

**MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE**  
**UZHHOROD NATIONAL UNIVERSITY**  
**DEPARTMENT OF ONCOLOGY**

## **Breast cancer**

Methodical instructions for 5, 6 year medical students' individual training

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# **BREAST CANCER**

## **I. Topic actuality:**

Breast cancer is the most common cancer cases among female and 2<sup>nd</sup> most common cancer related death between females .it is a malignancy originating from breast tissue from ductal or lobular origin

Prevalence is increasing, due to increased incidence and improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection and screening programs.

Gender and age play an important role in risk factors of breast cancer as well as family history, about a quarter of breast cancers occurring before age 50, and about 5% under age of 35, while the majority of cases occurs in ages > 50 years.

Clinically breast cancer can be localized (limited to the breast), locally advanced, or metastatic breast cancer, which should be very well evaluated by right diagnostic staging, pathological diagnosis and to know the intrinsic subtype of breast cancer in order to offer right therapeutic plan and to get better treatment outcome.

## **II. Teaching aim:**

### **2.1. The student must know:**

- Epidemiology
- Classification
- Risk factors
- Clinical presentation
- Clinical workup and staging
- Modern methods of diagnosis
- Treatment
- Screening
- Prognosis

### **2.2. The student should be able to:**

- Put clinical diagnosis, stage of disease, make a plan of examination and make differential diagnosis of breast masses.
- Put algorithm of treatment, Assess prognosis of patient.
- Screening of breast cancer

## **III. Basic level of knowledge and skills:**

- classification and presentation of benign and malignant tumors of mammary gland
- risk factors and molecular biology of breast neoplasms
- methods of investigation and work-up of breast neoplasm

#### **IV. The program of self-preparation of the students:**

| <b>№</b> | <b>Task Maintenance</b>    | <b>Task maintenance concrete definition</b>  |
|----------|----------------------------|--|
| 1.       | Collecting history         | 1. risk factors and family history of breast cancer<br>2. epidemiology<br>3 classification<br>4 common presentation and complains  |
| 2.       | Work up and treatment plan | 1 physical examination<br>2 biopsy, histological types of breast cancer, molecular types of breast cancer<br>3 differential diagnosis of breast masses.<br>4 modern methods of investigation, metastatic work-up<br>5 staging of breast cancer.<br>6 treatment plans for local, locally-advanced and metastatic breast cancer. |

#### **V. Short methodical instructions for practical study work.**

- After introductory teacher's word, control of the level of knowledge and skills of the students.
- The group carried out the individual educational tasks.
- The students acquaint with work of the department in oncological clinic.

## VI. Content of the topic

### Overview

Breast cancer is a malignancy originating from breast tissue. And it is the first diagnosed cancers in women.

Disease confined to a localized breast lesion is referred to as early, primary, localized, or curable.

Disease detected clinically or radiologically in sites distant from the breast is referred to as advanced or metastatic breast cancer (MBC), which is usually incurable.

### Incidence and epidemiology

In 2018, the predicted number of new breast cancers in 28 European Union (EU) countries was 404 920, with estimated age-adjusted annual incidence of breast cancer of 144.9/100 000 and mortality of 32.9/100 000, with 98 755 predicted deaths. Worldwide, there was about 2.1 million newly diagnosed female breast cancer cases in 2018, accounting for almost one in four cancer cases among women, and 630 000 died of it.

There is a steep age gradient, with about a quarter of breast cancers occurring before age 50, and about 5% under age of 35, while the majority of cases occurs in ages > 50 years.

The estimated 5-year prevalence of breast cancer (people with a diagnosis within the last 5 years and still alive, with or without disease) in Europe in 2012 was 1 814 572 cases and a staggering 6 875 099 cases worldwide. Prevalence is increasing, due to increased incidence and improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection. However, breast cancer Most common female malignancy & 2<sup>nd</sup> most common cause of cancer death.

Left sided cancers are slightly more common than right sided ones (relative risk 1.05). The peak age incidence is 50–70 years and only 0.5–1 per cent of cases arise in men. It is a disease of the Western world being much less prevalent in the Far East.

### Risk factors

The most important risk factors include: gender, age, genetic predisposition, exposure to estrogens [endogenous and exogenous, including long-term hormone replacement therapy (HRT)], ionizing radiation, low parity, high breast density and a history of atypical hyperplasia. The Western-style diet, obesity and the consumption of alcohol also contribute to the rising incidence of breast cancer

- **Age:** it is extremely rare below the age of 20 years but thereafter the incidence steadily rises that by the age of 90 years nearly 20% of women are affected, age peak is over 65 years.
- **Gender:** it is less than 1% of patients with breast cancer are male.
- **Geographical:** it occurs most commonly in the western world, accounting 3-5% of all death in women.
- **Genetics:** it occurs more commonly in women with a family history of breast cancer than in the general population. Breast cancer related to specific mutation account for

about 5% of breast cancer (BRCA1 and BRCA2 gene mutation and Other familial/hereditary breast CA: HER2/neo, TP53, PTEN, ATM gene mutation

- **Diet:** there is some evidence that there is a link with diets low in phytoestrogen, a high intake of alcohol is associated with increased risk.
- **Endocrine** Early menarche, late menopause, late parity, or nulliparity, hormone replacement therapies and oral contraceptives. It is more common in nulliparous women and breast feeding in particular appeared to be protective. Also protective in having a first child at an early age, especially if associated with late menarche and early menopause. It is known that in postmenopausal, breast cancer is more in obese. This is thought to be because of increased conversion of steroid hormones to estradiol in the body fat.
- **previous radiation exposure** or radiotherapy treatments for women with mantle radiotherapy as a part of the management of Hodgkin's lymphoma. The risk appears about decades after treatment and it is higher if radiotherapy administered during breast development
- **Benign breast conditions** (ductal hyperplasia, papilloma, radial scar, sclerosing adenosis); atypia (atypical ductal or lobular hyperplasia); dense breast, Cysts, fibroadenoma, columnar changes.

### **Pathology:**

breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of major lactiferous ducts to the terminal duct unit, which is in breast lobule. The disease may be entirely in situ, an increasingly common finding with the advent of breast cancer screening or may be invasive cancer. Tumor is usually described using three grades as well differentiation moderately differentiation or poorly differentiation. Commonly numerical grading system based on the scoring of the three individual factors (nuclear pleomorphism, tubular formation, and mitotic rate) is used in grade I-III cancers roughly equating the poorly differentiated.

