Review Article

Male breast cancer (MBC) – a review

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Abstract

About 1% of all breast cancers occur in males. The disease has shown increasing incidence in recent decades with the aging of global populace. Due to small size of breasts in male, the disease is easier to detect, yet the lack of awareness about this disease results in late reporting of patients. This article reviews the various aspects associated with the male breast cancer (MBC).

Keywords: Male breast cancer (MBC), risk factors, tamoxifen, mastectomy, chemotherapy, awareness.

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Introduction

Male breast cancer is considered a relatively rare disease but its incidence has been reported to be substantially increasing in recent times. [1-3] The disease bears similarity with female breast cancer as far as assessment, staging and management is concerned but the lack of awareness and the absence of screening protocols leads to delayed reporting of patients. [4-5] Multiple risk factors have been identified and the disease can have unusual presentation. This article is presented with the aim of reviewing male breast cancer in the light of recent literature.

Methods

Publications in English language on male breast cancer up to 2013 were obtained by searching Pub Med database. Data extracted from these papers included demographic data, pathogenesis, clinical features risk factors, staging, complications and management. Permission for usage of current UICC (Union for International Cancer Control) TNM classification for breast cancer was duly obtained from Springer, Rights and Permissions, 3300 AA Dordrecht, The Netherlands.

Epidemiology

Male breast cancer (MBC) is a rare disease in comparison to female breast cancer. In 2011 there were 2,140 new cases [6] with the median age at diagnosis of 67 years. However few cases of this disease in younger age have also been reported in literature. [7] Male breast cancer is slightly more prevalent in African American men compared to Caucasians. [8] The epidemiologic data regarding female breast cancer is quite extensive, but relatively little is known about the etiology of male breast cancer. This difference is attributed tomany factors [9] which include:

i. The rarity of this disease, which greatly limits the application of epidemiologic methodology to studies of male breast cancer.
ii. The rarity of the cancer and hence often a small the size of sample to observe an association between the risk factor and the disease.
iii. Limited tissue availability for research presents another challenge. Breast tumors in men are small due to small size of male breast, leaving little tissue for research purposes after the requisite pathology work up for molecular and genetic studies.

The recent literature however indicates that the analytical epidemiology of male breast cancer is generally similar to the epidemiology of female breast cancer, with a potential role of factors related to genetic and environmental factors.

Genetic factors

A positive family history of breast cancer has been found to be associated with increased risk of MBC similar to the female cancer. Friedman LS et al in a population-based series of 54 MBC cases from Southern Carolina observed that 17% of MBC patients have at least one first-degree relative with breast and/or ovarian cancer. [10] Similarly, a study by Hill et al. [11] observed that 19 of 123 (15%) patients had a first-degree relative with a history of breast cancer. It was further observed in that study that the presence of a family history did not have any statistically significant relation to the age at presentation, the duration of symptoms, the stage of disease at presentation, or the overall survival of the patient. Many other population based studies conducted over the last decade have observed that about 20% of male cases had a history of breast cancer in a female relative. [12-13] In general, analysis of recent literature suggests that a positive family history of either male or female breast carcinoma among first-degree relatives is associated with a 2- to 3-fold increase in MBC risk. [9]

Multiple studies have estimated that 4% to40% of MBC can be attributed to inherited mutations [14-15] in contrast to females where the figures go up to 86%. Genes that have been implicated in the etiology of MBC include BRCA2, AR gene, cytochromeP45017 (CYP17), Klinefelter syndrome (XXY karyotype), the PTEN tumor suppressor gene associated with Cowdensyndrome, and the CHEK2 gene.

BRCA2:

The BRCA2 gene is located on chromosome 13q12-13 and has been associated with the majority of inherited BCM. [16] BRCA2 regulates the intracellular

localization and DNA-bindingability of RAD51, and loss of these abilities followinginactivation of BRCA2 is postulated to be an important event leadingto genomic instability and tumorigenesis. The commonest reported mutation in the BRCA2 gene is a 999del5 mutation. The constitutional 999del5 mutation was shown to be involved in 40% of the patients of MBC in Iceland. [17] Other important mutation in BRCA2 in MBC mentioned in literature is duplication at 9p23-24. [18] BRCA1 mutations are however rare in MBC and most studies have observed no carriers of BRCA1 mutations. Few studies have however observed BRCA1 mutations in males with breast cancer like a study by Ottini et al. which concluded that 1 of 25 (4%) MBC cases from Florence, Italy, had a mutation in BRCA1. [19].

