An Introduction to BREAST DISEASES

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BREAST DISEASES

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1 Anatomy of the Breast

The breast is located above the pectoral fascia anterior to the major pectoral muscle, roughly between the 2nd and 6th ribs. It extends to the outer margin of the sternum medially and to the level of the anterior axillary line laterally. The breast itself consists of the mammary gland (*glandula mammaria*) and subcutaneous connective tissue. The nipple (*papilla*) and the areola are hyperpigmented and form areomamillary complex, which also contains smooth muscle cells that make nipple erection possible. Changes in the pigmentation of the nipple are commonly found during pregnancy. At the edge of the areola there are small elevations caused by the underlying Montgomery’s glands (*tubercula mammaria Montgomeryi*), which consist of rudimentary mammary glands (*glandula mammaria Montgomeryi*) and small **sudoriferous** and sebaceous glands. All of these glands are considerably more active during pregnancy. Fibrous connective tissue encapsulates the lobes of the mammary gland and forms a supportive network of fibrous bands that projects between the lobes (*ligamenta Cooperi, ligamentum suspensorium mammae, retinaculum cutis mammae*). The network ends in the subcutaneous tissue ventrally and connects to the pectoralis fascia dorsally. Although not officially recognized by anatomical terminology, the discreet space between the breast itself and the pectoralis fascia is commonly described in surgical anatomy as the retromammary bursa (Chassaignac’s bursa). The surrounding space is filled with adipose tissue. Clearly, the breast is not a homogenous organ, and it is best described as a combination of glandular, adipose, and connective tissue, with the glandular tissue only accounting for about half of the total mass of the breast. The breast is subject to fluctuations in both mass and size, which can be influenced by age, phase of the menstrual cycle, lactation, and gravidity. In adulthood, the breast can take several shapes:

- *mamma disciformis* – flat and shallow breast
- *mamma hemispheroidea* – “classic” hemispheroid shape
- *mamma piriformis* – the shape of the pear, typical for middle-aged women
- *mamma pendula* – saggy breast, typical for older women, caused by the loss of adipose tissue

**Arterial nutrition** of the breast is made possible by the rr. mammarii (branches of the internal thoracic artery), superior thoracic artery, and the second to fourth intercostal arteries. **The veins** form an anastomotic circle around the base of the papilla (first described as the
circulus venosus by Haller), which converge towards the gland and drain into the internal and lateral thoracic vein. The main destinations of the lymphatic drainage are the axillary lymphatic nodes, although other systems have also been described. To this day, the full intricacy of the lymphatic drainage of the breast remains unknown. Commonly accepted interpretations work with the subareolar lymphatic plexus, i.e. plexus subaerolaris Sappeyi. Modern anatomical methods using radioisotopes show that 97 percent of the lymph is drained by the axillary nodes and the rest by the lymph nodes proximate to the internal thoracic artery (a. mammaria interna). One of the axillary nodes is the Sorgius lymph node - often the sentinel node of the breast. Sensory innervation of the breast is through the fourth to sixth intercostal nerves. The area of the papilla belongs to the T4 dermatome. Autonomous innervations are brought via the periarterial plexus.

The mammary gland consists of 15 - 20 tubuloalveolar lobes that divide into smaller lobules. Every lobe of the mammary gland ends in a lactiferous duct (ductus lactiferus, width 2 - 4 mm). Close to the nipple, the lactiferous ducts dilate into sinuses (sinus lactiferus) and open on the nipple through constricted orifices (porus lactiferus, width 0.4 - 0.7 mm). Tubuloalveolar mammary glands are modified apocrine sweat glands and lie in the subcutaneous tissue. The lobes radiate from the papilla and further divide in what is known as the terminal duct lobular unit (TDLU) and are the basic unit of the breast. Every gland drains into a lactiferous duct, which leads to the nipple. The ends of the ducts are lined with keratinized squamous epithelium. The epithelial lining of the duct transitions gradually from keratinized squamous epithelium to stratified cuboidal epithelium in the lactiferous sinus and finally to simple cuboidal or simple columnar epithelium in the more proximal sections of the duct. The result of the division of the ducts is the aforementioned TDLU. The TDLU represents grape-like cluster of small secretory alveoli (lactating gland), or terminal ducts (inactive gland) surrounded by intralobular tissue. The TDLU consists of following (Fig. 2):

- **terminal ducts**, which are located in inactive glands. The epithelium changes and completely differentiates into fully functional secretory alveoli that produce milk during pregnancy and after birth;
- **intralobular collecting ducts** – these are multiple branches of transitional ducts that convey the products of the TDLUs to the lactiferous ducts;
- **intralobular stroma** – supporting matrix formed by specialized hormone-sensitive connective tissue that envelops the terminal ducts and alveoli and contains numerous adipocytes.
The most important cells of the mammary gland are the glandular epithelial cells lining the ductal system and the myoepithelial cells that are found between the superficial epithelial cells and basal membrane. Myoepithelial cells form a basket-like network in the secretory part of the ducts. The contraction of these cells facilitates milk ejection during lactation. Recent immunofluorescent studies have shown that the progenitor cells in the ductal epithelium give rise to both types of cells (i.e. the alveolar secretory cells and the myoepithelial cells). The morphology of the secretory part of the gland changes with the menstrual cycle. In the inactive gland, the glandular parts of the breast are sparse and consist primarily of ductal elements. During the follicular phase of the cycle, the intralobular stroma is sparse and the terminal ducts look like rods of cuboidal epithelium without a well-defined lumen. During the luteal phase, the epithelial cells enlarge and lumens, as well as small amounts of secretory product, become visible. The extracellular space is also filled with fluid during this part of the cycle. During the last few days of the cycle, an abrupt involution and apoptosis returns the gland to its inactive state.

The mammary gland also goes through dramatic changes in preparation for lactation and during lactation itself (see Physiology of the Breast).
**Fig. 1** Scheme of the main anatomical structures of the breast

**Fig. 2** Scheme of terminal duct lobular unit (TDLU)
2 PHYSIOLOGY OF THE BREAST

The breast is a secondary genital organ, whose primary function is to produce and secrete breast milk. The breast milk is the source of nutrition and antibodies for the newborn. For proper development of the mammary gland, several different classes of signal molecules are thought to be needed. Predictably, female sexual hormones play a major role in breast development, mainly estrogens (primarily responsible for duct proliferation), and progesterone, the main action of which is to promote cell differentiation within lobules. There is some experimental evidence that supports the role of prolactin in breast development. Unfortunately, this has only been proven in animal models - the exact role of prolactin in humans is yet to be determined. It is known that levels of prolactin rise continuously throughout pregnancy and the action of prolactin is irreplaceable in the full development of terminal ducto-lobular units. Despite this, process is still strongly influenced by high levels of estrogens and progesterone produced by placenta. Development of the gland also seems to be influenced by human growth hormone, even though in people with growth hormone deficiency (nanism) fully functional breast development can be observed. In men, the mammary gland regresses due to the effects of testosterone, however, its tissue still maintains the ability to react to the same signal molecules and stimuli as in women.

The growth and development of female mammary glands is influenced by the relatively high levels of estrogen and progesterone in women. Historically, most of the hormonal affects were attributed to estrogen. In women stricken with gonadal dysgenesis, estrogen substitution therapy alone is often sufficient to stimulate full development of the mammary glands. Studies that are more recent have shown that glandular epithelium proliferates much more actively during the luteal (second) phase of the menstrual cycle, which indicates the importance of progesterone. It is known that the morphology of the mammary gland changes not only with age, but also relative to changes associated with the menstrual cycle. It is also known, that during the luteal part of the cycle, the mitotic, as well as the apoptotic activity of the gland peaks. This cycle remains steady, even if the woman is taking hormonal contraception. It is possible to observe a slight increase in apoptotic activity in such cases. As would be expected, mitotic activity falls after menopause, however, this can by counteracted by hormonal substitution therapy. Although the reaction of the glandular epithelium of breast, to cycling levels of female sexual hormones, appears similar to that of the glandular epithelium lining the uterus, there is one significant distinction. The mitotic activity of the
endometrium is highest during the follicular, or estrogen dependent, phase of the cycle, whereas the mitotic activity of glandular epithelium reaches its maximum during the luteal, or progesterone dependent, phase of the cycle. Estrogen, without a doubt, plays a major role in not only normal epithelial proliferation, but also proliferation during malignant processes in the gland. However, the role of estrogen in the malignant transformation itself is less clear. Opinions on the role of progesterone in malignant processes are split. On the one hand, its role in differentiation and apoptosis points toward a protective effect, on the other hand they clearly stimulate mitosis, which is the most vulnerable part of the cell cycle, since carcinogenic insults are most effective during this period. It is well known, that the use of combined estrogen-progesterone products (as opposed to estrogen-only products) in peri- and postmenopausal women creates the highest risk of breast cancer. When considering the oncological processes happening in the mammary gland, it is important to realize that while there are many studies concerning the hormonal response of transformed malignant breast tissue, there are relatively few that examine the physiological endocrine response of mammary tissue to endogenous steroids; this means that the overall picture remains incomplete.

**Lactation**

In order to understand the phenomenon of lactation, one must realize that pregnancy and breastfeeding present themselves as two distinct developmental states in the life of the breast and, as such, fall under the category of specialized hormonal regulation. During pregnancy, the glandular epithelium fully differentiates, which occurs due to the hypophyseal hormone prolactin. Although the role of prolactin has been historically attributed to lactation, prolactin itself has 300 different receptors and serves many purposes in the human body. The secretion of prolactin is regulated by the central nervous system, through the hypothalamus. The most important regulatory neurons reside in the tuberoinfundibular arcuate nucleus (nucleus arcuatus). These secrete prolactin-inhibiting factor (PIF), which is simply dopamine that affects the D2 receptors of the lactotrope cells in hypophysis. Although the physiological regulation of dopamine is famous for its primarily inhibitory character, sometimes it is excitatory and can stimulate secretion, e.g. prolactin and thyrotropin-releasing hormone (TRH). Indeed, in some cases of lactation outside of pregnancy, the problem lies with the thyroid and its regulation. As mentioned previously, prolactin stimulates the production of breast milk. After the expulsion of the placenta, estrogen and progesterone levels plummet, which allows for the initiation of lactation. While the role of estrogens in the mammary glands is to stimulate the proliferation of the epithelium, estrogens perform many additional
functions, one of which is to stimulate lactation and antagonize prolactin. This is why estrogen diminution results in the enabling of prolactin to induce its physiological effects. The baby’s sucking reflex not only stimulates the production of oxytocin, but also the production of prolactin (through nipple stimulation). After the birth, a period of amenorrhea follows; women who breastfeed experience amenorrhea for a significantly longer period (roughly half a year) than women who do not breastfeed (roughly six weeks). This can be explained by one simple mechanism: breastfeeding stimulates the secretion of prolactin, which in turn inhibits GnRH secretion and counteracts the effect of gonadotropins in the ovary. This results in the cessation of ovulation. Indeed, amenorrhea can result in heightened levels of prolactin following the cessation of breastfeeding, which can lead to genital atrophy (Chiari-Fromell’s syndrome).

Human placental lactogen (hPL) is also involved in the complex regulation of the mammary gland during pregnancy. HPL appears in the blood during the sixth week, reaches its plateau in the third trimester, and disappears after the birth. It is produced exclusively by the placenta. Although its name suggests a similarity with prolactin, a structural homology with growth hormone can be observed. Its function probably lies “only” in the preparation of metabolism for lactation: it lowers insulin levels, thereby stimulating fatty acids oxidation needed for lactation (this effect can be described as lactogenic). Its diabetogenic effect can lead to the exacerbation of gestational diabetes. Although hPL has been known for some time, its full role has yet to be described.

When discussing lactation, it would be difficult not to mention oxytocin. The action of oxytocin is evident in the mammary gland and endometrium, but it may also have an effect on the degeneration of the luteal body at the beginning of pregnancy. The oxytocin receptor was first cloned from the myometrium, but it can be identified in both the ovary and mammary gland. In mammals, oxytocin facilitates the contraction of myoepithelial cells. These cells are similar to smooth muscle cells and they envelop the ductal system in the glands. Their contraction helps facilitate the movement of breast milk through the more distal parts of the ductal system and, finally, out of the breast (milk ejection). Normally, milk ejection is initiated by means of a neuroendocrine reflex, which begins via stimulation of the nipple. The stimulus travels via somatic tracts to the supraoptic and paraventricular nuclei (nucleus supraopticus et paraventricularis), where stimulation of the neurons causes secretion of oxytocin from the neurohypophysis. Oxytocin secretion can also be triggered by genital excitation, as well as certain emotions (erotic lactation). Oxytocin has not been called the
neuromodulator of intimacy without reason, as it also performs several related functions in the central nervous system (additional information can be found in neuroscience textbooks). We have mentioned the role oxytocin plays in lactation, but its best-known function has to do with the contraction of the myometrium. The number of oxytocin receptors in the myometrium continually rises during pregnancy and reaches its peak just prior to birth. The pressure exerted by the head of the fetus on the cervix causes afferent stimuli to the same centers mentioned for lactation. These centers allow the release of oxytocin, which then supports the contraction of the myometrium (the Ferguson reflex). During postpartal confinement, oxytocin helps regenerate the myometrium during involutionary changes.

The importance of insulin (or perhaps IGF-1), mineralocorticoids, and glucocorticoids has been demonstrated in tissue sample studies (including roles in inducing cell proliferation and differentiation into mature lobuloalveolar structures). Not only do these hormones influence the proliferation of the gland itself, they also affect trophic factor secretion of the surrounding myoepithelial cells. Complex interactions between stromal cells, the extracellular matrix and epithelial cells are necessary for proper differentiation of glandular tissues. Lobuli continue to change both functionally and structurally throughout a woman’s life. It begins with the L1 (type) lobulus that commonly found in women who are neither pregnant nor breastfeeding. During pregnancy, it changes to L2 and, finally, to L3, which is much more differentiated and divided. A fully differentiated ductal and alveolar system only appears in type L4, just prior to the end of gravidity. This also means that full differentiation of the gland is only achieved during lactation. Due to never fully completing the developmental stages or differentiation of the TDLU, one could indeed expect women who have never breastfed, nor been pregnant, to show a higher risk of developing breast cancer; and this does appear to be the case in population studies.
3 BREAST IMAGING

3.1 X-RAY MAMMOGRAPHY

Mammography is a specialized medical diagnostic procedure that utilizes a fine-tuned x-ray machine called a mammography unit. The main principle behind mammography lies in measuring the density of tissue that is permeable to soft x-rays (with an energy of 25-30 keV). Normal breast tissue is quite homogenous (i.e. the tissue density is virtually the same everywhere within the breast), and higher density areas point toward abnormal changes in the structure of the tissue. One of the mechanisms that allow mammography to be a more sensitive exam is a compression plate that puts pressure on the breast and reduced the thickness to 5 – 7 cm. A soft imaging technique is used, during which the median absorbed dose of ionizing radiation is about 0.002 Gy for two images. Levels below 0.01 Gy are generally considered harmless. The latest research in digital mammography has gradually lowered the doses of radiation used. In contrast to classical x-rays, digital mammography uses specialized digital receptors instead of film, and is connected to a computer in which an image is created using several sophisticated algorithms (reducing necessary radiation doses to even lower levels). Digital mammography has made this process faster; it has also made the detection of small, discreet lesions possible. This digital information can be enhanced, magnified, or manipulated for further evaluation more easily than information stored on film. Each breast is then screened in two projections: craniocaudal (CC) and oblique mediolateral (MLO, 45°). When needed, a perpendicular mediolateral projection (ML) may also be used. As a result, four 2D images are available. Another procedure currently being investigated is tomosynthesis. Three-dimensional (3D) mammography, also known as breast tomosynthesis, is a type of digital mammography that uses x-ray machines to take pictures of thin slices of the breast from different angles, and computer software to reconstruct the image.
In principle, one must differentiate between diagnostic and screening mammography. Diagnostic mammograms are used to check for breast cancer after a lump (or other sign or symptom of the disease) has been found. However, these signs may also be symptoms of benign conditions. Screening mammograms are used to check for breast cancer in women who have no signs or symptoms of cancer. Screening mammography works with groups instead of individuals, with precisely specified time intervals and patient age groups. This is done in order to reveal tumors that are not apparent during a physical examination. There are a number of imaging tools available, but only mammography succeeds in lowering the mortality rate of women with breast cancer (20 – 30 % in countries where screening programs exist). Although the efficiency of mammography is impressive, it is not perfect; according to the literature, 10 % of results are said to be false negatives. Most of these negative results can be discovered using one of the other imaging methods, of which ultrasound appears to be the most effective. False negativity is primarily a problem for younger women who have “glandular” breasts with tumors that are not easily approachable for mammography, i.e., they are either positioned too cranially, laterally or too close to the axilla. Potential limitations of screening mammography include false-positive results, over diagnosis and over treatment, false-negative results, and radiation exposure. The risk of radiation-induced cancer compared to the diagnostic benefit of such a procedure clearly speaks in favor of mammography.

