1. Guidelines for Reporting Carcinoma of the Breast

Compilation and editing of this volume:

Prof. Dilani Lokuhetty (Consultant Histopathologist)

List of contributors

Consultant Histopathologists
Dr. Ruchira Fernando
Dr. A.Illeperuma

Consultant Oncologists
Dr. Sujeewa Weerasinghe
Dr. Indrani Amarasinghe
Dr. Damayanthi Pieris

Coordinators
Consultant Histopathologists
Dr. Siromi Perera
Dr. Kamani Samarasinghe
Dr. Modini Jayawickrema

INDEX

CONTENT **PAGE NUMBER**

1.1 Introduction:

Breast carcinoma is a disease with a high prevalence in women. It is the commonest cause of death in the female from cancer accounting for 20% of such deaths [1]. The incidence of breast carcinoma continues to rise worldwide. Even though the incidence of breast carcinoma in Asia is lower than in the west, an increase of diagnosed breast cancers has been noted in several Asian countries that maintain cancer registries [2].

Based on year 2000 national cancer registry data, carcinoma of the breast is the commonest cancer in Sri Lankan females with an incidence of 14.0/100000 female population [3].

Modified radical mastectomy (including the breast, skin ellipse with the areola complex and the axillary tail) and simple mastectomy (including the breast and the skin ellipse with the areola complex) are the commonest surgical specimen encountered by pathologists in Sri Lanka. Information provided by the pathologist has therapeutic and prognostic implications in over all management of these patients. Therefore all pathologists and pathology trainees are advised to follow the standard format designed and recommended by the College of Pathologists of Sri Lanka for pathology reporting of breast carcinoma specimens. This reporting format while acting as a check list for pathologists will also allow easy access to pathology information by managing clinicians. It will simplify the auditing process and data entry in to cancer registries as well.

As breast carcinoma samples will be handled in hospitals with laboratory facilities headed by a

specialist pathologist, these guidelines will be applicable only to those hospitals (BH, GH, TH)

The recommended guidelines are also divided in to three levels taking due consideration that the availability of resources and facilities are different at different levels of hospitals that come under the Ministry of Health in Sri Lanka.

Strongly recommended guidelines (grade X) are very basic and every effort should be made to adhere to them as far possible.

Guidelines marked as grade Y are desirable to be adhered to.

Guidelines marked as grade Z are optional.

Strongly recommended…… Grade X
Desirable …….. Grade Y
Optional …… Grade Z

1.2 Modified Radical Mastectomy/ Simple Mastectomy for Breast Carcinoma

1.2.1 Dissection procedure and the gross description of the specimen: **(Category X)**

- Note down the number of containers/ specimens and whether the Specimen/s is/are received fresh or fixed.
- Orientate the specimen with the help of sutures (e.g. short suture-superior, long suture-lateral) or the axillary tail (when present) as a marker for lateral side.
- Examine measure and describe the external appearance of the mastectomy specimen. (Measurements in centimeters should include those of the total breast, skin ellipse and the axillary contents when present,)
- Note down the location and extent of any skin changes including scars, surgical incisions, erythema, oedema, flattening, retraction, ulceration and the appearance of nipple and areola (erosions, ulceration, retraction and inversion).
- Place the specimen on the cutting board, posterior side facing up with the inferior border towards the

dissector. When present, separate axillary tissue from the breast.

- Paint the surgical resection base with India ink, Alcian blue or any other commercially available marker after drying the surface. Use a fixative such as Bouin's or Carnoy's fixative or acetic acid to fix the paint. (If the surgeon has made one incision through the tumour starting at the deep surgical base to facilitate tumour fixation, take care when inking the specimen to prevent leakage of ink in to the incision made in the breast tissue)
- With a long sharp knife slice the entire breast sagitally from deep to superficial surface. These parallel slices should be as thin as possible (10mm). Cut the slices in such a way that the pieces remain attached together by skin.
  (If the specimen is received fresh it may be allowed to cool in the freezing compartment of a refrigerator for up to 20 minutes to facilitate slicing)
- Note down the following features of any suspicious lesions / masses observed.

