REVIEWS

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Breast Carcinoma – Diagnostics, Therapy and Resistance

Diagnostyka raka piersi – terapia i oporność na leczenie

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Abstract

Breast cancer is a pathologically and clinically heterogeneous disease with a variable prognosis. This type of cancer is the most common female cancer in Poland. According to data collected up to 2004, approximately 12,000 new breast cancer cases per year were diagnosed in women in Poland, and approximately 5000 patients died yearly of breast cancer. The authors present the histopathology, diagnostics, classification and general types of systemic therapy of breast cancer (**Adv Clin Exp Med 2011, 20, 1, 93–101**).

Key words: breast carcinoma, multidrug resistance.

Streszczenie

Nowotwory piersi są patologicznie i klinicznie heterogenicznymi chorobami z różną prognozą. Do 2004 r. diagnozowano u kobiet w Polsce 12000 nowych przypadków zachorowań na raka piersi rocznie; z tego około 5000 pacjentek rocznie umiera z powodu raka gruczołu sutkowego. W pracy zaprezentowano histopatologię, diagnostykę, klasyfikację oraz różne typy standardowo stosowanej terapii wykorzystywanej w leczeniu nowotworów gruczołu piersiowego (**Adv Clin Exp Med 2011, 20, 1, 93–101**).

Słowa kluczowe: rak piersi, oporność wielolekowa.

Breast cancer is the most common female cancer in Poland. According to data collected up to 2004, approximately 12,000 new breast cancer cases per year were diagnosed in women in Poland, and approximately 5000 patients died yearly of breast cancer. There were 106 registered cases of breast cancer in men in 2004. The incidence and death rate have increased within the last few decades. Breast cancer incidence and death rates generally increase with age. The median age at the time of breast cancer diagnosis is between 45 and 69 years (over 50% of breast cancer cases). The death rate increases in patients over 35 years old; the incidence increases in patients between 49 and 59 years old [1].

Breast cancer is a disease which, due to its heterogeneous pathological structure, progresses differently in different patients, and has varied prognoses. It forms in the tissues of the breast, usually the ducts and lobules. There are several known factors that are associated with breast cancer. A germ mutation induces approximately 5–10% of all breast cancers; approximately 50% of all hereditary breast cancers have a germline mutation of the genes BRCA1 and BRCA2. In other breast cancers, nulliparity, early menarche, advanced age and/or a personal history of a breast cancer may play an important role. Other factors that may also affect the prognosis and decisions about the choice of therapy include the patient's age and menopausal status, the stage of the cancer, the primary tumor's histological and nuclear grade, the tumor's estrogen-receptor (ER) and progesterone-receptor (PR) status, assessments of the tumor's proliferative capacity and human epidermal growth factor receptor 2 (HER2/neu) gene amplification [1–4].

Types of Breast Cancer

Breast cancers are classified according to a combination of pathological and clinical features that help to create prognostically significant categories; the structural features include the ana-

Table 1. Histological classification of breast cancer (based on data from the National Cancer Institute, www.cancer.gov, 2009) [37]

Tabela 1. Histologiczna klasyfikacja raka piersi (wg danych z NCI z 2009 roku, www.cancer.gov)

1. Ductal (Rak przewodowy)	2. Lobular (Rak zrazikowy)	3. Nipple cancer (Rak sutka)	4. Other (Inne)	5. Carcinoma NOS (not otherwise specified) (Rak niesklasyfkowany)
In situ (We wczesnej postaci – w miejscu)	*in situ*	Paget's disease	undifferentiated carcinoma	–
Invasive with predominant intraductal (in situ) component (Inwazyjny z dominującym elementem wewnątrzprzewodowym)	invasive with predominant in situ component	Paget's disease with intraductal carcinoma	–	–
Invasive (Inwazyjny)	invasive	Paget's disease with invasive ductal carcinoma	–	–
Comedo (Nieinwazyjna postać czopiasta)	–	–	–	–
Inflammatory (O podłożu zapalnym)	–	–	–	–
Medullary with predominant intraductal component (Rdzeniasty z dominującym elementem wewnątrzprzewodowym)	–	–	–	–
Mucinous (colloid) (Śluzowy/koloidalny)	–	–	–	–
Papillary (Brodawkowaty)	–	–	–	–
Scirrhous (Włóknisty)	–	–	–	–
Tubular (Cewkowaty)	–	–	–	–
Other (Pozostałe)	–	–	–	–

