BREAST CANCER

I. Epidemiology

Breast cancer is the most common malignancy in women in Western Countries.

- It accounts of 22% of all malignancies in women and 14% of cancer-related deaths in Poland. In 2017, an estimated 20,000 new breast cancer cases are expected to be diagnosed. About 1 in 7-8 women (about 12-15%) will develop invasive breast cancer over the course of her lifetime.
- Breast cancer is a global problem of public health – for example the expected number in 2017 in USA is over than 250,000 new cases of invasive cancer and more than 60,000 of non-invasive (in situ) carcinomas. It will be the cause of over than 40,000 deaths. Men account for 1% of breast cancer cases and breast cancer deaths.
- Widespread adoption of mammographic screening increases breast cancer incidence in a given population and changes the characteristics of cancers detected, with increased incidence of lower-risk invasive cancers, border-line/premalignant lesions, and preinvasive cancers (particularly ductal carcinoma *in situ* (DCIS).

II. Risk factors

The most significant risk factors for breast cancer are:

1. Gender: lifetime risk 12-15% for women vs 0.1% for men)

2. Increasing age (as for most cancers): just 12% of invasive breast cancers develop in women <45 years of age while about 66% are found in women >55)

3. Major inheritance susceptibility
   - Family history: a woman's risk of breast cancer nearly doubles if she has a first-degree relative (mother, sister, daughter) who has been diagnosed with breast cancer. Less than 15% of women who get breast cancer have a family member diagnosed with it.
   - Gene mutations: about 5-10% of breast cancers can be linked to gene mutations; mutations of the *BRCA1* and *BRCA2* genes are the most common. The estimated lifetime risk of developing breast cancer for women with *BRCA1* and *BRCA2* mutations is up to 85% and 45%, respectively. Carriers with a history of breast cancer have an increased risk of contralateral disease that may be as high as 5% per year. Breast cancer that is positive for the *BRCA1* or *BRCA2* mutations tends to develop more often in younger women. An increased ovarian cancer risk is also associated with these genetic mutations. In men, *BRCA2* mutations are associated with a lifetime breast cancer risk of about 6.8%; *BRCA1* mutations are a less frequent cause of breast cancer in men. About 85% of breast cancers occur in women who have no family history of breast cancer. These occur due to genetic mutations that happen as a result of the aging process and life in general, rather than inherited mutations.

4. Other risk factors are of minor significance and include the following:
   - Alcohol intake: women who have 2-3 alcoholic drinks per day have a 20% higher risk than non-drinkers (by the exposure to endogenous estrogen).
   - High breast density (high amount of glandular tissue compared with fat tissue on

mammogram): women with dense breast are 4-5 times more likely to get breast cancer than females with low breast density.

- Endogenous estrogen: menstrual history (early menarche <12 years of age, menopause >55), nulliparity, older age at first birth (in general, the more children a woman has given birth to, the lower her risk of breast cancer tends to be due to protective benefit from pregnancy).
- Hormone therapy history: taking combined hormone replacement therapy (estrogen plus progestin) for several years or more or estrogen alone for more than 10 years.
- Postmenopausal overweight, BMI >25; or obesity, BMI >30 (by the exposure to endogenous estrogen).
- Personal history of breast cancer (including DCIS): apart from a recurrent cancer women with breast cancer history have a higher risk of getting a new disease (so called second primary cancer) of ipsilateral breast (either breast after conserving therapy) and contralateral breast (opposite): about 5% of patients will get a second breast cancer within 8 years of their initial diagnosis while up to 14% within 25 years. On average, the estimated lifetime risk is about 10%. Women whose first breast cancer was hormone-negative may have higher risk when compared with hormone-positive cases.
- Personal history of proliferative breast disease (i.e. atypical hyperplasia, lobular carcinoma in situ).
- Radiation exposure to breast/chest: radiotherapy to the chest area at young age (e.g. for Hodgkin's disease) increases the risk of breast cancer for 3-7 times; low doses of radiation (such as from medical imaging) do not have much, if any, impact on breast cancer risk.

III. Protective Factors

Protective factors and interventions that may reduce the risk of breast cancer:

- Early pregnancy (by decreasing exposure to endogenous estrogen).
- Breast feeding (as above).
- Selective estrogen receptor modulators (SERMs, e.g. Tamoxifen, Raloxifene): can reduce the risk of estrogen receptor-positive breast cancers, neither drug reduces estrogen receptor-negative cancers. Tamoxifen is more effective in risk reducing while raloxifene has fewer harmful side effects.
- Aromatase inhibitors or inactivators (Exemestane, Anastrozole): may lower the risk by about half)
- Risk-reducing mastectomy (lowers the risk of breast cancer by up to 90%, never by 100%). Prophylactic mastectomy does not completely protect patient from breast cancer. The benefits seem to be greater in younger women because of more years of life ahead. For 30-year old *BRCA1/2* gene mutation carriers the procedure may add 3-5 years to her lifespan while for women at 60 years of age or older the gain in lifespan is very small.
- Exercise and physical activity (one large study, 2014).
- Risk-reducing oophorectomy (lowers the risk of breast cancer by 50-70%).

IV. Mammographic screening

Clinical trials have established that screening asymptomatic women using mammography (regardless of physical breast examination) decreases breast cancer mortality. In the randomized controlled trials, for women aged 40 to 74 years, screening with mammography has been associated with a 15% to 20% relative reduction in mortality from breast cancer. Absolute mortality benefit for women screened annually for 10 years is approximately 1% overall, ranging from 4 per 10,000 women who start screening at age 40 years to 50 per 10,000 women who start at age 50 years.

V. Diagnosis

1. Patient evaluation

When breast cancer is suspected, patient management generally includes the following:

- Confirmation of the diagnosis.
- Evaluation of the stage of disease.
- Selection of therapy.

Apart from physical examination the following imaging tests are used to diagnose breast cancer:

- Mammography.
- Ultrasound.
- Breast magnetic resonance imaging (MRI), if clinically indicated.

Each breast lesion is evaluated with regard to the risk of malignancy according to the BIRADS classification (Breast Imaging Reporting And Data System) based on mammography-, ultrasound- and MRI-dedicated lexicons. The management should be as follows:

Final Assessment Categories			
BIRADS Category		**Likelihood of cancer**	**Management**
0	Need more information and additional imaging	n / a	Recall for further assessment
1	Negative	Essentially 0%	Routine screening
2	Benign	Essentially 0%	Routine screening
3	Lesion of uncertain potential of malignancy*	>0% to ≤2%	Short-term follow-up (6 months)
4	Suspicious for malignancy	**4A** low suspicion >2% to ≤ 10% **4B** moderate >10% to ≤50% **4C** high suspicion >50% - ≤95%	Biopsy – tissue diagnosis
5	Highly suggestive of malignancy	> 95%	Biopsy – tissue diagnosis
6	Known cancer (biopsy proven)	n / a	Treatment

*formerly: probably benign

The following percutaneous procedures are used in minimally invasive investigations for lesions BIRADS-4 and 5 (recommended to be performed under the radiological guidance):

- FNA (fine-needle aspiration): needles 23-20 G (inner diameter 0.3-0.6 mm) cytology, low accuracy; generally not recommended
- CNB (core-needle biopsy): needles 18-14 G (0.8-1.6 mm); histology, cost-effective, most common
- VAB (vacuum-assisted biopsy): needles 11-7 G (2.4-3.8 mm); histology; highest sensitivity and specificity, very low underestimation rate; best but most expensive

If no malignancy is found on histological examination of specimen from core-needle or vacuum-

assisted biopsy of BIRADS-4C or BIRADS-5 lesion imaging-pathologic discordance occurs. In that case a recommended management is surgical excision to obtain a definitive diagnosis from histological examination of whole lesion.