- Multi centricity
- As far as possible locate the quadrant of the lesion
- Measure the size of the lesion in cm (give three dimensions) and note the presence of necrosis and haemorrhage.
- Describe the cut surface (optional) distance from the lesion to the skin and nipple, deep surgical margin and any other relevant surgical margins (superior and inferior)

➢ If an excision biopsy has been done previously mention the cavity dimensions and the distance to relevant margins and the skin. Describe the status of adjacent breast tissue (e.g. presence of cysts, size, number, location, and content)

➢ Remove the nipple and areola and cut one section horizontally from the **base.** Serially section the entire nipple perpendicular to the skin surface.

➢ Shred the axillary tissue (received attached to the mastectomy specimen or separately with each level in different container) and dissect out all lymph nodes. Lymph nodes are best identified in the axillary adipose tissue by combined palpation and inspection.

➢ Note the size of the largest lymph node isolated. Small nodes should be submitted entirely; nodes > 0.5cm in diameter are sliced and one half should be submitted. In grossly involved nodes only a sample may be submitted.

1.2.2 Sections to be taken for processing:

(Category X)

- Tumour / any suspicious area - Sample the tumor/suspicious area adequately and submit enough material to enable a definite diagnosis.
- Deep surgical margin – Sample the inked deep resection base separately. Blocks should be taken from all excision margins with in 10mm of the tumour
- Nipple with base – Submit one section from the base and one serial section of the nipple taken perpendicular to the skin surface.
- Any other relevant area – Sample any cysts, rubbery or any other area you may wish to sample in the adjacent breast tissue and macroscopically normal breast tissue.
- All lymph nodes isolated from the axillary tail/ each level should be submitted. If the lymph nodes are received according to the levels, each level should be submitted separately.

- If a previous excision biopsy has been done, sample tissue around the cavity.

The pathology report should contain specific information concerning the orientation of each block taken to facilitate subsequent microscopic interpretation or review.

1.2.3 Microscopic description:

(Category Z)

A detailed microscopic description is considered optional.

1.2.4 Microscopy and conclusion:

(Category X)

The microscopic findings and the conclusion are combined and documented in the following format.

1. Specimens received
2. Tumour type [4]
3. Tumour size*
4. Tumour location
5. Tumour grade (Nottingham grade) [5] Annexure 1
6. In situ component
   - present or not
   - ductal or lobular
   - when ductal in type, presence within or outside tumour
   - percentage
   - nuclear grade
   - architecture
   - necrosis

7. Presence or absence of lymphovascular invasion by tumour**
8. Lymphoplasmacytic response at host/tumour interface- good/ moderate/ poor.
9. State of overlying skin and nipple
10. Deep surgical margin ***
11. State of non neoplastic breast
12. Number of affected nodes out of the total number isolated (at each different level when received separately).

When lymph nodes are positive for tumour mention the following additional features.

- Focal or extensive involvement
- Extra capsular extension
- Size of largest involved node in cm.

* Tumour size should be the measurement of the invasive component. In situations where the lesion includes both in situ and invasive components, mention both the maximum dimension of the entire lesion (as seen macroscopically) as well as the maximum dimension of the invasive component (assessed microscopically). In small tumours if the macroscopic maximum tumour dimension is less than the dimension assessed microscopically in the section, the larger measurement should be taken.

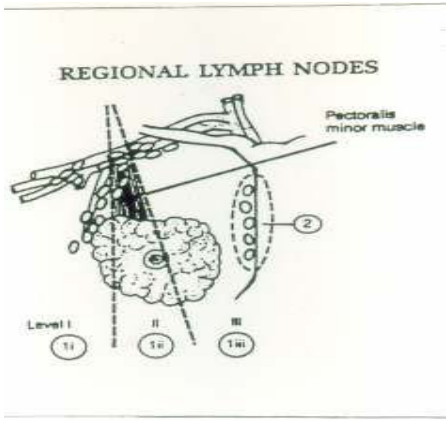
** Lymphovascular invasion should be assessed in the periphery of the tumour as the centre of the tumour may

contain artefactual retraction of tumour cells from the stroma. State whether Lymhovascular invasion is intratumoural or peritumoural when detected,

*** Surgical margins – Wide clear margins > 10mm should be stated as such. When the margin is <10mm the distance should be measured and stated in millimeters in the report

(Category Y)

13. Pathological tumour stage (pTNM) [6] Annexure 2
14. Nottingham prognostic index [7] Annexure 3
15. Breast prognostic markers – This is considered optional as most centers do not have the facilities to assess these markers. However as part of good practice the pathologist is encouraged to obtain this service from another centre on behalf of the patient or refer the patient appropriately.



