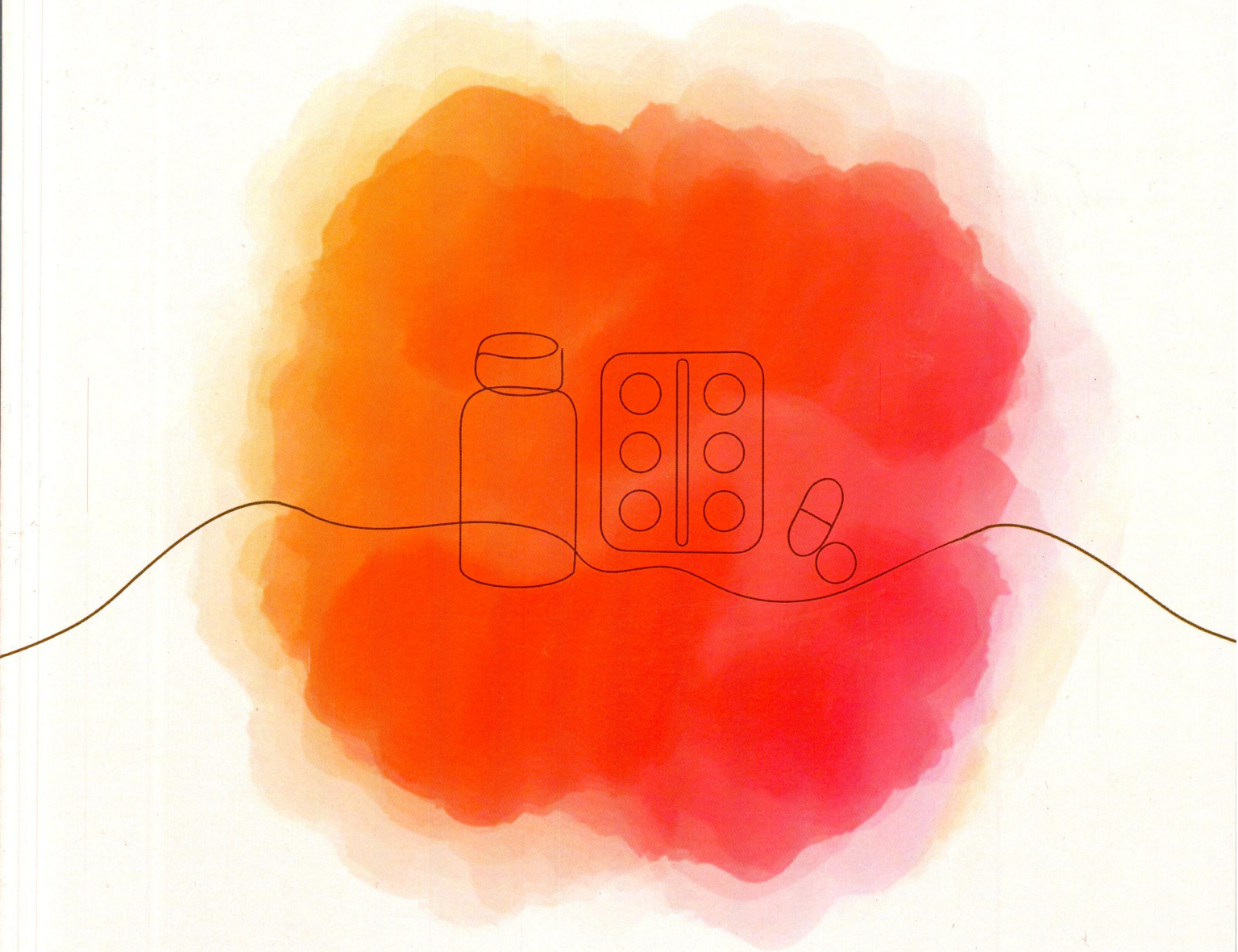
VOLUME-V

PrepLadder



MEDICINE

NEET SS VERSION 4.0

PREFACE

Dear Dreamer,

Pat your back and reward yourself, today you've taken an important step towards reaching your dream. Mark Twain said, "the secret of getting ahead is getting started". You have started in the right direction.

The next few months until your targeted exam or exams are crucial. Every moment counts and each step you take now, will help you reach your goal, your dream.

PrepLadder is your partner in this journey. We are in this together. So, don't worry, do not stress. Just focus on your preparation and stay positive. Set daily targets, achievable and realistic ones. If you pass the target, celebrate. However, if you miss a daily target, forgive yourself, move on and do better the next day.

Always remember that you are special and unique. Do not compare your preparation, your speed, your abilities with others. Believe us, it doesn't help.

Practice a lot. Solve the QBank. Take Grand Tests. Review your performance. But don't let ranks and results drag you down. Rather use them as a guiding light to know your strengths and weaknesses, to increase your speed and accuracy, and to get yourself ready for the exam day.

If you have a doubt or a question, ask us. We are here.

Lastly and most importantly. take care of yourself. You and your health are precious. So, keep up with exercise, eat healthy, get enough sleep and care for yourself.

We're behind you, cheering you on to the finish line. You might be feeling stressed, overwhelmed, and so tired, but you're nearly there. Give it everything you've got, and know that whatever happens next, you've got what it takes for the life you want. You are a Champion.

Own Your Dream
Team PrepLadder

CONTENTS

MEDICINE VOLUME - 5

1. MEDICAL ONCOLOGY

1.	Breast Cancer Part 1	2
2.	Breast Cancer Part 2	6
3.	Breast Cancer Part 3	12
4.	Treatment of Breast Cancer Part 1	16
5.	Treatment of Breast Cancer Part 2	20
6.	Metastatic Breast Cancer	23
7.	Testicular Cancer Part 1	28
8.	Testicular Cancer Part 2	32
9.	Testicular Cancer Part 3	36
10.	Pancreatic Cancer Part 1	39
11.	Pancreatic Cancer Part 2	45
12.	Renal Cell Carcinoma Part 1	49
13.	Renal Cell Carcinoma Part 2	53
14.	Urinary Bladder Cancer	57
15.	Gastric Neuroendocrine Tumors Part 1	63
16.	Gastric Neuroendocrine Tumors Part 2	70
17.	Pancreatic Neuroendocrine Tumors	77
18.	Lung Cancer Risk Factors and Pathogenesis	84
19.	Lung Cancer Clinical Features Diagnosis	90
20.	Lung Cancer Staging	95
21.	Treatment Small Cell Lung Cancer	102
22.	Treatment Non Small Cell Lung Cancer	105
23.	Thymic Tumors	109
24.	Prostate Cancer Part 1	111
25.	Prostate Cancer Part 2	118
26.	Prostate Cancer Treatment	122
27.	Thyroid Cancer Part 1	126
28.	Thyroid Cancer Part 2	132
29.	Thyroid Cancer Part 3	134

