BREAST CANCER

RISK FACTORS,AETIOPATHOGENESIS &TNM STAGING

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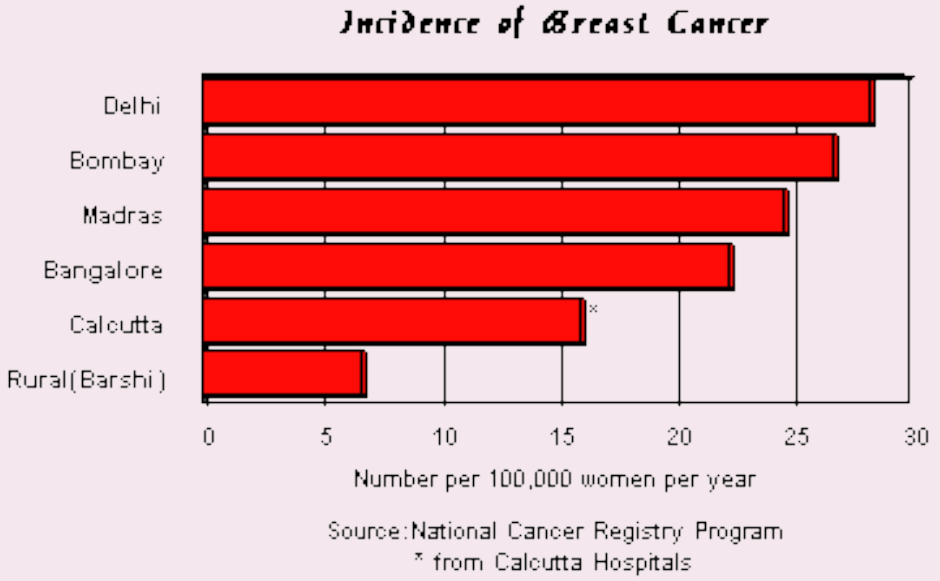
Epidemiology

- Major public health problem worldwide
- US, most frequent cancer in females & 2nd most common cause of cancer death
- In 201- 255180 new cases & 41070 deaths (American cancer Society)
- Worldwide 25% of cancer cases & 15% of cancer deaths
- 4-fold variation in mortality & 10-fold variation in incidence
- The highest incidence occurs in US, West Europe & lowest in Africa, Asia

IN INDIA

- Breast cancer is the second most prevalent cancer among Indian women.
- One in fifty eight women are affected by breast cancer in the age group of 30-70 years.
- Mainly seen in the urban areas.



Risk Factors of BREAST Cancer

(A)Established Risk Factors:

- Age
- Family history
- Genetic history
- Previous Radiation exposure
- Previous history
- Atypical hyperplasia
- Menstrual history
- Parity
- Age at 1st child birth
- Postmenopausal hormone therapy
- Obesity

(B)OTHER REPORTED RISK FACTORS:

- Using Birth control pills
- Tall height
- Regular Alcohol consumption
- Breast feeding
- Post menopausal BMI
- Jewish heritage

(C) POSSIBLE RISK:

- ✓High density breast on mammogram
- ✓Socio-economic condition
- ✓Physical activity
- ✓Dietary factors.

TABLE 79.2

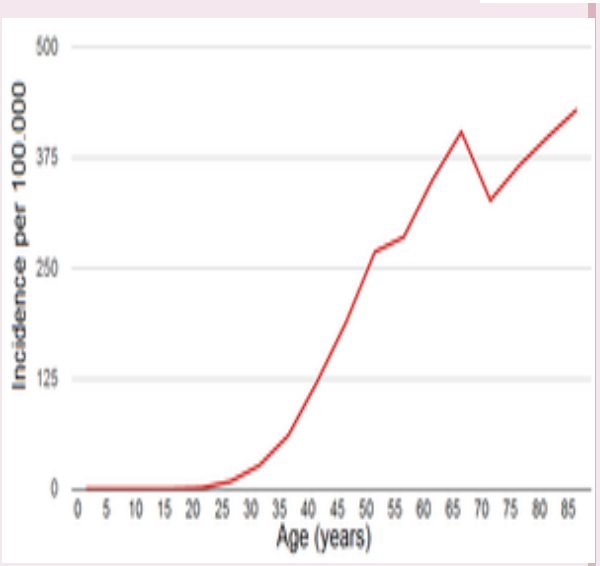
Magnitude of Risk of Known Breast Cancer Risk Factors