Mammography is, of course, also used in women of any age with palpable lesions. According to current legislature, any woman over the age of forty is eligible for a free mammography exam every two years. In women using hormonal substitution therapy, the interval is one year.
Mammography can be initiated by a gynecologist, surgeon, general practitioner, and medical oncologist. The exam is fully covered by health insurance. At present, mammography screening in Slovakia is not up to par with European Union guidelines.

Interpreting mammography images requires a specialized education and erudition of the diagnostician. According to EU guidelines, every image should be evaluated by two independent professionals (a double reading), and both of them should evaluate at least 5000 images every year. The mammography image of the breast itself is not uniform; it differs depending on the age and physical constitution of the woman. The basic types of breast parenchyma are listed in the tables and images. According to László Tabár, there are four basic types of mammography findings, each one can be combined with another, and additional signs can be described. In order to unify the classification, the **BI-RADS classification** is used (Breast Imaging Reporting and Data System); it is based on guidelines from the American Radiology Society, and is widely accepted.

**Tab. 1 Basic types of breast parenchyma**

<p>| |</p>
<table>
<thead>
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<tbody>
<tr>
<td>juvenile</td>
</tr>
<tr>
<td>fertile</td>
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<tr>
<td>transient (intermediate)</td>
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<tr>
<td>atrophic</td>
</tr>
</tbody>
</table>

**Tab. 2 Basic types of mammography findings**

<p>| |</p>
<table>
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<tbody>
<tr>
<td>circumscribed lesions</td>
</tr>
<tr>
<td>stellate lesions</td>
</tr>
<tr>
<td>architectural distortion of the breast parenchyma</td>
</tr>
<tr>
<td>calcifications</td>
</tr>
</tbody>
</table>

**Tab. 3 Susceptible mammography signs**

<p>| |</p>
<table>
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<th></th>
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<tbody>
<tr>
<td>thickened skin</td>
</tr>
<tr>
<td>retracted skin</td>
</tr>
<tr>
<td>retracted nipple</td>
</tr>
<tr>
<td>radial scar</td>
</tr>
<tr>
<td>local retraction of the parenchymal contour</td>
</tr>
<tr>
<td>focal asymmetry of breast tissue</td>
</tr>
<tr>
<td>density / masses with ill-defined or spiculated margins</td>
</tr>
<tr>
<td>suspicious microcalcifications</td>
</tr>
</tbody>
</table>
Fig. 4a Breast gland typology according to Tabár.
Type I (left): Gradually regressing parenchyma of the gland.
Type II (right): Well discernible tissue with an almost completely regressed gland.

Fig. 4b Breast gland typology according to Tabár.
Type III (left): Fibrous residual breast tissue is positioned retromammilary.
Type IV (in the middle): Non-reducing, adenous glandular type.
Type V (right): Disarranged and opaque non-reducing tissue with high-density parenchyma.
**Tab. 4 BI-RADS categories of mammography findings**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>incomplete finding, in need of further examination, additional imaging evaluation</td>
</tr>
<tr>
<td>1</td>
<td>normal, negative finding</td>
</tr>
<tr>
<td>2</td>
<td>benign</td>
</tr>
<tr>
<td>3</td>
<td>probably benign – receive a 6-month follow-up mammogram</td>
</tr>
<tr>
<td>4</td>
<td>suspicious abnormality</td>
</tr>
<tr>
<td>4a</td>
<td>low level of suspicion</td>
</tr>
<tr>
<td>4b</td>
<td>medium level of suspicion</td>
</tr>
<tr>
<td>4c</td>
<td>high level of suspicion</td>
</tr>
<tr>
<td>5</td>
<td>malignant finding</td>
</tr>
<tr>
<td>6</td>
<td>malignant finding – has been confirmed by biopsy</td>
</tr>
</tbody>
</table>

### 3.1.1 **SPECIAL MAMMOGRAPHIC PROCEDURES**

#### 3.1.1.1 **Ductography**

Ductography (galactography) is a mammography technique that uses x-ray contrast materials injected into the milk duct through the nipple to obtain pictures of the inside of the breast's milk ducts. It is primarily indicated for pathological discharge from the nipple. The images are then assessed for filling defects or contrast “stops” indicating pathological intraductal processes. A cytological assessment of the nipple discharge is needed prior to the ductography. Spontaneous, unilateral, single-duct discharge (bloody, serous, or clear) is the most common manifestation of solitary papillomas. In some cases (approximately 7% of patients with bloody discharge), an intraductal carcinoma can be found. Preoperative ductograms using a blue dye are routinely performed prior to ductectomy in patients with suspected papillomas, or those with breast cancer on diagnostic ductograms. During the operation, it aids the breast surgeon in identifying the specific milk duct in the breast tissue. The marked milk duct (and the surrounding breast tissue) will then be sent to a pathologist for further histologic evaluation by serial sectioning.

#### 3.1.1.2 **Pneumocystography**

Pneumocystography can be used to evaluate cystic lesions containing internal debris, mural nodules, solid components, or lesions that have irregular walls on ultrasound. After aspirating fluid from the cyst with a 20–22 gauge needle (via the free-hand technique, or under
ultrasound or stereotactic guidance), the same volume of air is injected into the cyst cavity. After the needle is removed and pressure is applied, a pneumocystogram can be obtained. The pneumocystogram should be obtained in both craniocaudal and mediolateral projections, showing an air-filled cavity with imperceptible walls and no intracystic masses. Occasionally, the fluid is not completely aspirated and an air-fluid level results. If the cyst displays suspicious mammographic features, a cytological examination of the fluid should be performed and correlated. Pneumocystography is useful in managing symptomatic cysts that are palpable or associated with breast pain: more than 90% do not recur after successful pneumocystography.

### 3.1.1.3 Stereotactic mammography

Stereotactic mammography is an interventional radiology technique that helps guide percutaneous breast procedures. This is done in order to install localization hook wires, or needles used during a biopsy. Stereotactic mammography has been used for more than 30 years; however, it has become increasingly popular in recent years thanks to screening mammography programs. Screening has made non-palpable lesions visible, but in order to localize them for further assessment, one has to visualize them in 2 planes. The procedure is either done on a dedicated stereotactic table with the patient in the prone position, or on an upright add-on unit that can be added to already-existing mammography equipment. The primary principle of stereotaxis is that the three-dimensional location of a lesion can be determined by analyzing changes in the lesion’s position in angled views (+15° / −15°). This three-dimensional information is calculated in terms of the lesion’s x, y, and z coordinates: For patients undergoing the biopsy in the prone position, the x axis is horizontal, y is vertical and z is the depth of the lesion. A guidance system is then used to place the biopsy needle or hook wire into the breast, in a precisely calculated location.

### 3.2 ULTRASOUND

Mammo-sonography (breast ultrasound imaging) is a diagnostic procedure that has its own place in breast cancer diagnostics. In mammo-sonography, a multi-frequency linear transducer (7.5 – 13 MHz) is used instead of the sector probes (3.5 MHz) used in ultrasounds of lesser pelvis organs. Higher frequencies allow for better resolution, but are limited in depth visualization; thus, findings close to the thoracic wall cannot be properly assessed by higher frequencies. During the procedure, the patient lies on her back on an examination table and
raises her arm above her head on the side of the breast to be examined. The examiner carefully examines all four quadrants and retromammary space of the breast. Lastly, the locoregional lymphatic nodes, as well as the axillary and infra / supraclavicular nodes are examined. When examining superficial findings, a mechanical device with an acoustic space can be used. This creates a layer of fluid between the sonographic transducer and the breast, which enables better resolution of the superficial lesion. During mammo-sonography, the examiner is expected to be highly erudite. Sonographic breast images change throughout a woman’s life. Using a small amount of compression is helpful when assessing the image. When using the perpendicular approach, the retromammilar space may be hidden in the shadow of the nipple, so an examination in tangential planes around the nipple is recommended. Individual findings are then assessed according to their features in the sonographic image. We assess the echo structure and echogenicity, margins, the effect of compression on the echo structure and posterior acoustic enhancement or shadowing of the lesions (Tab. 5 and Fig. 5).

**Tab. 5 Evaluation criteria for ultrasound imaging of breast lesions**

- anechoic area
- hypoechoic area
- homogenous / non-homogenous echotexture
- well circumscribed lesion / ill-defined borders
- hyperechoic border area
- compressivity
- posterior acoustic enhancement
- posterior acoustic shadowing
- lateral acoustic shadowing
Fig. 5 Hypoechoic area with ill-defined borders, non-homogenous echotexture and posterior acoustic shadowing (on the left). Histology: infiltrating ductal carcinoma.

Fig. 6 Elastographic study of a malignant tumor using 3D-reconstruction.

The irreplaceable role of sonography is apparent when distinguishing cystic structures from solid masses. Simple cysts have smooth, sharp edges, are anechogenic, and their fluid content enhances of the acoustic waves that go through them. Solid lesions are either well circumscribed with a homogenous echotexture (in the case of fibroadenomas), or hypoechoic...
("taller than broader") with spiculated margins, posterior acoustic shadowing and microcalcifications (carcinomas). The hyperechoic border zone caused by reactive fibrosis increases the suspiciousness of findings. Carcinomas usually do not react to compression, whereas benign findings can usually be slightly compressed and their echotexture becomes more homogenous. Although modern machines are quite capable of distinguishing microcalcification, one cannot assess their size, shape, or functional relationship with ultrasound imaging, which obviously diminishes the role of ultrasound in differential diagnostics in those types of small occult lesions. Nonetheless, ultrasound remains helpful in young woman with glandular parenchyma in the breasts. In such cases, it is difficult to accurately assess the image via x-ray due to the high density of the tissue. In this regard, ultrasound can reveal findings that are not available via mammography. Opinions asserting that ultrasound could be a valuable screening tool are exciting, but such claims would appear to be farfetched for now. Recognizing the in situ carcinoma remains the primary problem. When clinical assessment is improved with mammography, x-ray, and ultrasound, one can diagnose 97% of positive findings. Ultrasound also plays an important role in localizing occult lesions in preoperative preparations and in percutaneous biopsies, during which ultrasound can provide real-time assessment. The ultrasound is also equipped with color-coding techniques that display blood flow in tumors. This can aid in the differential diagnosis of solid cyst lesions, as well as guide percutaneous biopsies. Very recently a modified version of the ultrasound, known as elastography (ultrasound elasticity imaging), has increased in popularity. This technique color-codes changes in tissue elasticity based on different physical attributes of healthy tissue and the tumor. Changes in elasticity can either be assessed by direct tissue compression via the ultrasound head (strain elastography) or, more elegantly, via strong acoustic impulses from the head itself. The machine then analyzes the velocity of the newly created acoustic front, which is inversely proportional to the tissue elasticity in the examined area (shear-wave elastography) (Fig. 6).

3.3 THERMOGRAPHY AND THERMOVISION

Thermography and thermovision (which utilizes highly resolute and sensitive thermographic cameras) derive diagnostic indications from highly detailed, sensitive infrared images of the human body. The techniques analyzes changes in breast skin temperature and then displays the information using a defined color scheme. This method is no longer used, due to its low
specificity and sensitivity. In 2011, The FDA issued a public warning stating that breast 
thermography is not a suitable alternative to mammography.

3.4 MAGNETIC RESONANCE BREAST IMAGING

Magnetic resonance imaging (MRI) scans use magnets and radio waves (instead of x-rays) to 
produce very detailed, cross-sectional images of the body. MRI is not recommended as 
a screening tool by itself because, although it is a sensitive test, it can fail to detect some 
cancers that mammograms would reveal. Although breast MRI is more sensitive than 
mammography in many ways, this increased sensitivity may cause areas of the breast that do 
not have cancer to appear abnormal, producing an increased number of false-positive test 
results. At the same time, breast MRI cannot visualize the microcalcifications that typically 
occur in DCIS lesions. Lastly, breast MRI is more expensive than mammography. On the 
other hand, MRI is a valuable asset in the differential diagnosis of mammary tumors, and it 
can be helpful in the preoperative staging of tumors. Not only can one obtain a clear static 
image of the tumor, but additional data can also obtained by using a special contrast medium 
(gadolinium chelates, gadopentate) in the examined lesion (dynamic contrast-enhanced 
magnetic resonance imaging, DCE-MRI). A contrast accumulation and wash-out curve is 
calculated (Fig. 7). From this, one can distinguish between typical rates in malignant and 
benign lesions. Breast MRI prides itself on high sensitivity (nearly 100 %), but displays low 
specificity (60 – 80 %), which can be explained by the fact that benign lesions also absorb the 
contrast, and this leads to false positives. At the same time, when attempting to confirm 
negative findings, the predictive role of breast MRI is significant. When no pathological 
concentration of contrast material is present, one can say with high probability that there is no 
invasive carcinoma, nor high grade DCIS. Other advantages of breast MRI include the lack of 
ionizing rays and the fact that it is not dependent on tissue density (as is the case with x-rays). 
Still, there is some discussion about the role of NMR mammography in terms of its 
indications and the interpretation of its findings. The most heated debate pertains to its role in 
the preoperative staging of newly diagnosed tumors (Fig. 7).
Tab. 6 Indications for breast MRI

preventive care in BRCA 1.2 positive women, or other high-risk patients
preoperative staging in newly-diagnosed tumors (primarily infiltrating lobular carcinoma)
susceptible residual cancer after breast surgery
unknown primary source of the cancer (negative mammography and sonography)
assessing the efficiency of neoadjuvant chemotherapy
suspected cancer in patients with breast implants

3.5 COMPUTER TOMOGRAPHY (CT)

Although CT does not play a crucial role in the primary diagnosis of breast cancer, it is usually chosen to assess the stage of the carcinoma in terms of metastasis in the liver, lungs, brain, et cetera.