tomic origin and the presence or absence of invasion. Approximately 80% of carcinomas appear to arise from ducts. The histological classification of breast cancer includes five groups: ductal, lobular, nipple, undifferentiated and NOS (not otherwise specified).

Additionally, there are several tumor types that are not consider typical breast cancer but which may occur in the breast: angiosarcoma, phyllodes tumor, primary lymphoma

Noninvasive breast cancer (*in situ*) is a type of early breast cancer confined to the inside of the ductal system. The most common is a ductal carcinoma *in situ* (DCIS), which is histolopathogically heterogeneous, and often multifocal/multicentric. There are several subtypes of DCIS, the classification of which depends on the structural pattern: micropapillary, papillary, solid, cribriform and comedo. The comedo type is the most aggressive and has a higher probability of associated invasive ductal carcinoma.

Lobular carcinoma *in situ* (LCIS), also known as lobular neoplasia, is usually multicentric and frequently bilateral; it is an indicator for an increased risk of subsequent development of invasive breast cancer. This form of neoplasia occurs mainly in premenopausal women (see Table 1) [2, 5].

Diagnostics

The AJCC staging system TNM (American Joint Committee of Cancer) is commonly used for the classification of breast cancer and includes four parts: clinical, pathologic, recurrence and autopsy. It is useful in making decisions regarding the treatment of breast cancer [6].

Anticancer therapy is chosen according to staging categories, but also according to tumor size, lymph node status, estrogen-receptor (ER) and progesterone-receptor (PR) levels in the tumor tissue, human epidermal growth factor receptor 2 (HER2/neu) status, and the patient's menopausal status and general health.

ER and PR are steroid hormones that are located in a cell nucleus and which can be diagnosed in the tumor tissue by immunhistological methods. In breast cancer and some other cancer types, hormone-dependent growth factors may be produced which support the expansion of tumor cells. Information about the hormone status in the tumor tissue is an important step toward inhibiting tumor growth by using (anti)hormone therapy.

HER2 is a member of the ErbB protein family (epidermal growth factor receptor family). As

a cell membrane surface-bound receptor tyrosine kinase, it is involved in the growth and differentiation of cells. HER2/neu encodes HER2 and is a known proto-oncogene.

Approximately 15–30% of breast cancer cases show overexpression of HER2/neu's protein product or HER2/neu gene amplification, which is associated with a worse prognosis and an increased risk of cancer recurrence. HER2/neu amplification is commonly detected by immunhistological (IHC) methods: FISH (fluorescence *in situ* hybridization) and CISH (chromogenic *in situ* hybridization) [2, 4, 8, 34]

CA 15-3 and CEA (carcinoembryonic antigen) tumor markers, diagnosed in blood samples, can also be used as prognostic factors. There are also other proteins that are expressed in breast cancer tissue, but they are not sufficient known to be commonly used as tumor markers (e.g., piwil2, annexin A1) [2, 4, 7–10].

Apart from histological diagnostics, there are several imaging procedures that are used to diagnose and classify breast cancer.

Mammography

This conventional X-ray technique is the test of choice for women with no signs of breast cancer. For diagnosis, tailored mammographic views and sonography are used. Digital mammography entails recording X-ray images in computer code instead of on X-ray film (as in conventional mammography), which allows more accurate analysis of mammographic views. (In the USA approximately 80% of DCIS are diagnosed by mammography).

