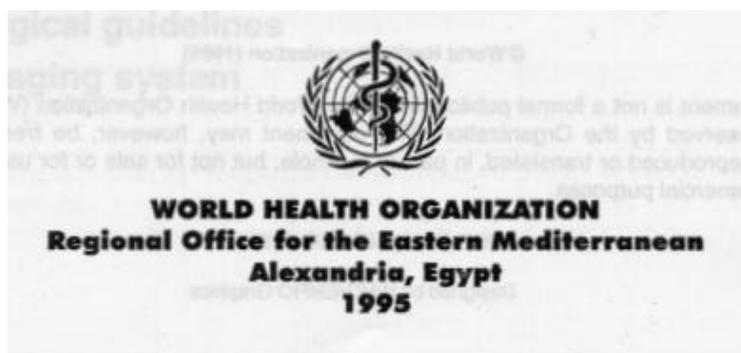


Guidelines for the Management Of Breast Cancer



Introduction

Breast Cancer is one of the most commonly occurring cancers in females in the Eastern Mediterranean Region (EMR). Unfortunately, cases are often seen in late stages and the outcome of treatment given is therefore unsatisfactory. Since no effective primary prevention is presently possible, efforts should be made to detect the disease in its early stages. Mammography has been found to be a useful procedure for early detection in elderly women but is not economically feasible as a means of mass screening in this Region, particularly because about two thirds of breast cancer patients in the EMR are premenopausal. Thus public and professional education is needed for early detection. Studies carried out in the Region have demonstrated the effectiveness of educating the public on breast self-examination in reducing the size of the primary tumour at presentation. In addition to public education, the medical profession should also be made conscious of the high rate of breast cancer in the Region.

The management of breast cancer continues to be one of the most controversial subjects in the field of oncology. There has been no universal consensus regarding the extent of surgery. The role of adjuvant radiotherapy is likewise highly debatable. Adjuvant chemotherapy has been shown to prolong the disease-free interval in premenopausal patients and improve overall survival. It has been less effectiveness in postmenopausal patients. Because of the availability of hormone receptor assays and the production of anti-estrogen medications during the last decade, there is a trend to use endocrine therapy as adjuvant treatment. The use of tamoxifen in postmenopausal women with operable breast cancer has improved disease-free and overall survival.

Amidst this confusion, clinicians are often uncertain of the best lines of treatment for individual patients. In order to minimize the problem and to help standardize the basic management of breast cancer in the Region, a task force has been created with an assignment to develop a protocol for the management of breast cancer. A meeting of the task force was convened in the Eastern Mediterranean Regional Office in Alexandria, Egypt, 18-19 December 1991. The task force took into consideration factors such as limited resources, paucity of specialized cancer centres, and cost of treatment without compromising the efficacy of the proposed protocol.

A protocol was developed to serve as guidelines in the management of breast cancer according to T.N.M.* a classification which appears on pages 27 and 28. The protocol was

* *T.N.M. Staging of tumours according to three basic components: primary tumour (T), regional nodes (N) and metastasis (M).*

further reviewed and produced in its final form by the WHO Regional Office for the Eastern Mediterranean and members of the task force during 1993.

Core clinical data

To help achieve uniformity of record keeping, a check list for recording core data of breast cancer cases has been prepared. The following data form the basis of breast cancer management. They are particularly useful where facilities are limited.