3.6 IMAGING USING NUCLEAR MEDICINE METHODS

Whole-body scintigraphy imaging, a method utilizing small amounts of radioisotope technetium (TC$^{99m}$), is predominantly used in bone metastases diagnostics. A special gamma camera is used to visualize areas with suspicious osteoblast / osteoclast activity. These areas are most likely to be associated with bone metastases, but the findings may be explained by other organic activity and, therefore, scintigraphy is not definitive. Differential diagnosis of bone metastases can be made using conventional x-ray imaging. Scintigraphy is first performed at the time of primary diagnosis, and may be repeated during treatment as needed. A scintigraphic camera is also used when localizing the sentinel lymph nodes in breast cancer patients.

Unfortunately, not all bone lesions are visible during a scintigraphy exam (mostly those that are destructive or osteolytic). In such cases, a PET scan (positron emission tomography) is the diagnostic tool of choice. PET scans are also effective in revealing other kinds of metastatic cancer. PET also makes use of radionuclides, but in a different manner than scintigraphy. Radionuclides are first bound to some sort of biological transporter (e.g. fludeoxyglucose (also known as fluorodeoxyglucose)), which is then administered to the patient. The radionuclides break apart and create a band of gamma rays, which are then detected using a special apparatus. One can then easily discern biologically active tissues (tissues that
consume the most glucose per unit time). It is well established that tumor cells tend to use glucose as their primary source of energy, thereby presenting us with a difference in metabolism that can be used in diagnostics. In the first step of glycolysis, hexokinase adds a phosphate to the molecule, thus creating fludexyglucose-6-phosphate. This molecule cannot pass through the cytoplasmic membrane and accumulates within the cell. This is the primary source of information for the PET scan. In contrast to scintigraphy, positron emission tomography forms 3-dimensional images, and is therefore classified as a separate technique (although both techniques use gamma cameras to detect internal radiation). PET scans are increasingly read alongside CT or MRI scans, with the resulting combination (known as "co-registration") providing both anatomic and metabolic information.
Fig. 7a Infiltrating ductal carcinoma in a patient – a carrier of the BRCA1 mutation, detected through magnetic resonance breast imaging (down) in non-reducing tissue with high-density during X-ray mammography (upper right) with obscure ultrasound presentation (upper left) (used with the permission of Dr. M. Schneiderová, MOÚ, Brno, CZ).
Fig. 7b Mammogram of a 59 year old patient with non-reducing parenchyma associated with a fibrocystic mastopathy (upper left), as well as a suspicious lymph node in the left axilla (upper right). The MRI (down) shows a multicentric tumor with a pathologic gadolinium contrast enhancement curve (in the middle). Histology: multicentric infiltrating ductal grade 3 carcinoma pT2 (m) pN3a.
4 INTERVENTIONAL BREAST PROCEDURES

Following the widespread application of screening mammography, a need to assess the impalpable breast lesions has arisen. Needle localization procedures have proven to be indispensable in their surgical treatment. Percutaneous breast biopsy techniques have been developed to diagnose lesions without the need for surgical biopsy. Percutaneous breast biopsies are the basis for an accurate diagnosis with the triple test (i.e. clinical examination + imaging techniques + non-excision biopsy). They can eliminate unnecessary general anesthesia, hospitalization, a number of two-step operations in cases of malignant tumors and, finally yet importantly, they spare patients the mental stress caused by uncertainty. Percutaneous biopsy completed under the guidance of mammographic stereotaxy (see above) or ultrasound is clearly preferred over free-hand techniques. Ultrasound is also the only method during which the biopsy can be visualized in real-time, allowing one to see the exact area in which the tissue sample is taken. In cases where lesions are only visible with X-ray mammography, a percutaneous biopsy should be guided by stereotaxy. The majority (more than 70 %) of palpable or impalpable cancers should receive a preoperative diagnosis from fine-needle cytology or large-core needle histology. A core needle biopsy can provide detailed information with regard to whether a lesion is benign or malignant, tumor invasiveness and grade, as well as other biological features (e.g. receptor status). Unnecessary surgical excisions should be minimized. For open surgical biopsies, the ratio of benign to malignant should not exceed 0.5 to 1 (European guidelines for quality assurance in the surgical management of mammographically detected lesions, 4th edition, 2006). Breast conserving surgery is the treatment of choice for the majority of small, screen-detected cancers, and is suitable in 70 – 80 % of cases. Every woman should receive information regarding treatment options (breast conserving surgery vs. mastectomy, immediate or delayed breast reconstruction, preoperative chemotherapy, etc.). Providing the patient with a detailed explanation of the nature of the disease is only possible after it has been explicitly evaluated with 3 tests (triple-test).

The aims of the triple-test are to:

- maximize diagnostic accuracy in breast diseases,
- maximize the preoperative diagnosis of cancer,
- minimize the proportion of excision biopsies for diagnostic purposes,
- minimize the proportion of benign excision biopsies for diagnostic purposes,
- shorten the interval between the diagnosis and treatment of breast cancer.

4.1 **FINE-NEEDLE ASPIRATION CYTOLOGY (FNAC)**

FNAC maintained a strong position in percutaneous breast interventions during the 1980s. It can be performed using a small-gauge (21 – 23 gauge) for sampling cells that (after being stained) are examined under a microscope. Local anesthetic may be given, but is not necessary. When the needle tip is felt to be at the edge of the lesion, negative pressure is applied through the syringe while the needle is pushed into the lesion. This procedure is repeated several times. Multiple passes must be made through the lesion in order to obtain the specimen, which is then smeared on glass slides and fixed with an appropriate fixative (methanol, Cytofix etc.). As regards the fluid contents of the cyst, the entire contents of the syringe will be sent to the laboratory, where it will be centrifuged and then placed on glass slides. This procedure has few complications, with hematomas being the most common. In clinical studies, sensitivity for this procedure ranges from 43 % to 92 %, and specificity ranges from 89 % to 96 %. FNAC results depend upon an experienced cytopathologist. The disadvantage of FNAC is the “gray zone” of the results; the cytologic features of some benign proliferative and precancerous lesions can overlap with characteristics typical of malignant cells (observed in 7 % to 10 % of cases). Another (and perhaps the biggest) disadvantage of FNAC is its inability to definitely confirm tumor invasiveness from the cytological picture, which is essential for the planning the primary surgery. Nevertheless, FNAC still has an important role among interventional breast procedures, mainly due to its safety, simplicity, and relatively low financial cost. To better understand cytological examination results relative to patient care, results are categorized into C-categories (Tab. 7).
Tab. 7 Reporting categories for breast cytopathology

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>insufficient for evaluation, non-representative sampling</td>
</tr>
<tr>
<td>C2</td>
<td>benign findings</td>
</tr>
<tr>
<td>C3</td>
<td>cell atypical, probably benign</td>
</tr>
<tr>
<td>C4</td>
<td>suspicious of malignancy</td>
</tr>
<tr>
<td>C5</td>
<td>malignant</td>
</tr>
</tbody>
</table>

4.2 LARGE-CORE NEEDLE BIOPSY (LCNB)

During the 1990s, there was a trend to move away from the use of FNAC in favor of large-core needle biopsy techniques. LCNB provides material for both morphological and cellular assessments. Compared to FNAC, LCNB provides significantly better sensitivity, specificity and positive predictive value for both benign and malignant tumors, and has a reduced rate of false-negative results. It is performed using a large-core needle (18 – 14 gauge) and an automatic biopsy gun. The core biopsy needle has a special cutting edge that allows for the removal of a larger tissue sample. The gun “fires” the needle at high speed into the breast lesion and the specimen is placed into the inner part (cutting edge) of the needle (Fig. 9). The
biopsy is performed under ultrasound or stereotactic guidance. The skin is cleansed, a local anesthetic is injected, and a small stab incision is made. By means of an external coaxial needle (1 gauge larger than the biopsy needle), the biopsy needle can be put through the breast parenchyma 3 to 6 times to obtain the samples (cores) without repeated damage, and while still preserving the parenchyma from possible needle track seeding of malignant cells (Fig. 9). The risk of false negative results from LCNB may be minimized by adopting a multidisciplinary approach during specimen sampling, and while interpreting the results, thereby ensuring adequate training and experience of the staff involved in all stages of this procedure. Histopathologic findings from LCNB are reported in B categories, similarly to the previously mentioned C categories for FNAC (Tab. 8). The routine correlation of pathology findings with clinical and imaging findings is important with regard to further management of the lesion.

**Tab. 8 Standardized reporting for LCNB samples**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>normal breast tissue</td>
</tr>
<tr>
<td>B1a</td>
<td>uninterpretable</td>
</tr>
<tr>
<td>B1b</td>
<td>normal tissue</td>
</tr>
<tr>
<td>B2</td>
<td>benign lesion</td>
</tr>
<tr>
<td>B2a</td>
<td>benign lesion – representative tissue sample</td>
</tr>
<tr>
<td>B2b</td>
<td>benign lesion – indeterminate tissue sample</td>
</tr>
<tr>
<td>B3</td>
<td>uncertain malignant potential</td>
</tr>
<tr>
<td>B3a</td>
<td>benign lesion, which may be associated with malignancy</td>
</tr>
<tr>
<td>B3b</td>
<td>lesions with atypical signs and increased risk of associated malignancy</td>
</tr>
<tr>
<td>B4</td>
<td>suspicious of malignancy</td>
</tr>
<tr>
<td>B5</td>
<td>malignant lesion</td>
</tr>
<tr>
<td>B5a</td>
<td>noninvasive carcinoma</td>
</tr>
<tr>
<td>B5b</td>
<td>invasive carcinoma</td>
</tr>
<tr>
<td>B5c</td>
<td>suspicious invasion</td>
</tr>
<tr>
<td>B5d</td>
<td>other malignancies (lymphoma etc.)</td>
</tr>
</tbody>
</table>
Fig. 9 Biopsy gun (on the left) with a large core needle (in the middle). Ultrasound-guided large-core needle biopsy (on the right).

Tab. 9 Advantages and disadvantages of FNAC versus LCNB

<table>
<thead>
<tr>
<th></th>
<th>FNAC</th>
<th>LCNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>inexpensive</td>
<td>generally more expensive</td>
<td></td>
</tr>
<tr>
<td>faster</td>
<td>histologic diagnosis</td>
<td></td>
</tr>
<tr>
<td>less invasive</td>
<td>more invasive</td>
<td></td>
</tr>
<tr>
<td>fewer complications</td>
<td>increased risk of complications</td>
<td></td>
</tr>
<tr>
<td>“gray zone“ of results</td>
<td>confirmation of invasivity</td>
<td></td>
</tr>
<tr>
<td>requires an experienced cytopathologist</td>
<td>evaluation of prognostic factors</td>
<td></td>
</tr>
</tbody>
</table>

4.3 DIRECTIONAL VACUUM-ASSISTED BIOPSY (VAB)

New breast biopsy techniques have been developed in recent years. The directional vacuum-assisted biopsy procedure was developed with the intention of making core biopsies simpler to perform, and providing more accurate diagnoses, particularly for difficult impalpable lesions (microcalcifications, small mass lesions < 1 cm in maximum diameter, and lesions that are difficult for pathologists to interpret). The volume of VAB samples is greater than in cases of LCNB. VAB can be used with ultrasound, stereotactic (Fig. 10), and eventually MRI guidance. The tissue is drawn into the biopsy needle through negative pressure produced by a vacuum pump. Multiple samples can be obtained from the region of interest via a single needle insertion. After the biopsy, a small staple or clip can be inserted in the breast for hook wire localization of the lesion prior to surgery. An X-ray of the cores in calcified lesions
should be performed to confirm the validity of the collected samples. Approximately 15 -- 20% of core biopsies identified as DCIS show invasive carcinoma on subsequent biopsy. Complications of this procedure are rare.

Fig. 10 Directional vacuum-assisted breast biopsy on a prone table

4.4 ADVANCED BREAST BIOPSY INSTRUMENTATION (ABBI)

The ABBI procedure involves the removal of a core sample of breast tissue measuring 5 -- 20 mm in size, while using stereotactic localization and an advanced biopsy device. The patient lies on a table in the prone position and the ABBI procedure is performed under stereotactic guidance. A localization needle is inserted into the lesion and, when the position is satisfactory, a wire is deployed to secure the lesion. Next, a rotation knife is activated that removes a cylinder of tissue up to 20 mm in diameter. In some cases, the entire lesion can be removed and examined by serial sectioning. As with the VAB procedure, a radiography specimen should be obtained to verify the presence of the lesion in the tissue sample. The ABBI procedure is time-consuming and takes from 30 to 60 minutes to complete. To stop the bleeding, an electrocoagulator is available as part of the ABBI device itself.
4.5 **THE INTACT™ BREAST LESION EXCISION SYSTEM (INTACT™ BLES)**

The Intact BLES System is uniquely able to deliver a sample with intact architecture and clear margins around the area of interest. The Intact BLES captures breast tissue for histological review, using R energy. The system can be used under stereotactic or ultrasound guidance. Unlike other procedures, the Intact BLES surrounds and excises the entire imaged abnormality using local anesthesia. The BLES probe consists of a suction biopsy “wand” connected to an extensible cutting radiofrequency ring wire (Fig. 11). It can envelop an area of tissue ranging from 10 to 20 mm in diameter (depending on wand size) in only 8 seconds. The radiofrequency is sufficient to excise and allow hemostasis without damaging the sample. The result is a complete surgical-quality specimen for histological evaluation and margin assessment that provides a definitive diagnosis (Fig. 11).

![Fig. 11 The Intact™ breast lesion excision system](image)

5 ABERRATIONS IN NORMAL BREAST DEVELOPMENT

Breast development begins in the embryo at about 6 weeks, when precursors of the mammary glands are formed in the ectodermal ridges of the ventral surface of the embryo. The multiple pairs of buds normally disappear during the third month; except for two breast buds in the pectoral region that eventually develop into the mammary glands. The breasts as a body organ are not fully developed in utero.

The breast overcomes a number of structural and functional changes throughout all periods of a woman’s life. Breast development as external sexual characteristics may indirectly point to developmental disorders in girls. The Tanner scale (also known as the Tanner Stages) is a scale of physical development in children, adolescents, and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia and the development of pubic and axillary hair. The scale was developed by British pediatrician James Tanner, and thus bears his name (Tab. 10).