30.	Evaluation of Thyroid Nodule	135
31.	Thyroid Cancer Toxic Multinodular Goiter	138
32.	Thyroid Cancer Non Toxic Goiter	141
33.	Paraneoplastic Syndromes Part 1	146
34.	Paraneoplastic Syndromes Part 2	149
35.	Hematological Paraneoplastic Syndromes	153
36.	Cholangiocarcinoma Part 1	158
37.	Cholangiocarcinoma Part 2	164
38.	Gall Bladder Cancer	166
39.	Hepatocellular Carcinoma	170
40.	Hepatocellular Carcinoma Diagnosis	175
41.	Hepatocellular Carcinoma Treatment Part 1	179
42.	Hepatocellular Carcinoma Treatment Part 2	184
43.	Hepatocellular Carcinoma Treatment Part 3	187
44.	Gastric Cancer Part 1	191
45.	Gastric Cancer Part 2	195
46.	Esophageal Cancer	198
47.	Gastric Lymphoma	204
48.	Gastrointestinal Stromal Tumors	207
49.	Small Bowel Neoplasm	208
50.	Head and Neck Cancer Part 1	211
51.	Head and Neck Cancer Part 2	214

2. EMERGENCY MEDICINE

1.	Approach to The Patient Coma	219
2.	COMA Part 1	223
3.	COMA Part 2	227
4.	Management of Coma	229
5.	ECMO	233
6.	Severe Brain Dysfunction	235
7.	Metabolic Encephalopathy Part 1	239
8.	Metabolic Encephalopathy Part 2	244
9.	Hypoxic Ischemic Encephalopathy	247
10.	Approach to Shock Part 1	251
11.	Approach to Shock Part 2	254

12.	Management of Shock Part 1	258
13.	Management of Shock Part 2	264
14.	Cardiogenic Shock and Pulmonary Edema Part 1	270
15.	Cardiogenic Shock and Pulmonary Edema Part 2	274
16.	Cardiogenic Shock and Pulmonary Edema Part 3	281
17.	Sudden Cardiac Death Part 1	287
18.	Sudden Cardiac Death Part 2	293
19.	Sudden Cardiac Death Part 3	296
20.	Respiratory Failure	303
21.	Complications of Mechanical Ventilator	307
22.	Approach to Patient with Critical Care Illness	311
23.	Complication of Critical Illness Part 1	317
24.	Complication of Critical Illness Part 2	320
25.	Critical Illness Polyneuropathy	323
26.	Venomous Snake Bite Part 1	326
27.	Venomous Snake Bite Part 2	334
28.	Scorpion Bite	340

3. NEUROLOGY

1.	Traumatic Brain Injuries	343
2.	Chronic Fatigue Syndrome	350
3.	Peripheral Neuropathy	353
4.	Dysautonomia	370
5.	Trigeminal Neuralagia	377
6.	Prion Disease	379
7.	Guillain Barre Syndrome Part-1	382
8.	Guillain Barre Syndrome Part-2	386
9.	Myasthenia Gravis Part-1	392
10.	Myasthenia Gravis Part-2	398
11.	Duchenne Muscular Dystrophy and BMD	403
12.	Mitochondrial Myopathies	407
13.	Progressive Supranuclear Palsy and CBS	414
14.	Amyotrophic Lateral Sclerosis and MND	416
15.	Diseases of Spinal Cord Part-1	421
16.	Diseases of Spinal Cord Part-2	425

17.	Encephalitis	432
18.	Neurocysticercosis	436
19.	Meningitis Part-1	440
20.	Meningitis Part-2	446
21.	Ataxic Disorders	451
22.	Chorea and Involuntary Movements	456
23.	Other Causes of Dementia	466
24.	Parkinsonism	471
25.	Lewy Body Dementia	476
26.	Vascular Dementia	479
27.	Fronto - Temporal Dementia	481
28.	Alzheimer's Disease	483
29.	Neuromyelitis Optica	491
30.	Multiple Sclerosis	494
31.	Trigeminal Autonomic Cephalgias	500
32.	Migraine and Tension Type Headache	508
33.	Subarachnoid Hemorrhage	514
34.	Intracerebral Hemorrhage	519
35.	Endovascular Therapy	524
36.	Transient Ischemic Attack	528
37.	Ischemic Stroke	533
38.	Epilepsy	542

MEDICAL ONCOLOGY

1 BREAST CANCER-PART 1

Breast Cancer

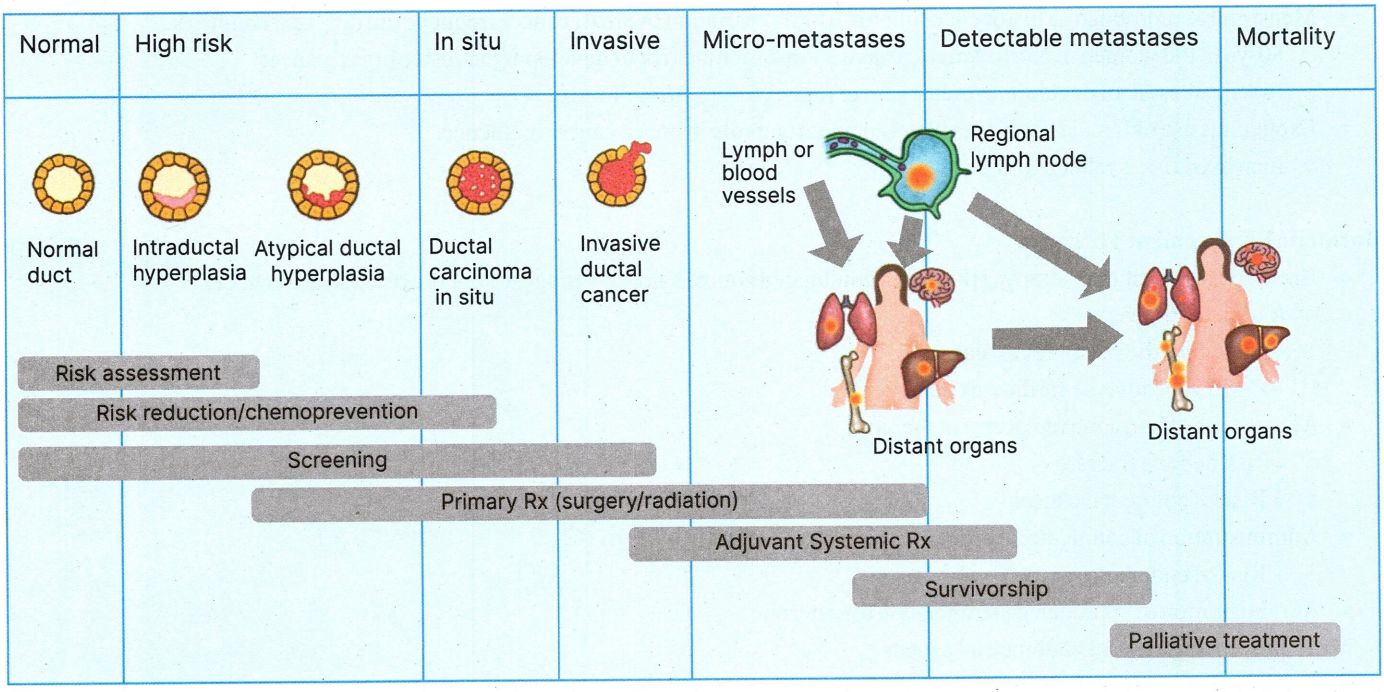
Conceptual & biological issues of breast cancer

- Breast cancer is a malignant proliferation of epithelial cells that line the ducts/lobules of the breast
- Epithelial malignancies of the breast:
  - M/c cancer in women, excluding skin cancer
  - Account for 1/3rd of all cancers in women
  - Mortality reduced by 1/3rd in past decade due to early diagnosis & prompt management

