

Breast Carcinoma and Treatment Modalities

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1. Summary

Breast cancer is a disease in which abnormal breast cells grow out of control and form tumours. If left unchecked, the tumours can spread throughout the body and become fatal.

Breast cancer caused 685 000 deaths globally in 2020. Roughly half of all breast cancers occur in women with no specific risk factors other than sex and age. Breast cancer occurs in every country in the world. Approximately 0.5–1% of breast cancers occur in men.

2. Introduction

In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life. Age-standardized breast cancer mortality in high-income countries dropped by 40% between the 1980s and 2020. Countries that have succeeded in reducing breast cancer mortality have been able to achieve an annual breast cancer mortality reduction of 2–4% per year [1].

Breast cancer is the most common cancer in Slovakia and its incidence increases each year. It is the most common type of cancer in women and its incidence grows each year from 1-2%. In men it occurs in Slovakia in ratio 1:140. In 2022 there had been diagnosed 2532 new cases, approximately 1 in 9 women. That is 27, 43 deaths on 100000 citizens [2]. Its incidence grows, so does the mortality, which is questionable because of improvements in survival began in the 1990s when countries established breast can-

cer early detection programmes that were linked to comprehensive treatment programs including effective medical therapies [1].

3. Etiology and Risk Factors

- a) Age – with higher age the incidence grows and is highest around 65 years
- b) Genetic predisposition – having carcinoma in personal or family history, genetically conditioned syndrome
 - Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with high risks for a diverse spectrum of childhood- and adult-onset malignancies. The lifetime risk of cancer in individuals with LFS is $\geq 70\%$ for men and $\geq 90\%$ for women [3].
 - BRCA gene 1 and 2
- c) Fibro-cystic lesions – the most common risk factor
- d) Nulliparity - generally higher risk in women, who didn't give birth
- e) Late pregnancy – 3 times higher risk in women, who gave birth after being 35-years old
- f) Estrogen substitution – in women with family history of carcinoma and in those with histological atypic hyperplasia
- g) Other types of cancer – carcinoma of ovary or endometrium
- h) Radiation of breast – too many RTG examinations
- i) Overweight
- j) Probable risk factors – smoking, alcohol, contraception

4. Clinical Signs

- 1) Palpable lesion – lesion that can be felt by self-examination although it doesn't hurt occurs in 75% of cases

- 2) Pain, growth, drawn in nipple, discharge, any changes of nipple
- 3) Lymphadenopathy of axilla
- 4) Bone pain
- 5) Weight loss
- 6) Paraneoplastic changes – dermatomyositis, neuro-muscular syndrome

5. Lymphatic Drainage of Breast

The breast is drained by 3 stages (etáž) (Figure 1).

6. TNM Classification – Staging

(Table 1)

Table 1:

T stage	Lymphatic nodes
TX, T0	NX, N0
pTis, Ca in situ (intraductal, lobular)	N1 – metastasis in axillary lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT1a – 1 – 5mm, pT1b – 6 – 10mm, pT1c – 11 – 20mm	N2a – metastasis in fixed or axillary lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT2 – 2 – 5cm	N2b – metastasis along arteria mammaria interna without metastasis into axillary lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT3 – tumor bigger than 5cm	N3a – metastasis in intraclavicular and axillary lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT4a – tumor of any size with growth into the thoracic wall, but not to breast muscle	N3b - metastasis along arteria mammaria interna and metastasis into axillary lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT4b – tumor of any size with right growth into the skin (edema, ulceration)	N3c – metastasis into supraclavicular lymph nodes on the same side as primary tumor (1 or more lymph nodes)
pT4c – tumor of any size with right growth into the skin and thoracic wall	
pT4d – inflammatory carcinoma	

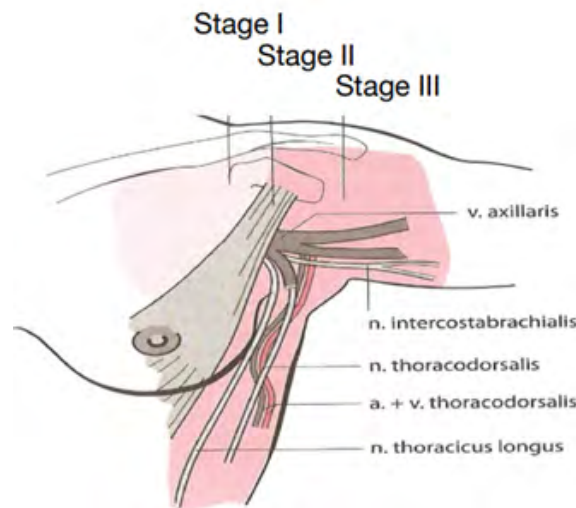


Figure 1:

7. Diagnostics

a) Clinical Examination

- anamnesis – personal, family and gynecological history
- aspection, palpation (all quadrants and axilla) – the most common occurrence of lesion is in 47% in upper lateral quadrant, in 22% nipple and in 14% upper medial quadrant

b) Imaging methods

- Mammography (BI-RADS 1 – 6 classification) – screening method, locuses and microcalcificates
- Ultrasound - completing mammography examination with high sensitivity up to 95%, but limited specificity
- Computer tomography – infiltration of thoracic wall by tumor

- Magnetic resonance imaging – sensitivity 94 – 100%, multicentricity, multifocality

c) Biochemistry

- Tumor markers – CEA, CA 15-3
- Hormone receptors – IHCH in tissue cut
- Biopsy – histology by core cut biopsy

d) Screening

- Mammography in women over 40 years of age

8. Genes Associated with Breast Carcinoma

1) HER 2

- In 20 – 30% of invasive carcinoma
- Higher risk and worse prognosis

2) BRCA 1 and BRCA 2

- Familiar occurrence in 5 -10% of women (Table 2).

9. Histopathology

The breast cancer most commonly origins in terminal lobes or ducts of the gland. It occurs first as non-invasive form of carcinoma in situ

a) ductal carcinoma in situ – special form – Pagets carcinoma of the nipple – in women in menopause, it has intradermal growth of tumorous cells, needs to be differentiated from eczema, cured by central quadrantectomy without axillary exenteration, eventual sentinel node biopsy (Figure 2).

b) lobular carcinoma in situ – not detectable by mammography, muticentric localization, very commonly contralateral breast occurrence in women in menopause



Figure 2: Pagets carcinoma of the nipple

Table 2:

Benign tumor lesions	Malignant tumor lesions
<p style="text-align: center;"><u>Epithelial</u></p> <ul style="list-style-type: none"> - Intraductal papilloma - Adenoma - adenomyoepithelioma 	<p style="text-align: center;"><u>Carcinoma of milk gland</u></p> <p style="text-align: center;"><u>DCIS</u></p>
<p style="text-align: center;"><u>Mesenchymal</u></p> <ul style="list-style-type: none"> - hemangioma 	<p style="text-align: center;"><u>Sarcoma of milk gland</u></p>
<p style="text-align: center;"><u>Mixed</u></p> <ul style="list-style-type: none"> - fibroadenoma <p style="text-align: center;"><u>Unclear biological behaving</u></p> <ul style="list-style-type: none"> - cystocarcoma phylloides 	<p style="text-align: center;"><u>Secretory breast carcinoma</u></p>

9.1. Invasive forms

- a) ductal – most common, occurs in 60 – 80%
- b) lobular – in 15%, mostly in upper lateral quadrant
- c) medullar – 3 – 4%
- d) mucinous – 3%
- e) inflammatory – 1 – 3%, the most malignant form with lymphangiopathy, induration of skin, in time of diagnosis it metastases in 50 – 70% into lymph nodes, needs to be differentiated from infection by histologisation, treatment by chemotherapy and followed by ablation of breast and axillary exenteration
- f) papillary – 2%
- g) cribriform
- h) tubular (Figure 3)



Figure 3: Inflammatory breast carcinoma

10. Therapy of the Breast Carcinoma

Definite treatment approach is multi-disciplinary team decision of surgeon, oncologist and radiotherapist.

1) Surgical treatment

- Targeted on locoregional control of the disease
- Finding out exact type of tumor, stage of disease according to TNM classification, differentiating risk groups

2) Systematic treatment

- Chemotherapy
- Hormonal therapy
- Biological treatment

3) Radiotherapy

- Breast gland, thoracic wall
- Lymphatic drainage

11. Surgical Treatment

Since 1882 is done by radical mastectomy by Halsted [4] with axillary exenteration, in that area they used to cut out the pectoral muscle and nerves. Followed by modified radical mastectomy, where the mammary gland is prepared from the fascia of breast muscle, nodes are extirpated from the upper stage locations, those under musculus pectoralis minor are left in situ. The break through the surgical treatment was brought in years 1985 – 1990 in USA by National Cancer Institute [5], when they recommended optimal treatment for women in early stages as tissue sparing operation of breast. In these years women in Europe and North America are indicated in stage I and II for this type of surgery. Therapy of breast cancer is multimodal, but surgical approach has its dominant status in early stages.