2. Risk of contralateral disease

Pathologically, breast cancer can be a multicentric and bilateral disease. Bilateral disease is somewhat more common in patients with infiltrating lobular carcinoma. At 10 years after diagnosis, the risk of a primary breast cancer in the contralateral breast ranges from 3% to 10%, although endocrine therapy decreases that risk. The development of a contralateral breast cancer is associated with an increased risk of distant recurrence. When *BRCA1*/*BRCA2* mutation carriers were diagnosed before age 40 years, the risk of a contralateral breast cancer reached nearly 50% in the ensuing 25 years.

Patients who have breast cancer must undergo bilateral imaging at the time of diagnosis to rule out synchronous disease, multicentric or bilateral. To detect either recurrence in the ipsilateral breast in patients treated with breast-conserving surgery or a second primary cancer in the contralateral breast, patients will continue to be followed-up and have regular breast physical examinations and mammograms.

The role of MRI in testing the contralateral breast and monitoring women treated with breast-conserving therapy continues to evolve. Because an increased detection rate of mammographically occult disease has been demonstrated, the selective use of MRI for additional imaging is occurring more frequently despite the absence of randomized controlled data. Because only 25-30% of MRI-positive findings represent malignancy, pathologic confirmation before treatment should be obtained. Thus, performing diagnostic MRI without ability of invasive investigation is not recommended. One has to remember that MRI is additional to mammography, not a substitute for. Despite very high sensitivity of MRI (particularly dynamic contrast-enhanced MRI) some cancers visible on mammography can be omitted on MRI (for example: small non-mass DCIS with no enhancement).

VI. Prognostic and Predictive Factors

In general, breast cancer is usually treated by various combinations of locoregional therapy, such as surgery and radiation therapy, and systemic treatment including chemotherapy, hormone therapy, and directed therapy. Prognosis and selection of therapy are influenced by the several features, including clinical factors, pathological features, and molecular profiling.

1. Clinical and pathological features:

- Menopausal status of the patient.
- Stage of the disease (TNM system, 0-IV prognostic groups)
- Grade of the primary cancer – measure of cell abnormality and histologic differentiation based on the resemblance of the tumour to the tissue of origin: well-differentiated G1 (low grade), moderately differentiated G2 (intermediate grade), poorly differentiated G3 (high grade), and undifferentiated G4 (anaplastic).
- Estrogen receptor (ER) and progesterone receptor (PR) status of the tumour.
- HER2 (HER2/neu) overexpression and/or amplification. HER2 is human epidermal growth factor type 2 receptor encoded by *ERBB2* gene. Other rarely use but still existing names include: epidermal growth factor type 2 receptor (EGFR2), protooncogene Neu, receptor tyrosine-protein kinase erbB2, CD340 (cluster of differentiation 340).
- Histologic type. Breast cancer is classified into a variety of histologic types. Some of which have prognostic importance - favourable histologic types include: mucinous, medullary, and tubular carcinomas.

2. Molecular profiling includes the following:

- ER and PR status testing.
- HER2 receptor status testing.
- Gene profile testing by microarray assay or reverse transcription-polymerase chain reaction (e.g., MammaPrint, Oncotype DX).

ER, PR, and HER2 status are important in determining prognosis and in predicting response to endocrine and HER2-directed therapy.

On the basis of ER, PR, and HER2 results, breast cancer is classified as one of the following intrinsic subtypes:

- Hormone-receptor positive.
- HER2-positive.
- Triple negative (ER, PR, and HER2-negative).

Gene profile tests include the following:

- MammaPrint:

The first available gene profile test was the MammaPrint gene signature (70 genes). Its prognostic utility primarily targets adjuvant therapy−decision making in women aged ≤61 years with stage I/II lymph node–negative breast cancer 5 cm or smaller (T1-2N0). In the near future ongoing trials will help determine if the assay should be used to decide whether adjuvant chemotherapy may benefit a patient.

- Oncotype DX:

The 21 gene profile test with the most extensive clinical validation thus far, albeit in a prospective–retrospective fashion. A recurrence score (RS) is generated based on the level of expression of each among the 21 genes (RS <18, RS ≥18 but <31, RS ≥31 defines low, intermedaite and high risk subgroup, respectively).

Many other gene-based assays may guide treatment decisions in patients with early breast cancer (Predictor Analysis of Microarray 50 [PAM50] Risk of Recurrence [ROR] score, EndoPredict, Breast Cancer Index, etc).

VII. Histopathologic Classification (WHO)

Table 1 describes the histologic classification of breast cancer based on tumour location. Infiltrating or invasive ductal cancer is the most common breast cancer histologic type comprising up to 80-85% of all cases.

Table 1. Tumour Location and Related Histologic Subtype

Tumour Location	Histologic Subtype
Carcinoma	
Ductal	Intraductal (in situ)
	Invasive with predominant component
	Invasive, NOS
	Comedo
	Inflammatory
	Medullary with lymphocytic infiltrate

	Mucinous (colloid)
	Papillary
	Scirrhous
	Tubular
	Other
Lobular	Invasive with predominant in situ component
	Invasive
Nipple	Paget disease, NOS
	Paget disease with intraductal carcinoma
	Paget disease with invasive ductal carcinoma
Other	Undifferentiated carcinoma
	Metaplastic

NOS: not otherwise specified; NST: no special type

The following malignant tumour subtypes occur in the breast but are not considered breast cancers:

- Malignant phyllodes tumour.
- Angiosarcoma.
- Primary lymphoma.

VIII. Stage (TNM)

The AJCC and UICC have designated staging by tumour, node, and metastasis (TNM) classification to define breast cancer. Tables 2-6 present the current version, modified in 2002.

Table 2. Primary Tumour (T)

Tx	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ*.
Tis (DCIS)	Ductal carcinoma *in situ*.
Tis (LCIS)	Lobular carcinoma *in situ*.
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumour ≤20 mm in greatest dimension.
T1mi	Tumour ≤1 mm in greatest dimension.
T1a	Tumour >1 mm but ≤5 mm in greatest dimension.
T1b	Tumour >5 mm but ≤10 mm in greatest dimension.
T1c	Tumour >10 mm but ≤20 mm in greatest dimension.
T2	Tumour >20 mm but ≤50 mm in greatest dimension.
T3	Tumour >50 mm in greatest dimension.
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules, invasion of the dermis alone does not qualify as T4).