Tab. 10 Tanner scale of breast development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner I</td>
<td>Prepubertal: no glandular tissue; areola follows the skin contours of the chest (typically age 10 and younger)</td>
</tr>
<tr>
<td>Tanner II</td>
<td>Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen (age 10 – 11.5)</td>
</tr>
<tr>
<td>Tanner III</td>
<td>Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast (age 11.5 – 13)</td>
</tr>
<tr>
<td>Tanner IV</td>
<td>Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast (age 13 – 15)</td>
</tr>
<tr>
<td>Tanner V</td>
<td>Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla (age 15 y. and older)</td>
</tr>
</tbody>
</table>

The mature or resting breast contains fat, stroma, lactiferous ducts and lobular units. Cyclic hormonal stimulation with hypertrophy is responsible for the clinically observed changes in breast morphology during menses and the administration of exogenous hormones. There is some clinical evidence suggesting that many benign breast conditions (especially pain,
nodularity, and cysts) are likely to have their pathogenesis in hormonal events during reproductive life. An attempt to formulate accurate and comprehensive terminology to aid in understanding and education led the EU to develop the **ANDI terminology** (Aberrations In Normal Development and Involution) (Tab. 11).

**Fig. 12** Tanner stages of breast development
Tab. 11 ANDI classification of benign breast disorders

Developmental disorders

- polymastia and polythelia (exposed to the same scope of disease as normal breast tissue)
- accessory axillary breast tissue
- congenital inversion of nipples
- macromastia
- fibroadenoma
- phylloides tumor
- adolescent hypertrophy – gross stromal hyperplasia

Cyclical change disorders

- mastalgia and nodularity

Involutional disorders

- fibrocystic breast disease – this includes a variety of changes in the glandular and stromal tissue in response to the levels of estrogen and progesterone

Fibrocystic changes:

- cysts
- fibrosis
- sclerosing adenosis
- duct ectasia with periductal mastitis

The most frequently observed abnormality is an accessory nipple (polythelia) (Fig. 13). It may appear at any point along the milk streak, from the axilla to the groin. True mammary glands rarely develop from accessory nipples, most often located in the axilla, though during pregnancy they may function (mamma accessoria). Asymmetry of the breasts is quite common in young women and can have many causes. A complete lack of breast development is called amastia, and when only a nipple is present it is called amazia. The lack of a breast nipple is called athelia. Poland syndrome (Fig. 14) can present with ipsilateral involvement of the chest muscles, skin and subcutaneous tissues, bones, and upper extremities. The classic ipsilateral features of Poland syndrome include the following: absence of the sternal head of the pectoralis major muscle; hypoplasia and / or aplasia of the breast or nipple (athelia); a deficiency of subcutaneous fat and axillary hair; and abnormalities of the rib cage or upper extremity anomalies, such as a short upper arm, forearm, or fingers (brachysymphalangism).
Juvenile (virginal) breast hypertrophy is an uncommon and benign disorder that typically occurs in peri-pubertal females. The etiology of this disorder is uncertain. It may represent hypersensitivity of the breast to normal levels of sex steroids. It is characterized by rapid enlargement of the breasts. It can cause breast pain, as well as back and neck pain. Dilatation of superficial veins may be present, and physical / psychological problems may develop.

Pseudoangiomatous stromal hyperplasia (PASH) of the breast, especially in its tumorous form, can occur in girls or young women as a rapidly growing enlargement of the breast. PASH is a benign and proliferative mesenchymal lesion with possible hormonal etiology. It typically affects women in the reproductive age group. Breast tissue affected by PASH is characterized by dense myofibroblastic proliferation of mammary stroma associated with interanastomosing capillary-like spaces. PASH is frequently an incidental histologic finding in breast biopsies performed for other benign or malignant lesions. Rarely, it can present as a breast mass, which has been referred to as nodular or tumorous PASH (Fig. 15).

Fibroadenomas are the most common benign tumors of the female breast and represent the most common benign breast tumor in young women with a peak incidence at 20 – 30 years of age. Phylloides tumors are usually large, benign tumors of epithelial and mesenchymal origin that occur primarily in the perimenopausal era. However, they may be observed in any age group. Both fibroadenomas and phylloides tumors will be discussed in a separate chapter.

Mastodynia (breast tenderness) and mastalgia (painful breasts) are the most common complaint associated with disorders of the breast. It denotes the symptom of pain in the breast parenchyma or stroma in the absence of any specific physical or pathological abnormality. It can be cyclical or non-cyclical. Both will be discussed in a separate chapter.

In the ANDR classification, the term nodularity is the most common symptom for which patients consult their doctor – i.e. a palpable "lump" in the breast. The breast is not a homogeneous organ; its components include subcutaneous fat, stromal, and parenchymal tissue supported by fibrous bands (see Anatomy of the breast). The breasts undergo changes throughout a woman's life and during each menstrual cycle; therefore, minor nodularity occurs in nearly every woman’s life and does not immediately indicate a serious illness. Most benign breast disorders are relatively minor aberrations of the normal processes of development, cyclical hormonal response, and involution. The glandular nodularity of breast tissue is most pronounced in the upper outer quadrant of the breast. During the estrogen-stimulated proliferative phase of the menstrual cycle, the nodularity and texture of the breasts can wax and wane as the stromal tissue becomes edematous with venous congestion. The
continuous expansion of terminal milk ducts (duct ectasia) can lead to stagnation of their contents and eventual spontaneous emptying (nipple secretions). The term fibrocystic breast disease (fibrocystic changes) includes a variety of changes in glandular and stromal tissue in response to hormonal levels, and often presents with cyclical breast pain (mastalgia).

Fig. 13 Polythelia. Normal (black arrows) and accessory nipples (red arrows).

Fig. 14 Poland syndrome
Fig. 15 Breast asymmetry caused by the tumorous form of pseudoangiomatous stromal hyperplasia in a 19-year-old woman before (on the left) and after surgical correction.
6 MASTALGIA AND MASTODYNIA

One of the most common symptoms that bring women to the clinic is breast pain. Breast pain (mastalgia) and breast tenderness (mastodynia) are more common in younger premenopausal women, and perimenopausal women. Mastalgia affects up to two-thirds of women at some time during their reproductive lives. Difficulties may be cyclic (dependent on menstrual cycle phases), or non-cyclic, (either lasting or intermittent, but not related to the menstrual cycle). More often, cyclic difficulties are associated with physiological changes of the breast parenchyma, as opposed to the menstrual cycle (see Physiology of the breast). They primarily occur during reproductive age and, since the terminal duct lobular unit glands that are under the influence of progestogen in the second phase of the cycle, they are filled with secretions; additionally, the entire gland is well perfused and often voluminous. In addition to estrogen and progesterone, mastodynia may also involve an aberrant pituitary response to thyrotropin (TSH) (in terms of excessive prolactin secretion).

Mastodynia is frequently associated with premenstrual syndrome and spontaneously disappears. It is more common in women with fibrocytic mastopathy and duct ectasia; the volume of the mammary tissue itself is not crucial. Mastodynia deteriorates in circadian rhythm disorders, or during the use of certain drugs that lead to hyperprolactinemia (e.g. psychotropic drugs).

A clinical evaluation is required to assess the cause, and the majority of women can be reassured after a clinical evaluation. Breast imaging techniques can exclude an organic cause of the mastalgia/mastodynia (e.g. cysts, fibroadenomas, etc.) About 20% of mastalgia patients request treatment and therapy may consist of a well-fitting bra, a decrease in dietary fat and / or caffeine intake, and the discontinuance of oral contraceptives or hormone replacement therapy. Well established treatments for mastalgia and mastodynia are Mastodynon® (an extract of Vitex agnus-castus, which is available in drops and tablets), or evening primrose oil. Evening primrose oil is extracted from seeds of the evening primrose plant (Oenothera biennis), which is a wildflower that grows in eastern and central North America. Evening primrose oil can also reduce the pains associated with premenstrual stress syndrome. Other treatment options include bromocriptine, lisuride, quinagolide, danazol, low-dosed monophasic contraceptives, or non-steroidal anti-inflammatory drugs during the second phase of the menstrual cycle. Progestogen substitution during the second phase of the menstrual cycle is recommended in patients with luteal insufficiency. If the cause of
mastodynia is an increasing, solitary growing cyst, or fibroadenoma, then causal treatment is the treatment of the choice (aspiration of cyst contents and extirpation of fibroadenoma, respectively).

It is usually difficult to find the real cause of non-cyclic mastalgia / mastodynia. One should first consider the possibility of pain transference from other organs or tissues such as costochondral cartilage inflammation on the anterior chest (Tietze's syndrome); pain transferred from the spine in vertebrogenic syndrome; painful inflammation of the nerve ganglia in shingles; or pleuritis, esophagitis, stenocardia linked to ischemic heart disease, etc. Mastalgia is often the result of an improper lifestyle (stress, excessive intake of caffeine, methylxanthine, nicotine, etc.). Transient mastalgia in peri- and postmenopausal age can be caused by age-specific physiological involution and transformation of glandular tissue. It is also known that breast surgery scars can be painful, often associated with changes in atmospheric pressure.
7 INFLAMMATORY BREAST DISEASES

Inflammatory breast diseases are frequently experienced by women, and thus present the prevailing cause of a medical consult. They can occur both in the context of lying-in and lactation, but also outside of this period in a woman’s life. Misdiagnosis and postponing the start of effective treatment may lead to a breast abscess, which may in turn lead to even more serious health complications. Inflammatory diseases, therefore, should not be underestimated and they must be given due weight.

7.1 THE SYNDROME OF PERIDUCTAL MASTITIS & SUBAREOLAR ABScesses

This syndrome is referred to in the literature in different contexts and with different terminology, as well as with different clinical and morphological manifestations. In the American literature, it is also known as mammary duct-associated inflammatory disease sequence (MDAIDS). It essentially expresses interactions across a series of putative causal factors that result in a wide range of clinical manifestations. In any case, it is assumed that a retention of thickened secretions in the extended terminal milk ducts (duct ectasia) plays an important role, and causes a mechanical obstruction of the lumen. Secondary bacterial infections that enter primarily through the nipple cause periductal inflammation. The following are microscopically visible: squamous metaplasia in dilated ducts, foam histiocytes around ductal epithelial cells, and signs of periductal lymphocytic infiltration. Staphylococcus can be detected in most cases as the primary source of infection, but mixed aerobic and anaerobic bacterial flora may be also present. Other etiological factors such as nicotine and relative hypovitaminosis A are also proposed in the literature. Congenital, or even acquired, inversion of the nipple (where the skin around the mammilla folds and creates an environment for dead epithelial cells, sebum and bacteria), is also a form of predisposition to this syndrome. Fig. 16 shows the gradual development of different stages of the syndrome. Continuous non-cyclic mastalgia / mastodynia with nipple discharge may also be an early manifestation of MAIDS. Radiographic features that can be associated with MAIDS are coarse calcifications and a flame-shaped shadow in mammography.

In the early stage of the syndrome, one usually starts with conservative treatment, i.e. local use of anti-inflammatory ointments combined with systemic anti-staphylococcal antibiotics.
When a subareolar abscess forms, one must often make a small incision, followed by irrigation, or even install a short-term drain. The problem lies with the chronic nature of this inflammation and its tendency to reoccur. This then results in periareolar fistulas in about 2% of patients, for whom surgical treatment is then needed. An optical contrast agent (methylene blue) is instilled into the affected duct and excised (ductectomy) together with the eventual skin fistula. Neighboring ducts, which can also be affected, are also frequently excised. The material is then sent for histological evaluation, which might reveal intraductal papillomatosis. Unfortunately, in some cases circumstances (repeated inflammation with the formation of fistulas) force us to remove the entire areolo-mammillary complex along with the affected gland through a **central quadrantectomy**. The operation must be performed during an inactive stage of the inflammation and under antibiotic therapy. If not managed carefully, the infection may spread to the entire gland, which may lead to the formation of multiple abscesses in the breast and the eventual development of sepsis. There are known cases of patients for whom the improper treatment of MAIDS resulted in the need to perform a **mastectomy**, since ignorance of this issue can often have fatal consequences for the patient (septic shock).

*Fig. 16* Evolutionary scheme of the mammary duct-associated inflammatory disease sequence.

### 7.2 Puerperal Mastitis

Puerperal mastitis is a common complication during puerperium. It is a typical nosocomial infection caused by (in most cases) *staphylococcus aureus*. When treatment is delayed, the woman is at high risk for a number of complications: mastitis may become chronic or
recurrent, or it may progress to a breast abscess. Improper breastfeeding technique, incomplete emptying of the terminal milk ducts during lactation, short intervals between feeding, a fatigued mother, and infectious hands of the mother and/or maternity staff are all known etiologic factors of mastitis. Nipple rhagades from improper breastfeeding are gateways for this infection. A typical manifestation of puerperal mastitis is the rapid onset of fever in women with painful swelling of the breast. It then starts to manifest as a defined erythema of the affected part of the breast with subcutaneous edema, which rapidly increases. If antibiotic treatment is not started in time, the inflammation rapidly develops into an abscess that may seriously jeopardize the health of the patient. In nursing women, the first-line of treatment prescribed is a beta lactamase-resistant penicillin, possibly with clavulanic acid or cephalosporins (cefuroxime); second-line treatment is erythromycin. This is, of course, supplemented by antipyretics and local anti-inflammatory ointments. The issue of breastfeeding during acute inflammation was often a subject of controversy in the past, but today’s views are much more liberal and do allow breastfeeding from the affected breast. There is no documented evidence of harm to the infant from nursing at the affected breast. Epidemiological studies have demonstrated that contamination of the infant's skin, mouth, or nose with the pathogen preceded the infection of his mother's milk. The infant, therefore, probably contaminates his mother rather than being contaminated by her. When breastfeeding is not possible, the milk should be manually expressed from the affected breast. Once an abscess has formed, the only effective treatment is incision, irrigation, and drainage. Breast abscesses often occupy several areas, all of which should be evacuated and drained. The irrigation and drainage procedure must be repeated in a few days and the patient should be instructed regarding proper hygiene regimes. Currently, abscess treatment consists of percutaneous puncture with a special two-way drain, which can be used to re-irrigate the abscess cavity and apply topical antibiotics without the need for a surgical incision.

7.3 NON-PUERPERAL MASTITIS

Inflammation of the breast may also occur outside the period of puerperium, although less frequently. The route of infection is, in most cases, similar to that during the puerperium, i.e. through the nipple. Skin microbes penetrate the system of main ducts of the nipple during irritation (via sport, sexual stimulation, etc.) and induce inflammation under appropriate circumstances (fatigue, viral associated disease). The transfer of infection per diapedesis from surrounding tissue structures of the chest is rare, like the transmission of infection through
blood. More frequent is the inflammation of the Montgomery glands, or folliculitis of a hair follicle at the edge of the areola, with consequent formation of atheroma and secondary infection. Sometimes, inflammation of the thickened contents of a cyst appears. Inflammation can spread diffusely to the breast parenchyma and may continue until it forms an abscess. Antibiotic therapy is administered in such cases and, if necessary, a small incision is made to empty the atheroma or follicular abscess.

7.4 **INFLAMMATORY BREAST CANCER**

Although this is not a true inflammation of the breast, but rather breast cancer, we consider it important to mention it at this point, given that ignorance of this issue can often have fatal consequences for the patient. We know from experience that women with this disease are often sent from one specialist to another, and treated with anti-inflammatory drugs and antibiotics for long periods without suspicion of malignant disease.