Relative Risk <2	Relative Risk 2–4	Relative Risk >4
Early menarche	One first-degree relative with breast cancer	Mutation *BRCA1* or *BRCA2*
Late menopause		LCIS
Nulliparity	*CHEK2* mutation	Atypical hyperplasia
Estrogen plus progesterone	Age older than 35 y for first birth	Radiation exposure before age 30 y
HRT	Proliferative breast disease	
Alcohol use	Mammographic breast density	
Postmenopausal obesity		

LCIS, lobular carcinoma in situ; HRT, hormone replacement therapy.

AGE

- Risk increases exponentially up to menopause
- About 1 out of 8 invasive breast cancers are found in women < 45 years age
- About 2 of 3 invasive breast cancers are found in women age 55 years or older.



GENDER

- Breast cancer is about 100 times more common among women than men.

RACE & ETHNICITY

- White women are slightly at more risk than African-American women but risk of death is lower.
- < 45 years of age- more common in African- American women.
- Asian, Hispanic, and Native-American women : lower risk (incidence & death)

Family history of breast cancer:

- one first-degree relative affected (mother, sister, or daughter) with breast cancer: 1.5 to 3 fold increased risk.
- Depends on: Number of relative affected, exact relationship, age at diagnosis
- Several models for risk assessment

Table 1. Breast Cancer Risk-Assessment Models

Model	Risk Factors	Comments
Gail	Age, age at birth of 1st child (if applicable), family history of breast cancer (mother, sister, daughter), number of past breast biopsies, number of biopsies showing atypical hyperplasia, race/ethnicity	Risk is underestimated in women with a genetic predisposition
Gail 2	History of affected 1st-degree family member, in addition to Gail risk factors listed above	Used extensively in clinical practice; most accurate in non-Hispanic white women receiving annual mammograms; low sensitivity
CARE	Gail model modified for black women	Good prediction
BRCA probability tools	Genetic risk factors	Estimate probability of absolute risk of developing breast cancer over time from genetic mutations

BRCA: *breast cancer gene; CARE: Women's Contraceptive and Reproductive Experiences.*
Source: References 3, 4.

Previous chest radiation

- Radiation therapy to the chest (eg. Hodgkin disease , non- Hodgkin lymphoma): significantly increased risk
- Highest risk if the radiation was given during adolescence in developing breasts, specially when within 6 months of menarche.
- Radiation treatment after age 40 does not seem to increase breast cancer risk.

Personal history :

A woman with cancer in one breast:

- 3- to 4-fold increased risk of developing second malignancy in contralateral breast
- 10-15% chance in contralateral breast cancer

Proliferative lesions:

WITHOUT ATYPIA (RR1.5-2.0)

- excessive growth of cells in the ducts or lobules of the breast tissue.
- raise a woman's risk of breast cancer slightly (1½ to 2 times normal).

They include:

- Usual ductal hyperplasia (without atypia)
- Complex fibroadenoma
- Sclerosing adenosis
- Several papillomas (called papillomatosis)
- Radial scar

WITH ATYPIA (RR4.0-5.0)

a stronger effect on breast cancer risk, raising it 4 to 5 times higher than normal.

These types of lesions include:

- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH)

Women with a family history of breast cancer and either hyperplasia or atypical hyperplasia have an even higher risk of developing a breast cancer.

MENSTRUAL PERIODS

- Early menarche (before age 12) & late menopause (after age 55) : slightly higher risk of breast cancer.

PARITY

- Nulliparous Women & first child after age 30: slightly higher breast cancer risk.

BREAST FEEDING

- Slightly lower breast cancer risk; especially if breast-feeding is continued for 1½ to 2 years

HORMONE THERAPY AFTER MENOPAUSE

- Combined HRT after menopause increases the risk of breast cancer. (RR 1.66)
- It may also increase the risk of death from breast cancer.
- Increase in risk : even with 2 years of use.
- Increases cancer in advanced stage presentation.
- Risk seems to return to that of the general population within 5 years of stopping combined treatment.