a) management of primary tumor

- diagnostic extirpation – in lesions that are non-palpable there is inserted Franke's driver
- limited treatment – tylectomy, quadrantectomy
- ablation of breast
- subcutaneous mastectomy

b) treatment of regional lymph nodes

- sentinel axillary lymph node biopsy
- axillary exenteration

12. Management of Non-Palpable Breast Lesions

1) Marking

- Under ultrasound control or mammography
- Insertion of localization driver under MRI control

2) Extirpation and peroperational histologization

3) RTG control of the resected area

4) Radicalization in case of finding malignancy

5) Decision about lymphonodectomy (Figure 4)

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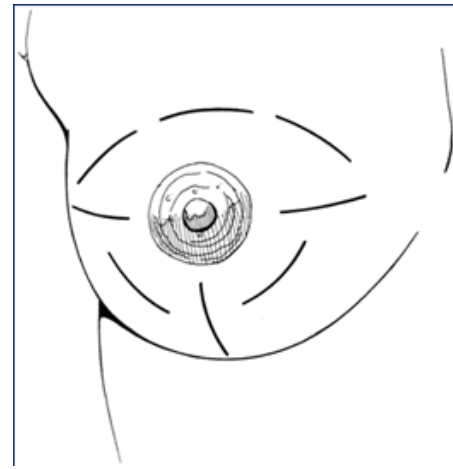


Figure 4: Spearing surgical treatment [6].

13. Management of Palpable Unicentric Breast Lesions

a) Lumpectomy

b) Tylectomy

c) Segmental resection

d) Partial mastectomy

e) Quadrantectomy

f) Wide excision

These are breast tissue sparing types of surgeries, although they have their contraindications:

1) Absolute

- Inflammatory breast carcinoma
- Previous radiotherapy
- Positive resection line

2) Relative

- Local recurrence after previous limited resection treatment
- Tumor bigger than 5cm, or big tumor in small breast
- Multicentricity
- Collagenousis
- Primary pulmonary diseases

14. Mastectomies

Figure 5-7

We differentiate mastectomies according to performed treatment into:

1) Simplex mastectomy

- Simplex amputation of the breast without axillary dissection
- Removing skin and central areolar-nipple complex (ANC)
- It is alternative for another types of carcinomas except invasive carcinoma
- Applicable in multicentric lesions

2) Hygienic (palliative) mastectomy

- It's range is identical to simplex mastectomy
- From oncologic point of view it is palliative treatment in advanced local carcinoma
- It's called debulking surgery with target on reduction of the tumor mass and avoid complications such as hemorrhagia, inflammation, spreading tumorous cells into the thorax (Figure 8-10).

3) Modified radical mastectomy

- From oncological point of view it is considered as sufficient radical treatment also for advanced types of breast cancer
- Amputation with dissection of the first two stages of axillary lymph nodes
- It replace Halsted's radical mastectomy

4) Subcutaneous mastectomy

- Indicated in big benign tumors
- Indicated in borderline tumors with malignant potential
- Indicated in cysto-sarcoma phylloides
- As a profylaxy in mutation of the gene BRCA 1 and BRCA 2 in lobular carcinoma in situ
- Tissue of the breast is removed, but skin is spared, so is the nipple
- Submammary cut is less used by surgeons

5) Skin sparing mastectomy

- Removing of ANC and the whole tissue of the breast gland
- It is considered as radical as modified radical mastectomy, but with skin left
- It can be done alongside with mammoplasty with implants or autologic tissue in form of myocutaneous lobe
- Removing of parenchyma followed by reconstruction done by small excision of areola and nipple, with skin left
- Indication

1. Multicentric ductal carcinoma in situ
2. T1 carcinomas
3. Local recurrent tumors after previous limited surgery
4. Prophylactic surgery

15. T3 and T4 Stage Advanced Breast Cancer

- a) Decision about neo-adjuvant therapy with cooperation of chemotherapist
- b) Biopsy of the tumor
- c) Ablation and axillary exenteration
- d) Marking of the resection lines in T3 by titan clips before follow-up chemotherapy