Inflammatory breast cancer accounts for about 3% of all breast cancers. It is associated with a high mortality rate in women, given its rapid growth and aggressiveness. This type of breast cancer is called inflammatory because the breast often appears swollen with red skin (as in an erysipelas infection) with the “peau d’orange” sign. This sign arises from skin edema created by a cluster of tumor cells in the subepidermal lymph vessels (*lymphangiomatosis carcinomatosae*). A histopathological examination of a small, securiform skin excision from the affected breast is the key to the diagnosis. Another common feature is that one does not find an obvious primary tumor (“lump”) within the breast. Skin thickening is virtually the only radiographic sign seen during mammography. The disease has a high potential for metastasis. Inflammatory breast cancer is initially treated with primary (neoadjuvant) systemic chemotherapy, followed by a modified radical mastectomy and radiation therapy. Adjuvant systemic therapy may be provided after surgery to reduce the chance of cancer recurrence. This therapy may include additional chemotherapy, hormonal therapy, targeted therapy, or some combination of these treatments. The prognosis of this disease is poor.
8 BREAST TUMOR CLASSIFICATION

The WHO series of monographs on tumor classification, published by the International Agency for Research on Cancer (IARC), covers all organ systems. The 4th edition of the WHO Classification of Tumors of the Breast (2012) is the most recent addition to this series, and provides a timely update to many new aspects of breast cancer classification that have occurred since the publication of the 3rd edition in 2003. Correct typing of the tumor and its inclusion in the adequate stage at the time of primary diagnosis is extremely important for the classification of patients into risk groups and treatment planning. Below, is a presentation of the new WHO classification for breast tumors (Tab. 12).

Tab. 12 Histopathologic classification of tumors of the breast (WHO, 2012)

- **Epithelial Tumors**
  - Microinvasive carcinoma

- **Invasive breast carcinoma**
  - Invasive carcinoma of no special type (NST)
    - Pleomorphic carcinoma
    - Carcinoma with osteoclast-like stromal giant cells
    - Carcinoma with choriocarcinomatous features
    - Carcinoma with melanotic features
  - Invasive lobular carcinoma
    - Classic lobular carcinoma
    - Solid lobular carcinoma
    - Alveolar lobular carcinoma
    - Pleomorphic lobular carcinoma
    - Tubulolobular carcinoma
    - Mixed lobular carcinoma
  - Tubular carcinoma
  - Cribriform carcinoma
  - Mucinous carcinoma
  - Carcinoma with medullary features
    - Medullary carcinoma
    - Atypical medullary carcinoma
    - Invasive carcinoma NST with medullary features
  - Carcinoma with apocrine differentiation
  - Carcinoma with signet-ring differentiation
  - Invasive micropapillary carcinoma
  - Metaplastic carcinoma of no special type
    - Low-grade adenosquamous carcinoma
- Fibromatosis-like metaplastic carcinoma
- Squamous cells carcinoma
- Spindle cell carcinoma
- Metaplastic carcinoma with mesenchymal differentiation
  - Chondroid differentiation
  - Osseous differentiation
  - Other types of mesenchymal differentiation
- Mixed metaplastic carcinoma
- Myoepithelial carcinoma
  - Rare types
    - Carcinoma with neuroendocrine features
      - Neuroendocrine tumor, well differentiated
      - Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)
      - Carcinoma with neuroendocrine differentiation
    - Secretory carcinoma
    - Invasive papillary carcinoma
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Polymorphous carcinoma
    - Onecytic carcinoma
    - Lipid-rich carcinoma
    - Glycogen-rich clear cell carcinoma
    - Sebaceous carcinoma
    - Salivary gland/skin adnexal type tumors
      - Cylindroma
      - Clear cell hidradenoma

- **Epithelial-myoepithelial tumors**
  - Pleomorphic adenoma
  - Adenomyoepithelioma
    - Adenomyoepithelioma with carcinoma
  - Adenoid cystic carcinoma

- **Precursor lesions**
  - Ductal carcinoma in situ
  - Lobular neoplasia
    - Lobular carcinoma in situ
      - Classic lobular carcinoma in situ
      - Pleomorphic lobular carcinoma in situ
    - Atypical lobular hyperplasia

- **Intraductal proliferative lesions**
  - Usual ductal hyperplasia
  -Columnar cell lesions including flat epithelial atypia
  - Atypical ductal hyperplasia
• **Papillary lesions**
  - Intraductal papilloma
    - Intraductal papilloma with atypical hyperplasia
    - Intraductal papilloma with ductal carcinoma in situ
    - Intraductal papilloma with lobular carcinoma in situ
  - Encapsulated papillary carcinoma
    - Encapsulated papillary carcinoma with invasion
  - Solid papillary carcinoma
    - In situ
    - Invasive

• **Benign epithelial proliferations**
  - Sclerosing adenosis
  - Apocrine adenosis
  - Microglandular adenosis
  - Radial scar/complex sclerosing lesion
  - Adenomas
    - Tubular adenoma
    - Lactating adenoma
    - Apocrine adenoma
    - Ductal adenoma

• **Mesenchymal Tumors**
  - Nodular fasciitis
  - Myofibroblastoma
  - Desmoids-type fibromatosis
  - Inflammatory myofibroblastic tumor
  - Benign vascular lesions
    - Hemangioma
    - Angiomatosis
    - Atypical vascular lesions
  - Pseudoangiomatous stromal hyperplasia
  - Granular cell tumor
  - Benign peripheral nerve-sheath tumors
    - Neurofibroma
    - Schwannoma
  - Lipoma
    - Angiolipoma
  - Liposarcoma
  - Angiosarcoma
  - Rhabdomyosarcoma
  - Osteosarcoma
  - Leiomyoma
  - Leiomyosarcoma
• **Fibroepithelial Tumors**
  - Fibroadenoma
  - Phylloides tumor
    - Benign
    - Borderline
    - Malignant
    - Periductal stromal tumor, low grade
  - Hamartoma

• **Tumors of the nipple**
  - Nipple adenoma
  - Syringomatous adenoma
  - Paget disease of the nipple

• **Malignant lymphoma**
  - Diffuse large B cell lymphoma
  - Burkitt lymphoma
  - T cell lymphoma
    - Anaplastic large cell lymphoma, ALK negative
  - Extranodal marginal-zone B cell lymphoma of MALT-type
  - Follicular lymphoma

• **Metastatic tumors**

• **Tumors of the male breast**
  - Gynecomastia
  - Carcinoma
    - Invasive carcinoma
    - In situ carcinoma

• **Clinical Patterns**
  - Inflammatory carcinoma
  - Bilateral breast carcinoma
9 BENIGN BREAST TUMORS

Breast cysts are benign, liquid-filled cavity structures in the breast parenchyma that occur in up to one third of women aged 35–50 years. Although most are not seen clinically (microcysts), about 25% of these cysts become clinically apparent in size as smooth, well-defined, easily movable, round or oval, and sometimes painful, breast lumps. Breast cysts develop when an overgrowth of glands and connective tissue (fibrocystic changes) block milk ducts, causing them to dilate and fill with fluid. They arise out of very small microcysts (dilated parts of terminal duct lobular units) to become palpable macrocysts (see Aberrations in normal breast development). The cause of breast cysts remains unknown. They can be the cause of mastalgia and/or mastodynia. The epithelial lining the macrocyst wall is usually flattened or completely absent and, in some cases, apocrine epithelial changes may occur. Cysts cannot be clearly distinguished from a tumor by simple palpation, as in mammography, where they present themselves as sharply-defined, circumscribed lesions with a homogeneous X-ray density and a halo sign. Breast ultrasound is considered the best option when diagnosing breast cysts (see Breast imaging). Treating breast cysts is not usually necessary unless they are painful or cause discomfort. Otherwise, fine needle aspiration can be performed under ultrasound guidance. Aspiration both diagnoses and removes cysts at the same time. Normal benign cyst fluid is usually yellow, green, or gray and does not need to be analyzed in a laboratory. Cysts will usually resolve after fine needle aspiration of the fluid contents. In complex (or complicated, or atypical) cysts which are characterized by internal echoes or thin septations, thickened and/or irregular walls, and absent posterior enhancement in ultrasound, the aspirated fluid should be examined (Fig. 17). All contents of the syringe will be sent to the laboratory for cytological examination. In order to exclude intracystic carcinoma in cases of intracystic growths, it is necessary to perform a histologic evaluation of the cyst after its complete surgical extirpation. Generally, however, an intracystic (intraductal) papilloma is a pathological correlate to an intracystic structure. Pneumocystography can be used to evaluate intracystic lesions or cysts that have irregular walls on ultrasound. Because cytologic evaluation of the cyst fluid is often inaccurate even in cysts with intracystic carcinoma, the pneumocystogram can provide a definitive diagnosis (Fig. 18). During pneumocystography, fluid from the cyst is aspirated through a fine needle and air is injected into the cyst cavity. Afterward, a repeated mammogram of the air-filled cyst cavity is obtained (see Special mammographic procedures).
**Fig. 17** Simple (on the left) and complex (on the right) cyst in the breast of the same patient.

**Fig. 18** Circumscribed lesions with well-defined margins in the left breast on mammography (on the left). Pneumocystography (on the right) shows suspicious intracystic structures that were suitable justification for surgery. Histology: centrally necrotizing breast carcinoma.

**Fibroadenomas** belong to the most common tumors of the breast, occurring in about 10 – 20% of the female population and especially in younger women, as a well-defined, rigid, round lump. The peak of their incidence is between the 15th to 35th years of a woman’s life, but they may occur also in postmenopausal age. Fibroadenomas are benign tumors made up of both glandular breast tissue and stromal connective tissue. They are best described by two main histological features: intracanalicular and pericanalicular types of fibroadenoma. A fibroadenoma is usually diagnosed through the triple test (see above): a clinical examination, ultrasound or mammography, and a percutaneous needle breast biopsy. In cases of fibroadenomas, imaging diagnostic methods usually provide a clear picture (Fig. 19); however, differential diagnosis through a needle biopsy is needed to distinguish phylloide tumors. These tumors are often multiple and bilateral. They are usually hormone-dependent, as evidenced by their growth during pregnancy and their involution during lactation and
postmenopause. Treating breast fibroadenomas is usually unnecessary unless they are painful or cause discomfort. The fibroadenoma itself is not an absolute indication for surgical treatment. Absolute indications for surgical treatment are cellular atypia in the cytology and histology of the percutaneous biopsy. Relative indications for its extirpation are the gradual increase of its size or the subjective discomfort of the patient. If necessary, they are treated by surgical excision (lumpectomy). The tumor should be removed with a small margin of surrounding breast tissue, since it is possible that a histopathological examination will diagnose a phylloide tumor. Fibroadenomas fitting the description of histological changes such as sclerosing adenosis and epithelial hyperplasia are referred to as complex fibroadenomas. An alternative method to the open surgical biopsy of fibroadenomas is ultrasound-guided cryoablation, i.e. the use of extreme cold to destroy tissue. The American Society of Breast Surgeons recommends the following criteria to establish a patient as a candidate for the cryoablation of a fibroadenoma: the lesion must be sonographically visible; the diagnosis of fibroadenoma must be confirmed histologically; and the lesions should be < 4 cm in diameter. In the case of multiplicity and / or bilaterality in mastopathy, treatment with danazol (200 – 400 mg / day for 3 – 6 months), GnRH analogs (i.e. one goserelin depot every 4 weeks for 6 months), or tamoxifen should be tried. Some fibroadenomas respond to treatment with ormeloxifene.

Fig. 19 Fibroadenoma ultrasound image

An adenoma is a pure epithelial neoplasm of the breast. This lesion is divided into tubular, lactating, apocrine, ductal, and pleomorphic (i.e. a benign mixed tumor) adenomas. They
occur more frequently than lactating adenomas during pregnancy and puerperium, and in reproductive women age they present as ductal and tubular adenomas, however, these adenomas are generally rare. Differential diagnosis should take phyllodes tumors, fibroadenomas, and well-differentiated carcinomas into consideration. Adenomas do not have typical characteristics in breast imaging; they should be verified by some form of percutaneous breast biopsy. Treatment is surgical and consists of their extirpation. A special form of adenoma (adenoma of the nipple) is also known as florid papillomatosis of the nipple ducts, or erosive adenomatosis. Histologically, this finding is characterized by proliferating ductal structures that invade the surrounding stroma. Nipple adenomas can be successfully treated by complete excision of the tumor with normal surgical margins.

A breast lipoma is a benign, usually solitary, tumor composed of mature fat cells. It presents itself as a semi-solid, well-circumscribed (sometimes lobed) lump, and usually without subjective disorders. Given the X-ray density of adipose tissue, a lipoma may not be easily recognized on mammography. An ultrasound must be performed carefully to distinguish lipoma and its thin wall from the surrounding fat and connective structures (Fig. 20). The diagnosis is verified by a percutaneous breast biopsy; a finding of fat cells does not indicate a non-representative sampling, but rather confirms the diagnosis. Treatment is usually unnecessary; in cases involving subjective disorders, or if the patient wishes, it may consist of surgical extirpation.

![Fig. 20 Lipoma ultrasound image](image)
Phyllodes tumor (cystosarcoma phyllodes, cystosarcoma phylloides, phylloides tumor). Although the name suggests a malignant mesenchymal tumor, phyllodes tumors are a group of tumors with a different relevance and prognosis. They are typically large, fast-growing masses. It is a typical biphasic fibroepithelial tumor consisting of epithelial and periductal stromal cells of the breast. They may be considered benign, borderline, or malignant, depending on histologic features. It occurs in women of young and reproductive age. They often manage to grow quite large in terms of size, which creates differential-diagnostic difficulties in comparison to fibroadenomas, or even sarcomas. Non-homogenous echotexture of the tumor is a characteristic property of phyllodes on breast ultrasound (Fig. 21). Sometimes a pathologic form of blood flow can be seen during a power Doppler examination. The common treatment for phyllodes tumor is a wide excision. Large malignant phyllodes tumors can necessitate mastectomy (Fig. 22). Possible predictors of locoregional recurrence are: stromal atypia, high mitotic rates and positive resection margins.

Fig. 21 Non-homogenous echotexture of a phyllodes tumor in an ultrasound image (on the left) and signs of increased vascularity during a power Doppler examination (on the right).
Hamartoma is a rare, benign solid tumor sometimes referred to as fibroadenolipoma, lipofibroadenoma, or adenolipoma, which reflect its composition. It consists of varying proportions of glandular, fatty, and fibrous tissue. It presents as a discrete, well circumscribed, and painless breast lump. The findings in breast imaging are the same as in fibroadenomas or phylloides tumors. The diagnosis is made from a percutaneous needle and/or open surgical biopsy. The pathologist should be cautious and also consider a coincidental epithelial malignancy occurring in the lesion.

A granular cell tumor is usually a rare form of benign tumor that originates from the Schwann cells of the peripheral nervous system. It is more frequently found on the head and neck, but can also occur (rarely) in the breasts. Granular cell tumors are usually fixed to the pectoral fascia, or skin, and consequently, can mimic breast cancer. Mammography and ultrasound findings can be misinterpreted as carcinoma. Diagnosis is made from a percutaneous needle and/or an open surgical biopsy.