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion.
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma.
T4c	Both T4a and T4b.
T4d	Inflammatory carcinoma.

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

Table 3. Regional Lymph Nodes - clinical (cN)

cNx	Regional lymph nodes cannot be assessed (e.g., previously removed).
cN0	No regional lymph node metastases.
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s).
	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted.
	OR
	Metastases in clinically detected***** ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases.
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures.
cN2b	Metastases only in clinically detected***** ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases.
	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement.
	OR
	Metastases in clinically detected***** ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases.
	OR
	Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.
cN3a	Metastases in ipsilateral infraclavicular lymph node(s).
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s).
cN3c	Metastases in ipsilateral supraclavicular lymph node(s).

*****Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for

example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine-needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Table 4. Regional Lymph Nodes - pathologic (pN)

pNx	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study).
pN0	No regional lymph node metastasis identified histologically.
Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumour cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.	
pN0(i–)	No regional lymph node metastases histologically, negative IHC.
pN0(i+)	Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC).
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR).
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC.
	Micrometastases.
	OR
	Metastases in 1–3 axillary lymph nodes.
	AND/OR
	Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected.*
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm).
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm.
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.****
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.****
	Metastases in 4–9 axillary lymph nodes.
	OR
	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases.
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit >2 mm).
pN2b	Metastases in clinically detected** internal mammary lymph nodes in the *absence* of axillary lymph node metastases.
	Metastases in ≥10 axillary lymph nodes.
	OR
	Metastases in infraclavicular (level III axillary) lymph nodes.
	OR
	Metastases in clinically detected** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes.

	OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*
	OR
	Metastases in ipsilateral supraclavicular lymph nodes.
	Metastases in ≥10 axillary lymph nodes (at least 1 tumour deposit >2.0 mm).
	OR
	Metastases to the infraclavicular (level III axillary lymph) nodes.
	Metastases in clinically detected[d] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes.
	OR
	Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected.*
pN3c	Metastases in ipsilateral supraclavicular lymph nodes.

Posttreatment ypN

–Posttreatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AD.

–The X classification will be used (ypNx) if no yp posttreatment SN or AD was performed.

–N categories are the same as those used for pN.

AD: axillary node dissection; H&E: hematoxylin and eosin staining; IHC: immunohistochemical; ITC: isolated tumour cells; RT-PCR: reverse transcriptase/polymerase chain reaction.

Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (SN) for "sentinel node," for example, pN0(SN).

*Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

Table 5. Distant Metastases (M)

M0	No clinical or radiographic evidence of distant metastases.
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases.
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm.

Table 6. Anatomic Stage/Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0	N1mi	M0
	T1*	N1mi	M0
IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

*T1 includes T1mi. **T0 and T1 tumours with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
M0 includes M0(i+). The designation pM0 is not valid; any M0 should be clinical. If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy. Postneoadjuvant therapy is designated with "yc" or "yp" prefix. No stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

IX. Treatment for Early Breast Cancer (Localized/Operable)

Standard treatment options for early, localized, or operable breast cancer may include the following:

1. Surgery:

1. Breast-conserving surgery (BCS) and sentinel node biopsy (SLNB) with or without axillary lymph node dissection for positive sentinel lymph nodes (SLNs).
2. Modified radical mastectomy (removal of the entire breast with axillary dissection of levels I and II) with or without breast reconstruction and sentinel node biopsy with or without axillary lymph node dissection (AD) for positive SLNs.

2. Postoperative radiation therapy:

1. Axillary node–negative breast cancer (postmastectomy):
    - No additional therapy.
    - Radiation therapy.
2. Axillary node–positive breast cancer (postmastectomy):

- For one to three nodes, the role of regional radiation therapy to the infra/supraclavicular nodes, internal mammary nodes, axillary nodes, and chest wall is unclear.
- For four or more nodes or extranodal involvement, regional radiation therapy is advised.

3. Axillary node–negative or positive breast cancer (post–BCS):
    - Whole-breast radiation therapy.

3. Postoperative systemic therapy:

1. Therapy depends on many factors including stage, grade, molecular status of the tumour (ER, PR, HER2). Adjuvant treatment options may include the following:
    - Tamoxifen.
    - Aromatase inhibitor (AI) therapy.
    - Ovarian function suppression.
    - Chemotherapy.

4. Preoperative systemic therapy:

1. Chemotherapy.
2. HER2 targeted therapy.
3. Endocrine therapy.

IX.1. Surgery

Stage I, II, IIIA, and operable IIIC breast cancer often require a multimodal approach to treatment.

The diagnostic biopsy and surgical procedure that will be used as primary treatment should be performed as two separate procedures:

- Biopsy. In most cases, the diagnosis of breast carcinoma is made by core needle biopsy, preferably under the radiological guidance.
- Surgical procedure. After the presence of a malignancy is confirmed by biopsy, the following surgical treatment options can be discussed with the patient before a therapeutic procedure is selected:
    - BCS.
    - Modified radical mastectomy (removal of the entire breast with axillary dissection of levels I and II) with or without breast reconstruction.

Selection of a local therapeutic approach depends on the following:

- Location and size of the lesion.
- Analysis of the mammogram (and USG/MRI when needed).
- Breast volume.
- Tumour size to breast volume ratio.
- Patient’s desire to preserve the breast.

Options for surgical management of the primary tumour include the following:

- Breast-conserving therapy (BCT: BCS plus radiation therapy). All histologic types of invasive breast cancer may be treated with BCT (BCS pus radiation therapy). However, the presence of inflammatory breast cancer, regardless of histologic subtype, is a contraindication to BCT. The presence of multifocal disease in the breast and a history of collagen vascular disease are relative contraindications to BCT.
- Mastectomy with or without breast reconstruction.

Survival is equivalent with any of these options - many prospective randomized trials found no

differences in distant metastases and long-term patient survival.

The rate of local recurrence in the breast with BCS is low and varies slightly with the surgical technique used (e.g., lumpectomy, quadrantectomy, segmental mastectomy, and others). Whether completely clear microscopic margins are necessary has been debated. However, results of a recent multidisciplinary consensus panel include the following:

- Positive margins (ink on invasive carcinoma or ductal carcinoma *in situ*) were associated with a twofold increase in the risk of ipsilateral breast tumour recurrence compared with negative margins.
- More widely clear margins were not found to significantly decrease the rate of ipsilateral breast tumour recurrence compared with no ink on tumour. Thus, it was recommended that the use of no ink on tumor be the new standard for an adequate margin in invasive cancer.
- There was no evidence that more widely clear margins reduced ipsilateral breast tumour recurrence for young patients or for those with unfavourable biology, lobular cancers, or cancers with an extensive intraductal component.

Axillary lymph node management

Axillary node status remains the most important predictor of outcome in breast cancer patients. Evidence is insufficient to recommend that lymph node staging can be omitted in most patients with invasive breast cancer. The axillary lymph nodes are staged to aid in determining prognosis and therapy.