1.3 Wide Local Excision of Breast Lump (WLE) /Lumpectomy

Small breast carcinomas may be subjected to wide local excision as part of diagnostic or treatment procedure with or without axillary node sampling. The dissection procedure, gross description and the reporting format for these specimens are described below.

1.3.1 Dissection Procedure and the Gross Description of the Specimen:

(Category X)

- Note down the number of containers/ specimens and whether the specimen/s is/are received fresh or fixed.
- Place on a cutting board and orientate the specimen (WLE) with the help of sutures (e.g. sutures indicating superior, superficial and either medial or lateral margins).
- Examine and measure the specimen in cm in three dimensions and describe.
- Paint the external surface of the specimen using India ink, Alcian blue or any other commercially available marker after drying the surface. Use a fixative such as Bouin's, Carnoy's fixative or acetic acid to fix the paint. (as an option each surgical margin may be painted in different colours. (Differential inking)

- Slice the entire specimen longitudinally as thinly as possible with a long sharp knife (preferably at 10mm). (If the specimen is received fresh it may be allowed to cool in the freezing compartment of a refrigerator for up to 20 minutes to facilitate slicing)

- Measure the size of tumour/ abnormal area in cm (or in mm if the lesion is small) and the distance to all 6 margins (superior, inferior, lateral, medial, superficial, deep).

- Describe the cut surface of the tumour/ lesion (fibrosis, cysts with size, number and content, calcifications, necrosis, colour).

1.3.2 Sections to be taken for Processing:

(Category X)

- Tumour / lesion – if the tumour / lesion is small submit all, if it is larger, sample adequately to enable a definite diagnosis.
- Sections should be taken to include all surgical margins if the margins are not included with the tumour/ lesion blocks.

The pathology report should contain specific information concerning the orientation of each block taken to facilitate subsequent microscopic interpretation or review.

1.3.3. Microscopic description:

(Category Z)

A detailed microscopic description is considered optional.

1.3.4 Microscopy and Conclusion:

(Category X)

The microscopic findings and the conclusion are combined and documented in the following format.

1.Specimens received

When a tumour is diagnosed mention the following;

2. Tumour type[4]

3.Tumour size *

4.Tumour grade (Nottingham grade [4]) Annexure 1

5.In situ component
- present or not
- ductal or lobular
- percentage of in situ component to determine presence of extensive carcinoma in situ (ECIS)
- nuclear grade
- architecture
- necrosis

6. Presence or absence of lymphovascular invasion by tumour**
7. Microscopic clearance of surgical margins***
8. Presence or absence of calcifications
9. State of non-neoplastic breast tissue

* Tumour size should be the measurement of the invasive component. In situations where the lesion includes both in situ and invasive components, mention both the maximum dimension of the entire lesion (as seen macroscopically) as well as the maximum dimension of the invasive component (assessed microscopically). In small tumours if the macroscopic maximum tumour dimension of an invasive tumor is less than the dimension assessed microscopically in the section, the larger measurement should be taken.

** Lymhovascular invasion should be assessed in the periphery of the tumour as the centre of the tumour may contain artefactual retraction of tumour cells from the stroma. State whether Lymhovascular invasion is intratumoural or peritumoural when it is detected.

*** Surgical margins – Wide clear margins > 10mm should be stated as such. When the margin is <10mm the

distance should be measured and stated in millimeters in the report. **(Category Y)**

10. Breast prognostic markers
    These markers are considered optional as most centers do not have the facilities to assess these markers. However as part of good practice the pathologist is encouraged to obtain this service from another centre on behalf of the patient or refer the patient for this.

1.3.5 Comment:

(Category X)

If the lesion detected is not a tumour, describe the lesion and give the diagnosis. If lymph nodes are also received in separate containers handle them as described under the section on mastectomy.