Previously, descriptive terms were used to classify breast cancer into scirrhous meaning woody or medullary meaning brain like. More recently the histological descriptions have been used. However, with the increasing application of molecular markers there will be a change in the way that the breast cancers are classified, and it is likely that much more information about individual tumor will be routinely reported, such as its likelihood of metastases, and to which therapeutic agents it will be suitable.

Macroscopically, most carcinomas arise in the upper outer quadrant of the breast and are usually solitary, although multifocal tumors can occur in the same or opposite breast. The tumor can be well circumscribed or diffusely infiltrating. The cut surface and texture will vary depending on the tumor type cancer might be invisible to the naked eye.

Microscopically, breast cancers are classified as 'lobular', arising in the lobules at the termination of the duct system of the breast, or 'ductal' arising from the extralobular ducts themselves. In situ carcinoma is diagnosed when all the malignant cells are confined to the lumen of the duct or lobule and do not breach the basement membrane. This contrasts with invasive carcinoma where malignant cells breach the basement membrane. The vast majority are ductal carcinomas but there are a number of variants including papillary, scirrhous, colloid, medullary. Estrogen and progesterone receptors are detectable, also HER2/neo gene mutation can be positive.

Table 1: Molecular classification of breast cancer

| Intrinsic subtype | Clinicopathological surrogate definition   |
|-------------------|--|
| Luminal A         | “Luminal A-like”<br>ER- positive<br>HER2-negative<br>Ki 67 low<br>PgR high<br>Low-risk molecular signature (if available)  |
| Luminal B         | “Luminal B-like” (HER2-negative)<br>ER-positive<br>HER2-negative<br>And either Ki 67 high or PgR low<br>High-risk molecular signature (if available)<br>“Luminal B-like” (HER2-positive)<br>ER-positive<br>HER2-positive<br>Any Ki 67<br>Any PgR |
| HER2              | “HER2-positive(non-luminary)”<br>ER and PgR absent   |
| Basal-like        | “Triple-negative”<br>ER and PgR absent<br>HER2-negative  |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; Ki 67, estimate tumor’s proliferation index.



Figure 1: Inflammatory carcinoma of breast



Figure 2: Paget’s disease of the nipple (male patient)

- Cases detected via screening program are often smaller and with better differentiation than those presenting to be symptomatic and are of a special type.

- Inflammatory carcinoma is a fortunately rare, highly aggressive that present as painful swollen breast which is warm with cutaneous edema; this is result of blockage of the subdermal lymphatics with cancer cells. Inflammatory carcinoma usually behaves aggressively with a high rate of local recurrence and distant metastases, also It may be misdiagnosed as a breast abscess.
- There is 80% overlap between ‘triple-negative’ and intrinsic ‘basal’ subtype, but ‘triple-negative’ also includes some special histological types such as carcinoma with a rich lymphocytic stroma (former medullary), secretory carcinoma, low-grade metaplastic carcinoma and adenoid cystic carcinoma.

Paget’s disease of the nipple is a superficial manifestation of underlying disease of the breast carcinoma. It presents as eczema- like condition of the nipple and areola which persists despite local treatment the nipple is eroded slowly and eventually disappears. If it left the underlying condition carcinoma will sooner or later become clinically evident.

Nipple eczema should biopsied if there is any doubt about its cause. Microscopically Paget’s disease is characterized by the presence of a large ovoid cells with abundant, clear, pale staining cytoplasm in the Malpighian layer of the epithelium.

### **Spreading of the breast cancer**

- Local spread: the tumor increases in size and invade another portion of the breast. It tends to involve the skin and to penetrate the pectorals muscles and even the chest wall if diagnosed later.
- Lymphatic metastasis: it occurs primarily to axillary and internal mammary lymph nodes. A tumor in the posterior one third tends to spread to internal mammary lymph nodes. The involvements of lymph nodes have both biological and chronological event in the spread of carcinoma and it also a marker of metastases potential of that tumor. Involvement of the supraclavicular lymph nodes and of any of the contra lateral breast represents advanced disease.
- Hematological spread: it is by this route skeletal metastases occur. In order of the frequency the lumbar vertebrae, femur, thoracic vertebrae, rib and skull are affected and these deposits are generally osteolytic. Metastases may also commonly occur in the liver, lung, brain, and occasionally adrenal glands and ovaries.

### **Clinical presentation**

Although any portion of the breast including axillary tail may be involved breast cancer is found most frequently in the upper outer quadrant most carcinoma will present as a hard lump which may be associated with indrawing of the nipple , as the disease advances locally there may be skin involvement with peau d orange or frank ulceration and fixation to the chest wall.

- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.
- A lump which is usually non-tender, well defined and most likely to be located in the upper outer quadrant, which contains the majority of the breast tissue. Breast discomfort is occasionally a presenting symptom. In advanced cases, the overlying skin can be dimpled or frankly invaded by tumor leading to reddening, induration and nodular irregularity. Fixation to the skin or chest wall will limit mobility of the lump, and this should be sought by the clinician during physical examination. A very large lump will lead to obvious asymmetry of the breasts. There may be enlargement of the ipsilateral



axillary lymph nodes, the mobility of which should be assessed as part of the clinical staging, and less frequently enlargement of the supraclavicular Lymph nodes. Hepatomegaly could suggest metastatic infiltration while intrathoracic signs of collapse, consolidation or pleural effusion could suggest pulmonary or pleural metastases. Bone metastases are most frequent in the thoracic and lumbar spine and can lead to tenderness when pressure is applied to the affected vertebrae

- Symptoms of Metastatic Breast Cancer depend on the site of metastases but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, and mental status changes, pathological fractures due to metastatic osteolytic process and bone pain

## Investigations

**mammography:** soft tissue radiographs are taken by placing the breast in direct contact with ultrasensitive film and exposing it to low- voltage, high amperage of x rays. The dose of radiation is very low so it is a safe investigation. The sensitivity of this investigation increases with age as the breast becomes less dense. In total, 5% of breast cancers are missed by population -based mammographic screening even in retrospect, such carcinoma is not apparent. program Thus, a normal mammogram does not exclude the presence of carcinoma. Digital mammography is being introduced, which allow manipulation of the images and computer aided diagnosis. Tomo- mammography is also being assessed as a more sensitive diagnostic modality.