Identification data

Name _____ **Date of birth** _____ **Sex**

History

1. Presenting symptoms

Breast mass
Breast pain
Nipple discharge
Nipple or skin retraction
Axillary mass or pain .
Arm swelling
Symptoms with reference to possible metastatic spread

2. Past medical history of breast disease

3. Family history of breast cancer

4. Reproductive history:

Menstrual history
Age at first delivery
Number of pregnancies, children and abortions
Age at onset of menopause
Breast-feeding
History of hormone use including contraceptive pills

5. Past medical history

Physical examination

1. Weight and height and surface area
2. Local examination: this should be carried out in both sitting and supine position; both breasts and glandular areas should be examined:

(a) Breast mass

Size

Location (specified by clock position and the distance from the edge of the areola)

Shape

Consistency

Fixation to skin, pectoral muscle or chest wall

(b) Skin changes

Erythema

Oedema (note location and extent)

Dimpling

Infiltration

Ulceration

Satellite nodules

(c) Nipple changes

Retraction

Erythema

Erosion and ulceration

Discharge (specify)

(d) Nodal status

Axillary nodes:

Number

Location

Size

Fixation to other nodes or underlying structures

Supraclavicular nodes

3. Full clinical examination
4. Radiological investigations

Chest X-ray

Mammography, particularly if breast conservation surgery is considered

- Ultrasonography of breast (if available)
- Ultrasonography of liver, particularly in T₃ IT₄ and N₁ tumours
- Isotopic bone scan (if available)
- X-ray of spine, pelvis including femora upper end and skull lateral view (when bone scan is not available)
- Other radiological investigations, if needed
- 5. Fine needle aspiration cytology, depending on the availability of local expertise in solid tumour diagnosis
- 6. Tissues (histopathology) diagnosis
- 7. A complete blood count; liver and kidney function tests
- 8. In institutions where more advanced laboratory facilities are available, additional investigations, such as hormone receptor assays and tumour markers, can be considered.

Treatment policy

The treatment policy is planned according to the staging (TNM classification) and also according to operability. Treatment is also influenced by clinical prognostic risk factors such as lymph node status. Biological prognostic factors such as hormone receptors and DNA ploidy may be considered particularly in node negative patients. In principle, no modality of breast cancer treatment can be undertaken without microscopic proof of malignancy.

The following guidelines are applicable in most cases.

Operable tumours			
T₁	N₀	N₁	M₀
T₂	N₀	N₁	M₀
Tumours less than 3 cm. No regional lymph nodes or metastasis to movable ipsilateral axillary nodes.			
(I 2' DUI uess man i.u cm)			

1 .1

- Breast conservation surgery
- +
- Axillary clearance
- +
- External radiotherapy to breast only + a booster dose may be recommended if the edge of the local excision is not completely clear.
- External radiotherapy will be given to internal mammary chain and ipsilateral supraclavicular region in medial quadrant or central tumours, and in all pathologically positive axillary lymph nodes.
- Adjuvant systemic chemotherapy only in positive axillary nodes and high risk, node negative, (grade III) RBS (Richardson Bloom Scarf) grading.

Tamoxifen may be used in estrogen receptor (ER) positive premenopausal women.
In premenopausal women and positive nodes .CMF x 6.
In postmenopausal (<3 years) positive nodes .CMF x 6.
In postmenopausal (>3 years)- Tamoxifen 10 mg b.d. daily for a minimum of 3 years.

Contraindications for breast conservation surgery

Clinical

- a) Multiple tumours
- b) Large breast if homogenous radiation dose distribution is difficult to achieve. Decision requires consultation between surgeon and radiotherapist.
- c) Retroareolar tumours

Mammographic Multiple tumours or microcalcification away from a single primary tumour.

Pathological Intraduct component >50% of the field examined. Lack of accessible, good quality radiotherapy facilities.

In case of contraindication, mastectomy with axillary clearance is the surgical treatment of choice. For adjuvant treatment, see above.

Tumours of 3 to 7 cm. No regional lymph node metastasis or metastasis to movable ipsilateral axillary nodes. No evidence of distant metastasis.

T₂	N₀	N₁	M₀
(T₂: 3-5 cm)			
T₃	N₀	N₁	M₀
(T₃: 5-7 cm)			

- Total mastectomy + axillary clearance

External radiotherapy will be given to the internal mammary chain and supraclavicular regions in medial quadrant and central tumours and in all pathologically positive axillary lymph nodes. Chest wall radiation in T₃ cases and if more than 4 axillary nodes are positive.