- SLNB is the initial standard axillary staging procedure performed in women with invasive breast cancer. The SLN is defined as any node that receives drainage directly from the primary tumour; therefore, allowing for more than one SLN, which is often the case. Injection of technetium-labeled (Tc99) sulfur colloid, vital blue dye, or both around the tumour or biopsy cavity, or in the subareolar area (Sappey plexus), and subsequent drainage of these compounds to the axilla results in the identification of the SLN in 92% to 98% of patients and a 97.5% to 100% concordance between SLNB and complete AD. SLNB alone is associated with less morbidity than axillary lymphadenectomy.
- AD is indicated when axillary disease is proven preoperatively or massive metastases with gross extracapsular extension are found in numerous SLNs
- AD is unnecessary after a positive SLNB in patients with limited SLN-positive breast cancer treated with breast conservation or mastectomy, radiation, and systemic therapy.
- AD and axillary radiation therapy provide excellent and comparable axillary control for patients with T1 or T2 primary breast cancer and no palpable lymphadenopathy who underwent BCT or mastectomy.
- The use of axillary radiation therapy is also associated with significantly less morbidity.

For patients who require an AD, the standard evaluation usually involves only a level I and II dissection, thereby removing a satisfactory number of nodes for evaluation (i.e., at least 6–10), while reducing morbidity from the procedure.

Breast reconstruction

For patients who opt for a total mastectomy, reconstructive surgery may be performed at the time of the mastectomy (immediate reconstruction) or at some subsequent time (delayed reconstruction). Breast contour can be restored by the following:

- Implant reconstruction: submuscular insertion of an artificial implant, silicone- (preferably) or saline-filled. If an immediate implant cannot technically be performed, a tissue expander can be inserted beneath the pectoral muscle. Saline is injected into the expander to stretch

the tissues for a period of weeks or months until the desired volume is obtained. The tissue expander is then replaced by a permanent implant.

- Autologous flaps: muscle flaps (LD: latissimus dorsi; TRAM: transverse rectus abdominis) or no-muscle flaps (DIEP/SIEP: deep/superficial inferior epigastric perforator artery; SGAP/IGAP: superior/inferior gluteal artery perforator) require a considerably more complicated and prolonged operative procedure, and blood transfusions may be required.

After breast reconstruction, radiation therapy can be delivered to the chest wall and regional nodes in either the adjuvant or local recurrent disease setting. Radiation therapy after reconstruction with a breast prosthesis may affect cosmesis, and the incidence of capsular fibrosis, pain, or the need for implant removal may be increased.

IX.2. Postoperative Radiation Therapy

Radiation therapy is regularly employed after BCS. Radiation therapy is also indicated for high-risk postmastectomy patients. The main goal of adjuvant radiation therapy is to eradicate residual disease thus reducing local recurrence.

Post–BCS

For women who are treated with BCS without radiation therapy, the risk of recurrence in the conserved breast is substantial (>20%) even in confirmed axillary lymph node–negative women. Although all trials assessing the role of radiation therapy in BCT have shown highly statistically significant reductions in local recurrence rate, no single trial has demonstrated a statistically significant reduction in mortality. However, a large meta-analysis demonstrated a significant reduction in risk of recurrence and breast cancer death. Thus, evidence supports the use of whole-breast radiation therapy after breast-conserving surgery.

With regard to radiation dosing and schedule, the following has been noted:

- Whole-breast radiation dose. Conventional whole-breast radiation therapy is delivered to the whole breast (with or without regional lymph nodes) in 1.8 Gy to 2 Gy daily fractions over about 5 to 6 weeks to a total dose of 45 Gy to 50 Gy. Some studies show that a shorter fractionation schedule of 42.5 Gy over 3 to 4 weeks can be a reasonable alternative for some early-stage breast cancer patients. However, additional studies are needed to determine whether shorter fractionation is appropriate for women with higher nodal disease burden.
- Radiation boost. A further radiation boost of 10-16 Gy is given to the tumour bed to minimize the risk of local recurrence from putative cancer cells that can exist in the immediate vicinity of primary tumour (clinically occult satellite foci or cells exfoliated during surgery). The local control benefit is about 3% at 5 years. If a boost is used, it can be delivered either by external-beam radiation therapy, generally with electrons, or by using an interstitial radioactive implant.

Postmastectomy

Postoperative chest wall and regional lymph node adjuvant radiation therapy has traditionally been given to selected patients considered at high risk for locoregional failure after mastectomy. Patients at highest risk for local recurrence have one or more of the following:

- Large primary tumours (T4 always; T3 optional if pN+).
- Very close or positive deep margins of resection of the primary tumour.

In this high-risk group, radiation therapy can decrease locoregional recurrence, even among those patients who receive adjuvant chemotherapy.

Regional nodal irradiation

- Four or more positive axillary nodes.
- The need of radiotherapy in cases with 1-3 positive axillary nodes is questionable; it remains

a subject of research and can be taken into account only when other risk factors are present (young patient's age, G3, ER/PR-negative, blood vessels tumour emboli).

- Grossly evident extracapsular nodal extension.

Patients with one to three involved nodes without any of the high-risk factors are at low risk of local recurrence, and the value of routine use of adjuvant radiation therapy in this setting is unclear.

Timing of postoperative radiation therapy

The optimal sequence of adjuvant chemotherapy and radiation therapy after BCS has been studied. Delaying radiation therapy for several months after BCS until the completion of adjuvant chemotherapy does not appear to have a negative impact on overall outcome. Additionally, initiating chemotherapy soon after BCS may be preferable for patients at high risk of distant dissemination. Delaying radiation therapy for up to 7 months after surgery had no effect on the rate of local recurrence. Delivering radiation therapy concomitantly with hormone therapy and trastuzumab appears to be safe (no associated increase in acute adverse events or frequency of cardiac events) and avoids additional delay in radiation therapy treatment initiation.

Late toxic effects of radiation

Late toxic effects of radiation therapy are uncommon, and can be minimized with current radiation delivery techniques and with careful delineation of the target volume. Late effects of radiation include the following:

- Radiation pneumonitis: the overall incidence of symptomatic radiation pneumonitis is 1%, increases to 3% with the use of a supraclavicular radiation field and over than 8% when concurrent chemotherapy is administered, but remains low (<1.5%) in patients treated with sequential chemotherapy.
- Cardiac events: in women treated with radiation therapy before 1980, an increased cardiac death rate was noted after 10-15 years, compared with women with nonradiated or right-side-only radiated breast cancer, probably caused by the radiation received by the left myocardium. Modern radiation therapy techniques introduced in the 1990s minimizes deep radiation to the underlying myocardium when left-sided chest wall or left-breast radiation was used and decreases cardiac mortality. Since 1980, no increased death rate resulting from ischemic heart disease in women who received left chest wall or breast radiation was found in USA by the National Cancer Institute (Surveillance, Epidemiology, and End Results – SEER Program data).
- Arm lymphedema: it remains a major quality-of-life concern for breast cancer patients. Single-modality radical treatment of the axilla (AD or radiation) is associated with a low incidence of arm edema. In patients who receive axillary dissection, adjuvant radiotherapy increases the risk of arm edema. Edema occurs in 2-10% of patients who receive axillary dissection alone compared with 13-18% of patients who receive axillary dissection and adjuvant radiation therapy. SLNB is associated with very low risk of lymphedema.
- Brachial plexopathy: is rare clinical entity. When 54 Gy in 30 fractions is delivered to the regional nodes, the incidence of symptomatic brachial plexus injury is 1%, compared with 6% when increased fraction sizes (45 Gy in 15 fractions) are used.
- Contralateral breast cancer: only one report suggested an increase in contralateral breast cancer for women younger than 45 years who received chest wall radiation therapy after mastectomy in the 80s. Nowadays, techniques to minimize the radiation dose to the contralateral breast are used to keep the absolute risk as low as possible.
- Risk of second malignancy: is very low. Sarcomas in the treated field are rare, with a long-term risk of 0.2% at 10 years. In non-smokers, the risk of lung cancer as a result of radiation exposure during treatment is minimal when current dosimetry techniques are used. Smokers, however, may have a small increased risk of lung cancer in the ipsilateral lung.

IX.3. Postoperative Systemic Therapy

Stage and molecular features determine the need for adjuvant systemic therapy and the choice of modalities used. For example, hormone receptor–positive (ER and/or PR) patients will receive hormone therapy. HER2 overexpression is an indication for using adjuvant anti-HER2 therapy (trastuzumab) usually in combination with chemotherapy. When neither HER2 overexpression nor hormone receptors are present (triple-negative breast cancer), adjuvant therapy relies on chemotherapeutic regimens, which may be combined with investigational targeted approaches.

An international consensus panel proposed a risk classification system and systemic therapy treatment options. This classification, with some modification, is described below:

Table 7. Systemic Treatment for Early Breast Cancer by Subtype

Subtype	Treatment Options	Comments
Luminal A–like		
ER/PR–positive		Consider chemotherapy if:
HER2-negative		
PR >20%		
Ki67 low (<20-30%)		– Grade 3
Luminal B–like		
ER/PR-positive		
HER2-negative		
Either Ki67 high or PR low		
		Use endocrine therapy, if also hormone receptor–positive
		May consider omitting chemotherapy plus anti-HER2, for small node-negative tumours
Triple-negative	Chemotherapy	May consider omitting chemotherapy for small, node-negative tumours

The selection of therapy is most appropriately based upon knowledge of an individual's risk of tumour recurrence balanced against the short-term and long-term risks of adjuvant treatment. This approach allows clinicians to help individuals determine if the gains anticipated from treatment are reasonable for their particular situation. The treatment options described below should be modified based upon both patient and tumour characteristics.

Table 8. Adjuvant Systemic Treatment Options for Women With Stages I, II, IIIA, and Operable IIIC Breast Cancer

Patient Group	Treatment Options
	No additional therapy
	Tamoxifen
	Tamoxifen plus chemotherapy
	Ovarian function suppression plus tamoxifen
	Ovarian function suppression plus aromatase inhibitor
	No additional therapy
	Chemotherapy

Patient Group	Treatment Options
Postmenopausal, ER/PR–positive	No additional therapy
	Upfront aromatase inhibitor therapy or tamoxifen followed by aromatase inhibitor with or without chemotherapy
	No additional therapy
	Chemotherapy

General points

- Chemotherapy is traditionally combined and given for 3-6 months on an every 3-week schedule.
- Anthracycline-based regimens (doxorubicin, epirubicin) are in slight advantage vs CMF program (cyclophosphamide, methotrexate, fluorouracil) in both premenopausal and postmenopausal women.
- In node-positive breast cancer the benefit from anthracyclines is higher in HER2-positive cases.
- Taxanes (paclitaxel, docetaxel) are added to an anthracycline-based adjuvant chemotherapy regimen for women with node-positive breast cancer.
- Dose-dense chemotherapy is a subject of research, However, evidence suggests that decreasing the duration between can improve clinical outcomes in women with HER2-negative cancer.
- Timing of postoperative chemotherapy: the optimal time to initiate adjuvant therapy remains uncertain. However, it is usually recommended to be started within 2-4 weeks after surgery (maximum 3 months)
- Toxic effects of chemotherapy: adjuvant chemotherapy is associated with several well-characterized toxic effects that vary according to the individual drugs used in each regimen. Most common toxic effects include the following: nausea and vomiting, myelosuppression, alopecia, and mucositis. Less common, but serious, toxic effects include the following: heart failure (if an anthracycline is used), thromboembolic events, premature menopause, and acute leukemia (anthracyclines plus cyclophosphamide, 02-1.7% risk at 5 years).

HER2-negative breast cancer

- For HER2-negative breast cancer, there is no single adjuvant chemotherapy regimen that is considered standard or superior to another. Preferred regimen options vary by institution, geographic region, and clinician.
- Triple-negative breast cancer (TNBC) is defined as the absence of staining for ER, PR, and HER2. TNBC is insensitive to some of the most effective therapies available for breast cancer treatment including HER2-directed therapy such a trastuzumab and endocrine therapies such as tamoxifen or the aromatase inhibitors.
- Combination cytotoxic chemotherapy remains the standard therapy for early-stage TNBC.
- Platinum agents (cisplatin, carboplatin): have emerged as drugs of interest for the treatment of TNBC. However, there is no established role for adding them to the treatment of early-stage TNBC outside of a clinical trial.
- PARP (Poly ADP-Ribose Polymerase) inhibitor agents: PARPs are a family of enzymes involved in multiple cellular processes, including DNA repair. Because TNBC shares multiple clinicopathologic features with *BRCA*-mutated breast cancers, which harbour dysfunctional DNA repair mechanisms, it is possible that PARP inhibition, in conjunction with the loss of DNA repair via BRCA-dependent mechanisms, would result in synthetic lethality and augmented cell death. The PARP inhibitors are currently being evaluated in ongoing clinical trials for patients with *BRCA* mutations and in TNBC.

HER2-positive breast cancer

- Trastuzumab: standard treatment for HER2-positive early breast cancer is 1 year of adjuvant trastuzumab (Herceptin) therapy. It lowers the risk of distant recurrence by up to 50% while the risk of death by up to 33%. The overall increase in long-term survival rates is about 10%. In multiple studies cardiac events associated with adjuvant trastuzumab have been observed: a 3-year cumulative incidence of cardiac events for trastuzumab-treated patients is up to approx. 4%.
- Lapatinib: lapatinib is a small-molecule tyrosine kinase inhibitor that is capable of dual-receptor inhibition of both epidermal growth factor receptor and HER2. As yet, there is no data supporting the use of lapatinib as part of adjuvant treatment of early-stage HER2-positive breast cancer.