Mammography below shows a spiculate density with flecks of microcalcification typical of carcinoma

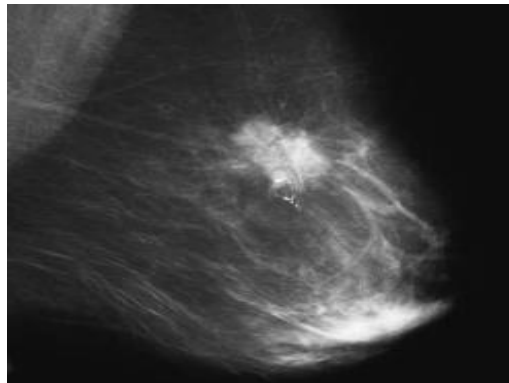


Figure 3: mammography of mammary gland typical for carcinoma

**Ultrasound :** ultrasound is particularly useful in young women with dense breasts in whom mammograms are difficult to interpret, and in distinguishing cysts from solid lesions. It also can be used to localize impalpable areas of breast pathology. It is useful as screening tool and remains operator dependent. Increasingly, ultrasound of the axillary tissue is performed when cancer is diagnosed and guided percutaneous biopsy of any suspicious glands may be performed.

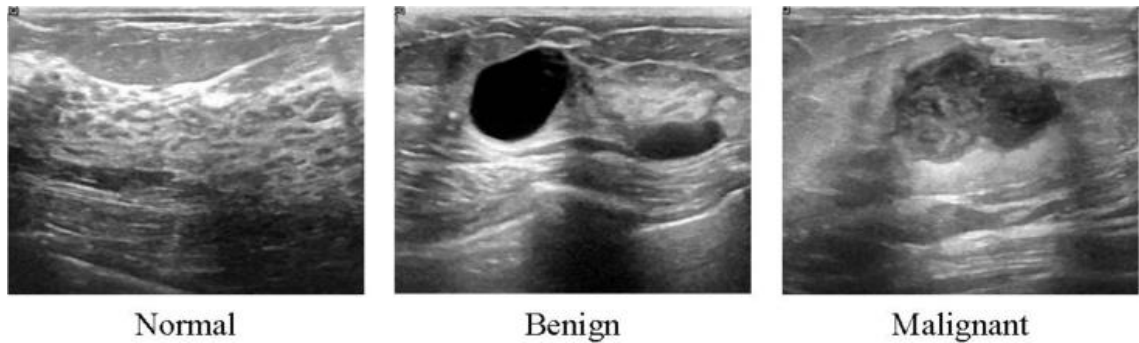


Figure 4: US of mammary gland (normal, benign - cyst and malignant conditions – invasive lobular carcinoma)

**Tomosynthesis:** or “3D” mammography is an advanced form of digital x-ray mammogram which creates 2D and 3D-like pictures of the breasts. This tool improves the ability of mammography to detect early breast cancers, and decreases the number of women visits for additional tests.

**Magnetic resonance imaging (MRI):** MRI is of increasing interest to breast surgeons in a number of setting; it distinguishes scar from recurrence in women who have had previous breast conservation therapy for cancer. It is the best imaging modality for the breast of women with implants. It has proven to be a useful as screening tool in a high-risk woman because of a family history. It is less useful than ultrasound in the management of the axilla in both primary breast cancer and recurrent diseases.

**positron emission tomography (PET)-CT:** may be useful when conventional methods are inconclusive. PET-CT scanning can also replace traditional imaging for staging in high-risk patients.

Also, PET-CT scanning is widely used for metastatic workup, Positron emission tomography combined with computed tomography (PET/CT) has been receiving increasing attention during the recent years for making the diagnosis, for determining the staging and for the follow-up of various malignancies. A study showed the PET/CT findings of 58 breast cancer patients (age range: 34-79 years old, mean age: 50 years) were retrospectively compared with the PET or CT scans alone. PET/CT was found to be better than PET or CT alone for detecting small tumors or multiple metastases, for accurately localizing lymph node metastasis and for monitoring the response to chemotherapy in breast cancer patients.

**Fine needle aspiration (FNA) cytology:** This is a rapid, safe, relatively non-traumatic procedure which can provide a tissue diagnosis within hours. It should be performed whenever a palpable lump or suspicious area of induration is found, and is applicable to the primary tumor, regional lymph nodes or suspicious skin lesions. Small, impalpable lesions might have to be localized by stereotactic mammogram or ultrasound. It cannot, however, distinguish a focus of in situ carcinoma from invasive carcinoma, and does not allow accurate grading of the tumor.

**Needle biopsy:** This is performed under local anesthetic and is a little more traumatic than FNA but gives a core(s) of tissue for histological analysis. This may allow a preoperative diagnosis of in situ versus invasive carcinoma, a preliminary grading and determination of hormone receptor status.

**Nipple discharge cytology:** This is useful in women presenting with a bloody nipple discharge in the absence of a palpable lump.

**Excision biopsy:** an excision biopsy is mandatory when it is not possible to obtain a tissue diagnosis by FNA or core biopsy. The procedure is usually performed under general anesthetic and the specimen can be sent for instant frozen section so that, if a more radical operation is deemed necessary, it can be performed immediately.

Triple assessment: the diagnosis should be made by a combination of clinical assessment, radiological imaging and a tissue sample taken for either cytological or histological analysis, the so-called triple assessment.

Table 2: Diagnostic work up for newly discovered breast cancer

|                                     |   |
|-------------------------------------|---|
| Assessment of general health status | History.<br>Menopausal status.<br>Physical examination.<br>Full blood count.<br>Liver, renal and cardiac function tests (in patients planned for anthracycline and/or trastuzumab treatment), alkaline phosphatase and calcium. |
| Assessment of primary tumor         | Physical examination.<br>Mammography.<br>Breast US.<br>Breast MRI in selected cases.<br>Core biopsy with pathology determination of histology, grade, ER, PgR, HER2 and Ki 67.  |
| Assessment of regional lymph nodes  | Physical examination.<br>US.<br>US guided biopsy (if suspicious).   |
| Assessment of metastatic disease    | Physical examination.<br>MRI<br>PET-Scan<br>Whole body bone scan  |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; US, ultrasonography; MRI, magnetic resonance imaging.

Evaluation of metastatic disease: the results of these investigations may influence the treatment planned, offer useful prognostic information and provide a valuable baseline assessment, which may be of assistance in the future care of the patient.