1.4. References:

1. McPherson K, Doll H. Oestrogens and breast cancer: exogenous hormones.
   British Medical Bulletin 1990; 47: 484-92

2. Kelsey JL, Horn-Ross PL. Breast cancer: Magnitude of the problem and descriptive epidemiology. *Epidemiology Review* 1993; 15: 7-16

3. Cancer registry 2000, Cancer Control Programme, Cancer Institute, Maharagama, Sri Lanka.

4. Tavassoli FA, Devilee P. World Health Organization Classification of the tumours of the breast and female genital organs. Lyon;IARC press, 2003.

5. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grading in breast cancer: experience from a large study with long term follow up. *Histopathology* 1991; 19:403-410

6. American Joint Committee on Cancer. 2002, Breast : In AJCC Cancer Staging Handbook , 6th Ed , Springer 2002 ;pp255-281

7. I.O.Ellis, S.E.Pinder, A.H.S.Lee, C.W.Elston. Tumours of the breast. In;Christopher D.M.Fletcher. Diagnostic Histopathology of tumours, Ed 2nd, Churchill Livingstone, 2001, p865.

8. Juan Rosai, Rosai and Ackerman's Surgical Pathology , 9th Ed. Mosby 2004.

9. www.rcpath.org

10. Recommendations of the Australian Cancer Network Working Party: In The pathology reporting of breast cancer, 2nd ed, Intramed Sydney, 2001.

1.5 Recommendations to Surgeons:

Provision of following information and adherence to these suggested protocols by surgeons will enable the pathologist to provide **quality information necessary for management of patients with breast carcinomas.**

1.5.1 For modified radical mastectomy/ simple mastectomy specimens;

1. Mentioning the side of the breast removed in the request form (right or left).

2. Send the breast in an oriented state – eg. short suture superiorly and a long suture laterally.

3. Send level 1, 2 and 3 lymph nodes in separate containers.

4. Due to logistic problems in our country most of the mastectomy specimens reach the pathologist already fixed in formalin and not in the fresh state. In this type of specimen the tumour preservation is poor, preventing its accurate grading. This may also affect assessment of steroid receptor status of the tumour. Therefore following measures are suggested to minimize autolysis of the tumour.

- Refrigerate the whole specimen in fixative if facilities are available or

- Make one incision though the tumour starting at the deep surgical margin up to the skin keeping the skin intact. Insert some gauze/cotton wool in to the incision. Immerse the whole specimen in adequate formalin to facilitate fixation of the tumour.

- Send the specimen in a large container preferably in a bucket with 10% buffered formalin entirely submerging the specimen.

- **Do not** squeeze the specimen in to a small container with inadequate formalin.

1.6 Annexure 1

1.6.1 Microscopic Grading of Breast Carcinoma

Nottingham Modification of the Bloom – Richardson Grading System.

Tubule Formation

1 point: Tubular formation in >75% of the tumour
2 points: Tubular formation in 10 to 75% of the tumour
3 points: Tubular formation in <10% of the tumour

Note: For scoring tubule formation, the overall appearance of the tumour has to be taken into consideration.

Nuclear Pleomorphism

1 point: Nuclei with minimal variation in size and shape
2 points: Nuclei with moderate variation in size and shape
3 points: Nuclei with marked variation in size and shape

Note: The tumour areas having cells with greatest atypia should be evaluated.

Mitotic count

The mitotic count is given 1, 2, or 3 points, according to the following table.

Table: Assignment of points for mitotic counts according to the field area, using several microscopes

	Leitz Ortholux	Microscope Nikon Labophot	Leitz Diaplan
Objective	X25	X40	X40
Field diameter(mm)	0.274	0.152	0.312
Field area (mm^2)	0-9	0-5	0-11
Mitotic count	10-19	6-10	12-22
1 point	>20	>11	>23
2 points			
3 points			

Note: Mitotic figures are to be counted only at the periphery of the tumour. Counting should begin in the most mitotically active area; 10 high-power fields (HPF) are to be counted in the same area (but not necessarily contiguous).The fields should be filled with as much tumour as possible; poorly preserved areas are to be avoided. Cells in the prophase should be ignored.