Adjuvant systemic chemotherapy

In positive axillary nodes and high-risk node-negative cases

In premenopausal and

] positive nodes

postmenopausal <3 years

In postmenopausal >3 years

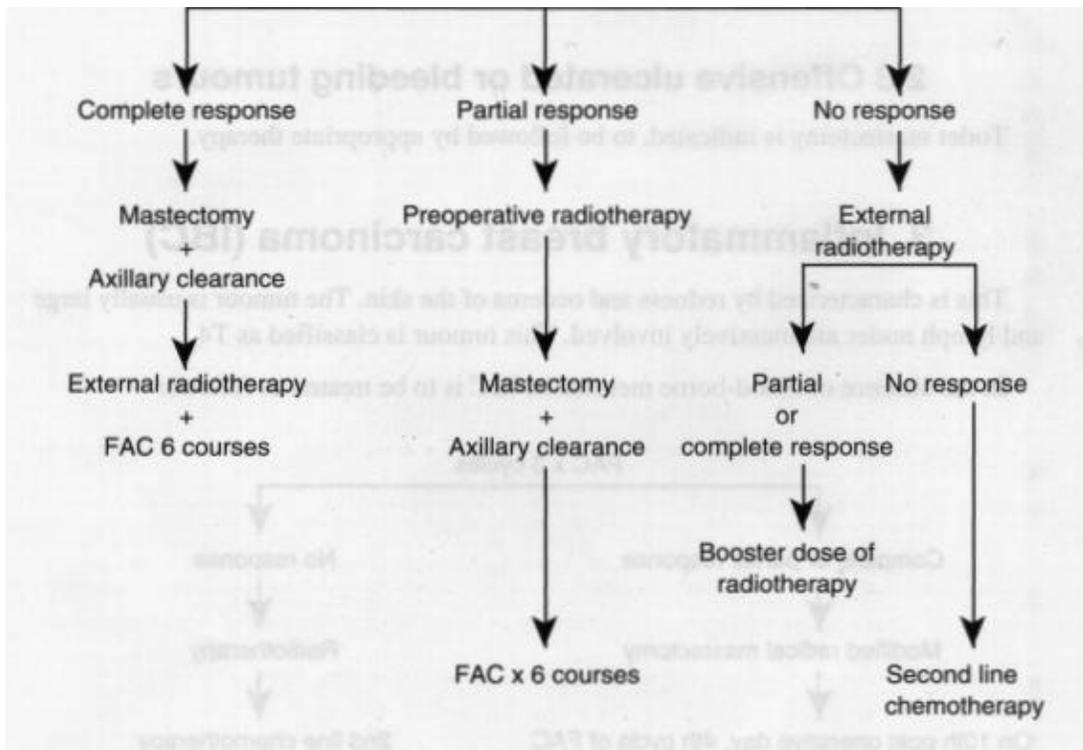
.tamoxifen 10 mg b.d. daily for 3 years

2. Inoperable (locally advanced tumours)

T₁ N₂ N₃ M₀
 T₂ N₂ N₃ M₀
 T₃ T₄, N₁ N₂ N₃ M₀
 (T₃ over 7 cm)