Spectrum of conditions for which different clinical considerations must be made

1. Risk assessment
2. Prevention
3. Screening
4. Evaluation
5. Local and adjuvant systemic treatments
6. Metastatic therapies
7. Survivorship issues

Breast cancer continuum



- Sub-types include expression of:
  - Estrogen receptor (ER)
  - Human epidermal growth factor receptor-2 (HER-2)
  - BRCA1 & BRCA2 - Tumor suppressor genes

    ↑

    Germline mutation & Somatic mutation

- Identifiable somatic mutations include:
  1. Mammalian target of Rapamycin -mTOR
  2. Cyclin-dependent kinase (CDK) 4 & 6
  3. Sphosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)
- Immune checkpoint inhibitors are applied to a specific type of breast cancer

Risk Factors

00:12:54

- 75% of breast cancers occur in women >50 years
- May occur in 20s, 30s & 40s
- Sex hormone-dependent disease
  - ↑ activity of estrogen receptor & its ligands
  - ↑ estradiol
  - ↑ estrone
- ♂:♀ is around 1:150
- Estrogen exposure:
  - Endogenous
  - Exogenous
- Risk is higher in women with early menarche
  - ↑ by exogenous HRT
- Low risk in:
  - Women without functioning ovaries
  - Early menopause
  - Women who never received combination estrogen/progesterone replacement therapy
- Duration of maternal nursing correlates with risk reduction, independent of parity/age
- Menstrual & reproductive history account for 70-80% variation in breast cancer frequency in different countries
  - 80-year-old women in North America have a 1 in 9 lifetime risk of developing invasive breast cancer
  - In Asia, the risk of developing breast cancer ranges from 1 in 5 to 1 in 10
- Exogenous use of female hormones plays an important role in breast cancer incidence
  - Increased risk is related to OCPs

Hormone Replacement Therapy

00:20:03

- Hormone replacement therapy (HRT) with conjugated equine estrone + progestins: ↑ the risk of breast cancer
  - If used for 6-7 years:
    → Doubles the risk of breast cancer
    → ↑ Risk of adverse cardiovascular events
- Advantages of hormone replacement therapy:
  - ↓Risk of bone fracture
  - ↓ Risk of colorectal cancer
- Administration of conjugated estrogens alone
  - ↑ Risk of endometrial cancer
- Administration of conjugated estrogens + Progesterone
  - Prevent high risk of endometrial cancer
- Single-agent estrogen replacement therapy in women who have undergone hysterectomy
  - No significant ↑ risk of breast cancer
- Epidemiological studies demonstrate that discontinuation of HRT reduces risk of breast cancer
- HRT is contraindicated in women previously diagnosed with breast cancer (expression of ER)
  - HRT counteracts the effectiveness of anti-neoplastic endocrine therapies

- Intravaginal estrogen therapy: Atrophic vaginitis
  - Associated with anti-estrogenic endocrine therapies
  - Systemic absorption leads to development of breast cancer
  - Avoided in high-risk patients of breast cancer

Other Risk Factors 00:29:25

Diet	• Controversial role • Associative links exist between breast cancer & total calorie & fat intake • Increased risk of breast cancer with: 1. High-calorie diet 2. Excess fat diet
Dyslipidemia	• Central obesity • Metabolic syndrome • Type 2 Diabetes Mellitus
Alcohol	• Moderate alcohol consumption ↑ risk of breast carcinoma • Folic acid supplementation modifies the risk in women who consume alcohol
Depression	• Associated with occurrence & recurrence of breast cancer
Benign pathologic findings	• Atypical hyperplasia • Radial scars
Prior Radiation	• Radiation therapy in adolescents & childbearing groups • Women <30 years exposed to radiation by multiple fluoroscopies (200-300 cGy) • Treatment for Hodgkin's disease (>3600 cGy) • Minimal carcinogenic effect of radiation exposure after 30 years of age • Radioactive iodine therapy for thyroid disease is not associated with ↑ risk of breast cancer
Mediastinal Radiation	• Powerful risk factor for breast carcinoma in younger women for lymphoma

Inherited Germline Susceptibility Factors 00:45:01

- Family history is recognized as a risk factor for breast cancer
  - 1st degree history (mother/sister) : 30-50% risk
  - Family history in other relatives : 10-15% risk

Genetics of Breast Cancer

1. Inherited causes
2. Germline genetic differences among individuals & acquired
3 .Somatic genetic changes within cancers

Inherited causes

- Mutations, more properly termed as Single-nucleotide polymorphisms (SNPs)
  - Synonymous SNPs:
    Do not change the encoded amino acid in the affected protein due to redundancy in genetic code
    ↓
    → No clinical significance

  - Non-synonymous SNPs:
    Change in the amino acid of the protein does not change the function of protein

↓

→ Clinically insignificant

- In most women, an increased risk of breast cancer is associated with breast cancer in a family member with:
  - Multigene germline susceptibility (M/c)
  - Exposure to environmental & lifestyle risk factors
- 10% of human breast cancers can be linked to single inherited germline SNP
- BRCA gene mutations
  - BRCA1: Chromosomal loci 17q21
  - BRCA2: Chromosomal loci 13q12
  - Greatest clinical significance in assessing genetic risk
  - If the mutation is inherited from parents, then:
    - → Risk of breast cancer: 60-80%
    - → Risk of ovarian cancer: 33%
- Cancers that arise within a BRCA1-mutated patient: Triple-negative breast cancers
  - ER negative
  - PgR negative
  - HER-2 negative
- Men who carry a mutant allele of BRCA-2 gene
  - ↑Risk of breast cancer & prostate cancer
- BRCA-2 mutation (Females > Males)
- SNPs in BRCA-1 & BRCA-2 are seen in:
  - < 1% of general population
  - < 5% of all patients with breast cancer
- 20% of women with triple negative breast cancers: Positive for deleterious germline BRCA-1 SNPs
- Compared to BRCA1 carriers, Cancers that arise in BRCA-2 contexts are more likely ER-positive
- In men with breast cancer, BRCA2> BRCA1

- **Other germline mutations:**
  - p53 : Putative tumor suppressor gene, also the part of Li-Fraumeni familial cancer syndrome
  - PTEN : Accounts for Cowden syndrome
  - PALB-1
  - They are readily detected in blood test of normal circulating WBCs

- **Consensus guidelines on who should be tested include:**
  - Women with a family history of breast cancer
  - Any breast cancer patient with triple-negative breast cancer with
  - Age < 40 years
  - Synchronous/metachronous contralateral breast cancer
  - Personal history of ovarian cancer
  - First-degree relative with breast or ovarian cancer

2 BREAST CANCER PART-2

PREVENTION OF BREAST CANCER

00:00:11

- Screening strategies: To prevent disease progression
  - Diet, Exercise
  - Avoidance of combined estrogen/progestin HRT: Reduces the associated ↑ risk of breast cancer
  - Bilateral prophylactic mastectomies: ↓ risk of breast cancer by > 95%
  - Because breasts are not encapsulated organs

    ↓

    Some normal tissues are left behind (In prophylactic mastectomy)

    ↓

    New breast cancer
  - Prophylactic mastectomy is most often chosen by germline genetic risk: ↓ mortality
  - For women with average or only mildly elevated risks such as diagnosis of unilateral breast cancer, survival is not ↑ by prophylactic mastectomy.
- Chemoprevention to lower breast cancer is achieved with treatment:
  - Directed towards ER/Estrogen signaling pathways
  - Includes administration of Selective estrogen receptor modulators(SERMs) & Aromatase inhibitors
  - Aromatase inhibitors should be applied in postmenopausal women → Result in paradoxical ↑ in circulating estrogen (with functioning ovaries).
- Chemoprevention with SERMs or aromatase inhibition

