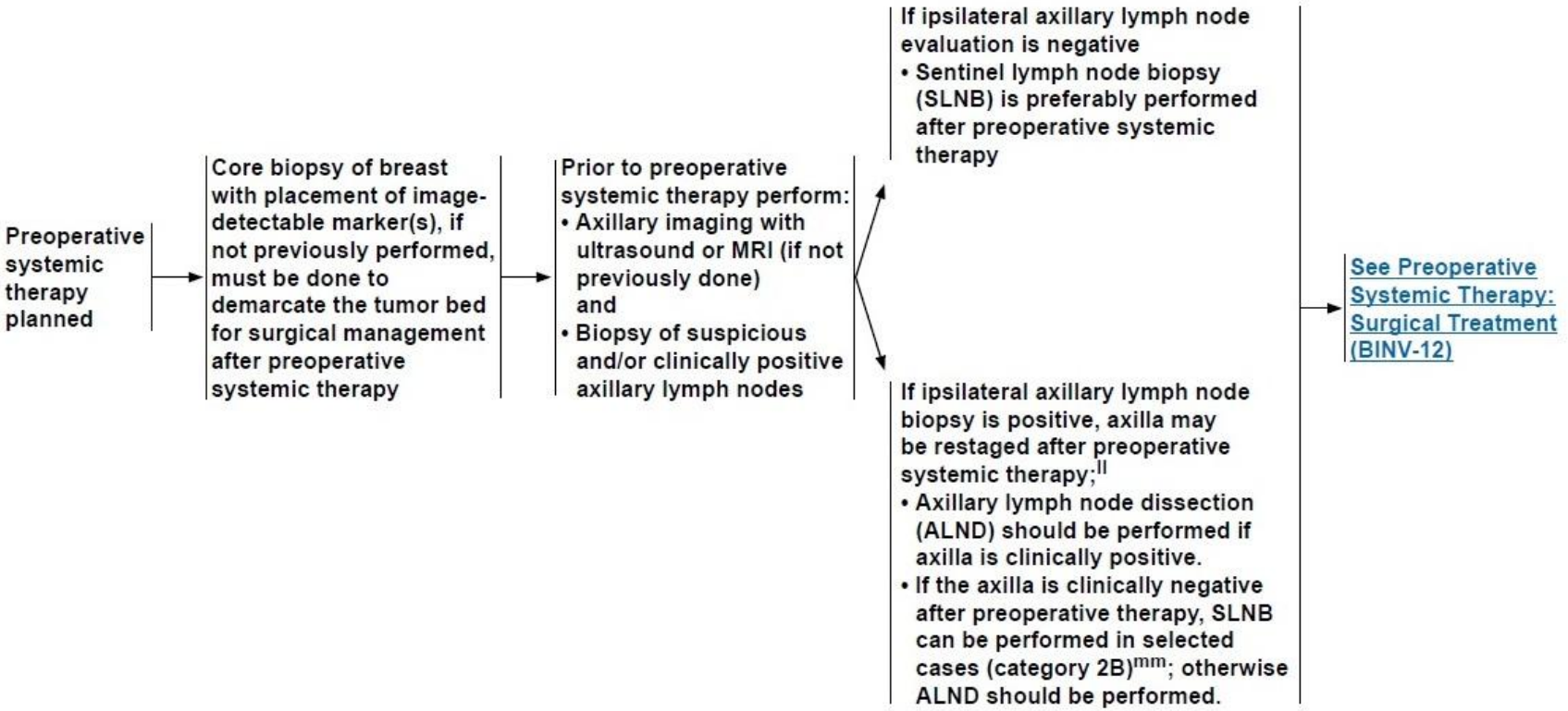
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-NEGATIVE DISEASE[c]



PREOPERATIVE SYSTEMIC THERAPY: BREAST AND AXILLARY EVALUATION



[ll]Marking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.

[mm]Among patients shown to be node-positive prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.