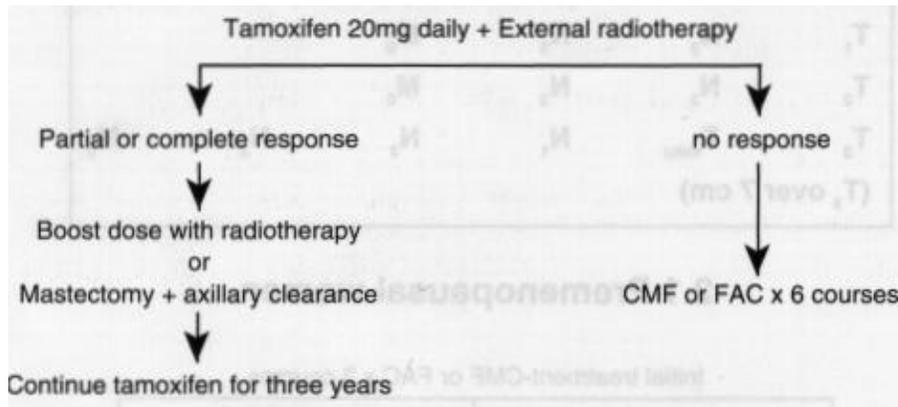
2.1 Premenopausal women

Initial treatment - CM F or FAC x 3 courses



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2.2 Postmenopausal women



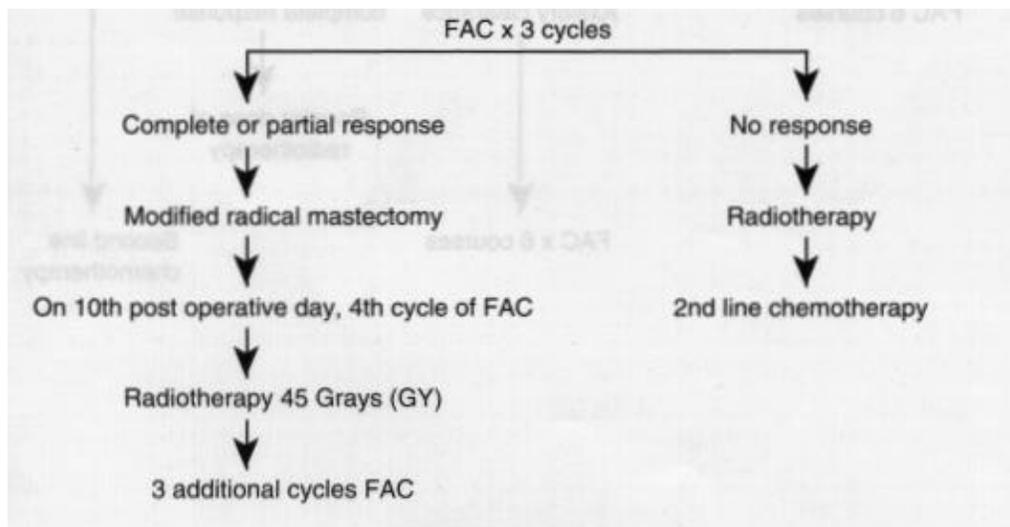
2.3 Offensive ulcerated or bleeding tumours

Toilet mastectomy is indicated, to be followed by appropriate therapy.

3. Inflammatory breast carcinoma (IBC)

This is characterized by redness and oedema of the skin. The tumour is usually large and lymph nodes are massively involved. This tumour is classified as T⁴d

In the absence of blood-borne metastasis, IBC is to be treated as follows:



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2.2 Postmenopausal women

Hormone therapy depends on the receptor status.

Evaluation of response should take into consideration regression of inflammatory signs.

4. Metastatic disease T N M

Any Any 1

Metastasis can either be present at diagnosis of the primary tumour or develop subsequently. In the latter, the disease-free interval between primary treatment and the development of metastasis influences management. The longer this period is, the more likelihood of response to hormonal therapy. On the other hand, short intervals indicate the requirement for systemic chemotherapy.

4.1 Premenopausal women

Prolonged disease-free interval or receptor positive cases: ovarian ablation by surgery or radiation castration or administration of anti-estrogens or leutenizing hormone releasing hormone (LH-RH) antagonist. Other hormones, such as progestogens or aromatase inhibitors, can also be used.

Short disease-free interval or receptor-negative or unknown status: chemotherapy in the form of CMF or FAC depending on the type of adjuvant treatment the patient has received. The number of courses would depend on the response and patient's tolerance.

4.2 Postmenopausal women

Tamoxifen is the first line of treatment. If there is no response, other hormonal treatments, such as progestogens or aromatase inhibitors, can be tried before shifting to chemotherapy.