  ↓

  ↓ the risk of ER +ve breast cancer by 50%

  ↓

  No effect on ER -ve breast cancers

- Prophylactic bilateral oophorectomy & salpingo-oophorectomy

  ↓

  BRCA1/2 deleterious SNPs

  ↓

  ↓ Breast cancer + ↓ Ovarian cancer

SCREENING FOR BREAST CANCER

00:14:02

- Screening mammography is useful for
  - Earlier diagnosis
  - Local & systemic therapy
- Overviews of 9 prospective randomized clinical trials demonstrate that Screening mammography ↓ breast cancer mortality by $1/5^{th}$ to 1/4 in women aged ≥ 50 years
- In addition to ↓ breast cancer mortality, screening mortality & early detection it helps to identify tumor stage → Plan treatment
- Parameters that improved the accuracy of mammography

1. Better technology which includes

- Digitized mammography
- Tomosynthesis

} improved the accuracy of mammography

- Routine use of magnified views

- Greater skill in interaction

2. Magnetic resonance spectroscopy
   - Higher sensitivity
   - Lower specificity than mammography

- In countries that have adopted widespread screening programs,

  ↓

  Nonrandomized, epidemiologic studies have demonstrated even greater magnitude reductions in breast cancer mortality > randomized trials

  ↓

  Annual screening is required in women aged 50-70 years & 40-50 years

- Magnetic resonance imaging is recommended for

1. Women with particularly dense breasts
2. Women whose first cancer was not detected by mammography
3. Women with an axillary breast cancer presentation but no definable breast mass on physical exam or mammography
4. High genetic risk such as BRCA1 or BRCA2 carriers
5. LiFraumeni,Cowden's or Bannayan-Riley-Ruvalcaba syndromes

- MRI might also be considered in women with a history of radiation therapy between 10-30 years

  ↓

  ↑ incidence of breast cancer

  ↓

  Planned for prophylactic mastectomy in case of any mass
- Self-examination or physical breast examinations done by a health professional has
  - Poor sensitivity
  - Poor specificity
- Screening breast imaging is not recommended for men
- Unilateral lesions in men should be evaluated in the same manner as in women sue to high index of suspicion.

EVALUATION OF BREAST MASSES

00:25:23

- Virtually all breast cancer is diagnosed by biopsy

  ↓

  Mammogram/palpation

  ↓

  No risk factors

PALPABLE BREAST MASSES

- Proper attention is given to the mass
- Most newly diagnosed breast cancer is asymptomatic
- Lesions with certain clinical features like

1. Firmness
2. Irregularity
3. Tethering or fixation to the underlying chest wall

} Worrisome for breast cancer

4. Dermal erythema or peau d'orange

- Painful masses and those that are cystic
  - O/E: Less likely malignant
- A negative mammogram /presence of a persistent lump in the breast does not exclude the malignancy
- In premenopausal women ,lesions that are either equivocal or nonsuspicious on physical examination

↓

Re-examined in 2-4 weeks

↓

During the follicular phase of menstrual cycle

- Day 5-7 : Considered the best time for breast examination
- A dominant mass in a postmenopausal woman/
- A dominant mass that persists through a menstrual cycle in a premenopausal woman

} Require evaluation like biopsy

ABNORMAL MAMMOGRAM

- Diagnostic mammography - After a palpable abnormality is detected
- Screening mammography - Performed in an asymptomatic woman with no previously identified abnormalities
- Suspicious mammographic abnormalities include

1. Clustered
2. Heterogenous
3. Linear
4. Branching microcalcifications
5. Densities (especially if spiculated)
6. New or enlarging architectural distortion

- These are suggestive of breast malignancy
- USG - Cysts/guided biopsy
- If a nonpalpable mammographic lesion has a low index of suspicion

↓

Mammographic followup in 3-6 months is reasonable

- The presence of a breast lump(persists/enlarging) and a negative mammogram\

↓

Biopsy is indicated

BREAST MASSES IN PREGNANCY OR LACTATION

- Breast cancer: 1 of 3000-4000 pregnancies
- The breast grows during pregnancy
  - Estrogen
  - Progesterone
  - Prolactin
  - HPL
- During lactation, the breast is under the influence of Prolactin

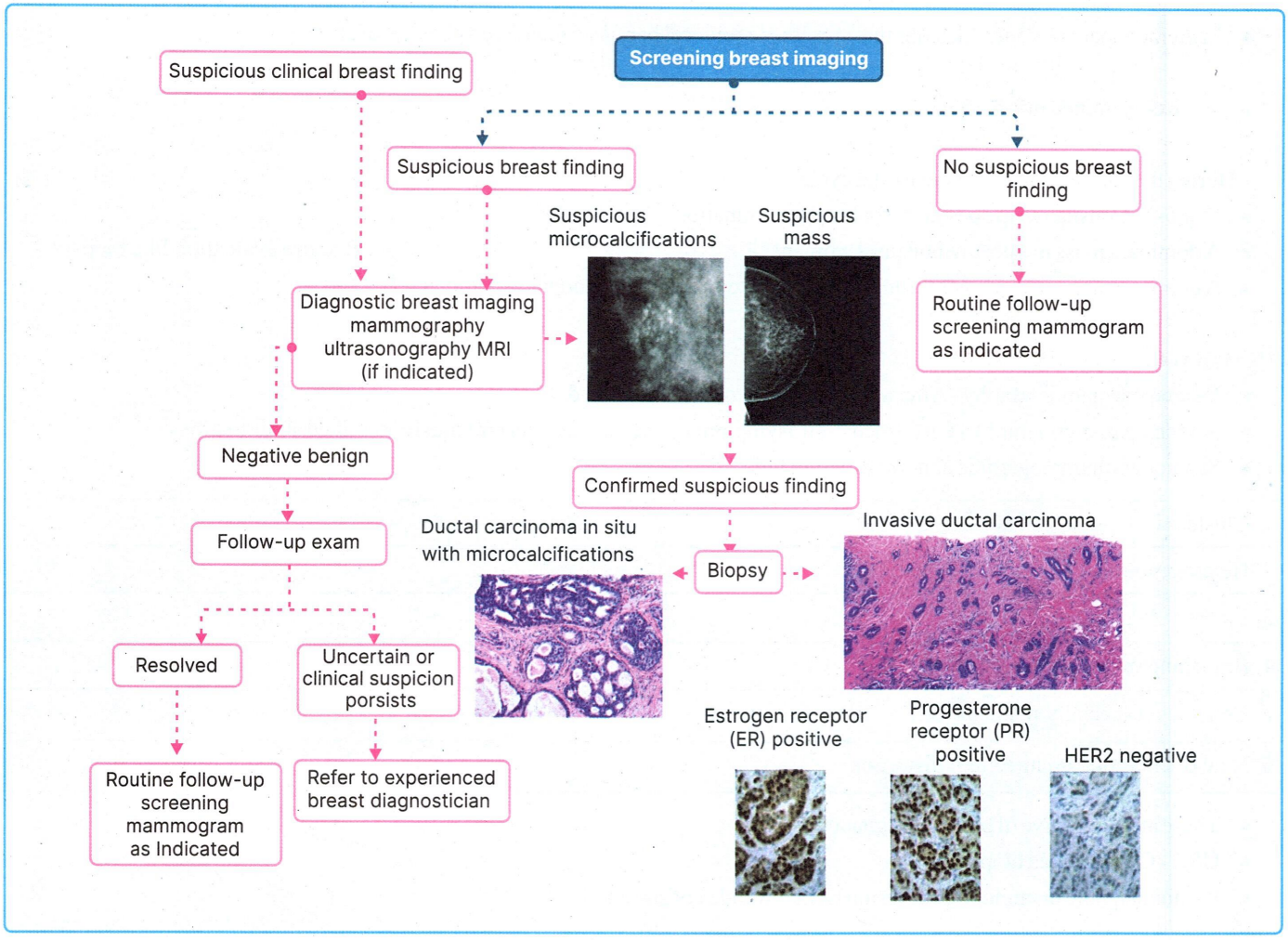
- Pregnant women have more advanced disease