Pseudoangiomatous stromal hyperplasia of the breast (PASH) is a benign, proliferative mesenchymal lesion with possible hormonal etiology. It typically affects women in the reproductive age group. Breast tissue affected by PASH is characterized by the dense myofibroblastic proliferation of mammary stroma associated with interanastomosing capillary-like spaces. PASH is frequently an incidental histologic finding in breast biopsies.

Fig. 22 Malignant form of a giant phyllodes tumor, which necessitated a mastectomy.
performed for other benign or malignant lesions. Rarely, it can present as a breast mass, which has been referred to as **nodular or tumorous PASH** (Fig. 23). Tumorous PASH presents as a unilateral palpable resistance in the breast with a relatively rapid progression of growth. PASH may occur (rarely) in men with gynecomastia. The exact etiology and pathogenesis of the disease is still not completely clear. It primarily affects young women, and therefore a hormonal etiology is considered.

![Fig. 23 Tumorous form of PASH during mammography (upper left) and on an ultrasound (upper right). A giant tumor (lower left) was removed from the breast through a reduction mammoplasty. Histologic examination showed myofibroblastic proliferation of the mammary stroma, associated with interanastomosing capillary-like spaces (PASH) (lower right).](image)

**Diabetic fibrous mastopathy** occurs rarely in premenopausal women with long-standing type 1 insulin-dependent diabetes mellitus. The etiology is unknown, although, an immune response to abnormal accumulations of altered extracellular matrix, resulting from the effect of diabetes on connective tissue is a possible explanation. The mammographic and ultrasound pictures of the lesions are highly suspicious for breast carcinoma; therefore, a percutaneous large-core needle biopsy should be performed to confirm the diagnosis. Breast MRI that fail to show an accumulation of gadolinium contrast material in the lesion are useful in
eliminating the possibility of a simultaneous malignancy. Treatment consists of good management of insulin-dependent diabetes; surgical extirpation of the lesions is not recommended due to concerns of impaired wound healing. Routine annual follow-up of patients with diabetic fibrous mastopathy is recommended.

**Intraductal papilloma** is a small benign tumor inside the mammary duct, which is often the cause of pathological secretion from the nipple. The disruption of vessels in the peduncle of a papilloma results in bloody discharge from the nipple. Imprint cytology from the nipple and a ductography (see Breast imaging) should be performed in these patients. In case of intraductal formation findings (localization of radiocontrast agent or intraductal shape change) (Fig. 24), a ductectomy should be performed after preoperative marking with an optical contrast agent (a blue dye). In most cases, intraductal papillomas will be detected morphologically. The central papillomas tend to be solitary, whereas peripheral papillomas are usually multiple. Solitary papillomas can be often seen as an intracystic structure on ultrasound (Fig. 24). Papillomatosis (multiple papillomas) is defined as a minimum of five clearly separate papillomas within a localized segment of breast tissue. This condition is considered premalignant lesion (see next chapter).

![Fig. 24](image)

*Fig. 24* Solitary intracystic and intraductal papilloma in an ultrasound image (left) and ductography (red arrow on the right).

Additional information on this topic will be presented in the chapter Premalignant breast lesions.
10 PREMALIGNANT BREAST LESIONS

The term ‘premalignant lesions of the breast’ designates a scale of morphological changes of breast tissue with the potential for cancer formation. They usually represent benign changes that are, in comparison to purely non-malignant lesions, associated with higher risk of malignancy. A synonym for this term is precancerous or high-risk lesions. Women with these lesions, i.e. ambiguous biological behavior, are in more danger of developing cancer throughout their lives than women without these lesions. The risk should be evaluated on a strictly individual basis and in relation to other pre-existing risk factors. Pathological results from breast core needle biopsies of premalignant lesions refer to the B3 category, i.e. benign lesions with uncertain biological potential (see Interventional breast procedures).

10.1 INTRADUCTAL PROLIFERATIVE LESIONS

The ductal, as well as lobular, epithelia of the terminal ductal-lobular units may proliferate. In comparison to lobular epithelium, which is primarily monomorphous, ductal epithelium is characterized by great variability of cytological changes. For the last few decades, there have been numerous attempts to create an appropriate classification of intraductal lesions, but no exact criteria that clearly classifies these lesions has been defined. Intraductal proliferative lesions are sometimes referred to as ductal intraepithelial neoplasia (DIN). Even though this classification is not officially accepted by the new WHO classification of tumors from 2012 (see Breast tumor classification), we consider it important to mention the classification at this point (Tab. 13).

<table>
<thead>
<tr>
<th>Former terminology</th>
<th>DIN classification</th>
</tr>
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<tbody>
<tr>
<td>Usual ductal hyperplasia without atypia (UDH)</td>
<td>Usual ductal hyperplasia without atypia (UDH)</td>
</tr>
<tr>
<td>Flat epithelial atypia</td>
<td>Ductal intraepithelial neoplasia grade 1A (DIN 1A)</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>Ductal intraepithelial neoplasia grade 1B (DIN 1B)</td>
</tr>
<tr>
<td>DCIS grade 1</td>
<td>Ductal intraepithelial neoplasia grade 1C (DIN 1C)</td>
</tr>
<tr>
<td>DCIS grade 2</td>
<td>Ductal intraepithelial neoplasia grade 2 (DIN 2)</td>
</tr>
<tr>
<td>DCIS grade 3</td>
<td>Ductal intraepithelial neoplasia grade 3 (DIN 3)</td>
</tr>
</tbody>
</table>
10.2 COLUMNAR CELL LESIONS
FLAT EPITHELIAL ATYPIA (FEA)

Columnar cell changes represent a wide range of changes from columnar metaplasia through usual columnar cell hyperplasia up to atypical columnar cell hyperplasia. FEA is one form of columnar changes that are benign and represent histopathological changes of the breast formerly described as blunt duct adenosis. We can say that columnar changes represent columnarily-changed cells (cuboid – cylindrical cells) in distended TDLU, where they substitute original ductal epithelium. The columnar cell lesions are a relatively common finding in breast biopsies and refer to benign changes with a minimal risk of breast cancer. FEA is considered a precursor lesion of low-grade carcinomas; thus, FEA findings in core needle biopsies should be verified by a follow-up surgical biopsy.

10.3 ATYPICAL DUCTAL HYPERPLASIA (ADH)

Atypical ductal hyperplasia presents as small atypical intraductal lesions that do not fully meet the criteria of ductal carcinoma in situ (DCIS). Despite numerous attempts, the diagnostic criteria to differentiate ADH from low-grade DCIS still have great variability. The increase in screening mammography has been accompanied by a rising number of detected ADH lesions, which affects women’s lives. Generally, the life-long risk of developing infiltrating carcinoma in women with ADH is approximately 5-fold greater in comparison to the general population. In cases where the woman has a positive family history (first-degree relatives), the risk rises by 10-fold. Even though the degree of risk refers to the ipsilateral breast, the contralateral breast is also at higher risk. Women with ADH should be informed of the risk and should have annual screening mammography. Medicamentous chemoprevention, or other prophylactic measurements, should be offered to women with ADH after a thorough evaluation of their individual risks (in relation to pre-existing risk factors).

10.4 DUCTAL CARCINOMA IN SITU (DCIS)

Ductal carcinoma in situ of the breast represents a malignant clonal proliferation of epithelial cells within the ductolobular system of the breast gland, which does not exceed the myoepithelial layer (basal membrane); thus, there is no invasion of surrounding tissue. Therefore, it is a non-invasive malignant disease which has been shown to be a direct non-obligatory precursor of invasive carcinoma. This means that, in some cases, the DCIS lesion progresses into invasive carcinoma and this risk is 8- to 11-fold greater than in the general
population. According to some retrospective trials, in cases of non-treated DCIS, 30% of lesions progress to invasive carcinoma during the course of 30 years. One typical feature of DCIS is a lack of any clinical signs or symptoms in the majority of cases. 80 – 85% of lesions present themselves with microcalcifications on mammography, without any other clinical sign. Therefore, the recent increase in detected DCIS lesions is connected with the application and increasing quality of mammography screening. Considering the fact that DCIS represents a direct precursor of invasive carcinoma, the primary treatment is surgical. In some cases, radiotherapy is administered after surgical treatment; the local recurrence rate after this standardized treatment is reported to be 10 – 15%. Fifty percent of these recurrences are represented by invasive carcinoma. Nevertheless, key information that could help predict the biological behavior of these lesions is still lacking. The most important predictor, relative to clinical practice, appears to be differentiation of DCIS lesions with high a risk of progression from their stable, indolent counterparts. In the past, the main criteria for the classification of these lesions were based on morphology, and various classification systems have been created as a consequence of DCIS heterogeneity. According to the growth pattern, lesions might be divided into cribriform, micropapillary, comedo-type, solid and mixed types.

According to cell differentiation (grading) and the presence of intraluminal necrosis, DCIS can be divided into three groups:

- low-grade DCIS (LG-DCIS),
- intermediate DCIS (IG-DCIS),
- high-grade DCIS (HG-DCIS).

Multifocality (the presence of more foci in one breast quadrant) and multicentricity (foci in more than one quadrant) may occur in all subtypes of DCIS.

Even though “clinically silent” lesions are the most common, some lesions can present with a palpable tumor. The primary diagnostic modality of DCIS is mammography carried out in two different projections (CC and MLO) and, in certain cases, completed by 90° projection or magnification views (differential diagnosis of microcalcifications). In some cases, a hypoechoic lesion can be seen during an ultrasound examination. Digital mammography increases detection of low- and intermediate-grade DCIS. The definite role of MRI has not been defined yet, but it might be beneficial in the pre-operative staging of HG-DCIS. The key method for verification of the diagnosis is a core needle biopsy. The most appropriate method seems to be stereotactic-guided VAB (vacuum-assisted large-core needle biopsy) followed by
a radiogram of the obtained tissue samples in order to visualize the microcalcifications. Surgical treatment has a primary role in the treatment of DCIS through the establishment of locoregional disease control, and determining the exact stage of the disease. The key is to remove the lesion together with a sufficient margin of adjacent healthy tissue, while trying to maintain an acceptably aesthetic result. Surgical treatment of non-palpable lesions demands special management, such as (for example) preoperative hook wire localization of the non-palpable lesion by mammographic stereotaxy. Perioperatively, a radiogram of the excised tissue (specimen radiography) is performed to confirm the presence of the lesion (and its completeness) in the excised tissue. The appropriate choice of surgical procedure involves first considering tumor size and distribution, as well as its size in relation to the breast. Most of the time, breast-conserving procedures (with or without radiotherapy) are standard treatment. DCIS lesions are not appropriate for perioperative frozen section pathology assessment; this is due to the reduction of tissue quantity, or the margin assessment being affected as a result of tissue processing. Waiting for results from paraffin-embedded slides is recommended. In some cases, biopsy of the sentinel lymph node is indicated. In cases of multicentricity or large multifocality, a mastectomy must be performed. The final therapeutic choice should be the result of a multidisciplinary discussion considering the patient’s wishes, (after having been thoroughly informed about their health status, treatment options and prognosis). The Van Nuys prognostic index (VPNII) can aid in the decision making process for the further management of patients with DCIS (Tab. 14). Patients with VNII scores of 4 to 6 can be considered for treatment with excision only. Patients with intermediate scores (7 – 9) should be considered for treatment with radiation therapy or be re-excised if the margin width is < 10 mm and cosmetically feasible. Patients with VNII scores of 10 – 12 have an extremely high local recurrence rates, regardless of irradiation, and should be considered for mastectomy. Tamoxifen is indicated in order to prevent recurrences in estrogen-positive DCIS.

**Tab. 14 Van Nuys prognostic index for DCIS patients**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>&lt; 15 mm</td>
<td>16 – 40 mm</td>
<td>&gt; 41 mm</td>
</tr>
<tr>
<td>Margins</td>
<td>&gt; 10 mm</td>
<td>1 – 9 mm</td>
<td>&lt; 9 mm</td>
</tr>
<tr>
<td>Grading</td>
<td>1.2 – necrosis</td>
<td>1.2 + necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60 years</td>
<td>40 – 60 years</td>
<td>&lt; 40 years</td>
</tr>
</tbody>
</table>
Paget disease (m. Paget) affects the nipple and is characterized by the presence of malignant epithelial cells within the squamous epithelial layer of the mammila-areolar complex. It presents clinically with eczematous changes of the nipple-areola area and is often associated with DCIS of the underlying ductal system (with or without invasion). In cases of clinically obvious Paget disease, the clinician should always search for DCIS or an infiltrating carcinoma in the affected breast.

10.5 LOBULAR NEOPLASIA. ATYPICAL LOBULAR HYPERPLASIA AND LOBULAR CARCINOMA IN SITU

Lobular neoplasia (LN) includes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ. Differentiation between these lesions is based on the extent of the affected lobular units. LCIS is divided into classical and pleomorphic types, with or without comedonecrosis. The classical type does not have the same biological potential as DCIS, and does not always progress into an infiltrating form of cancer. Moreover, it may regress after menopause. The differential diagnosis between ALH and classical LCIS can be difficult. In the past, LN was only considered an indicator of a higher risk for breast carcinoma (both lobular and ductal types). This hypothesis was based on observational studies of patients with lobular hyperplasia. In the case of LH representing a direct precursor lesion, we would expect the development of invasive lobular carcinoma in the ipsilateral breast in the same quadrant.

However, this hypothesis has recently been called into question by the results of recent molecular-biological studies. At present, LN is considered a non-obligatory precursor lesion, both in the ipsilateral and contralateral breast at the same time. LN is often a coincidental finding in breast needle biopsies, as it does not have perfect correlation with imaging examination methods. The diagnosis of LN in surgical tissue samples does not require further surgical intervention; in patients with LN findings from core-needle or vacuum-assisted biopsies, a complete surgical excision of the lesion is recommended. Patients with LN should be informed of the higher risk for breast cancer development (approximately a 7-fold higher risk over 10 years) and possible options for individual risk reduction. Preventive mammography is performed in annual intervals.

Cells of the pleomorphic variant of LCIS have some cytological differences relative to classical LCIS, especially where core morphology is concerned. Apocrine metaplasia necroses and microcalcifications are also typical. Pleomorphic LCIS can resemble DCIS and can make diagnosis difficult. Immunohistochemistry to verify the E-cadherin protein might be
helpful in these cases. However, the molecular profile is more similar to classical LCIS, and is therefore considered a special form. Taking into account its more aggressive biological behavior, pleomorphic LCIS is treated like DCIS, which is an important difference in comparison to classical LCIS.