Note: All recommendations are category 2A unless otherwise indicated.
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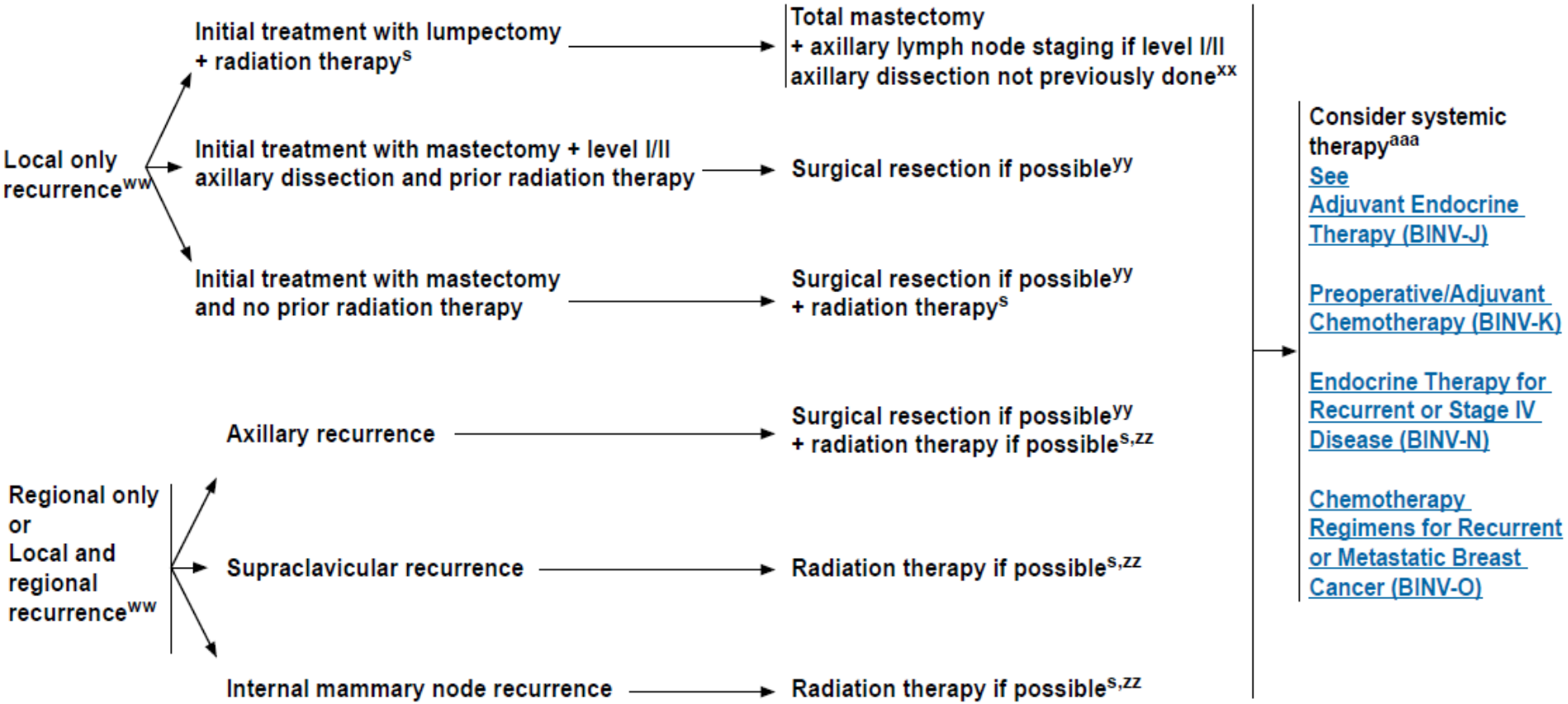
TREATMENT OF LOCAL and REGIONAL RECURRENCE