ER/PR–positive breast cancer

- Tamoxifen: therapy with tamoxifen is well established to be of benefit in women with hormone receptor–positive breast cancer. It reduces the annual breast cancer death rate by 31%, largely irrespective of patient's age, the use of chemotherapy, and other tumour characteristics.
- 10 years of tamoxifen is superior to shorter durations of therapy.
- For women who remained premenopausal after 5 years of adjuvant tamoxifen, continued tamoxifen for 5 more years is beneficial. Women who have become menopausal after 5 years of tamoxifen may also be treated for 5 more years with aromatase inhibitors (AI).
- The use of tamoxifen in women who received adjuvant chemotherapy does not attenuate the benefit of chemotherapy. However, concurrent use of tamoxifen with chemotherapy is less effective than sequential administration (post-chemotherapy).
- Ovarian ablation (surgical or pharmacological) alone is not an effective substitute for other systemic therapies. Further, evidence suggests that the addition of ovarian ablation to chemotherapy and/or tamoxifen does not significantly improve outcomes. It can be taken under consideration only for premenopausal women with contraindications to tamoxifen (combined with AI or alone).
- The use of AI (steroidal: exemestane, nonsteroidal: anastrozole, letrozole) in sequence with or as a substitute for tamoxifen is recommended in postmenopausal women.
- Switching to an AI after 5 years of tamoxifen is superior to stopping tamoxifen at that time.
- Side effects of tamoxifen and AI differ: patients on tamoxifen more frequently develop endometrial cancer and cerebrovascular accidents, whereas women on AI have more fracture episodes. Except for a continued increased frequency of endometrial cancer in the tamoxifen group, these differences did not persist in the posttreatment period.
- The role of bisphosphonates in adjuvant therapy for early-stage breast cancer is unclear.

IX.4. Preoperative Systemic Therapy

Preoperative chemotherapy, also known as primary or neoadjuvant chemotherapy, has traditionally been administered in patients with locally advanced breast cancer in an attempt to reduce tumour volume and allow for definitive surgery. In addition, preoperative chemotherapy is being used for patients with primary operable stage II or stage III breast cancer.

General points

- Preoperative chemotherapy is associated with identical disease-free and overall survival compared with the administration of the same therapy in the adjuvant setting.
- Current guidelines recommend preoperative chemotherapy based on anthracyclines and taxanes, because it is associated with higher response rates than alternative regimens (e.g., anthracycline alone).

- Ideally, the entire treatment regimen should be administered before surgery.
- A potential advantage of preoperative systemic therapy is the increased likelihood of success with definitive local therapy in those presenting with locally-advanced, unresectable disease. It may also offer benefit to carefully selected patients with primary operable disease by enhancing the likelihood of breast conservation and providing prognostic information where PCR is obtained (clear evidence whether the chemotherapy works and how effective it is). PCR (pathological complete response) is defined as no residual invasive cancer in the breast and axillary nodes with presence or absence of *in situ* cancer (ypT0/is ypN0). There is a very low risk of recurrence compared with a situation in which a large amount of residual disease remains.
- Postoperative radiation therapy may also be omitted in a patient with histologically negative axillary nodes after preoperative therapy, irrespective of lymph node status before preoperative therapy, allowing for tailoring of treatment to the individual.
- Potential disadvantages with this approach include the inability to determine an accurate pathological stage after preoperative chemotherapy. However, the knowledge of the presence of residual disease may provide more personalized prognostic information, as noted above.
- Regular clinical assessment of response to therapy is necessary after beginning preoperative therapy. Repeat radiographic assessment is also required if breast conservation is the surgical goal. Patients with progressive disease during preoperative therapy may either transition to a non–cross-resistant regimen or proceed to surgery, if feasible. Although switching to a non–cross-resistant regimen results in a higher pCR rate than continuing the same therapy, there is no clear evidence that other breast cancer outcomes are improved with this approach.

Patient selection, staging, treatment, and follow-up

- Multidisciplinary management of patients undergoing preoperative therapy by an experienced team is essential to optimize the patient selection, choice of systemic therapy, management of the axilla and surgical approach as well as decision to administer adjuvant radiation therapy.
- The tumour histology, grade, and receptor status have to be carefully evaluated before preoperative therapy is initiated.
- Patients whose tumours have a pure lobular histology, low grade, or high hormone–receptor expression and HER2-negative status are less likely to respond to chemotherapy and should be considered for primary surgery, especially when the nodes are clinically negative. Even if adjuvant chemotherapy is administered after surgery in these cases, a third-generation regimen (anthracycline/taxane based) may be avoided.

The optimal timing of sentinel lymph node biopsy (SLNB) in patients receiving preoperative therapy.

- The optimal timing of SLNB has not been established.
- If suspicious nodes are positive for malignancy at baseline, SLNB may be performed after preoperative therapy but is associated with a high false-negative rate. If the procedure is performed with both radiocolloid and blue dye and at least 3 nodes are sampled and are negative, then axillary dissection (AD) may be omitted. Alternatively, it is acceptable in this circumstance to perform AD, based on the possibility of undetected positive nodes.
- In patients with clinically negative nodes, SLNB may be performed before preoperative therapy because of the false-negative rates observed when performed after preoperative therapy. If the SLNB is negative, AD can be omitted.
- If SLNB is performed after preoperative chemotherapy, the baseline clinical and postchemotherapy pathological nodal status should be taken into consideration when deciding whether AD is necessary. AD is usually performed in the setting of node-positivity.

When considering preoperative therapy, treatment options include the following:

- HER2-negative breast cancer: an anthracycline-taxane based chemotherapy regimen.
- HER2-positive disease: chemotherapy and HER2-targeted therapy. It appears that dual targeting of the HER2 receptor (trastuzumab + pertuzumab) results in an increase in pCR rate; however, no survival advantage has been demonstrated to date with this approach. There is currently no role for the use of lapatinib in the preoperative or adjuvant settings.
- ER/PR–positive breast cancer, postmenopausal women: chemotherapy is an option. For those who cannot be given chemotherapy, preoperative endocrine therapy may be an option.
- ER/PR–positive cancer, premenopausal women: the use of preoperative endocrine therapy is under investigation.

Preoperative endocrine therapy

- Preoperative endocrine therapy may be an option for postmenopausal women with hormone receptor–positive breast cancer when chemotherapy is not suitable because of comorbidities or performance status. Although the toxicity profile of preoperative hormonal therapy over the course of 3 to 6 months is favourable, the PCR rates obtained (1–8%) are far lower than have been reported with chemotherapy in unselected populations.
- Longer duration of preoperative therapy may be required in this patient population. Preoperative tamoxifen is associated with an overall response rate of 33%, with maximum response occurring up to 12 months after therapy in some patients. Likewise, longer duration of AI therapy (letrozole) results in significantly higher PCR rate.
- Overall objective response to preoperative therapy with AI in postmenopausal women is better or comparable to tamoxifen-associated outcomes.
- The use of preoperative endocrine therapy in premenopausal women: the use of preoperative endocrine therapy remains investigational.