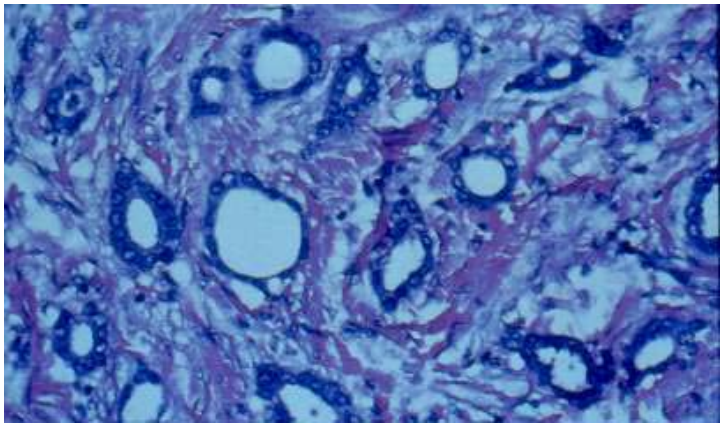
Final Grading

Add all the points scored for tubule formation, nuclear atypia and mitotic count.
Total score must be in the range 3-9.

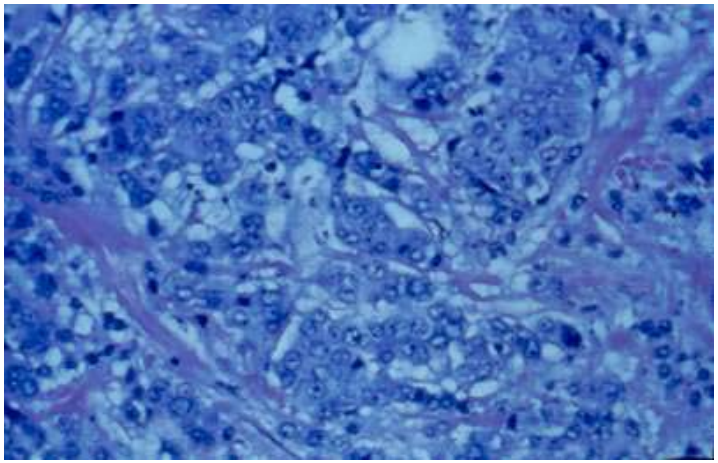
Total score 3, 4 or 5 = **grade 1** Total score 6 or 7 = **grade 2**
Total score 8 or 9 = **grade 3**

References:

1.Juan Rosai ,Rosai andAckerman's Surgical Pathology, 9th Ed. Mosby 2004.
2.www.rcpath.org



Nottingham Grade 1 tumour



Nottingham Grade 3 tumour

1.7Annexure 2

1.7.1 Pathological Tumour Staging of Breast Carcinoma

Pathologic Staging. Pathologic staging includes all data used for clinical staging, plus data from surgical exploration and resection as well as pathologic examination of the primary carcinoma, regional lymph nodes, and metastatic sites (if applicable), including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. A cancer can be classified pT for pathologic stage grouping if there is only microscopic, but not macroscopic, involvement at the margin. If there is tumor in the margin of resection by macroscopic examination, the cancer is coded pTX because the total extent of the primary tumor cannot be assessed. If the primary tumor is invasive and not only microinvasive, resection of at least the low axillary lymph nodes (Level I)—that is, those lymph nodes located lateral to the lateral border of the pectoralis minor muscle—should be performed for pathologic (pN) classification. Such a resection will ordinarily include six or more lymph nodes. Alternatively, one or more sentinel lymph nodes may be resected and examined for pathologic classification. Certain histologic tumor types (pure tubular carcinoma < 1 cm, pure mucinous carcinoma < 1 cm, and microinvasive carcinoma) have a very low incidence of axillary lymph node metastasis and do not usually require an axillary lymph node dissection. Cancerous nodules in the axillary fat adjacent to the breast, without histologic evidence of residual lymph node tissue, are classified as regional lymph node metastases (N). Pathologic stage grouping includes any of the following combinations of pathologic and clinical classifications: pT pN pM, or pT pN cM, or cT cN pM. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "y" should be used with the TNM classification, e.g., ypTNM.