↓

Due to endogenous hormone stimulation

SCREENING FOR BREAST CANCER

00:48:40



PATHOLOGIC FINDINGS OF THE BREAST

00:49:52

BENIGN BREAST HISTOPATHOLOGY

- Only ~ 1 in every 5-10 breast biopsies → Diagnosis of cancer
- The vast majority of benign breast masses is due to fibrocystic changes

↓

Fluid-filled cysts & fibrous tissue hyperplasia

- Women with ductal or lobular cell proliferation (~ 30% of patients)

↓

Particularly the small fraction(3%) with atypical hyperplasia

↓

Atypical hyperplasia has the 4-fold risk of breast cancer

↓

If the same individual has a 1st degree relative → Risk is even higher

- Chemoprevention with antiestrogen therapy

  ↓

  SERM/Aromatase inhibitors should be considered
- Prophylactic mastectomy is not normally indicated

NON-INVASIVE BREAST NEOPLASMS

00:55:19

- Breast cancer develops as a series of molecular changes in the epithelial cells

  ↓

  Malignant behaviour

- These changes range from

1. Noninvasive or more commonly in-situ carcinoma: Malignant cells confined within the basement membrane/duct.
2. Invasive or infiltrating cancer : Cancer cells invade through the basement membrane to the normal tissue

- These lesions fall into two groups

1. DUCTAL CARCINOMA IN SITU (DCIS)	2.LOBULAR CARCINOMA IN SITU (LCIS)/LOBULAR HYPERPLASIA IN SITU
• In situ proliferation of malignant epithelial cells within the ducts → Ductal carcinoma in situ	• The presence of malignant cells within the lobules ○ It does not cause breast mass ○ Mammogram - negative ○ Breast biopsy - incidental finding
• Atypical hyperplasia is difficult to distinguish from DCIS	• Unlike DCIS, which is confined to a single area of the breast • LCIS often spreads throughout the breast
• Premalignant condition	• Found on the contralateral breast as well
• At least 1/3rd of patients with untreated DCIS	• LCIS is not a marker for mortality • ↑ the risk of breast cancer • Those who have not undergone bilateral prophylactic mastectomy ↓ The incidence of invasive cancer is 1%
• Low grade DCIS do not appear to have progressed for many years	• LCIS (pre-malignant condition) > DCIS
• Mastectomy(100% effective) prevents future breast cancer ○ Prophylactic treatment	• Management options include careful observation with ○ Routine mammography ○ Chemoprevention is given for 5 years - SERM/Aromatase inhibitors
• Breast preserving therapy refers to excisional surgery alone with or without breast radiation	• Beyond 5 years, patients should be followed ↓ Annual mammography & semi-annual physical examination
• Addition of Tamoxifen or any Aromatase inhibitors to a DCIS patient who has undergone surgery & radiotherapy ↓ Further improvement in local control	• Bilateral prophylactic mastectomy is an alternative option ↓ Associated with cosmetic, emotional morbidity

• The largest trial comparing the two in DCIS
  ○ Anastrozole
  ○ Tamoxifen	

• At high risk for local recurrence after either lumpectomy/Lumpectomy with radiation therapy • Prognostic features include: 1. Extensive disease in the breast 2. Age < 40 years 3. Necrosis 4. Poor nuclear grade 5. Comedo subtype -Her-2	
• Breast preserving surgery is recommended for localized focus for DCIS ↓ Tamoxifen and Radiotherapy	

• Multifactorial gene expression assay
  ○ ↑ recurrence → Lumpectomy only
  ○ ↓ recurrence → Lumpectomy +Radiotherapy	

• The decision to irradiate such patients depends on:
  ○ Risk aversion to in-breast recurrence balanced
  ○ Against the risk associated with breast irradiation	

• For patients with small unicentric DCIS, Axillary lymph node dissection is unnecessary	
• Axillary sentinel lymph node (SLN) evaluation ↓ Indicated for larger/poor grade DCIS/microscopic invasion identified on core biopsy	

INVASIVE BREAST CANCERS

01:30:35

- Invasive breast cancers are of more concern than in situ lesions
  ↓
  The chances of metastasis are high
  ↓
  ↑ morbidity & mortality
- 85% of invasive breast cancers are ductal in origin
  - 10% are lobular or mixed(lobular/ductal)
  - 5% are made up of (special types)
  - Mucinous/colloid (2.4%)
  - Tubular(1.5%)
  - Medullary (1.2%)
  - Papillary (1%)
- The prognosis of the special types is slightly better than ductal/lobular

3 BREAST CANCER PART 3

Breast Cancer - Staging and Treatment

Staging and Diagnostic Considerations

- Staging is based on size, involvement of regional lymph nodes, and distant metastasis. ER/HER 2 has also been added to staging.

Types of Staging 00:00:41

- Clinical staging (cTNM): Performed before adjuvant systemic therapy
- Pathological staging (pTNM): Performed after adjuvant systemic therapy

Imaging for Distant Metastases

- Imaging for detection of distant metastases is not needed in patients with:
  - No signs and symptoms of widespread disease
  - Small tumor
  - <4 involved axillary lymph nodes
- Important prognostic findings:
  - Bone marrow micrometastases or circulating tumor cells (cM0(I+)) - both have worst prognosis

Staging Overview 00:10:22

- Stage 0: Carcinoma in situ (e.g., DCIS), no invasion of neighboring tissue
- Stage I: Small localized tumor with minimal lymph node involvement
- Stage II: Large tumor / greater regional lymph node involvement
- Stage III: More extensive local and regional spread, significant lymph node involvement
- Stage IV: Distant metastases - bone, liver, lungs, and brain

Treatment

Early-Stage Breast Cancer Components

- Goals of Therapy
- Prognostic and Predictive Factors
- Local/Primary treatment
- Evaluation and Treatment of the Axillary Lymph Nodes

Goals of Therapy

- Primary goal: Cure

Primary Considerations

- Primary therapies consist of surgical and radiation treatment directed towards breast and locoregional lymph nodes. The goal is to reduce recurrence.