Sonography (Ultrasound)

High-frequency sound-wave imaging is used to differentiate between solid tumors and cysts, for the evaluation of lumps and to guide needle biopsy. Some early cancer signs such as microcalcifications cannot be sufficiently diagnosed by sonography, which is why this method is not used for routine screening for breast cancer.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a highly sensitive imaging method without the use of radiation or radioactive agents that is used to solve problem cases (for example, when there is a suspicion of additional cancer foci that cannot be seen in standard imaging) or for post-treatment surveillance. MRI is not always suitable for distinguishing between cancerous and noncancerous breast tissue or for detecting microcalcifications, which is why it is not used as a routine diagnostic procedure.

Computer-Assisted Detection

Computer-assisted detection (CAD) is a sensitive method that helps to show and identify suspicious areas in tissues (e.g. microcalcifications). In breast cancer screening it can be used with mammography: A mammogram is scanned through a laser beam, then converted into a digital signal and processed by a computer; the digital image and the conventional image can be compared and evaluated.

Computed Tomography

Computed tomography (CT) can be used in diagnostics such as CT-guided needle biopsy or to diagnose distant metastases (e.g. in the abdomen). It is commonly used when planning radiation therapy.

Positron Emission Tomography Scans

Positron emission tomography scans (PET--scans) present images of chemical changes in the body tissues after a patient has been given Fluorine-18-Fluoro-D-glucose (FDG), a radioactive sugar that is absorbed by cancer tissue faster than by normal tissue, which can be detected through a PET-scanner. The diagnostic value for detecting primary tumors is limited, but this method can be used for monitoring the response to therapy [2, 11, 12].

Therapy

Breast cancer is commonly treated by various combinations of surgery, radiation therapy, chemotherapy, targeted therapy and hormone therapy.

Surgical Treatment

Surgical treatment of breast cancer includes mastectomy or breast conservation therapy (BCT).

A mastectomy is necessary in some stages of the disease (see below). It entails the removal of the entire breast, including the nipple; women who undergo a mastectomy have the option of breast reconstruction.

Mastectomies are often (depending on the stage of the disease) performed in conjunction with dis-

section of the axillary lymph nodes (lymphadenectomy). Sentinel lymph nodes are the first lymph nodes to which cancer cells metastasize and are thus predictors of lymph node status in breast cancer. To identify the sentinel lymph node(s), a radionuclide or blue dye or both are injected (vital blue dye lymphatic mapping or radioguided surgery – RGS). Positive lymph node(s) must be removed and intraoperatively histopathologically examined for the presence of cancer cells (sentinel lymph node biopsy). Studies have shown that the rate of detection of sentinel lymph node(s) is significantly higher when both procedures (vital blue dye lymphatic mapping and RGS) are used synchronously. This procedure should be restricted to early-stage cancers (tumor size up to 3 cm, clinically uninvolved axillary lymph nodes or DCIS) [2, 35].

BCT entails the removal of the tumor along with a margin of surrounding healthy breast tissue. Depending on the tumor location and size, BCT could mean a lumpectomy (surgical removal of a small tumor), partial mastectomy, segmental mastectomy or quadrantectomy. It is estimated that 75–80% of patients can be treated with BCT and a post-surgical therapy rather than mastectomy with excellent results. BCT is often followed by radiation therapy [2, 11, 35].

Radiation Therapy

Radiation therapy is a treatment that uses X-rays or radionuclides to help eliminate microscopic metastases in the remaining breast tissue. In some stages of the disease it can be used to shrink or eliminate the tumor. Radionuclides play a part in the diagnosis of breast cancer (see above).

Radiation therapy can be used in addition to breast-conserving surgery to eradicate local subclinical residual disease (with a reduction of local recurrence rates by about 75%) [2, 13, 36]. According to the American Society of Clinical Oncology, radiation therapy can also be used as a post-mastectomy treatment when the primary tumor was larger than 5 cm, when four or more lymph nodes are involved or when there are positive postmastectomy margins.