Klinefelter Syndrome:

About 4 – 7.5% of MBC cases have been reported to have Klinefelter syndrome. [20-21] The syndrome is characterized by a rare chromosomal abnormality of 47 XXY karyotype and is prevalent in 1 in 1,000 men. It is a hereditary disorder and usually recognized at puberty by exhibition of eunuchoidhabitus, gynecomastia, and small, firm testes and increased secretion of FSH (follicle stimulating hormone) but low levels of androsterone and normal to somewhat low levels of estrogens, resulting in a high estrogen/androgen ratio. MBC manifest in Klinefelter syndrome at the age of about 58 years, which is somewhat lower than the mean age at onset of breast cancer in the absence of the syndrome. Studies have shown that there is a 49-fold increased risk of the development of breast cancer for men with Klinefelter syndrome and this increased risk is explained by abnormal hormonal stimulation of cell proliferation in mammary ductalepithelium. [22] Another theory blames the treatment with exogenoustestosterone, which is converted to estrogens in peripheral adipose tissue. [22-23] Brinton LA [23] has however stressed the need for additional well-designed epidemiologic studies to identify the subsets of patients with Klinefelter Syndrome which are at a high risk of developing MBC and to distinguish between possible predisposing factors, including alteration in levels of endogenous hormones.

AR (androgen receptor) Gene Mutation:

Germ line mutations in the AR gene have also been proposed to lead to a decrease in androgen action within the breast cells accounting for the development of MBC by the loss of a protective effect of androgens on these cells. Wooster et al. in 1992 [24] were the first to reported an association between MBC and a germ line mutation in exon3 encoding the DNA-binding domain of the AR and since then , many other workers have reported this phenomenon. [25-26] The AR gene has highly polymorphic polyglutamine (CAG) and polyglycine (GGC) tracts within the coding area of exon 1 and Song et al have recently found the CAG repeat length and AR expression to be two independent prognostic indicators in MBC patients. [26] Furthermore, the CAG repeat length within the AR gene has been proposed to be one useful molecular biomarker to identify males at increased risk of breast cancer development. [26]

CYP17 Gene:

CYP17 is another gene hypothesized to be associated with male breast carcinoma. This gene codes for the cytochrome P450c17a enzyme which is involved in the synthesis of estrogens and androgens. Young I E et al in 1999 published a case-control study from the South East of Scotland showing that a polymorphism of the CYP17 gene is associated with an increased risk of MBC. [27] But more evidences are needed to establish the relation between CYP17 mutations and MBC.

Cowden Syndrome:

Cowden syndrome is an autosomal dominant cancer susceptibility syndrome characterized by multiple hamartomas and is associated with germ line mutations in the PTEN tumor suppressor gene. Fackenthal JD et al after studying two cases of Cowden's syndrome with MBC proposed PTEN gene mutations syndrome to contribute to development and early occurrence of MBC. [28]

CHEK2:

CHEK2 is a kinase that mediates cellular responses to DNA damage and acts as a cell cycle checkpoint. A protein truncating mutation 1100delC in exon 10 abolishes the kinase function of CHEK2 and has been found to impartan increased risk of MBC [29] though

some studies failed to demonstrate such relationship. [30]

Epidemiological risk factors

Several epidemiologic risk factors have been mentioned in literature in association with MBC including disorders associated with elevated estrogen levels, dietary factors, testicular disorders, benign breast disorders and occupational/environmental exposures.

Elevated estrogen levels

The increased estrogen levels in various states have been studied because estrogen-related risk factors have been strongly implicated in the etiology of female breast cancer. Accordingly the following factors which induce hyperestrogenism have been mentioned in literature to be associated with MBC:

1. Obesity
2. Trans-sexuality
3. History of prostate cancer
4. Liver cirrhosis

Testicular disorders

Various testicular abnormalities including cryptorchidism, post-mumps orchitis, testicular injury, post orchidectomy and congenital inguinal hernia have been associated with an increased risk of MBC. The testicular disorders are often associated with deficient androgen production, which may increase the risk of MBC.

Dietary Risk Factors:

Few studies have addressed the role dietary factors in MBC. Meat consumption has been found to be a risk factor in studies by Xu K[31] and Hsing et al [32] though Rosenblatt et al failed to illustrate any such association. [33] On similar lines, evidences for a protective association between fruit and vegetable intake and MBC risk are also inconsistent. Somestudies [31] have suggested protective effect for fruit and vegetable consumption, whereas others [33] did not find any statistically significant association. Chronic alcoholism has been found to cause 2-6 fold increase in risk of MBC. [34]

Occupational exposures:

Occupations involving exposure to high temperatures, night at light, electromagnetic waves, [35] chemicals (like polycyclic aromatic hydrocarbons (PAH), nitrogen oxides, nitrosamines, metal fumes) and fuels [36] (gasoline, vehicular combustion products) have been proposed to have association with MBC but without conclusive evidences.