Systemic Considerations

- Adjuvant systemic treatments consisting of:
  - Endocrine therapy: Tamoxifen (for ER-positive tumors)
  - Anti-HER2 therapy: For micrometastasis
  - Chemotherapy: As indicated

Prognostic and Predictive Factors

- Prognostic factors provide indication of how likely a cancer will reoccur either locally or distant organ in future
- Predictive factors will tell you if the given treatment will work or not

Anatomic Prognostic Features

- Visual and physical examination findings of locally advanced breast cancer:
  - T4 lesions
  - Skin erythema, edema (peau d'orange)
  - Nodules or ulceration
  - Tumor fixation

Biological Features

- Histologic tumor grade
- ER, PgR and HER2 status - tells prognosis
- Gene expression patterns/signatures have demonstrated that breast cancer is many different diseases and can be divided into series of subtypes
- These subtypes are driven by expression of ER, HER2 receptors and are clinically important

Four Different Intrinsic Subtypes

- Luminal
- HER2
- Basal
- Claudin low

Luminal Breast Cancer

- Characteristics: +ve for ER and -ve for HER2 amplification
- **Luminal A tumor:**
  - Highest level of ER
  - -ve or low HER2
  - Low grade and low proliferative thrust
  - Favorable prognosis
  - Respond to endocrine therapy (tamoxifen)
  - Less responsive to chemotherapy
- **Luminal B breast cancer:**
  - PgR -ve
  - HER2 expression low level
  - High grade tumor and higher proliferation rate compared to Luminal A
  - Worse prognosis than Luminal A
  - More sensitive to chemotherapy

HER2 Amplified Breast Cancer

- Exhibit co-amplification and overexpression of gene adjacent to HER2
- Poor prognosis, but with introduction of anti-HER2 treatment the prognosis is better

Basal Breast Cancer

- Mostly -ve for ER/PgR and HER2 (called triple negative malignancy)
- High-grade tumors
- Express:
  - Cytokeratins 5/6 and 17, as well as vimentin
  - p63
  - CD10
  - α-smooth muscle actin
  - Epidermal growth factor receptor (EGFR)

Normal Breast Like and Claudin Low Cancer

- Over the past decade - several multiparameter tests are done based on gene expression like Node -ve, ER +ve and HER2 +ve

Predictive Features for Target Therapy

- ER +ve: Require endocrine treatment - tamoxifen
- HER2: Anti-HER2 Trastuzumab
- BRCA 1/2: PARP inhibitors
- PIK3CA mutations: PIK3CA inhibitors

Local (Primary) Treatment

00:35:31

Historical Evolution

- In 1980s:
  - Halsted radical mastectomy was replaced with Modified radical mastectomy, where chest wall muscles are preserved and sampling of axillary LN is removed
  - Subsequently, breast-conserving treatment consists of surgical excision of the primary tumor that includes lumpectomy, quadrantectomy, and partial mastectomy, followed by locoregional radiation

Breast Conservation Treatment

- For women undergoing breast conservation post-lumpectomy, radiation is indicated
- May be less necessary in older women with ER-positive and node -ve breast cancer since their chance of recurrence is low
- Contraindications include:
  - Large tumor to breast ratio
  - Inability to achieve clear margins with adequate cosmesis after extensive surgery
  - Multifocal cancers
  - Extensive four-quadrant DCIS
  - Inability to receive radiation - commonly arises in women with dermal autoimmune disease like Lupus erythematosus, prior radiation to site, lack of radiation treatment

Mastectomy Options

- For patients who do undergo mastectomy - nipple areola sparing mastectomy preserves dermis and epidermis of nipple but removes major ducts from within nipple lumen
- Nipple sparing mastectomy is contraindicated in:
  - Inflammatory breast cancer
  - Carcinoma involving nipple areola complex
  - Nipple retraction
  - Paget's disease
  - Bloody nipple discharge
  - Multicentricity
- Clinical Evidence:
  - In a meta-analysis of 20 studies (5594 patients), overall and disease-free survival and locoregional recurrence rates appeared similar to those of patients undergoing modified radical mastectomy.

Breast Reconstruction

00:52:53

- Breast reconstruction can be achieved by:
  - Exogenous implant
  - Transferring autologous tissue from another site, like the abdomen, L. Dorsi and gluteus area.
- Risks of reconstruction:
  - Infection and hemorrhage

- Reconstruction does not hinder future recurrence
- Silicon implants can rupture and require surgical removal

- Complications:
  - Breast implant associated anaplastic large cell lymphoma
  - Metastatic lymphoma

Post-mastectomy Radiation 00:58:11

- Indications for post-mastectomy chest wall and regional nodal radiation:
  - High recurrence risk
  - Tumor >5 cm
  - 4 or more +ve axillary LN
  - Post-operative +ve margins
  - Will reduce locoregional recurrence and improve survival
- Post-mastectomy radiation is NOT indicated in:
  - Cancer <2cm
  - -ve margins
  - -ve LN
- Considered for women who fall into:
  - Tumor size 2-5 cm
  - 1-3 +ve nodes

Important Information

- The survival of patients who have a recurrence is worse
- Thus, locoregional recurrence is a -ve prognostic variable

Evaluation and Treatment of the Axillary Lymph Nodes 01:00:35

Sentinel Lymph Node (SLN) Mapping and Biopsy

- SLN mapping and biopsy (SLNB) for localized breast cancer and clinically negative axilla
- Procedure involves injecting dye/radioactive tracer into involved breast and 4-24 hr later resection of axillary node containing the dye
- If resected node is negative for tumor, more extensive surgery not required
- Even in presence of sentinel lymph node involvement, axillary surgery is not required
  - Axillary surgery is NOT required in:
    - → Older women
    - → ER +ve patients

4 TREATMENT OF BREAST CANCER PART-1

Adjuvant regimens

Endocrine therapy

00:00:35

- Adjuvant endocrine therapy is indicated for
  - ER positive breast cancer
  - Never indicated for ER negative individuals
  - 2 adjuvant endocrine therapy strategies
    → Tamoxifen/Estrogen ablation

Tamoxifen

- Effectively reduces new cancers
- ↓ risk of locoregional recurrence particularly in DCIS
- Also ↓ distant recurrences
- ↓ death due to invasive breast cancer by almost 40%
- Equally effective in premenopausal and postmenopausal woman
- Slightly less effective in very young patients (age<40 years)
- Mechanism of action: Mixed mechanism of action- It is a SERM- acts as Estrogen receptor antagonism in breast and brain and acts as ER agonist in bone, liver and uterus
- Given in prevention of breast cancer
- Given as adjuvant in breast cancer
- Given in metastatic settings
- Side effects are predictable and based on ER antagonism
  - Frequent hot flashes, vaginal discomfort
  - Sexual dysfunction
  - Myalgia
  - Arthralgia
- Agonistic effects results in
  - ↓ in osteopenia and osteoporosis especially in postmenopausal women (Used for the treatment of Osteoporosis in Postmenopausal women).
  - ↑ thrombosis risk and endometrial cancer → due to effect on liver and uterus respectively
- Estrogen depletion can be achieved surgically in
  - Premenopausal woman – oophorectomy
  - Gonadotrophin releasing hormone (GnRH) superagonist- Goserelin, Leuprolide
  - GnRH antagonist- Triptorelin
  - However, women with nonfunctioning ovaries → Whether induced or by natural menopause } Produce small amount of estrogen by adrenal synthesis of estrogen precursors
- Estrogen precursors
  - Testosterone, DHEA → Converted to Estradiol, Estrone by aromatase activity in peripheral fat and possibly in the cancer cells
  - Estradiol, Estrone can act on ER positive breast cancer → breast malignancy
- In postmenopausal women
  - Circulating estrogen can be reduced to nearly imperceptible levels with use of oral Aromatase Inhibitors:
    → Anastrozole
    → Letrozole
    → Exemestane
    → More effective in treatment of breast cancer compared to Tamoxifen
  - Toxicities of AIs based on Very low estrogen levels