Dense breast tissue

- Breast density is partly determined genetically.
- Mammographic breast density: an important risk factor.
- >75% breast density-4.7 fold increase in odds of breast cancer development compared to >10% density (Boyd NF et al 2007).

Oral contraceptive use

- slightly greater risk of breast cancer in current users (RR 1.14).
- RR of spread of disease is less than non users.
- Women who stopped using oral contraceptives more than 10 years : decreased risk.

Lobular carcinoma in situ

- Not a true premalignant condition
- 30% risk for invasive carcinoma- usually IDC
- 1/3rd of cases are bilateral
- Often ER positive
- Clinically not palpable, mammographically silent
- Observation is enough for majority of the patient
- Pleomorphic LCIS - should be managed like DCIS

Dietary & lifestyle factors

OBESITY

- after menopause increases risk by raising estrogen levels.
- BMI>31.1 increases 2.5 fold risk than BMI <22.6

ALCOHOL

- Risk increases linearly with consumption

DIET

- High fat diet and deficiencies of nutrients like vit C, folate & beta -carotene: not proved in meta analysis

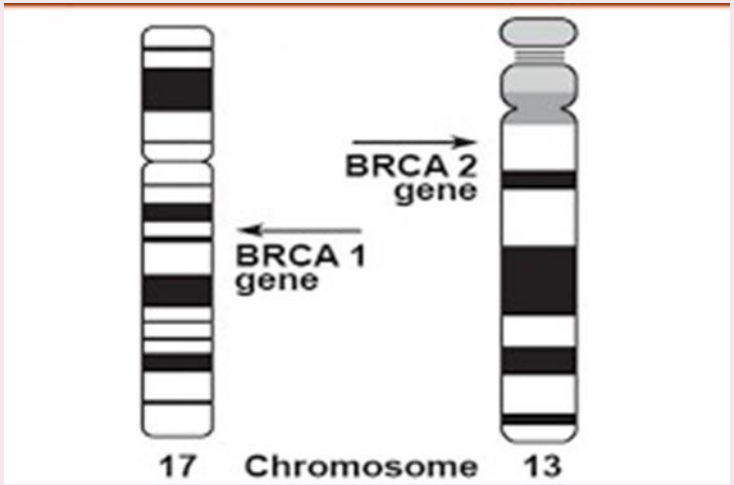
PHYSICAL ACTIVITY

- In one study from the Women's Health Initiative (WHI) as little as 1.25 to 2.5 hours per week of brisk walking reduced a woman's risk by 18%.

Variables	GAIL	CLAUSE	FORD	TYRER	MANNUAL
Personal information					
Age	Y	Y	Y	Y	Y
BMI	N	N	N	Y	N
Hormonal Factors					
Menarche	Y	N	N	Y	Y
First Live Birth	Y	N	N	Y	Y
Menopause	N	N	N	Y	Y
Personal Breast Disease					
Breast Biopsy	Y	N	N	Y	Y
Atypical Hyperplasia	Y	N	N	Y	Y
LCIS	N	N	N	Y	Y
Family History					
FDR	Y	Y	Y	Y	Y
SDR	N	Y	Y	Y	Y
Age of onset of CA	N	Y	Y	Y	Y
Bileteral Breast Cancer	N	N	Y	Y	Y
Ovarian carcinoma	N	N	Y	Y	Y
Male Breast carcinoma	N	N	Y	N	Y

GENETIC RISK FACTORS

- About 5% to 10% are hereditary.
- BRCA1 and BRCA2 mutations: The most common cause of hereditary breast cancer.



BRCA 1

- Chromosome 17q21
- Autosomal dominant
- ~ 2000 mutations, specific one (del 185) in Ashkenazi Jews, present in 1/100 vs. 1/1000 of general population.
- 50-85 % lifetime risk of breast cancer.
- 15-45 % lifetime risk of ovarian cancer, also risk of colorectal and prostate cancer
- Often triple negative and p53 mutation : Basal phenotype.
- Carriers have annual MRI from age 30

BRCA2

- Chromosome 13q12
- Autosomal dominant.
- 20-60% lifetime risk of breast cancer .
- 11-16% lifetime risk of ovarian cancer , also risk of melanoma, prostate ca, bladder ca, NHL.
- Males : 6% lifetime risk Breast cancer .
- Breast cancer at late stage than in BRCA1
- Often ER+, PR+ at high grade
- Carriers have annual MRI from age 30.

