Chapter 2
Staging of Breast Cancer

Zeynep Ozsaran and Senem Demirci Alanyalı

2.1 Introduction

Five decades ago, Denoix et al. proposed classification system (tumor node metastasis [TNM]) based on the dissemination of cancer according to the features of the primary tumor (localization, size, and extension to the surrounding structures), regional lymph nodes, and the presence of metastases. Currently, the TNM system which was formulated by Union International Cancer Centre (UICC) and the American Joint Committee on Cancer (AJCC) is being used for every cancer site [1].

The most important function of staging is to anatomically group patients to determine the treatment algorithm and prognosis. Accurate staging carries substantial importance to compare the treatment results among the studies [2].

In 1960, the UICC published the TNM staging system adapted for breast cancer. Revisions to the staging system were updated in 1962 and the seventh edition was published in 2009 [3]. The differences between the sixth and the seventh edition of the staging system are:

- T1mic changed to T1mi to indicate microscopic disease.
- Clarification of wording of "not clinically detected" and "clinically detected" internal mammary nodes.
- Subdivision of Stage I into IA and IB (IB includes T0-T1 with nodal micrometastases).
- New cM0(i+) category defined for the presence of either disseminated tumor cells detectable in bone marrow or circulating tumor cells or found incidentally in other tissues if not exceeding 0.2 mm.
- The category of "yc" or "yp" was introduced to distinguish stage after preoperative, or "neoadjuvant" systemic therapy and surgery.

Z. Ozsaran (✉) • S.D. Alanyalı
Department of Radiation Oncology, Ege University, Bornova, Izmir 35100, Turkey
e-mail: zeynep.ozsaran@ege.edu.tr; senem.demirci@ege.edu.tr

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2.2 Rules for Classification

2.2.1 Clinical Staging

Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathologic examination of the breast or other tissues as appropriate to establish the diagnosis of breast carcinoma. Imaging and clinical findings obtained after a patient has been treated with neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy are not considered elements of initial clinical staging. If recorded in the medical record, these should be denoted using the modifier prefix "yc."

2.2.2 Pathologic Staging

Pathologic staging includes all data used for clinical staging, in addition to data from surgical exploration and resection as well as pathologic examination (gross and microscopic) of the primary carcinoma, regional lymph nodes, and metastatic sites, including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "yp" should be used with the TNM classification [2].

2.3 American Joint Committee on Cancer Staging of Breast Cancer

2.3.1 Primary Tumor

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner should use the major headings (T1, T2, and T3). If other measurement, such as mammographic or pathologic, is used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- *Tx* Primary tumor cannot be assessed
- *T0* No evidence of primary tumor
- *Tis* Carcinoma in situ

- *Tis* (*DCIS*) Ductal carcinoma in situ
- *Tis* (*LCIS*) Lobular carcinoma in situ
- *Tis* (*Paget's*) Paget's disease of the nipple with no tumor
- *T1* Tumor 2 cm or less in greatest dimension

  $T1_{mic}$ Microinvasion 0.1 cm or less in greatest dimension
  T1a Tumor greater than 0.1 cm but not more than 1 cm in greatest dimension
  T1b Tumor greater than 0.5 cm but not more than 1 cm in greatest dimension
  T1c Tumor greater than 1 cm but not more than 2 cm in greatest dimension

- *T2* Tumor greater than 2 cm but not more than 5 cm in greatest dimension
- *T3* Tumor greater than 5 cm in greatest dimension
- *T4* Tumor any size with direct extension to chest wall or skin, only as described below
  Note: Invasion of the dermis alone does not qualify as T4

  T4a Extension to chest wall, not including pectoralis muscle
  T4b Edema (including peau d'orange or ulceration of the skin of the breast or satellite skin nodules confined to the same breast)
  T4c Both (T4a and T4b)
  T4d Inflammatory carcinoma.

2.3.2 Regional Lymph Nodes

Definitions for classifying the regional lymph nodes (N) are different for clinical and for pathologic classification.

2.3.2.1 Clinical Lymph Node Classification (cN)

- *Nx* Regional lymph nodes cannot be assessed (e.g., previously removed)
- *N0* No regional lymph node metastases
- *N1* Metastases to movable ipsilateral level I,II axillary lymph nodes
- *N2* Metastases to ipsilateral level I,II axillary lymph nodes 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 axillary lymph node metastases

- *N3* Metastases to ipsilateral infraclavicular (level III) axillary lymph node(s) with or without level I,II axillary lymph node(s) 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 Metastases in ipsilateral infraclavicular lymph node(s)
N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c Metastases 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 biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

2.3.2.2 Pathologic Classification (pN)

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

Note: Isolated tumor cell clusters (ITC) are defined as single tumor cells or small cell clusters not 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 usually detected only by immunohistochemistry (IHC) or molecular methods but which may be verified on hematoxylin and eosin stains. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction)

pN0 (*i*−) No regional lymph node metastases 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 metastasis histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
pN0 (*mol*+) Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

– *pN1* Micrometastases or metastases in one to three 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 one to three axillary lymph nodes, at least one metastasis greater than 2.0 mm
  pN1b Metastases in internal mammary lymph 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 four to nine axillary lymph nodes, or in clinically detected** internal mammary lymph nodes in the absence of axillary lymph node metastases

  pN2a Metastases in four to nine 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 metastasis

– *pN3* Metastases in 10 or more axillary lymph nodes, or in infraclavicular (level III) lymph nodes, or clinically detected** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I,II axillary lymph nodes, or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected** or in ipsilateral supraclavicular lymph nodes

  pN3a Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastases to the infraclavicular (level III axillary lymph) nodes
  pN3b Metastases in clinically detected** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes, or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**
  pN3c Metastases in ipsilateral supraclavicular lymph nodes.

*"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.
**"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 biopsy with cytologic examination.

Table 2.1 AJCC 7th Edition Staging for Breast Cancer

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0-T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

2.3.3 Distant Metastasis (M)

- *M0* No clinical or radiographic evidence of distant metastases
- *cM0*(*i*+) No clinical or radiographic evidence of distant metastases, but deposits of moleculary or microscopically detected tumor cells detected in circulating blood, bone marrow, or other nonregional nodal tissues, that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- *M1* Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proved larger than 0.2 mm.

2.3.4 Staging

The staging grouping is summarized in Table 2.1.

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.

- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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