10.6 Papillary Breast Lesions

Papillary breast lesions are a major issue in breast pathology. In general, papillomas consist of two layers of cells: one layer of ductal epithelial cells and a second myoepithelial layer, supported by a fibrovascular core. This group of changes comprises a high number of lesions described with different pathological terminology. The latest WHO classification from 2012 divides these lesions as follows:

- Intraductal papilloma
  - Intraductal papilloma with atypical hyperplasia
  - Intraductal papilloma with ductal carcinoma in situ
  - Intraductal papilloma with lobular carcinoma in situ
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
  - Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma
  - In situ
  - Invasive

Solitary papillomas (discrete, small tumors of the main ducts) are a common cause of spontaneous, brownish, or bloody nipple discharge. They can sometimes be seen on native mammography as small circumscribed subareolar masses, or as solitary dilated ducts. Standard diagnostic management involves a cytology examination of discharge from the affected nipple, in order to exclude atypical cells. This is followed by special X-ray mammography of the affected duct, which is performed after cannulation and the injection of contrast material (i.e. ductography / galactography). A solitary papilloma usually manifests with a contrast-agent filling defect in the system of terminal ducts, usually a few centimeters beyond the areola-mamillary complex. The primary therapeutic procedure (ductectomy after catheterization and visualization with an optical contrast material, such as isosulfan blue) is therapeutic (as well as being the diagnostic method of choice), as it brings relief to the patient by stopping the discharge. The probability of carcinoma incidence in such cases is estimated
to be 2 – 7 %. Multiple papillomatosis of the ducts is defined by the presence of at least 5 or more separated papillomas within one breast segment. Multiple papillomatosis is found in about 10 % of women with a solitary papilloma, more often at a younger age than in perimenopausal age. A bilateral appearance is common and might be associated with DCIS. Juvenile papillomatosis, which is unusual, is a severe form of papillomatosis that occurs in young women. It presents with painful, movable circumscribed tumors in the retromamillary area of the breast. Fine-needle aspiration cytology seems to be insufficient for a differential diagnosis and a core-needle biopsy should be used to minimize diagnostic difficulties. Complete surgical excision of papillary lesions (particularly the intracystic papillary lesions) with a margin of healthy adjacent tissue is recommended by most authors.

### 10.7 Radial Sclerosing Lesion (Radial Scar)

From the term “radial sclerosing lesion” (RSL) this lesion is observed to be a rosette-like, proliferative lesion of the breast (radiological as well as histological). The terminology for CSL varies, but most authors agree on the term “radial scar” in cases where the lesion size is < 1 cm, and “radial complex sclerosing lesion” in cases where the lesion is > 1 cm. The prevalence of RSL is reported to be around 0.04 %. Radial scars and complex sclerosing lesions are characterized by central sclerosis with a corona of epithelial proliferation; it can be benign, but can also comprise cellular atypia or malignant changes. The presence of glandular structures compressed in the center of the lesion may imitate carcinoma, especially the tubular subtype. Moreover, the epithelial compound is often accompanied by different changes, such as ADH, LN, and DCIS. The malignant changes within RSL are usually of lower biological potential (LG-DCIS, invasive carcinoma grade 1). In various trials concerning premalignant changes in RSL, DCIS was found in 0 – 40 % cases. Based on these findings, many authors believe that evidence of RSL in breast tissue samples from core-needle biopsies does not exclude the presence of malignancy; therefore, all such findings should be completely excised. On the other hand, there has been an increase in the number of trials that do not consider surgical excision necessary if an adequate number of samples have been obtained by percutaneous biopsy (preferably VAB), and histological results correlate with clinical findings.
10.8 APOCRINE BREAST LESIONS

Apocrine metaplasia of the breast is a common finding in women after the 25th year of age, and is considered a normal part of the breast gland. However, the presence of apocrine metaplasia may only be considered normal in cases of apocrine sudoriferous glands in the axilla, or in the periareolar sudoriferous glands of the breast. Apocrine cells may occur in a number of breast lesions, some of which may include malignant features. Generally, apocrine breast lesions are divided as follows:

- apocrine metaplasia in fibrocystic mastopathy,
- apocrine adenosis,
- apocrine changes in sclerosing adenosis,
- apocrine changes within other changes (RSL, papilloma, fibroadenoma, phylloides tumor),
- atypical apocrine hyperplasia,
- apocrine DCIS,
- infiltrating carcinoma with apocrine features.

Apocrine adenoma is an extremely rare lesion and the studies published thus far do not enable one to define its biological potential (from the view of malignancy); however, it is generally considered a benign change. Apocrine changes within sclerosing adenosis represent changes of uncertain malignant potential. In the past, the lesion was also known as apocrine adenosis, but this term was also used for a completely different histopathological unit. Therefore, it is recommended to use the term “apocrine change” in sclerosing adenosis, in order to avoid confusion with changes associated with another rare lesion called adenomyoepithelioma. The literature refers to the term “apocrine DCIS” only rarely, and many authors assume it is because these lesions often go unrecognized. Even though there have long been claims suggesting there is too little evidence to declare a special apocrine phenotype of carcinoma, recent trials have defined a “pure” apocrine-infiltrating carcinoma.

10.9 MUCOCELE-LIKE LESIONS

A mucocele is defined as an accumulation of mucus in any dilated, e.g. in a hollow organ. Breast mucocele-like lesions (MLL) include dilated areas with mucus (mucin) that discharge their contents into the surrounding stroma. The epithelial lining of these areas may be of benign or malignant potential, or may be characterized by heterogeneity, including benign,
atypical or malignant epithelial proliferation within one lesion. Pathogenesis is not fully understood, but may be explained by increased production of mucus in TDLU followed by duct obstruction. They present themselves in a broad spectrum of imaging findings, ranging from different masses to clusters of microcalcifications of unknown origin on mammography, to hypoechogenic lesions on ultrasound image. Core-needle biopsies with a finding of MLL with cell atypia always require surgical excision. In cases of MLL in surgical tissue samples, it is always necessary to consider and look for possible histological DCIS and / or mucinous carcinoma.
11 MALIGNANT BREAST TUMORS

11.1 BREAST CARCINOMA

11.1.1 EPIDEMIOLOGY OF BREAST CARCINOMA

Breast carcinoma is currently the most common cause of death from cancer in women in more-developed countries, closely followed by lung cancer in a few countries. It causes 3 -- 5 % of all deaths in developed countries. In western countries, breast cancer is the most common cause of death within the age group of 39 – 58 years. Among all such deaths, women from the USA comprise 29 %, and the remainder is represented by women from western Europe and Australia. In Slovakia, nearly 1,500 new cancer cases are diagnosed every year. According to data from the National Oncological Register of the Slovak Republic, the incidence of breast cancer is approximately \( \frac{80}{10^4} \), with mortality being around \( \frac{25}{10^5} \). While the incidence in western countries has been declining during the last few years, incidence in Slovakia shows the opposite tendency. Even though incidence rates vary throughout the world depending on population, this difference changes with time. Future generations of migrants from less-developed countries are affected by the same incidence rate as women from the majority population. This means that not ethnic, but rather social, dietary, cultural and other possible factors significantly influence the incidence of breast cancer. Nowadays, not only is the number of new cancer diseases increasing, but the aggression of these diseases is higher, as well (especially in young women). Today, every 9th woman from well-developed countries, and every 8th woman from the USA, develops breast cancer. It is estimated that by the beginning of the 3rd millennium, the world-wide incidence of breast cancer will be around 1 million women.

11.1.2 ETIOLOGY OF BREAST CANCER

The etiology of breast cancer is uncertain. Similarly to other malignant diseases, breast cancer is a disease of the cell genome. Various environmental factors are mentioned in relationship to it.

Genetic factors seem to be conspicuous. It has been shown that 5 – 10 % of illnesses are associated with genetic proneness. A sporadic form of cancer means there has been no previous occurrence of malignant disease in the patient’s family. The term hereditary
carcinoma is used for tumors with proved genetic mutations; however; familial incidence of carcinoma (carcinoma in patients with a family history of cancer incidence without evidence of genetic mutation) does not need an underlying genetic cause. An association with certain genes has been shown; particularly autosomal dominant genes i) BRCA1, localized on the 17th chromosome (17q-21), and ii) BRCA2, localized on chromosome 13 (13q12). Among other genes, p53, CHK2, STK11, ATM, PTEN, and MMR are often mentioned. At present, not all genes related to cancer development have been discovered. The BRCA1 gene is a tumor-suppressor gene responsible for genome stability, and a malfunction in DNA repair mechanisms is believed to be crucial in the process of carcinogenesis. Women with this mutation have an 80% risk of breast cancer and a 60% risk of ovarian cancer, both in young age (for BRCA2, the risks are 85% and 35%, respectively). In cases with a suspected mutation in the family, these women may undergo a special examination using genetic-molecular methods. If the results are positive, the women participate in a special preventive program. The genetic risk of developing breast cancer may also be due to a malfunction of other genes (e.g. p53, STK11, ATM, PTEN, MMR and others), or the activation of some oncogenes (e.g. the HER-2 oncogene). Oncogenes may also be activated by certain viruses. Hereditary breast cancer can be also be a component of syndromes with multiple cancer development, such as Li-Fraumeni, Lynch, Fanconi anemia, familial diffuse gastric cancer, Cowden syndrome and others.

Among dietary factors, the most discussed is higher fat intake (particularly animal fat). It is presumed that obesity leads to a higher conversion of androgen intermediate products into estrogens during the process of hormone synthesis, and into relative hyperestrogenism. It is further presumed that fatty tissue works as a reservoir for various carcinogens from the external environment (e.g. polychlorinated biphenyls or pesticides). In addition, aromatized hydrocarbon compounds, considered typical carcinogens, are usually fat-soluble. The relation between obesity and breast cancer has only been observed in postmenopausal women; it has not been proven in younger women, and there is still ambiguity concerning this issue.

Another important carcinogenic factor is ionizing radiation. A classic example would be the trials studying cancer incidence in women who were irradiated in Japan during World War II. Observational studies on women irradiated with high X-ray doses at young ages (due to mastitis or tuberculosis) confirmed results from previous studies. Breast radiation with high X-ray doses during breast development seems to be critical. Neither postoperative therapeutic
dosages, nor dosages associated with mammography, have been shown to increase the risk of cancer development.

Hormonal imbalances in women are a frequently discussed factor and a clear correlation has yet to be established.

11.1.3 RISK FACTORS FOR BREAST CARCINOMA

Breast cancer primarily affects women from developed, industrialized countries, with the exception of Japan. Nulliparous women have a 3-fold higher risk than multiparous women; however, this is mainly true when the first birth occurs before the age of 20. In cases where the first child is born after the age of 30, a woman’s risk for developing breast cancer is the same as in nulliparous women. Moreover, primiparous women older than 35 have an even higher risk. Breast-feeding has a protective effect, but only in premenopausal carcinomas. The greatest risk factor is an incidence of breast carcinoma in the family history, especially in first-degree relatives (mother, sister, or daughter). This factor multiplies in cases of familial incidence of tumors diagnosed in young woman and / or in cases of bilateral tumors (see Early menopause, both natural and artificial, increases the risk of breast cancer). Breast radiation with high doses of ionizing radiation at an age close to menarche increases the risk of disease. Exogenous administration of hormones (e.g. HRT during postmenopause) slightly increases the relative risk of cancer diagnosis in relation to the regimen and duration of therapy. Among negative alimentary factors, fat and alcohol have been described. Vitamins A, D, E, C, and calcium seem to have a protective influence.

Among benign breast diseases, breast cancer risk is mildly increased by some types of premalignant breast diseases, particularly if they are accompanied by epithelial hyperplasia (see Premalignant breast lesions). Atypical ductal and lobular hyperplasias are of greatest importance. One basic condition for the diagnosis is a morphological examination of the breast tissue. Even though the morphological description is relatively well established, there is still confusion during evaluation. Atypical hyperplasias have some (but not all) of the histological features of in situ carcinomas and represent so-called “borderline” lesions. Atypical lobular hyperplasia, which is very similar to lobular carcinoma in situ (LCIS) (and why both lesions are known as lobular neoplasia (LN)), means a greater risk of invasive carcinoma in both breasts. In comparison to lobular atypical hyperplasia, ductal atypical hyperplasia shares only a few features with ductal carcinoma in situ, and endangers patients
with a dominant risk of cancer development in the ipsilateral breast. This risk is significantly increased in patients with a positive family history.

Since the genetic, hormonal, and molecular biology mechanisms of breast cancer formation are still not clear, the risk factors are only of limited importance (the exact role in the mechanisms they influence is also not known). The one and only apparent risk factor is incidence of breast carcinoma in the contralateral breast. Generally, we can say that, at present, all women are at high risk for developing breast cancer and, in some women, the risk is even higher.

### 11.1.4 Histopathological Classification of Breast Cancer

Histopathologic classification of malignant breast tumors is based upon the current WHO classification (see Table 12 in Breast tumor classification). Histological typing of breast tumors (identification of the correct tumor type) is crucial for the management of the disease. For better comprehension of further aspects of the breast cancer issue, we consider it necessary to mention some important morphological and molecular-genetic terms.

Breast carcinoma develops through the malignant transformation of ductal cells (ductal carcinoma accounts for around 80% of cases) or acinar cells (lobular cells). Other variants of breast cancer (tubular, medullar, mucinous and papillary) represent variations of these two types. In addition to these, there are also mixed-types comprising the ductal and acinar epithelia, and precise differentiation between the two is impossible. Paget carcinoma also arises from ducts, but it spreads intra-epidermally in the mamillary area. Inflammatory carcinoma is a special form of carcinoma. Sarcomas of the breast occur only rarely. The TNM classification of tumors (see below) should be strictly respected, since tumor size and number of affected lymph nodes remain the most important prognostic factors. By the N+ state, it is also recommended that the exact number of positive lymph nodes from the entire number of examined nodes (e.g. 3 / 15) be stated. Reporting the levels of removed lymph nodes provides information pertaining to how radical the surgical procedure in the axilla was. The M-state is also important when considering the high potential of lymphogenic and hematogenic dissemination. Regarding the localization of the disease, approximately half are localized in the upper outer quadrants. A less common location for breast cancer is the lower medial quadrant, and this location has the worst prognosis. **Multifocality** in breast cancer may be defined as the presence of two or more tumor foci (usually, microscopic connections between the foci are found) within a single quadrant. **Multicentricity** means the presence of
additional separate tumor foci within different quadrants of the same breast. Studies of mastectomy samples show that even in the T1 stage (tumor size < 2 cm), multicentricity was present in 25% of cases and affected other breast quadrants. This finding has led to the currently routine irradiation of the rest of the breast after breast conserving surgery.

More than 50% of invasive ductal carcinomas send intraductal *in situ* projections to their margins. If these projections form more than 25% of the tumor mass, it is termed an **extensive intraductal component (EIC)**. Its importance is especially obvious in breast conserving therapy, where *in situ* projections may become a source of recurrences.

The morphological examination of the tumor is not simply focused on macro- and microscopic descriptions of tumor tissue, but rather the examination also evaluates certain **prognostic factors** in order to provide important information for clinicians. The differentiation and appearance of the cells is described by tumor grade. **This grading** is stated in relation to the presence of hyperchromatic nuclei, nuclear pleomorphism and the number of mitoses figures per view field per high-powered field. Information about tumor grading is subjective and often affected by subjective mistakes made by the pathologist. The cellular nuclei are also examined by flow cytometry in order to determine the nuclear DNA content and ploidy level, as well as the distribution of cells in major phases of the cycle.

These methods are relatively objective and can be performed on fresh tissue samples, frozen samples, cytology material, or paraffin-embedded tissue. The term **DNA index** (DI) is used to express the nuclear DNA content, and a DNA index of 1 corresponds to diploidy. DNA indices that are < 1.0 (hypodiploidy) or > 1.0 (hyperdiploidy, tetraploidy etc.) are referred to as DNA aneuploidy. In general, diploid tumors have a more favorable prognosis than aneuploid tumors. The number of tumor cells in the synthetic cellular phase is determined by the **S-phase**. The rest of the cells are either in the pre-synthetic phase (G0/G1), or the post-synthetic and mitotic phase (G2+M). A lower tumor S-phase has a better prognosis than a higher tumor S-phase, which is also expressed by index.