- CT scan of the brain, thorax, abdomen and pelvis
- isotope bone scan
- serum CA 15-3 breast cancer tumor marker assay. A very high preoperative level or persistently high level after surgery may suggest distant metastatic disease
- a biopsy should be carried out to confirm histology and re-assess tumor biology (ER, PgR, HER2)
- A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with: • clinically positive axillary nodes; •

large tumors (e.g. >5 cm); • aggressive biology; and • clinical signs, symptoms or laboratory values suggesting the presence of metastases



Figure 5:Osteolytic process of bone tissue due to bone metastasis

### **Staging**

The TNM classification is the most frequently used and can be used as a guide to management and prognosis:

**T0** No evidence of primary tumor

**TX** Primary tumor cannot be assessed

**Tis** Carcinoma in situ

**T1** tumor 2 cm or less in greatest dimension –

**T2** tumor >2 cm but not >5 cm in greatest dimension

**T3** tumor >5 cm in greatest dimension

**T4** Tumor of any size with extension to chest wall and/or skin

**N0** No lymphadenopathy

**NX** lymphadenopathy cannot be assessed

**N1** Ipsilateral mobile axillary nodes

**N2** Ipsilateral axillary nodes fixed to one another or to adjacent structures

**N3** Ipsilateral internal mammary node metastases

**M0** no supraclavicular lymph node involvement of distant metastasis

**M1** Involvement of supraclavicular nodes or distant metastases.

- Stage 1 T1NOMO

- Stage 2A T1N1M0, T2N0M0
- Stage 2B T2N1M0, T3N0M0
- Stage 3A T1N2M0, T2N2M0, T3N1M0, T3N2M0
- stage 3b T4N0M0, T4N1M0, T4N2M0
- Stage 3c any T N3M0
- Stage 4 Any T Any N and M1

### **PROGNOSIS:**

the best indicator of likely prognosis in breast cancer remains tumor size, lymph node status and the presence of metastasis. It is realized that some large tumors remain confined to the breast for decades whereas some very small tumors are incurable at time of diagnosis. Hence the prognosis of a cancer depends not on chronological age but on its invasive and metastatic potential.

HER2/neu (HER2) overexpression is associated with transmission of growth signals that control aspects of normal cell growth and division. Overexpression of HER2 is associated with increased tumor aggressiveness, rates of recurrence, and mortality. Genetic profiling tools provide additional prognostic information to aid in treatment decisions for subgroups of patients with otherwise favorable prognostic features.

Noninvasive breast cancer, Ductal carcinoma in situ (DCIS), Lobular carcinoma in situ (LCIS), Paget's disease – good prognosis (more than 85%-90% 5-years surviving)

- Invasive breast cancer

Stage I 93% 5-year survival rate

Stage II 72% 5-year survival rate

Stage III 41% 5-year survival rate

Stage IV 18% 5-year survival rate

Other adverse prognostic factors:

- Young age <35 year
- increasing TNM stage
- poorly differentiated tumours
- poorly differentiated tumors
- lymphatic vessel and/or vascular channel invasion
- estrogen and progesterone receptor negativity
- positivity for the HER2 oncogene.

### **Treatment of breast cancer:**

the two basic principles of treatment are to reduce the chance of local recurrence and the risk of metastatic spread. The treatment of early breast cancer will usually involve surgery with or without radiotherapy. Systemic therapy such as chemotherapy or hormone therapy is added if there are adverse prognostic factors such as lymph nodes

involvement, indicating a high likelihood of metastases relapse. At other end of spectrum locally advanced or metastatic disease is usually treated by systemic therapy to palliate symptoms with surgery playing a much smaller role, Algorithm for management of breast cancer is shown in summary as

- Achieve local control
- Appropriate surgery includes (a) wide local excision (clear margin) + radiotherapy  
(b) mastectomy- radiotherapy immediate or delayed.

Combined with axillary procedure.

- Treat risk of systemic disease by chemotherapy if prognostic factors are poor and hormone therapy if estrogen and progesterone receptor are positive.

Details of local treatment of early breast cancer: local control is achieved through surgery and/or radiotherapy. The aim of treatment is to

- (1) cure: likely in some cases but late recurrence is possible.
- (2) Control local disease in breast and axilla.
- (3) Conservation of local form and function.
- (4) Prevention or delay of occurrence of distant metastases.

### **Surgery**

Surgery: still has central goal to play in the management of breast cancer but have seen gradual shifts toward more conservative techniques, that might show equal efficacy between mastectomy and local excision followed by radiotherapy. It was initially hoped that avoiding mastectomy would help to alleviate the considerable psychological morbidity associated with breast cancer but recent studies as has shown that over 30% of women develop significant anxiety and depression following both radical and conservative surgery.

Mastectomy indicated for (1) a large tumor in relation to size of the breast (2) central tumor beneath or involving the nipple (3) multifocal disease (4) local recurrence (5) patient preference.

Types of operation: the radical Halsted mastectomy including excision of breast axillary lymph nodes + pectorals major and minor, this operation is no longer performed it causes excessive morbidity with no survival benefits. The modified radical (Patey) mastectomy is more commonly performed by preservation of pectorals major and division of pectorals minor. Simple mastectomy, wide local excision.

Conservative breast surgery is aimed at removing the tumor plus a rim of at least 1 cm of normal breast tissue this called wide local excision. Lumpectomy is removal of benign lump. Removing of entire segment of the breast that contains the tumor called Quadrantectomy.

### **Radiotherapy**

Radiotherapy is indicated in all patients treated by breast-conserving surgery. Such an approach produces long-term survival equivalent to that of mastectomy. External beam radiotherapy to the breast alone typically comprises a 5-week course of treatment to the whole breast to reflect the increased risk of recurrence at the site of the original primary but also the possibility of recurrence elsewhere within the breast owing to occult foci of DCIS and LCIS. An extra 'boost' can be delivered specifically to the tumor bed when the margins of excision are narrow or focally involved, and is recommended in all women under 50 years of age.

it performs to the chest wall after mastectomy in selected patient in whom the risk of local recurrence is high. This includes patient with large tumor and those with large numbers of nodes or extensive lymph vascular invasion. It improves survival in women with node positive breast cancer. It is conventional to combine conservative surgery with radiotherapy to remaining breast tissue

radiotherapy can be given intraoperatively at one sitting or as accelerated post-regulatory course.

**Brachytherapy** The most common type of brachytherapy for women with breast cancer is the intra-cavitary brachytherapy, a device is put into the space left from tumor and is left there until treatment is complete. There are several different devices available, most of which require surgical training for proper placement. They all go into the breast as a small catheter (tube). The end of the device inside the breast is then expanded like a balloon so that it stays securely in place for the entire treatment.