Postoperative therapy

- There is currently no clear role for adjuvant chemotherapy in cases in which PCR is not obtained after receipt of an anthracycline/taxane combination chemotherapy regimen. Clinical trials of novel therapies should be considered in these individuals (after neoadjuvant or preoperative trials).
- Radiation therapy is administered after breast conservation in most women who have received preoperative therapy to reduce the risk of locoregional recurrence. Baseline clinical and subsequent pathologic staging should be considered in deciding whether to administer postmastectomy radiation.
- Other adjuvant systemic treatments may be administered either postoperatively, during, or after completion of adjuvant radiation, including adjuvant endocrine therapy for patients with ER/PR–positive disease and adjuvant trastuzumab for those with HER2-positive disease.

X. Post-therapy Surveillance

- Recommended follow-up in asymptomatic patients who complete treatment for stages I-III breast cancer is limited to physical examination and annual mammography.
- The frequency of follow-up and the appropriateness of screening tests after the completion of curative treatment remain controversial. Evidence from randomized trials indicates that periodic follow-up with bone scans, liver sonography, chest x-rays, and blood tests of liver function does **not** improve survival or quality of life when compared with routine physical examinations. Even when these tests permit earlier detection of recurrent disease, patient survival is unaffected.

XI. Locally Advanced or Inflammatory Breast Cancer

Based on available evidence, multimodality therapy delivered with curative intent is the standard of care for patients with locally advanced or inflammatory breast cancer. The standard treatment options for locally advanced or inflammatory breast cancer may include the following:

- BCS or total mastectomy with AD.
- Chemotherapy.
- Radiation therapy.
- Hormone therapy.

Initial surgery is generally limited to open biopsy (e.g. T4b/T4c tumours, inflammatory cancers not eligible for minimally invasive image-guided biopsy) to permit the determination of histology, ER/PR receptor levels, and HER2 overexpression/amplification.

Clinical trials have confirmed that patients with locally advanced and inflammatory breast cancer can experience long-term disease-free survival when treated with initial chemotherapy.

- The standard chemotherapy regimen for initial treatment is the same as that used in the adjuvant setting.
- For patients who respond to preoperative chemotherapy, local therapy may consist of total mastectomy with AD followed by postoperative radiation therapy to the chest wall and regional lymphatics. BCT can be considered for patients with a good partial or complete response to preoperative chemotherapy.
- Subsequent systemic therapy may consist of further chemotherapy.
- Hormone therapy is administered to patients with ER-positive or ER-unknown tumours.
- All patients with locally advanced and inflammatory breast cancer are considered candidates for clinical trials to evaluate the most appropriate manner in which to administer the various components of new multimodality regimens.

XII. Locoregional Recurrent Breast Cancer

Recurrent breast cancer is often responsive to therapy, although treatment is rarely curative at this stage of disease. Patients with locoregional breast cancer recurrence may become long-term survivors with appropriate therapy.

- The estimated risk of local recurrence after BCT is 10-22% at 10 years with the median time of appearance of 3-4 years (5-7 years if adjuvant systemic therapy was given). It is believed to represent more commonly a second primary malignancy (new breast cancer) than true locally recurrent tumour. However, the differential diagnosis is often difficult, sometimes even impossible, but the prognostic and therapeutic significance of this difference is not clear yet.
- The rates of true locoregional recurrence have been reduced over time, and a meta-analysis of 17 randomised trials suggests a recurrence rate of <3% in patients treated with BCT.
- The rates are somewhat higher (5-15% at 10 years) for those treated with mastectomy. 80-90% appear within 5 years, nearly all in first 10 years.
- 9-25% of patients with locoregional recurrence have distant metastases or locally extensive disease at the time of recurrence. Sooner or later, 50% of patients with recurrence after mastectomy will develop distant metastases.

Before treatment for recurrent breast cancer, re-staging to evaluate the extent of disease is indicated. Cytologic or histologic documentation of recurrent disease is obtained whenever possible. When therapy is selected, the ER/PR status and HER2 status at the time of recurrence and previous

treatment are considered, if known.

- ER status may change at the time of recurrence: 36% of hormone receptor–positive tumours can be receptor negative in biopsy specimens isolated at the time of recurrence.
- In patients with unknown ER/PR status the site(s) of recurrence, disease-free interval, response to previous treatment, and menopausal status are useful in the selection of chemotherapy or hormone therapy.

Treatment options for locoregional recurrent breast cancer include the following:

- Chemotherapy.
- Hormone therapy.
- Radiation therapy.
- Surgery.
- Targeted therapy (e.g., trastuzumab).

Patients with locoregional recurrence should be considered for further local therapy. Treatment options depend on the site of recurrence, as follows:

- Cutaneous: a phase III randomized study showed that local control of cutaneous metastases could be achieved with the application of topical miltefosine.
- Chest wall: local chest wall recurrence after mastectomy is usually the harbinger of widespread disease, but, in a subset of patients, it may be the only site of recurrence. For patients in this subset, surgery and/or radiation therapy may be curative. Patients with chest wall recurrences <3 cm, axillary and internal mammary node recurrence (not supraclavicular, which has a poorer survival), and >2-year disease-free interval before recurrence have the best chance for prolonged survival.
- Breast: all resectable recurrence after mastectomy should be excised. Recurrence after BCT is usually treated with mastectomy. However, more individual approach is an option: patients who are not willing to undergo mastectomy can be offered a re-excision followed or not by the re-irradiation.

Because of substantial risk of distant metastases and dissemination, adjuvant systemic therapy should be administered whenever possible, even after complete resection of isolated locoregional recurrence.

- All patients with recurrent breast cancer are considered candidates for ongoing clinical trials.

XIII. Metastatic Breast Cancer

Treatment of metastatic disease is palliative in intent. Goals of treatment include prolonging life and improving quality of life. Although median survival has been reported to be 18 to 24 months, some patients experience long-term survival or even complete clinical remission.

Treatment options for metastatic breast cancer include the following:

- Hormone therapy (tamoxifen, AI).
- Targeted therapy.
- Chemotherapy.
- Local therapy for patients with limited symptomatic metastases.
- Bone modifier therapy, for patients with bone metastases.
-

Cytologic or histologic documentation of metastatic disease is obtained whenever possible.

ER/PR–positive or ER/PR–unknown breast cancer

- For postmenopausal patients with newly diagnosed metastatic disease hormone therapy is

generally used as initial treatment. It is especially indicated if the patient's disease involves only bone and skin/soft tissue and the patient either has not received adjuvant endocrine therapy or has been off such therapy for more than 1 year.