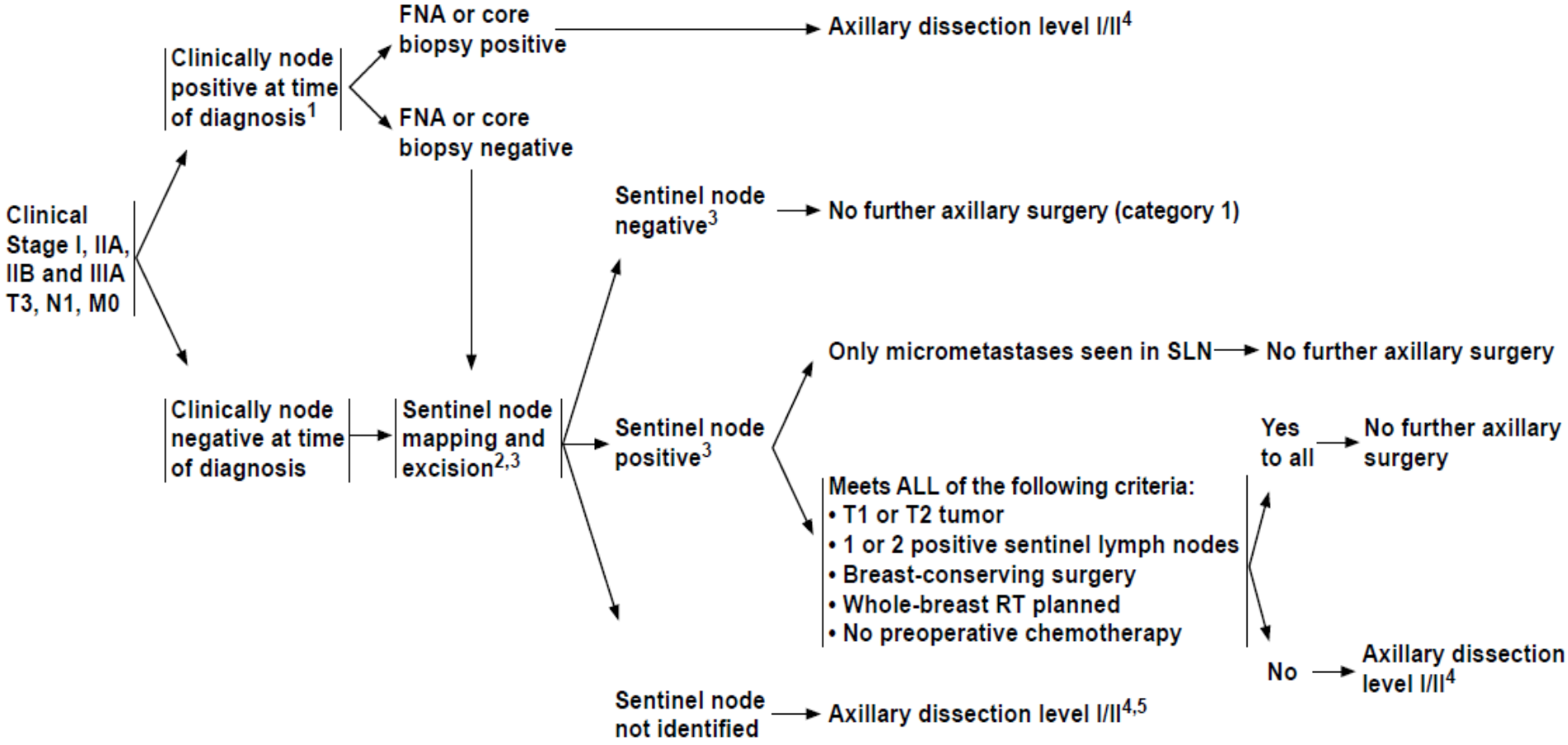


[s]See Principles of Radiation Therapy (BINV-I).

[ww]Multidisciplinary approach is especially important in the management of breast cancer recurrence to consider all potential treatment options for optimal outcomes.

[xx]In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel node biopsy (SNB), a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.

SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



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Paget's Disease

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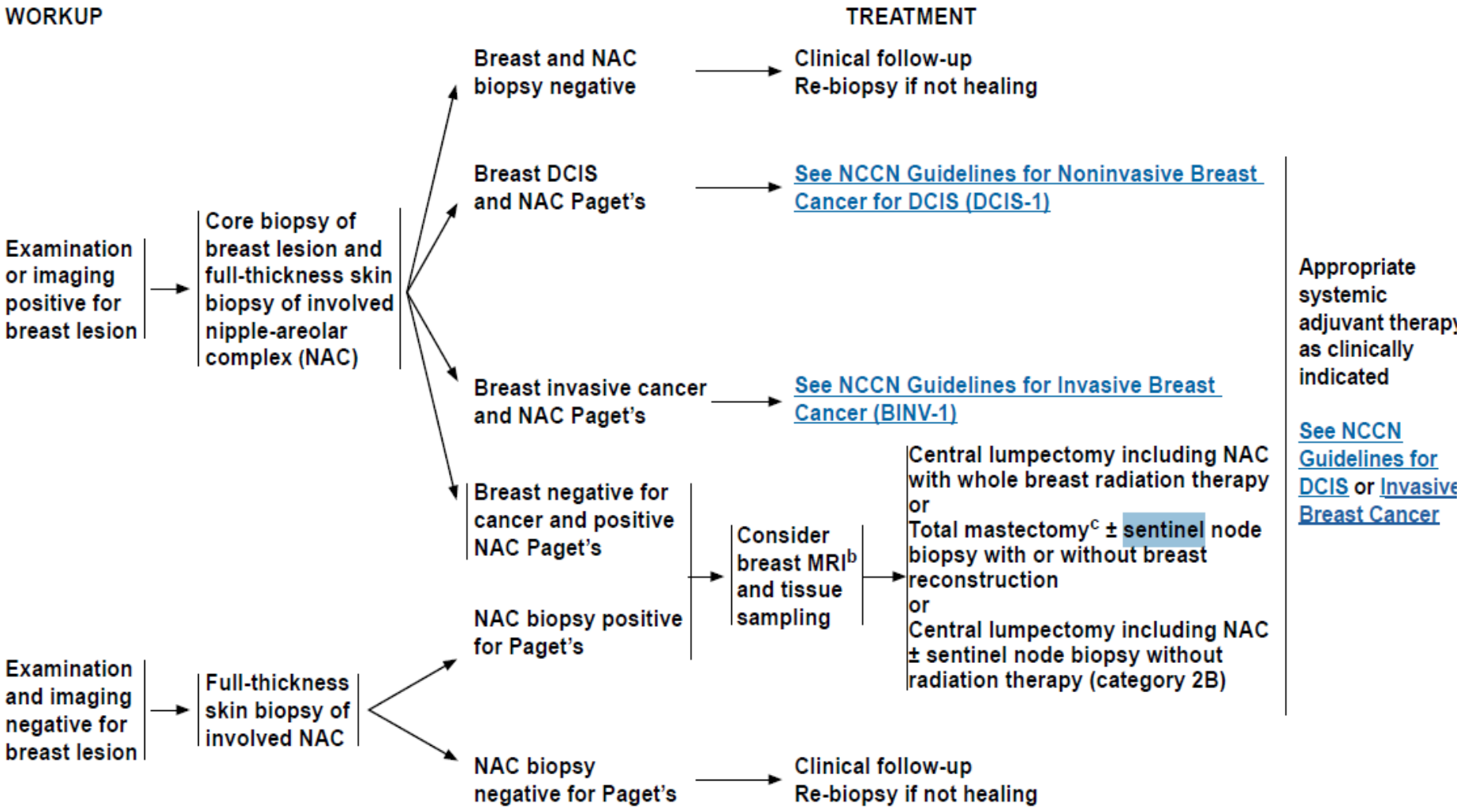
Discussion



Ganglion santinela dupa NAC

Recomandari OMS:

Utilizare de rutina IHC

Orice celule tumorale: Macrometastaze, micrometastaze, ITC=positive

Appropriate Role for Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Patients With Early-Stage Breast Cancer

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Among 649 evaluable patients who were enrolled onto the ACOSOG Z1071 (Alliance) trial with biopsy-proven (cN1) disease, no sentinel lymph node (SLN) was identified in 7% and only one SLN in 12% after NAC.[14] The observed FNR was 31.5% when only one SLN was resected and 12.6% when two or more were examined, prompting the investigators to conclude that greater sensitivity would be necessary to support the use of SNB in this setting.[14] In another recent study

FNR was as high as 24.3% in those with only one SLN removed.[15] In a recent systematic review of 15 published studies of patients with clinically node-positive ESBC undergoing NAC, the identification rate ranged from 78% to 98% (overall, 89%), whereas the FNR ranged from 5% to 25% (overall, 14%).[16] Therefore, the recently updated ASCO SNB guideline continues to warn that, although the data are limited, the FNR reported with SNB after NAC seems greater than the FNR found when SNB is performed before chemotherapy.[8] In the opinion of the Guideline Panel, in patients with metastatic nodes that are identified before NAC, the FNRs reported in the range of 10% to 30% are unacceptable and may result in inaccurate staging and undertreatment. The guideline panel emphasized that transitioning the use of SNB to after NAC is also associated with a learning curve and requires considerable surgical expertise.

Appropriate Role for Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Patients With Early-Stage Breast Cancer

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The SN FNAC (Sentinel Node Biopsy Following Neoadjuvant Chemotherapy) study, reported by Boileau et al[17] in the article that accompanies this editorial, adds important data to this discussion while also providing additional testable hypotheses that may be addressed in future studies. In this prospective multicenter phase II trial, 153 patients with biopsy-proven, node-positive breast cancer (T0-3, N1-2) before NAC underwent both SNB and CND on completion of NAC. Importantly, patients with larger tumors, N3 disease, previous axillary surgery, or preoperative breast or axillary radiation therapy were excluded. The overall SNB identification rate was 87.6%, and the FNR was 8.4%. However, immunohistochemistry was mandated, and SLNs with isolated tumor cells were considered positive. The authors acknowledge that if the isolated tumor cells were considered negative, as at most institutions, the FNR would have been 13.3%. At the same time, they argue that consideration of any size metastasis as positive with routine immunohistochemistry evaluation of SLNs after NAC would enable up to 30% of patients to avoid CND.