Less commonly the Interstitial brachytherapy may be used. which is, several small, catheters are inserted into the breast around the area where the cancer was removed and are left in place for several days. Radioactive pellets are inserted into the catheters for short periods of time each day and then removed.

**RT doses and fractionation:** Doses used for local and/or regional adjuvant irradiation have traditionally been 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy with a typical boost dose of 10–16 Gy in 2 Gy single doses. Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose) have shown similar effectiveness and comparable side-effects [I, A].

## **TREATMENT OF EARLY BREAST CANCER**

### **Local-Regional Therapy:**

- Surgery alone can cure most patients with in situ cancers, 70% to 80% of stage I cancers, and approximately one half of those with stage II cancers.
- Breast-conserving therapy (BCT) is often primary therapy for stage I and stage II disease; it is preferable to modified radical mastectomy because it produces equivalent survival rates with cosmetically superior results. BCT includes removal of part of the breast, surgical evaluation of axillary lymph nodes, and radiation therapy (RT) to prevent local recurrence.
- RT is administered to the entire breast over 3 to 5 weeks to eradicate residual disease after BCT. Reddening and erythema of the breast tissue with subsequent shrinkage of total breast mass are minor complications associated with RT.

### **Systemic Adjuvant Therapy:**

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or in combination) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. The goal of such therapy is cure.
- Administration of chemotherapy, endocrine therapy, targeted therapy, or some combination of these agents results in improved disease-free survival (DFS) and/or overall survival (OS) for all treated patients.

### **Adjuvant chemotherapy**

- Early administration of effective combination chemotherapy at a time of low tumor burden should increase the likelihood of cure and minimize emergence of drug resistant tumor cell clones.
- Anthracycline-containing regimens (eg, doxorubicin and epirubicin) reduce the rate of recurrence and death as compared with regimens that contain cyclophosphamide, methotrexate, and fluorouracil.

- The addition of taxanes, docetaxel and paclitaxel, to adjuvant regimens resulted in reduced risk of distant recurrence, any recurrence, and overall mortality compared with a non-taxanes regimen.
- Initiate chemotherapy within 12 weeks of surgical removal of the primary tumor. Optimal duration of adjuvant treatment is unknown but appears to be 12 to 24 weeks, depending on the regimen used.
- Dose intensity refers to the amount of drug administered per unit of time, which can be achieved by increasing dose, decreasing time between doses, or both.
- Dose increases in standard regimens appear to not be beneficial and may be harmful.
- Avoid dose reductions in standard regimens unless necessitated by severe toxicity.
- Short-term toxicities of adjuvant chemotherapy are generally well tolerated, especially with the availability of serotonin-antagonist and substance P/neurokinin 1– antagonist antiemetics and myeloid growth factors.

Table 3: different regimes of chemotherapy

|   |  |
|---|--|
| <b>AC</b>   | <b>TC</b>  |
| Doxorubicin 60 mg/m <sup>2</sup> IV, day 1                            | Docetaxel 75 mg/m <sup>2</sup> IV, day 1   |
| Cyclophosphamide 600 mg/m <sup>2</sup> IV, day 1                      | Cyclophosphamide 600 mg/m <sup>2</sup> IV, day 1                                     |
| Repeat cycles every 21 days for 4 cycles                              | Repeat cycles every 21 days for 4 cycles   |
| <b>FAC</b>  | <b>TAC</b>   |
| Fluorouracil 500 mg/m <sup>2</sup> IV, days 1 and 4                   | Docetaxel 75 mg/m <sup>2</sup> IV, day 1   |
| Doxorubicin 50 mg/m <sup>2</sup> IV continuous infusion over 72 hours | Doxorubicin 50 mg/m <sup>2</sup> IV bolus, day 1                                     |
| Cyclophosphamide 500 mg/m <sup>2</sup> IV, day 1                      | Cyclophosphamide 500 mg/m <sup>2</sup> IV, day 1 (doxorubicin should be given first) |
| Repeat cycles every 21–28 days for 6 cycles                           | Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)  |

**Adjuvant biologic therapy** Trastuzumab in combination with or sequentially after adjuvant chemotherapy is indicated in patients with early stage, HER2-positive breast cancer. The risk of recurrence was reduced up to 50% in clinical trials.

**Adjuvant endocrine therapy** Tamoxifen, toremifene, luteinizing hormone–releasing hormone (LHRH) agonists, and aromatase inhibitors (AI) are hormonal therapies used in the treatment of primary or early-stage breast cancer.

- Tamoxifen was the gold standard adjuvant hormonal therapy for three decades and is generally considered the adjuvant hormonal therapy of choice for premenopausal women. It has both estrogenic and antiestrogenic properties, depending on the tissue and gene in question.
- Tamoxifen 20 mg daily, beginning soon after completing chemotherapy and continuing for 5 years, reduces the risk of recurrence and mortality. It is usually well tolerated; however, symptoms of estrogen withdrawal (hot flashes and vaginal bleeding) may occur but decrease in frequency and intensity over time.
- Tamoxifen reduces the risk of hip radius and spine fractures.



- It increases the risks of stroke, pulmonary embolism, deep vein thrombosis, and endometrial cancer, particularly in women age 50 years or older.
- Premenopausal women benefit from ovarian ablation with LHRH agonists (eg, goserelin) in the adjuvant setting, either with or without concurrent tamoxifen.
- Aromatase inhibitors (anastrozole, letrozole, and exemestane) are recommended to be added into adjuvant hormonal therapy for postmenopausal, hormone-sensitive breast cancer.