The most common is external beam therapy (EBT), which works through a beam of high-energy X-rays targeting the tumor from outside the patient. In some breast cancer cases intensity-modulated radiation therapy (IMRT) can also be used. It is an advanced mode of high-precision radiotherapy that is planned using three-dimensional computed tomography, which allows the radiation dose to be precisely focused on a tumor or specific areas of a tumor while minimizing the radiation of surrounding structures. This allows higher radiation doses and reduces treatment toxicity.

Brachytherapy uses a type of energy called ionizing radiation and entails the temporary placement of radioactive materials within the breast, usually to give an extra dose of radiation (called a "boost") to the area of the excision site. This form of therapy allows a higher total dose of radiation to be used on a smaller focused area in a shorter period of time, which helps to reduce the possible side effects. The radiation material comes from radioactive iodine 125, strontium 89, phosphorous, palladium, cesium, iridium, phosphate or cobalt and is placed as radioactive seeds or pellets inside or next to the tumor. Brachytherapy may be permanent (in which case the radioactive material is left in the body; the radioactivity level diminishes after some weeks/months, and the material becomes inactive) or temporary (in which the radioactive material is removed from the body after some time). Temporary brachytherapy can be administered at a low- or high-dose rate. This sort of a therapy can be used to treat different types of cancer [2, 11, 13].

In some stages of breast cancer it is necessary to use chemotherapy or hormone therapy to minimize the risk of metastases.

Chemotherapy

Chemotherapy can be used in practically all stages of breast cancer: in the early stages depending on the risk and hormone receptor status (adjuvant or neoadjuvant treatment) and in all advanced stages as well (palliative treatment).

Most anticancer agents work by influencing DNA. Alkylating agents (e.g. cyclophosphamide) and platinum drugs (e.g. cisplatin, carboplatin) prevent the cancer cells from reproducing, but they are not phase-specific; they work in all cell cycles. Antimetabolites (e.g. 5-fluorouracil, capecitabine, gemcitabine, methotrexate) damage cells during the S-phase of a cell cycle. Antitumor antibiotics (e.g. doxorubicin, epirubicin, bleomycin, mitoxantrone) interfere with the enzymes involved in DNA replication. Topoisomerase inhibitors (e.g. topotecan, etoposide) interfere with topoisomerase enzymes and in this way help to separate the strands of DNA so that they can be copied. Mitotic inhibitors (e.g. paclitaxel, docetaxel, vinorelbine, vinblastine, vincristine) are active during the M phase of a cell cycle, but they can damage cells in all phases of a cycle. They can stop mitosis or inhibit enzymes that are necessary for the production of proteins needed for cell reproduction [2, 10, 14].

Resistance to chemotherapy among patients with cancer is a common clinical problem. The neoplastic cells often show a cross-refractoriness to a variety of drugs that have different structures and functions. This phenomenon is known as multidrug resistance (MDR) and it occurs in the treatment of infections as well. The mechanisms leading to MDR are caused by molecules that belong to the superfamily of ATP-binding cassette transporters (ABC). ABC transporters are proteins that are embedded in the cell membrane and regulate traffic of different molecules in and out of the cell. They are found in tumor cells and in normal cells in the digestive system, including the small and large intestine, liver and pancreas; and in epithelial cells in the kidneys, adrenals, brain, testes and endothelial cells as well [15, 20, 21, 22].