Bone lesions usually respond to hormone and localized radiotherapy. At times, stabilization of pathological and impending fractures is needed.

Drainage of fluid when accumulated, as in pleura, is needed to relieve symptoms. For brain metastasis, corticosteroids and radiation have a good palliative effect.

Pain relief should be given priority by providing effective analgesics and narcotics such as codeine and oral morphine (see *Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee, Technical Report Series No. 804. WHO,1990*).

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2.2 Postmenopausal women

5. Carcinoma *in situ* (intraductal carcinoma)

Many views were expressed, but the Task Force agreed that mastectomy with sampling of axilla is recommended. Adjuvant treatment is decided according to lymph node status. Clinical trials in the USA and Europe on localized ductal carcinoma *in situ* have recently reported that lumpectomy plus irradiation provide good results.

6. Bleeding from the nipple

Investigations consisting of mammography, ductography, cytology and sector excision for biopsy should be done. Management depends on the pathology of the lesion.

7. Paget's disease

Paget's disease, without an associated lump, is to be treated as intraductal carcinoma. When a lump is present, treatment should be according to the TNM classification.

8. Bilateral breast cancer

Each breast disease should be treated according to the stage of the disease in the particular breast.

9. Breast cancer in the elderly (70 years and above)

In view of their age and often poor general condition, these patients can be treated conservatively by limited surgery and tamoxifen or radiotherapy and tamoxifen.

10. Breast cancer and pregnancy

In the first trimester

- a) A precious pregnancy should be allowed to continue. Surgery is performed. No adjuvant therapy is recommended. The patient should be informed of the untoward effects of retaining her fetus.

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2.2 Postmenopausal women

- b) Pregnancy should otherwise be terminated after discussion with the patient. Treatment is given according to the stage of the disease.

In the second trimester

- a) A precious pregnancy is to be continued after explaining the possible hazards to the patient. Surgery is performed without adjuvant therapy.
- b) Pregnancy is otherwise terminated after explaining the hazards to the patient of retaining the pregnancy. If the patient refuses termination, then surgery should be carried out. Radiotherapy can be given following surgery after explaining the potential risk of morbidity to the fetus.

In the third trimester

Wait until the fetus is viable, then induce labour. Carcinoma is treated according to the stage of the disease.

11. Future pregnancies

There is no solid evidence on which conception advice following completion of treatment is based. However, it may be recommended to delay pregnancy for some time, for example, for 2 to 3 years in high-risk patients.

12. Breast reconstruction

Immediate reconstructive surgery is advisable in intraductal carcinoma. Otherwise, delayed reconstruction is usually undertaken six months to one year after surgery.

13. Male breast cancer

The classification of male breast cancer is the same as in females. Due to the lack of breast tissues, early invasion of the pectoralis fascia and muscle occurs. Thus, there is no place for conservation surgery in male breast carcinoma. Mastectomy with axillary dissection is the primary mode of treatment in the early cases. However, Halstead radical mastectomy or modified mastectomy combined with radiotherapy is advised if the tumour has involved the pectoralis fascia. Adjuvant therapy depends on the stage of the disease.

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2.2 Postmenopausal women

Assessment of response to treatment

Assessment of response to treatment should be carried out at each visit and before shifting from one modality to another. Side-effects and complications of treatment should be documented in detail.

Criteria for response

1. Complete response: complete disappearance of the disease (clinical, isotopic and radiological scan)
2. Partial response: more than 50% regression of disease
3. No change: less than 50% regression or stationary disease
4. Progressive disease: 25% increase in extent of disease.

Frequency of follow-up

1. Every 3 months in the first year
2. Every 4 months in the second and third year
3. Every 6 months in the 4th and 5th years
4. Every year 5 years onwards.