### **TREATMENT: OF LOCALLY ADVANCED BREAST CANCER (STAGE III)**

- Primary chemotherapy (neoadjuvant chemotherapy) is the initial treatment of choice.
- Primary chemotherapy with an anthracycline- and taxanes-containing regimen is recommended. The use of trastuzumab with chemotherapy is appropriate for patients with HER2-positive tumors.
- Surgery followed by adjuvant chemotherapy and adjuvant RT should be administered to minimize local recurrence.
- Other options include:
  - vinorelbine 25 mg/m<sup>2</sup> days 1 and 8 of a 21-day cycle
  - capecitabine 2500mg/m<sup>2</sup> divided into two oral doses per day for days 1 to 14 of a 21-day cycle
  - carboplatin (AUC 6) repeated every 21 days
  - methotrexate 35 mg/m<sup>2</sup> and mitozantrone 11 mg/m<sup>2</sup> (MM) repeated every 21 day

### **TREATMENT OF METASTATIC BREAST CANCER (STAGE IV)**

#### **Biologic or Targeted Therapy:**

- The most important factors predicting response to therapy are the presence of HER2, estrogen, and progesterone receptors in the primary tumor tissue (Triple negative is most aggressive)
- Four Anti-HER2 agents are available: trastuzumab, lapatinib, pertuzumab, and adotrastuzumab emtansine.
- Consider combination endocrine plus HER2-directed therapy when chemotherapy is not tolerated or after achieving maximal response with chemotherapy-HER2 therapy approach.
- Immune checkpoint inhibitors have the potential to produce durable tumor remission and induce long standing anti-tumor immunity in a subgroup of breast cancer patients. Pembrolizumab is a highly selective, humanized immunoglobulin (Ig) specific for PD-1, currently FDA-approved for use in advanced melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, and classical Hodgkin lymphoma. Pembrolizumab has been recommended in breast cancer both as monotherapy and in combination with chemotherapy, for both advanced and early stage breast cancer as well as in triple negative BC.
- The mammalian or mechanistic target of rapamycin (mTOR) pathway plays a crucial role in regulation of cell survival, metabolism, growth and protein synthesis in response to upstream signals in both normal physiological and pathological conditions, especially in cancer. There is an unmet therapeutic need in endocrine-resistant, hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (BC). The addition of everolimus to exemestane for women with HR-positive metastatic BC is now considered a new therapeutic strategy as a second line treatment.

### **Endocrine Therapy:**

- Endocrine therapy is the treatment of choice for patients who have hormone receptor–positive metastases in soft tissue, bone, pleura, or, if asymptomatic, viscera. Compared with chemotherapy, endocrine therapy has an equal probability of response and a better safety profile.
- AIs are generally first line therapy in postmenopausal women. AIs reduce circulating and target organ estrogens by blocking peripheral conversion from an androgenic precursor, the primary source of estrogens in postmenopausal women.
- When compared with tamoxifen, patients receiving AIs had similar response rates as well as lower incidence of thromboembolic events and vaginal bleeding.
- Tamoxifen, a selective estrogen receptor modulator (SERM) is the preferred initial agent when metastases are present in premenopausal women except when metastases occur within 1 year of adjuvant tamoxifen.
- Surgical or chemical ovarian ablation is considered by some to be the endocrine therapy of choice in premenopausal women and produces similar overall response rates as tamoxifen.
- Progestins are generally reserved for third-line therapy. They cause weight gain, fluid retention, and thromboembolic events.

### **Chemotherapy:**

- Chemotherapy is used as initial therapy for women with hormone receptor–negative tumors; and after failure of endocrine therapy.
- Single agents are better tolerated, an important consideration in the palliative metastatic setting.
- Treatment with sequential single agents is recommended over combination regimens.
- Anthracyclines and taxanes produce response rates of 50% to 60% when used as first-line therapy for MBC.

### **Radiation Therapy**

- Commonly used to treat painful bone metastases or other localized sites of disease, including brain and spinal cord lesions. Pain relief is seen in approximately 90% of patients who receive RT.

### **Geriatric recommendations for patients with BC.**

- Treatment of elderly early breast cancer patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard Chemotherapy, a standard multidrug regimen should be used [II, B].
- A geriatric assessment should be carried out before making treatment decisions [II, A].

### **Differential diagnosis of breast cancer**

- **fibroadenoma:** - this is usually arising in the fully developed breast between the age of 15-35 years although occasionally they occur in much older women. they arise from hyperplasia of single lobule and usually grow up to 2-3 cm in this case, they surrounded by well-marked capsule and can thus be enucleated through cosmetically appropriate incision. fibroadenoma does not require excision unless associated with suspicious cytology, it becomes very large or the patient expressly desire the lump to be removed. Giant fibroadenoma occasionally occur during puberty they are over 5cm in diameters and are often rapidly growing but in other respects are similar to smaller fibroadenoma and can be enucleated through sub mammary incision.

- **Phyllodes Tumors:** - these benign Tumors previously sometimes known as serocystic disease of Brodie or cystosacroma phyllodes, usually occur in women over the age of 40 years, but can appear in younger women. They present as large, sometimes massive, tumor with unevenly bosselated surface, occasionally ulceration of over lying skin occurs because of pressure necrosis, despite their size they remain mobile on the chest wall.
- **Galactocele:** is rare, usually present as a solitary, subareolar cyst and always dates from lactation, it contains milk and in longstanding cases its wall tend to calcify
- **Duct ectasia** :-( periductal mastitis): This is dilatation of the breast ducts which is often associate with periductal inflammation. The pathogenesis is obscure and almost certainly not uniform in all cases. Although the disease is much more common in smokers. it is dilatation in one or more of the larger lactiferous ducts which fill with a stagnant brown or greenish secretion, this may discharge. these fluids then set up an irritant reaction in surrounding tissue leading to periductal mastitis or even abscess and fistula formation. In some cases, a chronic induration has forms. beneath the areola, which is mimes as carcinoma. fibrosis eventually develops which cause may slit like nipple retraction. Some believes it is anaerobic bacterial infection and smoking causing arteriopathy. Clinical features: nipple discharge of any color, subareolar mass, abscess, mammary duct fistula and nipple retraction are the most common symptoms.
- **Bacterial mastitis:** it is the most common variety of mastitis and is associated with lactation in majority of the cases. Etiology: lactational mastitis is seen less frequently than previously. Most of the cases caused by staphylococcus, infective from the hospital or from infants who 50% of them harbor staph in their nasopharynx. Although ascending infection from a sore and cracked nipple may initiate mastitis, in many cases the lactiferous ducts will first become blocked by epithelial debris leading to stasis, this theory is supported by relatively high incidence of mastitis in women with a retracted nipple. Clinical features: classical signs of acute inflammation (pain, fever, rigor, edema, erythema, tender swelling) and start as general cellulitis end by abscess formation. Treatment: during cellulitis stage patient should be treated by a appropriate antibiotics as flucloxacillin or amoxiclav.
- **Breast abscess:** if there is lactational abscess and marked skin thinning drainage can be done under local or general anesthesia. Drainage is done by opening all loculi by removing septi between loculi to make one room or loculi, with this procedure we ensure we draining the entire abscess.
- **Mondor's disease:** it is superficial thrombophlebitis of superficial veins of the breast and anterior chest wall; it appears as subcutaneous cord. It should be distinguished from cancer permeation.
- **Gynecomastia:** hypertrophy of a male breast, may be unilateral or bilateral. The breast enlarges at puberty and sometimes present the characteristic female breast causes:
  1. Hormonal cause as in patient with carcinoma of prostate and treated by stilbestrol (now rarely used), in teratoma of the testis, anorchism, after castration, bronchial carcinoma, adrenal and pituitary disease and using of steroids in young body builder.
  2. associated with leprosy due to bilateral testicular atrophy.
  3. associated with liver failure as in cirrhosis due to failure of metabolism of estrogen.
  4. drugs as cimetidine, digoxin and spironolactone.
  5. Klinefelter, s syndrome: sex chromosome anomaly has 47 XXY trisomy.