1.7.2 TNM Classification of Breast Carcinoma Staging

Primary Tumor (T)

Determining Tumor Size

The clinical measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (that is, physical examination or imaging such as mammography or ultrasound). The pathologic tumor size for the T classification is a measurement of *only the invasive component*. For example, if there is a 4.0-cm intraductal component and a 0.3-cm invasive component, the tumor is classified T1a. The size of the primary tumor is measured for T classification before any tissue is removed for special studies, such as for estrogen receptors. In patients who have received multiple core biopsies, measuring only the residual lesion may result in significantly underclassifying the T component and thus understaging the tumor. In such cases, original tumor size should be reconstructed on the basis of a combination of imaging and all histologic findings.

Tis Classification

Carcinoma *in situ*, with no evidence of an invasive component, is classified as Tis, with a subclassification indicating type. Cases of ductal carcinoma *in situ* and cases with both ductal carcinoma *in situ* and lobular carcinoma *in situ* are classified Tis (DCIS). Lobular carcinoma *in situ* is increasingly defined as a risk factor for subsequent breast cancer, although there is some evidence that it may occasionally be a precursor of invasive lobular carcinoma. For example, this may be the case with LCIS with more atypical cytology (pleomorphic) as well as more extensive and locally distorting examples of well-developed LCIS.[1] Regardless of this controversy, LCIS is reported as a malignancy by national database registrars and should be designated as such in this classification system—e.g., Tis (LCIS). Paget's disease of the nipple without an associated tumor mass (clinical) or invasive carcinoma (pathologic) is classified Tis (Paget's). Paget's disease with a demonstrable mass (clinical) anywhere within that breast or an

invasive component (pathologic) is classified according to the size of the tumor mass or invasive component.

Microinvasion of Breast Carcinoma

Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.) The presence of multiple foci of microinvasion should be noted and/or quantified, as it is with multiple larger invasive carcinomas.

Multiple Simultaneous Ipsilateral Primary Carcinomas

The following guidelines are used in classifying multiple simultaneous ipsilateral primary (infiltrating, macroscopically measurable) carcinomas. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic foci. Most conservatively, tumors are defined as arising independently only if they occur in different quadrants of the breast.

1. Use the largest primary carcinoma to designate T classification. Do not assign a separate T classification for the smaller tumor(s).
2. Enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinomas. The outcome of such cases should be analyzed separately.

Simultaneous Bilateral Breast Carcinomas

Each carcinoma is staged as a separate primary carcinoma in a separate organ.

Inflammatory Carcinoma

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying palpable mass. These clinical findings should involve the majority of the skin of the breast. Classically, the skin changes arise quickly in the affected breast. Thus the term *inflammatory carcinoma* should not be applied to a patient with neglected locally advanced cancer of the breast presenting late in the course of her disease. On imaging, there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor emboli within dermal lymphatics, which may or may not be apparent on skin biopsy. The tumor of inflammatory carcinoma is classified T4d. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings. In addition to the clinical picture, however, a biopsy is still necessary to demonstrate cancer either within the dermal lymphatics or in the breast parenchyma itself.

Skin of Breast

Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4d may occur in T1, T2, or T3 without changing the classification.

Regional Lymph Nodes (N)

Macrometastasis

Cases in which regional lymph nodes cannot be assessed (previously removed or not removed for pathologic examination) are designated NX or pNX. Cases in which no regional lymph node metastasis is detected are designated N0 or pN0.

In patients who are clinically node-positive, N1 designates metastasis to one or more movable ipsilateral axillary lymph nodes, N2a designates metastasis to axillary lymph nodes that are fixed to each other (matted) or to other structures, and N3a indicates metastasis to ipsilateral infraclavicular lymph nodes. Metastasis to the ipsilateral internal mammary nodes are designated as N2b when they are detected by imaging studies

(including CT scan and ultrasound, but excluding lymphoscintigraphy) or by clinical examination and when they do not occur in conjunction with metastasis to the axillary lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as N3b when they are detected by imaging studies or by clinical examination and when they occur in conjunction with metastasis to the axillary lymph nodes. Metastasis to the ipsilateral supraclavicular lymph nodes are designated as N3c regardless of the presence or absence of axillary or internal mammary nodal involvement.