The overexpression of some ABC transporters in cancer cells is associated with a resistance to specific drugs due to the ability of ABC transporters to increase the efflux of cytotoxic substances from a cancer cell and in this way to lower the intracellular concentration of anticancer agents. The ABC transporter superfamily consists of over 40 members. One of the proteins is the so-called P-glycoprotein (P-gp). It is an adenosine triphosphate-dependent (ATP-dependent) membrane transporter that acts as a drug efflux pump and is able to affect not only cytotoxic drugs such as taxanes, anthracyclines, vinca alkaloids, epipodophyllotoxins, dactinomycin and mitomycin C, but also other exogenous compounds, such as digoxin or verapamil, opiates, immunosupresants (e.g. cyclosporin A) and others. The so-called MDR-related proteins (MRP) and breast cancer resistance proteins (BCRP, mitoxantrone resistance proteins, MXR) are also ATP-dependent and can decrease the intracellular drug concentration, the activation of detoxifying enzymes and apoptotic pathways, although they show some differences in their amino acid sequence, gene locus, structure and substrate [22, 25, 27].

Multidrug resistance (MDR) in tumor cells is a significant obstacle to achieving success in cancer therapy. MDR is especially problematic in cases of acquired drug resistance. The significant mechanisms that are known so far are the alteration of genes and the proteins involved in the control of apoptosis (p53, Bcl-2), the activation of the enzymes of the glutathione detoxification system and the activation of the transmembrane proteins effluxing different substances from the cell (e.g. P-gp). The solution to this problem is yet not known. It cannot be solved by using high doses of anticancer agents because of their enormously high toxicity. In some cases it is possible to use anticancer drugs which are not substrates of the ABC transporters and thus to bypass the resistance mechanism, but the use of this method is limited and not possible in all types of tumors [16, 17, 19, 24].

The most promising and intensively investigated method for overcoming MDR is the simultaneous use of substances – so-called MDR modulators, MDR reverters or chemosensitizers – which work as

Table 2. Selected adjuvant treatments in breast cancer, based on the 2009 Recommendations of the European Society for Medical Oncology (ESMO) Guidelines Working Group [28]

Tabela 2. Wybrane schematy terapii adjuwantowej, stosowanej w raku piersi (na podstawie zaleceń ESMO z 2009 r.)

Regimen (Schemat)	Number of cycles (Liczba cykli)	Duration of cycle – weeks (Czas trwania cyklu – tygodnie)
CMF	6	4
A-CMF	4–4 (–8)	3–4
CEF	6	4
CAF	6	4
AC-T	4–4	3–3
AC-T (G-CSF)	4–4	2–2
DAC	6	3
FEC-D	3–3	3–3
FEC100	6	3
A-D-CMF	3–3–3	3–3–4
DC	4	3

A: doxorubicin, C: cyclophosphamide, D: docetaxel, E: epirubicin, F: 5-flurorouracil, G-CSF: filgrastim, M: methotrexate, T: paclitaxel.

A: doksorubicyna, C: cyklofosfamid, D: docetaksel, E: epirubicyna, F: 5-fluorouracyl, G-CSF: filgrastym, M: metotreksat, T: paklitaksel.

competitive substrates of the ABC transporters and could in this way inhibit resistance to anticancer agents. These substances (e.g. verapamil) could be used as chemosensitizers to reverse resistance to anticancer drugs. The *in vitro* influence of phenothiazine derivates and verapamil on breast cancer cells (sensitive and resistant to doxorubicin) was one of the problems investigated in a study conducted at Wroclaw Medical University [18, 23, 26].

Adjuvant treatment of breast cancer has been estimated to be responsible for from 35% to 72% of the reduction of breast cancer mortality [2, 5, 11, 30]. Adjuvant therapy treats micro-metastases and cancer cells which have spread in the body but which have not yet created identifiable metastases, thus reducing the risk of recurrence. Generally the choice of adjuvant therapy is based on lymphnode status, receptor status and menopause status. Patients with tumors of uncertain endocrine responsiveness are commonly treated with hormone therapy in combination with chemotherapy and patients with endocrine non-responsive tumors are treated with chemotherapy alone [28]. Patients with HER2 overexpression should be given adjuvant treatment with a combination of hormone- and chemotherapy plus trastuzumab [28, 34]. Adjuvant chemotherapy is commonly recommended as a combination treatment. Some therapy regimens are presented in Table 2 [11, 28].