### Screening

The European Guidelines for quality assurance in breast cancer screening and diagnosis recommend performance parameters and indicators that should be monitored in any screening program. The European Commission Initiative on Breast Cancer (ECIBC) has produced evidence-based recommendations for mammography screening, with the strongest

recommendation for women aged 50–69 years and with conditional recommendations for women in younger and older age groups. The greatest mortality reduction benefit has been shown in the 50- to 69-year-old age group, while evidence for effectiveness of mammography screening in women aged 40–49 years is more limited, especially for women aged between 40 and 44 years. This was also the conclusion in the 2015 breast cancer screening report from the International Agency for Research on Cancer (IARC). There is no consensus about the exact effect of mammography screening on breast cancer mortality reduction, as the reported estimates vary. In a UK review of the randomized controlled mammography trials, a 20% relative breast cancer mortality reduction was estimated in women aged between 50 and 70. In women with familial breast cancer, with or without proven BRCA mutations, annual screening with magnetic resonance imaging (MRI) of the breast, in combination with mammography, can detect the disease at a more favorable stage compared with mammography screening alone (70% lower risk of being diagnosed with breast cancer stage II or higher).

#### **Recommendations of ESMO for breast cancer screening:**

- Regular (annual or every 2 years) mammography is recommended in women aged 50–69 years [I, A]. Regular mammography may also be done for women aged 40–49 and 70–74 years, although the evidence for benefit is less well established [II, B].
- In women with a strong familial history of breast cancer, with or without proven BRCA mutations, annual MRI and annual mammography (concomitant or alternating) are recommended [III, A].

#### **VII. QUESTIONS FOR SELF-CONTROL:**

1. Epidemiology and risk factors of breast cancer.
2. Pathology of breast cancer, modes of spreading.
3. Histological classification of malignant tumors of the breast, intrinsic subtypes of breast cancer.
4. Clinical approach to patient with breast masses, clinical presentation of breast cancer.
5. Breast cancer staging, diagnostics and follow up.
6. Differential diagnosis of breast masses.
7. Surgical treatment of breast cancer, radical mastectomy, breast conserving surgery, reconstructive surgery.
8. Role of radiotherapy in treatment of breast cancer.
9. Role of chemotherapy in treatment of breast cancer.
10. Breast cancer treatment, role of endocrinological and target therapies.
11. Breast cancer, prognosis, prevention.
12. Screening of breast cancer.

#### **VIII. Tasks for verification of concrete teaching aims achievement:**

- 1- A 40-year-old African-American woman presents to your clinic for an annual health examination. She has hypertension and hyperlipidemia, for which she takes hydrochlorothiazide and a statin, respectively. Otherwise, she is in good health, and she exercises regularly. Her main concern today is her risk of breast cancer. She has a close friend who was recently diagnosed with breast cancer, and she is now very worried that she might one day get it. Which of the following statements regarding the risk factors for breast cancer is true?
  - A. Because of germline mutations of either BRCA1 or BRCA2, the breast-ovarian cancer syndrome is inherited in an autosomal recessive fashion
  - B. Reproductive risk factors include late menarche, early menopause, and increasing parity
  - C. The diagnosis of breast cancer in first-degree relatives younger than 50 years is associated with a threefold to fourfold increased risk

- D. Women between the ages of 40 and 50 years are at greatest risk; 75% of all breast cancers are diagnosed in that age group.
- 2- On clinical examination, a 54-year-old woman is noted to have a nontender mass in the upper outer quadrant of her left breast. There are no overlying skin changes, and there is no palpable adenopathy in the axilla. The other breast is without masses. A mammogram obtained 1 year ago was normal. You immediately set up an appointment for mammography, but your patient is obviously disturbed. She has several questions regarding the therapy for breast cancer. Which of the following statements regarding breast cancer therapy is true?
- A. For women with stage I or II breast cancer, the survival rate with breast conservation therapy involving lumpectomy and radiotherapy is identical to the survival rate with modified radical mastectomy
  - B. Sentinel lymph node mapping is difficult to perform and offers no benefit to axillary lymph node dissection
  - C. The benefit of tamoxifen is limited to 5 years, and therefore, the recommendation is to discontinue therapy after 5 years
  - D. Aromatase inhibitors offer a viable alternative to tamoxifen therapy for premenopausal women
- 3- A 54-year-old woman presents with a breast mass she discovered 2 days ago. She has been performing breast self-examinations monthly and noted a new mass in the upper outer quadrant of her left breast. She denies having any breast pain or nipple discharge. She has experienced no weight loss, headache, shortness of breath, or bony pain. On examination, she is found to have a 0.5 cm × 1 cm hard, mobile mass that is easily palpated. No skin abnormalities or other masses are detectable by palpation in either breast. There is no axillary or supraclavicular lymphadenopathy, and the remainder of a detailed physical examination is normal. A biopsy is performed of the patient's breast mass, which is found to have infiltrating ductal carcinoma. Results of a complete blood count, liver function tests, and metabolic panel are all within normal limits. At this point, the interventions that would provide the best survival and least morbidity for this patient include which of the following?
- A. Modified radical mastectomy
  - B. Lumpectomy with axillary lymph node dissection
  - C. Radiation therapy
  - D. Modified radical mastectomy and radiation therapy
  - E. Lumpectomy with axillary lymph node dissection and radiation therapy
- 4- A 70-year-old woman presents for evaluation. Five years ago, she was diagnosed with stage II infiltrating ductal carcinoma of the right breast and was treated with lumpectomy and radiation. Over the past several weeks, she has experienced increasing fatigue and right upper quadrant pain. She denies having any bone pain. Physical examination reveals a hard, 3 cm palpable mass in the left breast (contralateral to her previous cancer); the examination is otherwise unremarkable. Results of laboratory testing include the following: AST, 78; ALT, 40; alkaline phosphatase, 200; total bilirubin, 1.3; and albumin, 3.0. CT of the abdomen shows three liver lesions that are consistent with metastases. Mammography reveals a speculated mass in the left breast; a biopsy is performed, and the mass is found to be invasive ductal carcinoma that expresses both estrogen and progesterone receptors. In this patient, first-line treatment should begin with which of the following?
- A. Surgical resection of the breast nodule
  - B. Radiation of the left breast
  - C. Hormonal therapy
  - D. High-dose chemotherapy with autologous stem cell transplantation
  - E. Cytotoxic chemotherapy