Other Rare Mutations:

. **ATM:**

- Inheriting one mutated copy :high rate of breast cancer

p53:

- Inherited mutations of the p53 tumor suppressor gene cause the ***Li- Fraumeni syndrome*** .
- increased risk of breast cancer, as well as other such as leukemia, brain tumors and sarcomas.

CHEK2:

- also causes ***Li-Fraumeni* syndrome .**
- mutated CHEK2 :breast cancer risk of about two fold.

PTEN:

- Inherited mutations cause ***Cowden syndrome*** ,
- a rare disorder with increased risk for both benign and malignant breast tumours, tumours of the digestive tract, thyroid, uterus and ovaries.

CDH1:

- Inherited mutations ***Heditary diffuse gastric cancer***.
- increased risk of invasive lobular breast cancer.

STK11:

- can lead to **Peutz-Jeghers syndrome** .
- Pigmented spots on their lips and mouths, polyps in the urinary and gastrointestinal tract.
- increased risk of many types of cancer including breast cancer.

Aetiopathogenesis of BREAST Cancer

- Mostly unknown
- Origin – Ductal
  Lobular
- Factors influencing- Breast tissue density
  Hormones eg. Estrogen
  Oncogenes
  Growth factors
  Others eg. Alcohol
  LCIS
- Cells loose their normal differentiation and control of proliferation.

AJCC 8th Edition

Breast

Ame ican Joint Committee on Cancer

Validating science. Improving patient care.

Outline

- Changes to the TNM Staging System in the 8th edition
- Established prognostic factors in primary breast cancer
- Effect of prognostic factors on TNM staging
- Inclusion of Genomic Profiles
- Clinical implications

Summary of Changes

- Two stage group options:
  - Anatomic – For use where biomarker (grade, ER, PR, HER2) not available
  - Prognostic – For use on all U.S.A. patients
- T, N, M changes
- Clarifications for post neoadjuvant therapy classification
- Inclusion of grade, HER2, ER, PR
- Inclusion of multigene panels

T, N, M Categories

T Category

- Lobular carcinoma in situ removed from Tis category
- Rounding tumor size
  - Exception for tumors between 1.0 - 1.5 mm
  - Do not round down, do not classify as microinvasive T1mi
- Multiple tumors (m) uses dimension of largest tumor
- T4b satellite tumor nodules
  - Must be separate from primary tumor
  - Must be macroscopically identified
  - Those identified on microscopic exam only do not qualify for T4b

N Category

- cN0 assigned when
  - Evaluation of nodes is possible
  - Physical exam or imaging is negative for nodal involvement
- cNX only valid if nodal basin removed
  - Cannot be examined by imaging or physical exam
- Criteria for microscopic measurement of node metastases
  - Largest contiguous tumor deposit used for pN
  - Do not use dimension of area containing several or multiple tumor deposits

M Category

- pM0 is not a valid category

- Valid M categories for clinical and pathological staging
  - cM0 – no signs or symptoms of distant mets
  - cM1 – signs, symptoms, or imaging evidence of distant mets
  - pM1 – microscopic confirmation of distant mets

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) 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 (round any measurement >1.0–1.9 mm to 2 mm).
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 macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see section "Rules for Classification")

**Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th*

Definition of Regional Lymph Nodes – Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases

cN Category	cN Criteria
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with 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
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Definition of Regional Lymph Nodes – Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)

pN Category	pN Criteria
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

*Note that imaging studies are not required to assign the cM0 category

Selecting Stage Group

Selecting Appropriate Stage Group Table

- Anatomic Stage Groups
  - Based solely on anatomic extent of cancer
  - Defined only by T, N, and M categories
- Appropriate for regions of world where biomarkers cannot be routinely obtained
- Not appropriate where biomarkers are used for patient care

Selecting Appropriate Stage Group Table

- Prognostic Stage Groups
  - Based on populations of breast cancer patients offered and mostly treated with endocrine and/or chemotherapy and/or anti-HER2 therapy
    - Includes T, N, M, tumor grade, HER2, ER, PR
    - Includes multi-gene panels
    - Can be based on clinical or pathological findings
- Preferred for patient care
- Must be used for reporting of all cancer patients in U.S.