- While tamoxifen has been used for many years in treating those women, randomized trials suggest equivalent or superior response rates and progression-free survival (PFS) for the AI (anastrozole, letrozole, exemestane, or vorozole).
- Another initial treatment option for postmenopausal women is AI therapy combined with cyclin-dependent kinase (CDK4 and CDK6) inhibitor therapy (palbociclib, ribociclib).
- In premenopausal women with newly diagnosed metastatic disease hormone therapy can include tamoxifen, LH-RH agonists or both. It is still not determined whether combined hormone therapy is superior to either approach alone.
- Second-line hormone therapy: women with bone or skin/soft tissue metastases only, and who have been treated with tamoxifen, may be offered second-line hormone therapy including AI (anastrozole, letrozole, exemestane, vorozole), megestrol acetate, and an ER down-regulator fulvestrant.
- Mammalian target of rapamycin (mTOR) inhibitor therapy: patients inevitably develop resistance to endocrine therapy. Preclinical models and clinical studies suggest that mTOR inhibitors (everolimus) might enhance the efficacy of endocrine therapies.
- Cyclin-dependent kinase inhibitor therapy: cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) have been implicated in the continued proliferation of hormone receptor–positive breast cancer resistant to endocrine therapy. CDK inhibitors (palbociclib) are currently approved in the first-line setting to enhance the efficacy of endocrine therapy.
- Patients with visceral metastases are candidates for cytotoxic agents.
- Patients with disease progression during hormone therapy are also candidates for cytotoxic chemotherapy.
- Combinations of chemotherapy and hormone therapy do not have an advantage over the sequential use of these agents regarding patient's survival.

ER/PR–negative Breast Cancer

- The treatment of choice for metastatic ER/PR–negative breast cancer is chemotherapy.
- There are no data suggesting that combination therapy results in survival benefit over single-agent therapy.
- Single agents that have shown activity in metastatic breast cancer include anthracyclines (doxorubicin, epirubicin, liposomal doxorubicin, mitoxantrone), taxanes (docetaxel, paclitaxel, albumin-bound nanoparticle paclitaxel), alkylating agents (cyclophosphamide), fluoropyrimidines (capecitabine, 5-fluorouracil), antimetabolites (methotrexate), Vinca alkaloids (Vinorelbine, Vinblastine, Vincristine), platinum (cisplatin, carboplatin), and others (gemcitabine, mitomycin C, eribulin, ixabepilon).
- At this time, no data support the superiority of any particular regimen. Sequential use of single agents or combinations can be used for patients who relapse with metastatic disease. Combination chemotherapy is often given if there is evidence of rapidly progressive disease or visceral crisis.
- Addition of one or more chemotherapy drugs to a chemotherapy regimen in the attempt to intensify the treatment improves tumour response but has no effect on patient's survival.

HER2–Positive Breast Cancer

- Antibody therapy targeting the HER2 pathway has been used since the 1990s and has revolutionized the treatment of HER2-positive stage-IV breast cancer. Currently, a number of HER2-targeted agents are approved for treatment of metastatic disease, including monoclonal antibody therapy using trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and tyrosine kinase inhibitor therapy using lapatinib.

Decisions regarding the duration of chemotherapy may take into account the following:

- Patient preference and goals of treatment.
- Presence of toxicities from previous therapies.
- Availability of alternative treatment options.

Due to the absence of data suggesting overall or relapse-free survival benefit from high-dose chemotherapy with stem cell support, this should be considered only as part of a clinical trial.

Because there is no standard approach for treating metastatic disease, patients requiring second-line regimens are good candidates for clinical trials.

Surgery

Surgery with palliative intent may be indicated for select patients. For example, patients may need surgery if the following issues occur:

- Fungating, painful, ulcerated or bleeding breast tumour (mastectomy).
- Parenchymal brain or vertebral metastases with spinal cord compression.
- Isolated lung metastases.
- Pathologic (or impending) fractures.
- Pleural or pericardial effusions.

Radiation Therapy

Radiation therapy has a major role in the palliation of localized symptomatic metastases. Indications for external-beam radiation therapy include the following:

- Painful bony metastases.
- Unresectable central nervous system metastases (i.e., brain, meninges, and spinal cord).
- Bronchial obstruction.
- Fungating/painful breast or chest wall lesions.
- After surgery for decompression of intracranial or spinal cord metastases.
- After fixation of pathologic fractures.

Other

- Strontium 89 (Sr-89), a systemically administered radionuclide, can be administered for palliation of diffuse bony metastases.
- The use of bone modifier therapy to reduce skeletal morbidity in patients with bone metastases should be considered. It includes bisphosphonates (pamidronate, clodronate, zoledronate) and denosumab, the monoclonal antibody inhibiting the receptor activator of nuclear factor kappa beta ligand (RANKL).
- The role of bevacizumab, a humanized monoclonal antibody directed against all isoforms of vascular endothelial growth factor–A in the treatment of metastatic breast cancer remains controversial.

All patients with metastatic breast cancer are considered candidates for ongoing clinical trials.

XIV. Ductal Carcinoma *In Situ* (DCIS)

General points

- Ductal carcinoma *in situ* (DCIS) is a noninvasive condition that can progress to invasive cancer, but estimates of the probability of this vary widely. DCIS accounts for about 16% of all newly diagnosed breast cancers and approximately 25% of screen-detected cancers; frequency of its diagnosis has increased markedly since the use of screening mammography became widespread.
- Very few cases of DCIS present as a palpable mass, with more than 90% being diagnosed

by mammography alone.

- DCIS comprises a heterogeneous group of histopathologic lesions that have been classified into the following subtypes primarily on the basis of architectural pattern: micropapillary, papillary, solid, cribriform, and comedo.
- Comedo-type DCIS consists of cells that appear cytologically malignant, with the presence of high-grade nuclei, pleomorphism, and abundant central luminal necrosis. Comedo DCIS appears to be more aggressive, with a higher probability of associated invasive component.

Treatment options for DCIS include the following:

- BCT (BCS plus radiation therapy) with or without tamoxifen.
- Total mastectomy with or without tamoxifen.

In the past, the customary treatment for DCIS was mastectomy. The rationale was based on:

- 30% incidence of multicentric disease
- 40% prevalence of residual tumour at mastectomy after wide excision alone
- 25-50% incidence of in-breast recurrence after limited surgery for palpable tumour
- 50% of those recurrences were invasive

The combined local and distant recurrence rate after mastectomy is very low: 1-2%.

Because BCT (BCS combined with breast radiation therapy) is successful for invasive carcinoma, this conservative approach should be extended to DCIS:

- Radiation therapy reduces the overall rate of in-breast tumour recurrence rate from 26-32% to 15-16%, occurrence of invasive cancer from 13-17% to 8%, and recurrent DCIS from 14-15% to 7-8%.
- There is, however, no significant effect of radiotherapy on breast cancer mortality.
- To identify both the most favourable group of patients for whom postoperative radiation therapy could be omitted, and the highest risk group for whom mastectomy could be more effective than BCT, several staging systems and algorithms and nomograms have been developed, with the most widely used the University of Southern California/Van Nuys Prognostic Index (USC/VNPI), which include tumour size, margin width, nuclear grade and comedonecrosis.
- However, since its testing has been retrospective and noncontrolled (selection bias might occur) consensus recommendations have not been achieved.
- As yet, any prospective trial did not identify any subset of patients who did not benefit from the addition of radiation therapy to BSC in the management of DCIS.

Women receiving tamoxifen or AI (anastrozole) after BCT due to DCIS have decreased incidence of ipsilateral breast cancer events (invasive and in situ) as well as contralateral breast tumours. However, they have no survival advantage. Thus, decision to prescribe or not endocrine therapy after a diagnosis of DCIS should involve a discussion with the patient about the potential benefits and side effects of each agent.