Pathophysiology

Approximately 90% of MBCs are invasive ductal carcinomas. Male breasts lack terminal ductal lobular units, thus lobular carcinoma is extremely rare accounting for only 1.5% occurring predominantly in cases with estrogenic exposure. Ductal carcinoma in situ (DCIS) accounts for about 7% of cases and occurs more frequently in an intraductal papillary form, and is more often low-grade. Paget's disease and inflammatory breast cancer are rare variants of MBC.

Approximately 85-93 percent of MBCs express estrogen receptor (ER progesterone receptor (PR). [37] As with female breast cancer, rates of hormone receptor positivity increase with age. ER/PR expression by carcinoma cells is considered to provide a growth advantage as shown by the positive association between the phenotype (ER+/PR+) and high proliferative activity. [38] Androgen receptor - (AR) expression is detected in 34 to 95 percent of MBCs but there are no reports of association between AR expression and other clinic-pathologic features or measures of outcome. [39] HER2/neu (Human Epidermal Growth Factor Receptor 2) amplification and/or overexpression has been seen in only 2-5% of cases and Wang-Rodriguez J et al in 2002 found Her2-neu was associated with shorter disease-free survival and correlated with positive lymph nodes. [40] Axillary lymphadenopathy is present in 40-55% cases and is an important prognostic factor as in female breast cancer. [41]

Clinical features

The commonest presentation of male breast cancer is a painless hard, fixed lump in the sub-areolar region in 75% of cases. [41] The nipple involvement occurs earlier then in the female cancer. Other less common symptoms include nipple discharge, nipple retraction or a skin lesion such as an ulcer. However, there are reports of disease presenting in an unusual form. Serra R et al reported a 70-year-old man who presented with superficial vein thrombosis

of right upper limb and on evaluation had invasive ductal carcinoma. [41] Lee ZH reported MBC presenting as metastases to face and buccal cavity. [42]

The rarer variants of MBC include Paget's disease and inflammatory cancer. Paget's disease presents frequently as ulceration, eczema, nipple discharge, bleeding, and crust formation and 50% of the cases have an associated breast mass, positive lymph nodes, or both. The symptoms are usually present for 6 months or more before the diagnosis is made. [43-44] Inflammatory cancer presents as erythema and thickening like in females. [45] Cases of synchronous bilateral breast cancers (invasive as well as in-situ) are also reported in literature, [46-47] signifying the importance of evaluation of both breast even in absence of bilateral symptoms.

Differential diagnosis

i. Gynecomastia
ii. Fat necrosis
iii. Breast metastases
iv. Lymphoma

Diagnosis /Screening

Thorough clinical examination is the corner stone in the evaluation of symptoms related to breasts in male. If the clinical features are equivocal or suggestive of malignancy, then additional evaluation with mammography and/or ultrasound/ may be appropriate. MRI studies are indicated if chest wall invasion is suspected.

The patients having high risk of breast cancer (family history, genetic predisposition, personal history of breast cancer) are recommended screening measures including monthly breast self-examinations, semi-annual clinical breast examinations, and baseline followed by yearly mammography if gynecomastia or breast density is seen. [48]

Staging

Staging for male breast cancer anal is done currently by seventh edition of the staging system that has been described by the AJCC and the International Union against Cancer [49] as shown in Tables 1-5.

Management

The standard treatment for male breast cancer is modified radical mastectomy with sentinel node biopsy. About 90% of these tumors are hormone-receptor positive; hence, tamoxifen is the standard choice for adjuvant chemotherapy.

The outcomes of breast conserving surgeries (BCS) like lumpectomy in MBC have recently got attention and multiple studies have been published in last few years. Cloyd JM et al in 2013 found the breast cancer-specific survival to be unaffected by the type of surgery [50] though, in another study, they concluded that the men with breast cancer are less likely to receive lymph node staging or adjuvant radiation therapy following breast conserving surgeries (BCS) compared to women. [51]

Radiation therapy has a role in locoregional disease management like in female breast cancer but recent data shows great underutilization of this modality of cancer management in MBC with regional spread. [52]

Health Education

There is a need to increase awareness about MBC so that the cases may be detected in early stages. [4] Increased awareness is also important to prevent the attrition of patients before any active management or during follow-up. Male self breast examination (MSBE) is a simple screening method and can be performed independently and should be promoted among men who are at high risk for breast cancer. [53]

Conclusion

Breast cancer in males is a rare disorder but has shown an increasing trend in recent times. There is a tendency in patients to report late in spite of symptoms. The disease has multiple risk factors and is treated by surgery and adjuvant therapy. There is a need to improve awareness among masses and general practitioners about the disease to achieve the aim of early detection of MBC.