→ Hot flashes
→ Musculoskeletal symptoms → Atrophic vaginitis, sexual dysfunction
→ Worsening of osteoporosis → fracture → Prevented by bone modifying agents: Bisphosphonates and RANK ligand antagonist: Denosumab

- Adverse effects of tamoxifen and Ais
  - Arthralgia and osteoarthritis → treatment:
    → Physical therapy
    → NSAIDs
    → Switching between one aromatase inhibitor to another → relieve the symptoms in approximately in 1/3rd of patients
    → Acupuncture
    → Duloxetine
  - Contraindications for Tamoxifen and Ais
    → Past history of thrombosis
    → High risk of cerebrovascular accidents
- Hot flashes from either class of drugs → reduced in half of patients with use of several different antidepressant drugs
- For premenopausal women- optimal endocrine therapy depends on prognosis and antidepressant choice
- Complete estrogen depletion is slightly more effective than Tamoxifen alone.
- Complete estrogen depletion leads to:
  - Hot flushes
  - Vaginal dryness
  - Sexual dysfunction
- Complete estrogen depletion achieved by
  - B/L Oophorectomy
  - Chemical suppression of gonadotrophins + Aromatase inhibitor → indicated for woman with worst prognosis
  - Worst prognosis present in individuals with nodal positivity
  - For individuals with more favourable prognosis: Tamoxifen alone/ ovarian suppression → better quality of life
- The AIs should not be administered to women with
  - Functioning or dormant ovaries
    → AIs completely ↓ estrogen levels → hypothalamic pituitary axis → rebound overproduction of ovarian estrogen
    → The duration of adjuvant endocrine- unclear, standard recommendation is 5 years of treatment - ↓ the risk of recurrence
    → Annual risk of recurrence in subsequent 15 years → 0.5 to 3% → completely depends on initial tumor size and nodal status
- Extended adjuvant endocrine therapy
  - Tamoxifen/ Aromatase inhibitors for 5 years →↓ late risk of relapse
  - After 5 years whether to continue or not depends on
    → Initial tumor size: nodal status and grade of breast carcinoma
    → Current side effects
    → Potential cumulative toxicities
    → Patient's perception of relative and absolute benefits and risk

Chemotherapy

00:39:16

- Multiple agent adjuvant chemotherapy is more effective than single agent chemotherapy.
- Given usually in combination → efficacy is more than it is given as single therapeutic agent
- Sequential single agent chemotherapy is effective and maybe slightly less toxic although requires longer duration to deliver
- Administration of 4 to 6 cycles of chemotherapy is optimal, one cycle is less effective than 6 cycles
- >6 cycles generally toxicity without further efficacy
- Importantly -although chemotherapy + anti HER2 therapy in patients with HER2 positive cancers
- Adding Tamoxifen is antagonistic with chemotherapy. Should be added sequentially.

- Endocrine therapy → completion → chemotherapy
- Several chemotherapeutic agents have activity in adjuvant settings

Chemotherapy Agents	Examples
Alkylating agents	Cyclophosphamide,
Anthracyclines	Doxorubicin, Epirubicin
Antimetabolites	5 Fluoro uracil, Capecitabine, Methotrexate
Taxanes	Paclitaxel, Docetaxel
The platinum salts	Cisplatin, Carboplatin

- Between the classes superiority of one agent vs the other agent is not demonstrated.Example: Paclitaxel and Docetaxel are equally efficacious.
- Escalation above optimal dose is not more effective, only optimal dose to be given
- Antineoplastic advantage of more frequent scheduling for most individual agents have been demonstrated in a well-done meta-analysis
  - Paclitaxel: weekly/ every other week paclitaxel superior than giving Paclitaxel every 3rd week
  - Frequent scheduling has been found to be more efficacious → dose dense fashion
- The oldest combination regimen consists
  - Cyclophosphamide
  - Methotrexate
  - 5- Fluoro uracil

  } Addition of Anthracycline or substitution of Anthracycline for antimetabolites have improved outcomes
- Adverse effects of Anthracycline derivatives
  - Risk of heart failure
  - Secondary leukemia
- Addition of Taxane to Anthracycline based regimen, further reduce chance of distant recurrences and death
  - Anthracycline+ Taxane is more effective than adding Taxane + Cyclophosphamide alone
  - Regimen appropriate for patient must be individualised based on:
    - → Prognosis
    - → Comorbid conditions
    - → Perspective of patient

Neoadjuvant chemotherapy

00:51:01

- Preoperative or neoadjuvant treatment involves the administration of adjuvant systemic therapy → m/c chemotherapy before surgery and radiotherapy
- Neoadjuvant therapy given for patients with ER positive diseases
- Given preoperatively for nearly around 4-6 months however generally reserved for patients for whom reasons for surgical delay already exists
- The objective partial or complete response rates of patients with breast cancer to neoadjuvant therapy range from 10-75%
- Response rates → 10-75% depending on intrinsic subtypes of cancer and regimen which is being used, many patients down staged by neoadjuvant chemotherapy however overall survival not been improved by this approach as compared with the same drugs given postoperatively
- Patients who achieve a pathologic complete remission (PCR) → substantially improved survival after neoadjuvant chemotherapy than individuals who do not have pathological complete remissions
- Pathological remissions not achieved in some patients due to worst initial prognosis
- Clearly non chemotherapeutic strategies
  - Adjuvant endocrine therapy → ER positive breast cancer
  - Adjuvant anti-HER2 if cancer is HER2 positive

- Adding or changing systemic therapy may benefit the selected group of patients who do not have pathological complete remission

- Approximately 6 months of post-surgical following drugs has reduced distant metastasis in patients with triple negative breast cancers who have residual diseases after non Fluoro pyridine containing neoadjuvant chemotherapy
  - Oral Fluoro pyridine
  - Capecitabine
- Similarly, postoperative therapy with an antibody drug conjugate consisting of Transtuzumab and anti-tubulin emtansine: Ado-Transtuzumab → both the drugs considered superior to continuing unconjugated Transtuzumab in patients with HER2 positive breast cancer

Chemotherapy toxicities

01:04:19

- Chemotherapy is associated with
  - Nausea
  - Vomiting
  - Alopecia

  } Found in almost 100% of patients
- Nausea and vomiting well controlled with anti-emetics
- By cooling, constriction of blood flow to scalp → reduce the alopecia
- Chemotherapy causes potentially life threatening or life changing toxicities → observed in 2-3% of individuals
  - Neutropenia: prevented with appropriate use of growth factors (Filgrastin)
  - Fever
- Secondary myelodysplasia and leukemia
  - 0.5-1% of patients treated with Anthracycline
  - High doses of Cyclophosphamide
  - Occurs within 2-5 years of treatment
  - Anthracyclines cause cumulative dose related congestive heart failure → occurs in 1% of patients treated with standard 4-6 cycles at dose of 60mg/m^2
- Peripheral neuropathy is the major dose limiting and life changing toxicity of Taxanes
  - Occurs in almost 15-20% of patients
  - Development of permanent chronic neuropathy in ~3-5% patients
  - Many patients complain of cognitive dysfunction – Chemobrain, occurs due to
    → Anxiety
    → Depression
    → Fatigue
  - Cognitive functions usually returns to age adjusted baseline several months after discontinuation of therapy