- 5- . You are seeing a 62-year-old woman in the clinic with a family history of breast cancer. She is worried about her future risk of breast cancer, since her mother died of breast cancer at the age of 63. Which of the following features is also a recognized risk factor for breast cancer?
- A. early onset of menopause
  - B. early onset of menarche
  - C. late-life radiation exposure
  - D. multiparity
  - E. early full-term pregnancy
- 6- A 53-year-old woman presents to the clinic for evaluation of a new left breast lump that she discovered 1 week ago. The nodule is not painful; she feels well and has no other symptoms. On physical examination the lump is palpable, and there are no axillary lymph nodes. The mammogram confirms the presence of a 1-cm breast mass which on biopsy is positive for invasive breast cancer. Which of the following is the most appropriate local therapy for her tumor?
- A. simple mastectomy with axillary dissection
  - B. radiation therapy to breast and axilla
  - C. local excision plus radiation therapy
  - D. local excision and axillary dissection followed by radiation therapy
  - E. local excision and axillary sampling
- 7- A 53-year-old woman notices a lump in her left breast. She reports no symptoms of breast discharge or previous breast disease. She is postmenopausal, menarche was at age 13, and her family history is negative for breast cancer. Physical examination reveals a 2-cm palpable lump in the left breast, which is mobile and nontender, and there are no axillary lymph nodes. The right breast and axilla are normal. Biopsy of the lump is positive for breast cancer, and she undergoes a lumpectomy and lymph node dissection. Which of the following factors is important in deciding about adjuvant therapy for breast cancer?
- A. menopausal status
  - B. tumor size
  - C. endocrine receptor status
  - D. lymph node status
  - E. all of the above
- 8- A 66-year-old postmenopausal woman presents with a painless breast mass and is found to have a 3- cm infiltrating ductal breast cancer. Sentinel node sampling reveals metastatic cancer in the sentinel node; a formal axillary node dissection shows that 4 of 13 nodes are involved by the malignant process. Both estrogen and progesterone receptor are expressed in the tumor. There is no evidence of metastatic disease outside the axilla. In addition to lumpectomy and radiation therapy to the breast and axilla, what should her treatment include next?
- A. No further treatment at this time
  - B. Radiation therapy to the internal mammary nodes
  - C. Platinum-based adjuvant chemotherapy
  - D. Bilateral oophorectomy
  - E. Adjuvant hormonal therapy (tamoxifen or aromatase inhibitor)
- 9- Among women younger than 60 years of age who die from cancer, which of the following is the most common primary organ of origin?
- A. Breast
  - B. Cervix

- C. Colon
  - D. Bone marrow
  - E. Lung
- 10- A 34-year-old woman is seen by her internist for evaluation of right breast mass. This was noted approximately 1 week ago when she was showering. She has not had any nipple discharge or discomfort. She has no other medical problems. On examination, her right breast has a soft 1 cm × 2 cm mass in the right upper quadrant. There is no axillary lymphadenopathy present. The contralateral breast is normal. The breast is reexamined in 3 weeks, and the same findings are present. The cyst is aspirated, and clear fluid is removed. The mass is no longer palpable. Which of the following statements is true?
- A. Breast MRI should be obtained to discern for residual fluid collection.
  - B. Mammography is required to further evaluate the lesion.
  - C. She should be evaluated in 1 month for recurrence.
  - D. She should be referred to a breast surgeon for resection.
  - E. She should not breastfeed any more children.
- 11- At what age do women most often suffer from breast cancer?
- A. 25-45 years
  - B. 45-65 years
  - C. 65-85 years
  - D. over 90 years
  - E. 65-85 years
- 12- Early findings of carcinoma of breast include:
- A. Skin ulceration
  - B. Skin retraction
  - C. Single non-tender, firm to hard mass with ill-defined margins
  - D. All of the above
- 13- Treatment of breast cancer T1N0M1 is considered as:
- A. Radical
  - B. Palliative
  - C. Chemotherapeutic
  - D. Surgical
  - E. Target
- 14- The most common localization of breast cancer?
- A. The upper inner quadrant
  - B. Upper-outer quadrant
  - C. Lower outer quadrant
  - D. The lower inner quadrant
  - E. Axilla
- 15- Paget`s carcinoma is usually an infiltrating carcinoma of:
- A. Skin of axilla
  - B. Lymph-nodes
  - C. Breast areola
  - D. Breast lobula
  - E. Lungs

Correct answers: 1-C ,2-A ,3-E ,4-C, 5-B ,6-D, 7-E, 8-E, 9-A, 10-C ,11-E, 12-C, 13-B, 14-B, 15-C.

**IX. Suggested Literature:**

### **IX 1. Basic:**

1. Cancer principles and practice of oncology – DeVita, Hellman and Rosenberg's ,10<sup>th</sup> edition.
2. manual of clinical oncology (Lippincott manual), 7<sup>th</sup> edition -2017.
3. NCCN clinical practice Guidelines of breast cancer ,2021.
4. ANNALS OF ONCOLOGY, ESMO Clinical Practice Guidelines of metastatic breast cancer treatment, 2021, ESMO Guidelines Committee.
5. ANNALS OF ONCOLOGY, ESMO Clinical Practice Guidelines of early breast cancer treatment, 2019, ESMO Guidelines Committee.

### **IX 2. Additional:**

1. Textbook of complex general surgical oncology -SHYNE Y. MORITA, CHARLES M. BALCH, V. SUZANNE KLIMBERG, TIMOTHY M. PAWLIK, MITCHELL C. POSNER, KENNETH K. TANABE, 2018.
2. Clinical oncology, basic principles and practice – Anthony J. Neal and Peter J. Hoskin ,4<sup>th</sup> edition.



## **X. CONTENT**

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