At follow-up

1. For early cases
 - Assess morbidity of treatment
 - Assess performances status and measure weight
2. Look for recurrence or dissemination
3. Investigations
 - Chest X-ray: every year for 3 years
 - Ultrasound of liver: every year
 - Mammogram: every year
 - Other investigations, including bone scan or skeletal survey, according to symptoms and physical findings.

The frequency of investigations at follow-up should be modified according to the extent of the disease on presentation and risk factors.

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2.2 Postmenopausal women

Details of radiotherapy

- | | |
|-------------------------|---|
| 1. Following lumpectomy | Breast-50 Gy in 5 weeks with Co ⁶⁰ or linear accelerator
+
Booster dose to tumour bed with a small field 15-20 Gy in two weeks, or by iridium implant delivering 20 Gy |
| 2. Following mastectomy | Chest wall- 50 Gy in 5 weeks with Co ⁶⁰ or linear accelerator |
| 3. Glandular areas | Supraclavicular and axillary regions Gy in 5 weeks with Co ⁶⁰ IMC-50 Gy in 5 weeks with Co ⁶⁰ or linear accelerator |
| 4. Ovarian ablation | 15 Gy in 5 fractions to whole pelvis. 20 Gy in 5 fractions in young women (<40 years) |

2.2 Postmenopausal women

Chemotherapy regimes

1. FAC .	5 Fluorouracil	500 mg/m ²	i.v.	every 3 weeks
	Adriamycin	50 mg/m ²	i.v.	
2. CMF .	Cyclophosphamide	500 mg/m ²	i.v.	every 3 weeks
	Cyclophosphamide	600 mg/m ²	i.v.	
	Methotrexate	40 mg/m ²	i.v.	
3. MV .	5 Fluorouracil	600 mg/m ²	i.v.	every 6 weeks
	Mitomycin	15 mg/m ²	i.v.	
		Vinblastine	6 mg/m ²	i.v.

Note: – Adjuvant chemotherapy should be started within 10-15 days following surgery.

- Radiotherapy should follow two days after first course.
- During course of radiotherapy, two days of rest should be given following the chemotherapy courses.

2.2 Postmenopausal women

Hormone therapy

i. Tamoxifen	10mg b.d.
ii. Megestrol acetate	80 mg b.d.
iii. Aminoglutethemide	250 mg b.d. medical adrenalectomy
+	
Cortisone acetate	25-37.5 mg

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2.2 Postmenopausal women

Surgical procedures

1. Lumpectomy is the removal of the lump surrounded by a 2-3 cm safety margin of breast tissue. The excision is performed down to the pectoralis fascia. Occasionally a skin ellipse overlying the lump is removed to ensure better cosmetic results. In case of positive margin or frozen section, proceed to mastectomy.
2. Axillary clearance is removal of levels 1 and 2 with the axillary vein used as the cephalic boundary. The head of the pectoralis major and minor muscles are retracted and the dissection is carried out medially to the chest wall, preserving the long thoracic nerve. The apex is then left intact. The lower boundary is the fifth rib at the lowermost origin of the pectoralis minor. The posterior border consists of the subscapular fascia and latissimus dorsi muscle while trying to preserve the subscapular pedicle and thoracodorsal nerve. The lateral border is marked by the lateral edge of the latissimus dorsi muscle. The highest lymph node is marked with stitches.

Physiotherapy is to be started in the early postoperative period.

3. Total mastectomy, modified radical mastectomy and radical mastectomy are to be performed according to classical, established techniques.

2.2 Postmenopausal women

Histological guidelines

The specimen should preferably be sent to the pathologist fresh, without creating any distortion. This makes it easier for the pathologist to examine grossly the main tumour and to dissect the axillary lymph nodes. However, if the fresh specimen cannot be sent immediately to the pathologist, it should be fixed in formalin without any interference and then sent to the laboratory.

If axillary clearance is done, the highest lymph node should be marked with stitches.

As soon as the specimen is received in the laboratory, the gross examination is carried out measuring the size of the tumour in three dimensions (biggest diameter), the condition of the skin, nipple, and areola.