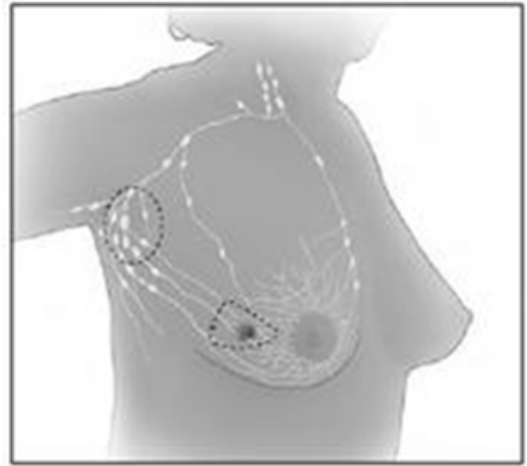


Figure 5: Partial mastectomy, quadrantectomy [6]

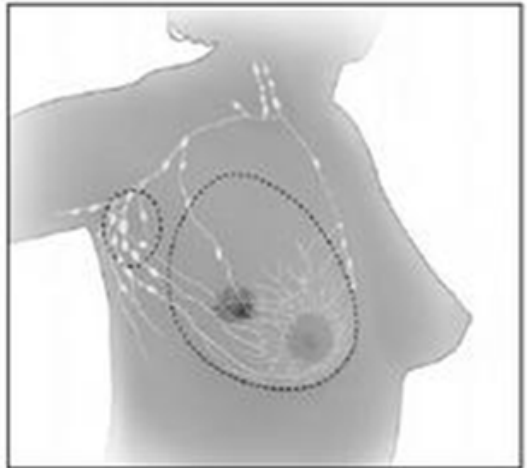


Figure 6: simplex and total mastectomy [6]

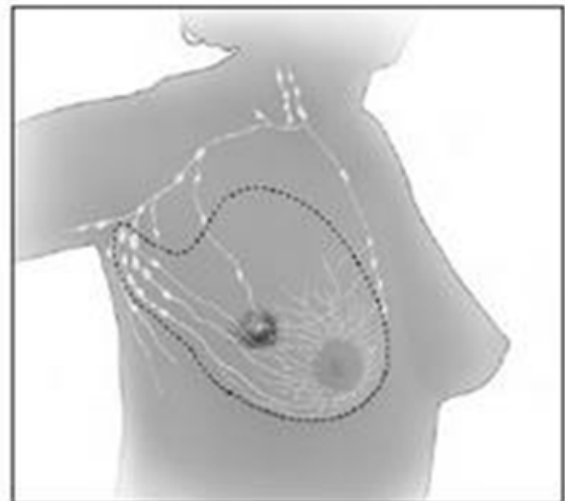


Figure 7: radical mastectomy [6]



Figure 8: simple and total mastectomy [6]



Figure 9: simple, total and skin sparing mastectomy with pexy (modelation) [6]

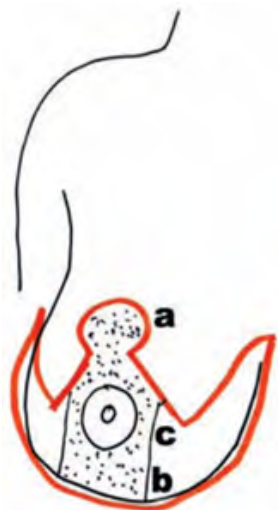


Figure 10: subcutaneous mastectomy with modelation, where the nipple is moved cranial [6]

16. Surgery of Lymph Nodes

Status of axillary lymph nodes is the main prognostic factor and main indication factor for systematic therapy. Surgical treatment of regional lymph nodes has staging-prognostic meaning. In clinical practice there are two types of surgery treatment on axillary lymph system:

- a) Sentinel biopsy
- b) Axillary dissection

16.1. Sentinel Biopsy

In theory the tumor is primary drained by one lymph node. Coloring the sentinel lymph node by Paten blue or combination of Paten blue with insertion of gamma sond is needed to determine the stage of disease and increase negative outcome. In stages T1 and T2 can occur lymphedema, neuropathy, mostly in tumors bigger than 5cm. Indications is T1 invasive breast carcinoma in early stage of the disease without any clinical and paraclinical axillary lymphadenopathy and multifocal eventually multicentric lesions.

In the state of examination there are conditions before and after systematic chemotherapy and primary carcinomas of T2 (Figure 11 and 12).