5 TREATMENT OF BREAST CANCER PART- 2

Anti-HER2 Therapy

- The humanised anti-HER2 monoclonal antibody:
  - TRANSTUZUMAB
    → ↓ Recurrence
    → ↓Mortality → Early stages
  - Transtuzumab delivered concurrently with Chemotherapy (Taxane)
- Concurrent treatment with an Anthracycline:
  - Avoided
  - Transtuzumab → cardiac dysfunctions
  - Transtuzumab + Doxorubicin → more chances of cardiac dysfunction
    → Associated with high pathological complete remission rates (PCR)
- In patients with reasonably favourable prognosis:
  - T1/T2
  - Node -ve
    → Paclitaxel+ Transtuzumab → Regimen
- The addition of a second anti-HER2 monoclonal antibody:
  - Pertuzumab + Tanstuzumab combination superior to Transtuzumab alone
    → Associated with high pathological complete remission rates (PCR)
- At least in patients with poor prognostic features:
  - Positive axillary LN
    ↓
    Combination → distant metastasis & mortality

- Neoadjuvant studies have demonstrated that:
  - Post. op Ado-Transtuzumab emtansine → superior → PCR
    → Given weekly or every 3 weeks
    → Given for 12 months → no additional benefits beyond 12 months
    → Treatment for 6 months is effective than no Transtuzumab therapy
    → 6 months therapy is inferior to 12 months therapy of Transtuzumab
- U.S FDA-approved s/c application of Transtuzumab
- Selected anti-HER2 tyrosine kinase inhibitors-
  - Activity against HER-2 positive breast cancer but benefit in adjuvant setting is limited
- Lapatinib does not add to Transtuzumab therapy but single agent Lapatinib considered inferior to that of Transtuzumab
- Another anti-HER2 tyrosine kinase inhibitors:
  - Neratinib → superior to no anti-HER2 therapy

Toxicities of Anti-HER2 Adjuvant Therapies

00:12:32

- Allergic reactions observed only with initial cycles of Transtuzumab
- Cardiac muscle dysfunction: rare to observe symptomatic congestive heart failure
- Base line & serial echo-monitoring required on starting Transtuzumab
- Patients with past history of cardiac abnormalities should not receive Transtuzumab or should be followed and treated by a cardiologist
- Pertuzumab is associated with:
  - Loose stools & diarrhea → Rx-loperamide
- The chemotherapy payload of ado-Transtuzumab:

- Emtansine – A/E:
  → Thrombocytopenia
  → Peripheral neuropathy

Skeletal Strengthening Agents

- Rx- osteoporosis - Bisphosphonates
- Post menopausal women → limited activity in preventing recurrent breast cancer
- The benefit is not significantly associated with -
  - Any specific bisphosphonate class → Bone fractures decreased
  - Treatment schedule
  - ER status
  - Nodal status
  - Tumor grade, or
  - Concomitant chemotherapy
- Joint guidelines from the American Society of Clinical Oncology and Cancer Care Ontario recommend that,
  - If available, zoledronic acid - 4mg IV/every 6 months
  - Clodronate - 1600 mg/day - orally → adjuvant for post-menopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy
  - The rank-ligand inhibitor:
  - Denosumab → does not prevent relapse in the bone or other sites and will not reduce mortality

Novel Adjuvant Systemic Agents

00:27:05

- Other exciting adjuvant strategies are being tested
- These include PARP inhibitors: given in patients with known germline BRCA-1/BRCA-2 mutation and in triple negative cancers
  - Olaparib
  - Talazoparib
- mTOR inhibitor - Everolimus
- CDK4/6 inhibitor - Palbociclib, Ribociclib, Abemociclib
  ↓+
  Anti-estrogen therapy
- The remarkable results of immune checkpoint inhibitors:
  - Metastatic & post. Adjuvant Chemotherapy settings
  - Activity with chemotherapy in Triple negative diseases appears to be promising

Stage III Breast Cancer

00:32:28

- 10-25% → locally Advanced breast cancer
- Many of these cancers are technically operable (T3)
- Other cancers like the following, can not be managed by surgery initially
  - Particularly cancers with chest wall involvement
  - Inflammatory breast cancers, or
  - Cancers with large matted axillary lymph nodes (T4 or N2-3)
- Neoadjuvant downstaging therapy facilitates local therapy
- Radiotherapy either to the chest wall after mastectomy or
- To the breast after tumor excision -
- Adjuvant anti-HER-2 & endocrine Rx used appropriately
- These patients should be managed in multi-modality clinics to coordinate the local as well as systemic therapies

Simultaneous New Primary With Detectable Metastases

- In the screening era, only a small fraction of patients - 5% present with new primary lesion & simultaneous metastasis detected due to Symptoms of distant diseases or staging scans due to locally advanced diseases
- Several retrospective single institutional experiences have suggested that Neo adjuvant systemic therapy followed by local therapy (breast surgery and radiation) is associated with prolonged survival

6 METASTATIC BREAST CANCER

DIAGNOSTIC CONSIDERATIONS

00:00:14

- 15-20% treated for localized breast cancer develop metastatic breast cancer
- Metastasis to soft tissue, bone and visceral organs (Lung and liver)
- Bone metastases are the most common but not the most fatal
- Recurrence can appear at any time after primary therapy
  - ½ occur after 5 years
  - Seen in estrogen receptor (+) cases
- Factors that can influence recurrence rates
  - Depression
  - Central obesity
  - No past history of recurrence/ mets → lesion of physical examination or radiographic lesion → biopsy (for confirmation of mets)
  - Apparent abnormality is NOT breast cancer mets
- Conditions mimicking recurrence of breast cancer
  - TB
  - Gallstones
  - Sarcoidosis
  - Hyperparathyroidism
  - Other non-malignant diseases
- If biopsy (+) for mets
  - Re-evaluation of ER status
  - Re-evaluation of HER-2
  - ER/ HER-2 status can be different in 15% of cases between the primary and recurrent conditions
  - Analysis of PIK3CA mutation (if ER (+))
- Predictors of immune checkpoint inhibitor susceptibility
  - PDL1 expression (Triple negative breast cancer)
- Once a recurrence/ mets established → should undergo body imaging
  - Scintigraphic bone scan
  - Chest/ abdominal CT
  - PET-CT
- Brain scanning (CT/ MRI) not indicated in the absence of cognitive/ neurological signs and symptoms
- HER-2 (+) have high recurrence rate → CNS imaging done
- Body scans provide → extent of the disease → therapeutic decisions → ancillary treatments
- Bone modifying agents → skeletal mets (+)

CONSIDERATIONS REGARDING GOALS OF THERAPY

00:14:57

- Median survival of metastatic breast cancer < 3 years
  - Depending upon the intrinsic subtype and treatment effects
- Patients with:
  - Triple negative metastatic breast cancer → shortest expected survival rate
  - ER (+) disease → live longest
  - HER2 (+) very poor prognosis in metastatic breast cancer
- Treatment modalities has improved the prognosis of ER(+) distant mets
- Palliation: over all goal of treatment in metastatic disease
- Overall survival has not been improved by advocating more aggressive or toxic therapies (high dose or combination chemotherapy)