In patients who are pathologically node-positive with one or more tumor deposits greater than 2 mm, cases with 1 to 3 positive axillary lymph nodes are classified pN1a, cases with 4 to 9 positive axillary lymph nodes are classified pN2a, and cases with 10 or more positive axillary lymph nodes are classified pN3a. Cases with histologically confirmed metastasis to the internal mammary nodes, detected by sentinel lymph node dissection but not by imaging studies (excluding lymphoscintigraphy) or clinical examination, are classified as pN1b if occurring in the *absence* of metastasis to the axillary lymph nodes and as pN1c if occurring in the *presence* of metastases to 1 to 3 axillary lymph nodes. (If 4 or more axillary lymph nodes are involved, the classification pN3b is used.) Clinical involvement with histologic confirmation of the internal mammary nodes by imaging studies (excluding lymphoscintigraphy) in the absence or presence of axillary nodal metastases are classified as pN2b and pN3b, respectively. Histologic evidence of metastasis in ipsilateral supraclavicular lymph node(s) is classified as pN3c. A classification of pN3, regardless of primary tumor size or grade, is classified as Stage IIIC. A case in which the classification is based only on sentinel lymph node dissection is given the additional designation (sn) for "sentinel node"—for example, pN1 (sn). For a case in which an initial classification is based on a sentinel lymph node dissection but a standard axillary lymph node dissection is subsequently performed, the classification is based on the total results of the axillary lymph node dissection (that is, including the sentinel node).

Isolated Tumor Cells and Micrometastases

Isolated tumor cells (ITCs) are defined as single cells or small clusters of cells not greater than 0.2 mm in largest dimension, usually with no histologic evidence of malignant activity (such as proliferation or stromal reaction). If an additional immunohistochemical examination was made for ITCs in a patient with histologically negative lymph nodes, the regional lymph nodes should be designated as pN0(i−) or pN0(i+), as appropriate.

Micrometastases are defined as tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension that may have histologic evidence of malignant activity (such as proliferation or stromal reaction). Cases in which only micrometastases are detected (none greater than 2 mm) are classified pN1mi. The classification is designated as (i+) for "immunohistochemical" if micrometastasis was detected only by IHC [e.g., pN1mi (i+)].

If histologically and immunohistochemically negative lymph nodes are examined for evidence of metastasis using molecular methods [reverse transcriptase–polymerase chain reaction (RT-PCR)], the regional lymph nodes are classified as pN0(mol−) or pN0(mol+), as appropriate.

Distant Metastasis (M)

Cases where distant metastasis cannot be assessed are designated MX, cases in which there is no distant metastasis are designated M0, and cases in which one or more distant metastases are identified are designated M1. A negative clinical history and examination are sufficient to designate a case as M0; extensive imaging or other testing is not required. Note that positive supraclavicular lymph nodes are now classified as N3 rather than M1.

DEFINITION OF TNM

Primary Tumor (T)

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 will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are 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

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below

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

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis 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)

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Pathologic (pN)[a]

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

pN0(i−)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol−)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

[b]RT-PCR: reverse transcriptase/polymerase chain reaction.

pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

***Not clinically apparent* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

1.7.3 Reference:

American Joint Committee on Cancer. 2002, Breast : In AJCC Cancer Staging Handbook , 6th Ed , Springer 2002 ;pp255-281

1.8Annexure 3

1.8.1 Nottingham Prognostic Index

NPI = 0.2 ×Tumour size in cm + Stage (1, 2 & 3) +
Nottingham grade (1, 2 & 3)

Stage 1 – Node negative
Stage 2 – Up to 3 nodes +
Stage 3 – 4 or > nodes positive

1.8.2 Interpretation

< 2.4	–	Excellent prognosis
2.4 – 3.4	–	Good prognosis
3.41 – 4.4	-	Moderate prognosis
4.41 – 5.4	–	Poor prognosis
>5.4	–	Very poor prognosis

1.8.3 Reference:

Ellis IO, Pinder SE, Lee AHS, Elston CW. Tumours of the breast. In;Christopher D.M.Fletcher. Diagnostic Histopathology of tumours, Ed 2nd, Churchill Livingstone, 2001, p865.