Neoadjuvant treatment is used in cases of large and locally advanced tumors (> 3 cm, stages III A-B and inflammatory breast cancer), to minimize operable tumors and to enable breast conservation therapy. It can be used in regimens similar to those that are used in adjuvant therapy –mostly the EC (epirubicin, cyclophosphamid) and FEC (5-fluorouracil, epirubicin, cyclophosphamid) regimens [11, 28]. Approximately 5-10% of breast cancer patients have metastases at presentation [2]. Surgical treatment can be appropriate for a few patients who can benefit from the resection of an isolated recurrence, but generally patients with metastatic breast cancer are treated with systemic therapy (chemotherapy or hormone therapy). It is impor-

Table 3. Selected single-agent regimens in metastatic breast cancer (based on the 2008 Recommendations of the ESMO Guidelines Working Group) [11]

Tabela 3. Wybrane schematy monoterapii w przypadku raka piersi z przerzutami (na podstawie zaleceń ESMO z 2008 roku)

Drug (Lek)	Overall Response Rate (Całkowity odsetek odpowiedzi) %
Capecitabine	30
Docetaxel	30–68
Doxorubicin	35–50
Doxil (liposomal encapsulated doxorubicin)	–
Epirubicin	35–50
Gemcitabine	–
Nabpaclitaxel	(33%–) 58–62
Paclitaxel	25–50
Vinorelbine	35–45
Trastuzumab	10–15

Table 4. Selected regimens applied for metastatic breast cancer (based on the 2008 Recommendations of the ESMO Guidelines Working Group) [11]

Tabela 4. Wybrane schematy terapii stosowanych w przypadku raka piersi z przerzutami (na podstawie zaleceń ESMO z 2008 r.)

Chemotherapy (Chemioterapia)	Cycle (Cykl)	Chemotherapy (Chemioterapia)	Cycle (Cykl)
Capecitabine Docetaxel	every 3 weeks	HER2 Positive Metastatic Breast Cancer	
Capecitabine Paclitaxel	every 3 weeks	Trastuzumab Paclitaxel	weekly weekly
Capecitabine Navelbine	every 3 weeks	Trastuzumab Docetaxel	every 3 weeks
Gemcitabine Paclitaxel	every 3 weeks	Tarstuzumab Vinorelbine	weekly weekly
Carboplatin Paclitaxel	every 3 weeks	Lapatinib Capecitabine	every 3 weeks
Carboplatin Docetaxel	every 3 weeks	Lapatinib Paclitaxel	every 3 weeks
Paclitaxel Bevacizumab	every 28 days	–	–

tant to choose a regimen that assures the patient the best possible quality of life. The choice is also influenced by the patient's personal history of prior drug exposure. Tables 3 and 4 (below) present examples of single and combination chemotherapies in breast cancer [11, 28, 29].

Hormone Therapy

For patients who have hormone receptor positive disease (ER and/or PR) without systemic symptoms requiring immediate aggressive chemotherapy, hormone therapy is usually the first treatment of choice. Also, about 50% of the patients with relapses can benefit from second-line hormone therapy [8, 30]. Response rates are higher when combined hormone/chemotherapy is used, but toxicity is higher in this case too. Common hormone therapies are listed in Table 5 [2, 4].

Table 5. Hormone therapy in breast cancer (modified from Pfeifer B, Preiss J, Unger C.: Onkologie integrativ) [37]

Tabela 5. Terapia hormonalna stosowana w raku piersi (na podstawie schematów z: „Onkologie integrativ", Pfeifer B., Preiss J., Unger C.)