Anatomic Stage Grouping

When T is…	And N is…	And M is…	The Stage Group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB

Anatomic Staging Groupings - 2

When T is…	And N is…	And M is…	The Stage Group is…
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Post Neoadjuvant Therapy Classification

Post Neoadjuvant Therapy Staging

- Assigned after neoadjuvant therapy and surgical resection
- ypT category
  - Largest focus of residual tumor
  - Treatment-related fibrosis near invasive tumor NOT used
  - Multiple foci of residual tumor, use (m)
- ypN category
  - Largest focus of residual tumor in nodes
  - Treatment-related fibrosis near nodal tumor deposits NOT used
- M category
  - If M1 prior to therapy, remains M1 following neoadjuvant therapy
  - Regardless of observed response to therapy
- Pathological complete response (pCR), no residual tumor
  - ypT0 ypN0 cM0 no stage group assigned

Post-neoadjuvant Prognostic Stage Groups

- This part of the AJCC Staging System is under preparation.
- It will include Anatomic TNM, Grade, ER, PR and HER2

Grade, ER, PR, HER2-neu Categories

Biomarkers

- All invasive carcinomas should have the following determined by appropriate assays whenever possible
  - – Estrogen receptor (ER) status
  - – Progesterone receptor (PR) status
  - – Human epidermal growth factor receptor 2 (HER2) status – best scored by 2013 ASCO/CAP standards
- Modified Nottingham (Bloom Scarf Richardson) tumor grade should be documented
- Marker of proliferation is also recommended
  - –Ki-67
  - – Mitotic count

Grade

- All invasive breast ca should be assigned by histologic grade
  - Nottingham modification of SBR grading system recommended
- Nottingham grade determined by totalling scores for
  - Tubule formation
  - Nuclear pleomorphism
  - Mitotic count
- Grade table to equate SBR score of points to G1-G3

G	G Definition
GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable), SBR score of 3–5 points
G2	Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points
G3	High combined histologic grade (unfavorable); BSR score of 8–9 points

ER and PR

- ER & PR expression measured primarily by IHC
- ≥1% of cells stained considered positive for ER & PR
- Multiple results always use positive results
  - If biopsy and resection specimens are tested, and
  - One is positive, while the other is negative, then
  - Use the positive results to assign the stage group

HER2

- HER2 measurement by IHC or ISH
- 2013 ASCO/CAP Guidelines provide standards
  - Sequential performance of tests to determine HER2 status
- Summary of standards
  - IHC
    - Negative: 0 or 1+ staining
    - Equivocal: 2+ staining
    - Positive: 3+ staining
  - ISH, dual probe (Fluorescent – FISH or Chromogen – CISH)
    - Possible negative:
      - HER2/CEP17 ratio < 2.0 and HER2 copy number < 4
    - Possible equivocal:
      - HER2/CEP17 ratio < 2.0 andHER2 copy number ≥ 4 but < 6
    - Possible positive:
      - HER2/CEP17 ratio ≥ to 2.0 by ISH, or
      - HER2 copy number ≥ to 6 regardless of ratio by ISH

HER2 Equivocal

- HER2 determined to be “equivocal”
  - By ISH (FISH or CISH) testing
  - Under the 2013 ASCO/CAP HER2 testing guidelines
- Categorize HER2 “equivocal” by ISH as HER2 “negative”
  - For assigning stage in Prognostic Stage Group Table

Multigene Panels

- Patients with
  - ER/PR-positive, HER2-negative, node-negative tumors
  - Size less than or equal to 5 cm

  - Combined with any of the following multigene panels
    - Oncotype Dx® recurrence score <11
    - Mammaprint® low risk score
    - EndoPredict® low risk score
    - PAM50 risk of recurrence score in low range
    - Breast Cancer Index in low-risk range

- Stage IA: Are in same prognostic category as T1a-T1b N0 M0 with ER Positive, HER2 negative

Prognostic Stage Groups

Notes for Prognostic Stage Group Table

- Prognostic value of these Prognostic Stage Groups
  - Based on populations of patients with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy
- Stage groups marked by asterixes ***
  - Changed by more than one stage group from 7th Edition
  - Due to use of grade and prognostic factors
  - Comparing 7th edition anatomic stage to 8th prognostic stage
  - Example of patient staged by 7th and 8th editions
    - Anatomic Stage Group IIB in 7th edition
    - Prognostic Stage Group IB in 8th edition