All the axillary lymph nodes must be sampled, irrespective of size.

If laboratory services are not available at the time of surgery, a fragment of tumour, free of fat, is to be taken and put immediately in dry ice in order to be sent for evaluation of estrogen and progesterone receptors. It is preferable to contact the laboratory twenty-four hours before the operation to make the necessary arrangements.

The following microscopic points should be included in the report:

1. Tumour

- a) Histologic type of tumour
- b) Grading of the tumour

All carcinomas should be graded according to the following histological criteria:

- 1) tubule formation
- 2) hyperchromatism and mitosis
- 3) irregularity of the size, shape and staining of the nuclei.

1. Tubule formation

Well-marked tubule formation or acinar arrangement, with cells grouped more or less regularly round the central space, is characteristic of a high degree of differentiation and indicates a favourable prognosis.

One point is awarded if the section shows well-marked tubule formation, two points if tubule formation is moderate, and three points if there is little or no differentiation with cells growing in sheets or strands.

2.2 Postmenopausal women

2. Hyperchromatism and mitosis

The greater the number of hyperchromatic or mitotic nuclei, the worse is the prognosis.

One point is awarded if only an occasional hyperchromatic or mitotic figure is seen per high power field, two points if there are two or three such figures in most fields, and three points if the nuclei are higher.

3. Irregularity of size, shape and staining of nuclei

One point is awarded if the nuclei are fairly uniform in size, shape and staining, two points if there is moderate variation and three points if pleomorphism is marked.

The points allocated for each of the three criteria are added together:

A total of 3-5 points is considered low grade (Grade I)

A total of 6-7 points is considered intermediate grade (Grade II)

A total of 8-9 points is considered high grade (Grade III)

- c) Margins of the tumour, specially when lumpectomy is done
- d) Presence or absence of lymphoplasmocytic infiltrate
- e) Lymphatic and/or vascular invasion
- f) Extent of the tumour
- g) Status of the remaining breast

2. Lymph nodes

- a) Number of lymph nodes dissected
- b) Number of lymph nodes infiltrated
- c) Capsular infiltration of the lymph nodes
- d) Whether the highest lymph node is infiltrated or not
- e) Reactive changes in the non-metastatic lymph nodes

2.2 Postmenopausal women

Symbol Meaning

TNM system

TX	Primary tumour cannot be assessed
TO	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i> : intraductal carcinoma, lobular carcinoma <i>In situ</i> , or paget's disease of the nipple with no tumour
T1	Tumour = 2 cm
T2	2-5 cm
T3	>5 cm
T4	Tumour of any size with direct extension to chest wall or Skin
a	Extension to chest wall
b	Oedema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
c	Both of the above
d	Inflammatory carcinoma
NX	Regional lymph nodes cannot be assessed (e.g. Previously removed)
NO	No regional lymph-node metastasis
N1	Metastasis to movable ipsilateral axillary nodes
N2	Metastasis to ipsilateral axillary nodes fixed to one Another or to other structures
N	Metastasis to ipsilateral internal mammary lymph nodes
MO	No evidence of distant metastasis
MI	Distant metastasis (including metastasis to ipsilateral Supraclavicular lymph nodes)

Clinical Stage

I	Ti, NO, MO
IIA	TO,N1,MO Ti, Ni, MO
	12, NO, MO

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TNM staging system for cancer of the breast*

Clinical Stage (*cont.*)

IIB	T2, Ni, MO T3, NO, MO
IIA	TO or Ti, N2, MO T2, N2, MO T3, Ni or N2, MO
IIIB	T4, any N, MO Any T, N3, MO
IV	Any T, any N, M1

* According to the Union internationale contre le cancer and the American Joint Commission on Cancer Staging and End-Results Reporting, the chest wall includes the ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscle.

Dimpling of the skin, nipple retraction, or any other skin changes, except those listed for T4b may occur in Ti, T2 OR T3 without affecting the classification.