Acknowledgement

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TABLES 1-5

Table 1. Primary Tumor (T)[a,b]

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma *in situ*.
Tis (DCIS)	DCIS.
Tis (LCIS)	LCIS.
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension.
T1mi	Tumor ≤1 mm in greatest dimension.
T1a	Tumor >1 mm but ≤5 mm in greatest dimension.
T1b	Tumor >5 mm but ≤10 mm in greatest dimension.
T1c	Tumor >10 mm but ≤20 mm in greatest dimension.
T2	Tumor >20 mm but ≤50 mm in greatest dimension.
T3	Tumor >50 mm in greatest dimension.
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).[c]
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion.
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peaud'orange) of the skin, which do not meet the criteria for inflammatory carcinoma.
T4c	Both T4a and T4b.
T4d	Inflammatory carcinoma.

DCIS = *ductal carcinoma* in situ; LCIS = lobular carcinoma *in situ*.

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Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.

[b]The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

[c]Invasion of the dermis alone does not qualify as T4.

Table 2. Regional Lymph Nodes (N)[a]

Clinical	
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 node(s).
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted.
	OR
	Metastases in clinically detected[b] 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[b] ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases.
N3	Metastases in ipsilateralinfraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement.
	OR
	Metastases in clinically detected[b] 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 ipsilateralinfraclavicular lymph node(s).

Clinical	
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s).
N3c	Metastases in ipsilateral supraclavicular lymph node(s).

[a]*Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.*

[b] 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.

Table 3. Pathologic (pN)[a,b]

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study).
pN0	No regional lymph node metastasis identified histologically.
Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by 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 metastases histologically, negative IHC.
pN0(i+)	Malignant cells in regional lymph node(s) ≤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.
pN1	Micrometastases.
	OR
	Metastases in 1–3 axillary lymph nodes.

	AND/OR
	Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected.[c]
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm).
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm.
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.[c]
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
	Metastases in clinically detected[d] internal mammary lymph nodes in the *absence* of axillary lymph node metastases.
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit >2 mm).
pN2b	Metastases in clinically detected[d] internal mammary lymph nodes in the *absence* of axillary lymph node metastases.
pN3	Metastases in ≥10 axillary lymph nodes.
	OR
	Metastases in infraclavicular (level III axillary) lymph nodes.
	OR
	Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes.
	OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.[c]
	OR
	Metastases in ipsilateral supraclavicular lymph nodes.
pN3a	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm).

	OR
	Metastases to the infraclavicular (level III axillary lymph) nodes.
pN3b	Metastases in clinically detected[d] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes.
	OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.[c]
pN3c	Metastases in ipsilateral supraclavicular lymph nodes.
PosttreatmentypN	
–Posttreatmentyp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND.	
–The X classification will be used (ypNX) if no yposttreatment SN or AND was performed.	
–N categories are the same as those used for pN.	

AND = axillary node dissection; H&E = hematoxylin and eosin stain; IHC = immunohistochemical; ITC = isolated tumor cells; RT-PCR = reverse transcriptase/polymerase chain reaction.

[a]Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.

[b]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).

[c]"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

[d]"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 4. Distant Metastases (M)[a]

[a]Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.	
M0	No clinical or radiographic evidence of distant metastases.
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or

	microscopically detected tumor cells in circulating blood, bone marrow, or other non regional nodal tissue that are ≤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 proven >0.2 mm.

Posttreatmentyp M classification. The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.[1]

Table 5. Anatomic Stage/Prognostic Groups[a,b]

Stage	T	N	M
0	Tis	N0	M0
IA	T1[b]	N0	M0
IB	T0	N1mi	M0
	T1[b]	N1mi	M0
IIA	T0	N1[c]	M0
	T1[b]	N1[c]	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[b]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0

Stage	T	N	M
IV	Any T	Any N	M1

[a]*Reprinted with permission from AJCC: Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 347-76.*

[b]*T1 includes T1mi.*

[c]*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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