Oncotype Dx® in Prognostic Stage Groups

- Oncotype Dx® applicable only for assigning prognostic stage group to patients with
  - T1–2 N0 M0
  - ER -positive
  - HER2 -negative
- Prospective Level I data supports use for patients with score <11
- OncotypeDx® not performed, not available, or score ≥11
  - Group assigned based on anatomic and biomarker categories
- Future updates may include other multigene panels
  - When high level data available to support these assignments

Clinical Prognostic Stage Groups

- Based on history, physical exam, imaging, biopsies and biomarkers (Grade, ER, PR and HER2 status)
- Relevant to all patients, including those who will receive pre-operative systemic or radiation treatments)
- Determined prior to any treatment
- Allows determination of changes between baseline and pre-operative treatments.
- Allows comparison between groups treated with surgery first or other treatment modalities

Clinical Prognostic Stage Grouping- 1

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 MO T0 N1mi M0 T1* N1mi M0	1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB

*Includes T1mi

Clinical Prognostic Stage Grouping - 2

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T0 N1** MO T1 N1** M0 T2 N0 M0	1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

**Does not include N1mi

Clinical Prognostic Stage Grouping - 3

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T2 N1 MO T3 N0 M0	1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

Clinical Prognostic Stage Grouping - 4

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T0 N2 M0 T1 N2 M0 T2 N2 M0 T3 N1 M0 T3 N2 M0	1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC

Clinical Prognostic Stage Grouping - 5

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1 M0 T4 N2 M0 Any T N3 M0	1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

Pathologic Prognostic Groups

- Based on pathologic findings at definitive surgery and biomarkers (Grade, ER, PR and HER2, as well as multigene prognostic panels).

- Relevant to all patients treated with definitive surgery as initial treatment.

- Not appropriate for patients receiving neoadjuvant systemic or radiation treatment.

- It is the recommended staging system for use in the USA by all tumor registries.

Pathologic Prognostic Stage Grouping- 1

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Pathologic Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 MO T0 N1mi M0 T1* N1mi M0	1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
	2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

*Includes T1mi

Pathologic Prognostic Stage Grouping - 2

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Pathologic Prognostic Stage Group is…
T0 N1** MO T1 N1** M0 T2 N0 M0	1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

**Does not include N1mi

Pathologic Prognostic Stage Grouping - 3

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Pathologic Prognostic Stage Group is…
T2 N1 MO T3 N0 M0	1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA

Pathologic Prognostic Stage Grouping - 4

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Pathologic Prognostic Stage Group is…
T0 N2 M0 T1 N2 M0 T2 N2 M0 T3 N1 M0 T3 N2 M0	1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

Pathologic Prognostic Stage Grouping - 5

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is	And PR Status is	The Pathologic Prognostic Stage Group is…
T4 N0 M0 T4 N1 M0 T4 N2 M0 Any T N3 M0	1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
	2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

Clinical Implications of the New Staging System

TNM Groups	Anatomic Staging Groups	Pathologic Prognostic Staging Groups
T1 N0 M0	IA	IA IB
T1 N1 M0	IIA	IA IB 2A
T3 N0 M0	IIB	IA IB IIA IIB IIIA
T3 N2 M0	IIIA	IA IB IIA IIB IIIA

Genomic Profile for Pathologic Prognostic Staging

- Level 1 evidence generated with the 21-gene assay suggests that:
  - When the Recurrence Score is less than 11, and
  - The Tumor is a T1-2 N0 M0
    - Any Grade
    - HER2-negative
    - ER-positive
    - Any PR
  - Then the Pathologic Prognostic Stage is: IA

- Other Genomic Profiles (MammaPrint, ProSigna, Breast Cancer Index, EndoPredict, IHC4, etc.) provide similar prognostic information, although appropriately formatted data are as yet unavailable.

Selection of Genomic Profile for Prognostication

The AJCC Manual is NOT a practice guideline and the Expert Panel is NOT a guideline developer. Physicians are to use the best information available at the time to plan treatment, including the determination to use (one or several) genomic panels, and which genomic panel to select.


Thank
You …