Postmenopausal (Po menopauzie)	Premenopausal (Przed menopauzą)
Tamoxifen Or	Tamoxifen Or
Aromatase inhibitor: Anastrozole Letrozole Exemestane Or	Aromatase inhibitor+ LHRH: Leuprolide Goserelin Megestrol
Fulvestrant Or	–
Megestrol	–

Targeted Therapy

The HER-2/neu oncogene is one of the epidermal growth factor receptors and it encodes a transmembrane tyrosine kinase receptor. The humanized monoclonal antibody trastuzumab was developed as a therapy targeted against the human epidermal growth factor receptor 2 (HER-2), which is overexpressed in approximately one fourth of patients with invasive breast cancer. Lapatinib is a tyrosine kinase inhibitor and it blocks the epithelial growth factors EGFR (HER-1) and HER-2. It has been approved for the treatment of metastatic breast cancer in HER-2 positive patients after progression under trastuzumab-based therapy. Trastuzumab in combination with chemotherapy improves the disease-free survival rate in adjuvant therapy and slows down the progression of the disease in cases of metastatic breast cancer [2, 4, 8, 9].

Antiangiogenic Therapy in Breast Cancer

Angiogenesis seems to be a key process in the progression and metastasis of breast cancer. Bevacizumab is a humanized monoclonal antibody that acts against the vascular endothelial growth factor (VEGF), which affects the process of new bloods vessel formation in tumors. Bevacizumab in combination with chemotherapy prolongs progression-free survival in metastatic breast cancer [9, 30].

Monitoring and Follow-Up

Recommendations vary for monitoring the response to therapy in metastatic breast cancer. Usually it consists of a physical examination every

Table 6. Follow-up recommendations for breast cancer survivors (modified from the 2008 Recommendations of the ESMO Guidelines Working Group) [11]

Tabela 6. Zalecenia badań u kobiet po zakończonym leczeniu raka piersi (na podstawie zaleceń ESMO z 2008 r.)

	Year 1 (Rok)	Year 2 (2 lata)	Year 3–5 (3–5 lat)	Year 6+ (6 lat i więcej)
History and physical examination (Wywiad i badanie lekarskie)	every 3-4 months	every 4 months	every 6 months	annually
Mammography (Mammografia)	annually or every 6 months after breast conserving therapy	annually	annually	annually
Pelvic examination – for patients with an intact uterus on tamoxifen (Badanie ginekologiczne – dla pacjentek z zachowaną macicą biorących tamoksyfen)	annually	annually	annually	annually

4–6 weeks; blood tests including tumor marker and imaging are individually tailored to each patient [2, 11]. Physical examination is also important in case of long-term breast cancer survivors. The majority of relapses occur within the first three years. Follow-up recommendations for breast cancer survivors (according to the NCCN Guidelines) are presented in Table 6.

Chest X-ray, bone scan, blood counts, liver function tests and tumor marker blood tests are not routinely recommended; rather, they are used only in cases where there are clinical indications. Bone density tests are recommended for patients at risk for osteoporosis [11, 28, 31–33].

Conclusions

The conclusions that can be drawn from this study are that there are two essential aspects in breast cancer prevention: early detection and risk reduction. Screening may help in the identification early noninvasive cancers and allow for proper therapy before they become invasive, or in recognizing invasive cancers at an early treatable phase. However, screening does not prevent cancer. Breast cancer prevention really must be understood as risk reduction. In extremely high-risk patients, e.g. those with BRCA mutations, risk reduction may involve prophylactic surgical removal of the breasts and ovaries. For the typical patient, lifestyle modifications (diet, exercise, weight-loss, etc.) may be suggested, and may have several other benefits. For patients who have an increased risk based on other factors, the use of hormone-blocking agents, in addition to the usual lifestyle recommendations, may also be considered. Although there are several treatment standards, in cases of diagnosed breast cancer an anticancer therapy is commonly chosen individually for each patient. Breast cancer survivors as well as patients with metastatic breast cancer should undergo regular clinical control examinations.

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