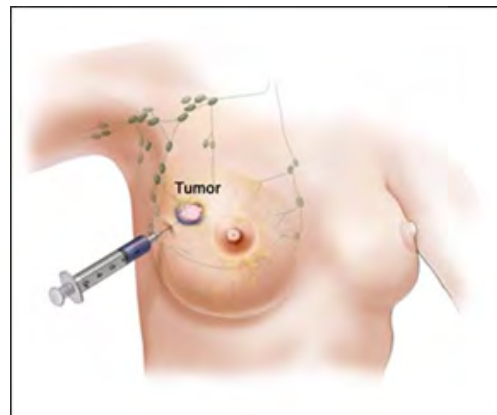


Figure 11: marking of the tumor [6]

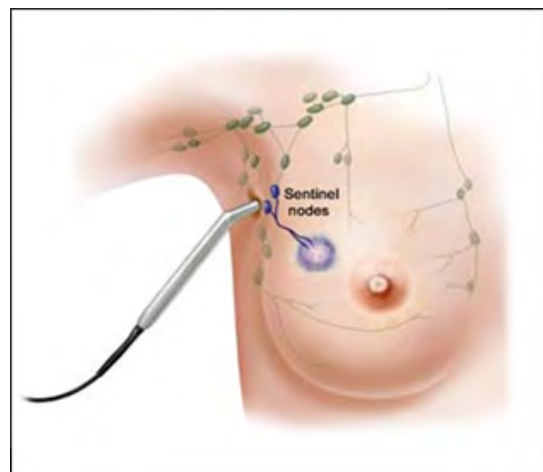


Figure 12: sentinel lymph nodes coloring with Paten blue and gamma sond [6]

16.2. Contraindications of Sentinel Lymph Node Biopsy:

- Status after extensive surgical treatment of breast and axilla
- Inflammatory carcinoma
- Generalized carcinoma
- Pregnancy
- Positive axillary lymph nodes

16.3. Axillary Lymph Node Dissection (ALND)

It is defined as en-block resection of fat-lymphatic tissue of axilla and the main condition of the staging of the disease is removing minimally 10 lymph nodes in I and II stage. It's possible to be done by continuous approach from one cut, where there is tissue and breast and axillary tissue removed. Also possible is discontinuous approach from separate incisions on mammary gland and in axillary skin wrinkle on the lower part. Therapeutic effect is disputable, in cases of early stage carcinomas with negative lymph nodes there is minimally affected survival rate. The best results are in patients with stage T1 and with 1 – 3 metastatic axillary lymph nodes.

16.4. Reconstruction Surgeries of the Breast

There is special article for these types of surgeries, which are

- a) Reconstruction by silicone implants
- b) Reconstruction by tissue expander
- c) Reconstruction by own autologous tissue

And they can be done in one standing alongside removal of the tumor or later approximately 1 year after mastectomy.

17. Local Recurrence

Depending on the locality there are types of surgery performed:

- a) Breast
 - Ablation
 - Limited surgery
- b) Axilla
 - Extirpation

18. Chemotherapy

Breast carcinoma is very sensitive on many cytostatic treatments, but the best result is their combination. The basic combination is CPM Cyclophosphamine, 5-FU, methotrexate, or the combination with anthracyclines. The therapy can be done:

- a) Neo-adjuvant – in higher stages
- b) Adjuvant – before menopause in positive lymph nodes, shall not be given in carcinoma in situ or tumor which is smaller than 1cm
- c) Palliative – in case the disease is already disseminated, it can significantly prolong the survival rate

19. Hormonal Therapy

It is also given neo-adjuvant, adjuvant or palliative. In premenopausal women it is literally castration surgically and pharmacologically meant.

20. Biological Treatment

It's done by inhibition of membrane receptors – Ig against receptors HER 2/neu Herceptin.

21. Radiotherapy

Breast carcinomas have limited radiosensitivity. RT is indicated in cases after tissue sparing surgeries and the result is identical to treatment by surgical ablation. It is given adjuvant. Brachyradiotherapy is application of Iridium wires into the breast tissue. In cases of bone metastases it is indicated as palliative treatment.

22. Discussion

Management of diagnostic treatment of the breast carcinoma must be multidisciplinary as had been written above. And it is still questionable why according to the techniques and treatment possibilities, women are still neglecting the early screening because of the psychological fear. There is need of clinicians to explain patients that early diagnosis of the disease is leading to better outcomes

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