Another important method is the examination of **estrogen and progesterone receptors** in the tumor cells. These can be examined by biochemical methods from fresh frozen tissue samples or in cytology material and paraffin-embedded tissue samples by immunohistochemistry. The results provide semiquantitative information about the hormonal status, which is important information for the further planning of adjuvant therapy.
Immunohistochemistry is also important for the examination of other prognostic and predictive factors of tumor tissue, such as cathepsin D, Ki-67, HER2 receptors, protein p53, and others. Of these, the most important seems to be human epidermal growth factor receptor 2 (HER2), which has become a routinely examined factor in invasive carcinomas. It is a transmembrane receptor from the tyrosine-kinase family. Patients with a high expression of HER2 have a poorer prognosis and undergo special anti-tumor treatment.

A mark of significant progress is the new breast cancer diagnosis method of gene expression profiling, which uses microarrays methods. It is used to analyze genes with a statistically significant association with breast carcinoma recurrences, genes with predictive value for tumor responsiveness to chemotherapy, and genes regulating the gene expression of other genes (e.g. Oncotype DX®, Mammaprint®). The results from these examination methods are important for further therapy planning and selecting the correct therapy (e.g. tamoxifen / CHT / CHT + tamoxifen) for specific breast cancer cases.

11.1.5 MOLECULAR CLASSIFICATION OF BREAST TUMORS

The cardinal publication of Dr. Perou and his colleagues in 2000 brought new insight into the tumor stratification issue based on their molecular-genetic profile. The profile counts the etiopathogenetic characteristics of tumors and their response to treatment. There are two types of epithelial cells in glandular breast tissue: basal and luminal. Apart from these well-differentiated cells, glandular breast tissue consists of undifferentiated stem cells and progenitor cells. An analysis of hundreds of genes regulating the growth and cell division of glandular and stromal breast cells led to the following breast tumor classification:

**Basal-like tumors**

Basal-like tumors are from cells that resemble basal cells of the epithelial lining in terminal ductal-lobular units. During immunohistochemistry staining, they show a positive expression for certain cytokeratins (CK 5, 6) and negative expression for estrogen, progesterone, and HER2 receptors. They represent tumors with the worst prognosis.

**Luminal tumors (luminal A, luminal B)**

Luminal tumors consist of cells that are similar to luminal epithelial cells within the terminal ductal-lobular units. They are defined by their gene and protein expression profile with positive immunohistochemistry staining against special cytokeratins (CK 8, 18) and they can be divided into two (some authors state three) subgroups based on expression of estrogen
receptors. The A subgroup is typical of greater expression of estrogen receptors in comparison to the B subgroup. Generally speaking, luminal tumors have the best prognosis.

**HER2 positive / estrogen receptor negative tumors**

HER2 tumors form a separate group of tumors due to their special molecular-genetic profile. During immunohistochemistry evaluations, they typically show positive staining for human epithelial growth receptor 2 (HER2 receptors) and negative staining for estrogen receptors. In comparison to luminal breast tumors, they have a poorer prognosis. On the other hand, the presence of HER2 receptors enables the use of modern biologic therapy with anti-HER2 substances.

**Normal breast-like tumors**

This group of tumors has a gene expression profile similar to the normal, non-malignant cells of terminal ductal-lobular units or benign breast tumors. Their exact clonal origin is not fully known.

### 11.1.6 Disseminated and Circulating Tumor Cells (DTCs, CTCs)

The metastatic process starts in the early stages of tumor development. In order to form a depot of the metastatic cells, the malignant cell or group of cells need to break away from the primary tumor, invade the host tissue and remain there to proliferate and form a metastatic tumor. Early detection of circulating tumor cells in the bloodstream, or disseminated tumor cells in the bone marrow of patients with breast carcinoma may enable early intervention in order to better stratify the risk. DTCs are usually identified by cytochemical staining methods after fine-needle bone marrow aspiration taken from the back of the hipbone. For CTC identification, polymerase chain reaction (PCR) methods, cytochemical methods and modern, commercially-produced diagnostic machines based on immunomagnetic cell separation (such as CellSearch), are used. Several trials have confirmed the independent prognostic value of DTCs but because of the invasive examination associated with their detection (bone marrow needle aspiration biopsy), recent research studies have focused instead on CTC detection methods.

A combination of morphological (TNM state, grading, S-phase, ploidy, receptors, molecular subtype, etc.) and clinical determinants (history, age, menopause, etc.) aid in the assessment of tumor aggressiveness and disease prognosis. New prognostic factors on a molecular level are still being sought, but their real value can only be validated by large studies with long-term patient follow-up.
11.1.7 TNM CLASSIFICATION OF BREAST CARCINOMA

Defining the extent of the malignant breast disease according to UICC rules (Union for International Cancer Control) is performed using the TNM classification with respect to primary tumor size (T), nodal status (N) and the presence / absence of distant metastases (M) (staging). The classification has been accepted worldwide and should be strictly followed. It is only applicable to carcinomas, and a pathological-anatomical examination is necessary. For each disease, there are two different TNM classifications: i) clinical (cTNM), based upon clinical and imaging examinations, and ii) pathological (pTNM), based upon postoperative histological examination. If the letter “y” comes before the “P,” it represents preoperative neoadjuvant therapy of the tumor.

The “L” category denotes the presence or absence of lymphangiosis carcinomatosa (L0 / L1), which is important in some cases of carcinoma. In cases of multiple simultaneous tumors present in one breast, the tumor with the highest T category should be classified and multiplicity, or the number of tumors, should be indicated in parentheses. In cases of bilateral simultaneous breast cancer, each tumor should be classified independently. The preoperative TNM classification is indicated according to clinical examination and imaging methods.
The regional lymph node groups are:

A. Ipsilateral axillary lymph nodes, interpectoral nodes and lymph nodes along the axillary vein and its tributaries which are divided by the margins of m. pectoralis minor into the following levels (Fig. 25):

**Fig. 25** Regional lymph nodes of the breast

I. **Level I.** (low-axilla): lymph nodes located lateral to the lateral border of the pectoralis minor muscle;

II. **Level II.** (mid-axilla): lymph nodes between the medial and lateral border of the pectoralis minor muscle and the interpectoral lymph nodes;

III. **Level III.** (apical axilla): apical lymph nodes and those medial to the medial margin of the pectoralis minor muscle, excluding those designated as subclavicular or infraclavicular.

Note: Intramammary lymph nodes are coded as axillary lymph nodes.

B. Ipsilateral lymph nodes along the arteria mammaria interna;

C. Supra- and infraclavicular lymph nodes.

Any other lymph node metastasis is coded as distant metastasis (M1).
A newly-revised breast cancer staging system classifying clinical and pathological breast cancer stages was published and implemented by the AJCC (American Joint Committee on Cancer) in January 2003. The changes in the revised system reflect new staging procedures concerning lymph nodes (sentinel lymph node biopsy, immunohistochemical examination of the lymph nodes etc.) and some new sites of lymph nodes within the N-stage. The last revision of this staging system was updated in 2010 (7th edition) and the main changes are as follows:

1. Micrometastases in ipsilateral lymph nodes differ from the isolated tumor cell cluster (ITCC) by their size and histological characteristics of malignancy. All metastatic elements in ipsilateral lymph nodes no greater than 0.2 mm (detected by HE or immunohistochemistry) are defined as pN0(i+). Micrometastases greater than 0.2 mm, but no greater than 2.0 mm, are designated with pN1mi.

2. Sentinel lymph node biopsies and their processing via immunohistochemistry or molecular biology methods are designated with special symbols.

3. The number of affected lymph nodes examined by classical hematoxylin-eosin staining (still the preferred method), or by immunohistochemical methods, influence pN status (pN1 for 1 – 3 lymph nodes, pN2 for 4 – 9 nodes, and pN3 for 10 or more affected nodes).

4. Metastases into infraclavicular lymph nodes are classified as N3 stage.

5. Metastases into supraclavicular lymph nodes are designated as N3 (in the past, these belonged to M1).

6. Metastases into lymph nodes along the internal mammary artery influence classification according to the method of metastases detection, and with respect to the simultaneous affection of axillary lymph nodes:
   A. N1: positive lymph nodes along the internal mammary artery detected by sentinel lymph node biopsy
   B. N2: positive lymph nodes detected by clinical (e.g. imaging) methods
   C. N3: for cases of simultaneous metastases in the axillary lymph nodes

7. The new cM0(i+) stage was added to express the presence of disseminated tumor cells in bone marrow, and / or circulating tumor cells in the bloodstream, without clinical evidence of distant metastases.
Clinical TNM classification

T: Primary tumor

TX. Primary tumor cannot be assessed

T0. No evidence of the primary tumor

Tis. Carcinoma in situ: intraductal or intralobular carcinoma in situ, or Paget disease of the nipple without a verified breast tumor (Paget’s carcinoma of the nipple with a verified breast tumor is classified according to tumor size).

T1. Tumors 2 cm or less in greatest dimension

T1mic. Microinvasion 0.1 cm or less in greatest dimension

T1a. More than 0.1 cm but not more than 0.5 cm in greatest dimension

T1b. More than 0.5 cm but not more than 1 cm in greatest dimension

T1c. More than 1 cm but not more than 2 cm in greatest dimension

T2. Tumors more than 2 cm but not more than 5 cm in greatest dimension

T3. Tumors more than 5 cm in greatest dimension

T4. Tumors of any size with direct extension to the chest wall or skin only, as described in T4a to T4d

Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscles, but not pectoral muscles.

T4a. Extension to the chest wall

T4b. Edema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c. Both 4a and 4b, as described above

T4d. Inflammatory carcinoma

Note: The T4b stage comprises only the above-mentioned changes. Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N: Regional Lymph Nodes

NX. Regional lymph nodes cannot be assessed

N0. No regional lymph node metastasis

N1. Metastasis in movable ipsilateral axillary lymph node(s)

N2. Metastasis in fixed ipsilateral axillary lymph node(s) or in clinically apparent* ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis

N2a. Metastasis in axillary lymph node(s) fixed to one another or to other structures
N2b. Metastasis only in clinically apparent internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis

N3. Metastasis in ipsilateral infraclavicular lymph node(s);

N3a. Metastasis in infraclavicular lymph node(s)

N3b. Metastasis in internal mammary and axillary lymph nodes with or without axillary lymph node involvement

N3c. Metastasis in supraclavicular lymph node(s)

M: Distant Metastasis

MX. Distant metastasis cannot be assessed

M0. No distant metastasis

MO (i+): No clinical or radiological evidence of metastases, but molecularly or microscopically detected tumor cells in the bone, marrow and / or in blood or other non-regional lymph nodes ≥ 2mm with absence of any symptoms or clinical signs of metastases

M1. Distant metastasis that is clinically evident via classical and / or imaging examination methods, or histologically verified, and greater than 0.2 mm.

Postoperative TNM classification

pT: primary tumor

The pT categories correspond to the T categories.

Note: When classifying pT, tumor size is a measurement of the invasive component. If there is a large in situ component (e.g. 3 cm) and a small invasive component (e.g. 5 mm), the tumor is coded as pT1a. Microinvasion of 1 mm or less is classified as pT1mic.

pN: regional lymph nodes

Pathological classification requires the resection and examination of lymph nodes with or without a sentinel lymph node biopsy. If classification is based solely on sentinel node biopsy without subsequent axillary lymph node dissection, it should be designated “(sn)” for sentinel node. A thorough examination of lymph nodes also categorizes findings of isolated tumor cell clusters (i) which are not greater than 0.2 mm in size, and are verified by immunohistochemical staining or molecular-biology methods (RT-PCR). A clinically-detected lymph node is defined as one that is detected by clinical examination or imaging studies.

pNX. Regional lymph nodes cannot be assessed

pN0. No regional lymph node metastasis

pN0(i-). No regional lymph node metastases histologically, negative immunohistochemistry

pN0(i+). Malignant cells in regional lymph nodes no greater than 0.2 mm detected by immunohistochemistry
**pN0(mol-)**. No histological metastases, negative RT-PCR

**pN0(mol+)**. No histological metastases, but positive RT-PCR evidence of metastases

**pN1.** Metastasis in 1 – 3 ipsilateral axillary lymph node(s), and / or in ipsilateral internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent

**pN1mi.** Micrometastasis (larger than 0.2 mm and / or more than 200 cells, but not larger than 2 mm in greatest dimension)

**pN1a.** Metastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension

**pN1b.** Internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent

**pN1c.** Metastasis in 1 – 3 axillary lymph nodes and internal mammary lymph nodes

**pN2.** Metastasis in 4 – 9 ipsilateral axillary lymph nodes, or in clinically apparent ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis

**pN2a.** Metastasis in 4 – 9 axillary lymph nodes, including at least one that is larger than 2 mm

**pN2b.** Metastasis in clinically apparent internal mammary lymph node(s), in the absence of axillary lymph node metastasis

**pN3.** Has the following subgroups:

**pN3a.** Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infraclavicular lymph nodes

**pN3b.** Metastasis in clinically apparent internal mammary lymph node(s) in the presence of positive axillary lymph node(s); or metastasis in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent

**pN3c.** Metastasis in ipsilateral supraclavicular lymph node(s)
Stage grouping

Based upon TNM staging, breast cancer can be classified into the following final stages (Tab. 15):

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T0, T1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N1mic, N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0, T1b, T2</td>
<td>N1, N1, N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2, T3</td>
<td>N1, N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0, T1&lt;sup&gt;b&lt;/sup&gt;, T2, T3</td>
<td>N2, N2, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T1, 2, 3, 4</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T1, 2, 3, 4</td>
<td>N1, 2, 3, M1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>b</sup> = T1 including T1mi
<sup>c</sup> = T0 and T1 tumors with micrometastases in lymph nodes are reclassified from IIB stage to IB
M0 also includes M0(i+)

11.1.8 CLINICAL MANIFESTATION AND PATIENT EXAMINATION

The majority of breast tumors are found by patients. Unfortunately, the median size of these tumors is greater than 2 cm. Most of these tumors have already metastasized and, therefore, have a poor prognosis. This means that self-examination detects small (< 2 cm) tumors, which have a better prognosis, in very few cases. The main objective of preventive oncological check-ups is to detect the smallest possible tumors before generalization or, even better, before infiltration (non-invasive stages, in situ carcinomas). This is only successful when the preventive examination is performed together with mammography, which is (so far) the only examination that significantly decreases breast cancer mortality, thanks to its early detection.
**History.** The main points of interest relative to a patient’s personal history can be found in the chapter “Risk factors.” The clinician should particularly ask about breast cancer in first-degree relatives (mother, grandmothers, sisters, daughters); age at first parturition; breast-feeding; and data regarding menarche, menopause, and estrogen intake. Subjectively, patients usually mention undefined symptoms such as the sensation of pins and needles in the breast, breast tenderness, a burning sensation, and others that have no association with a woman’s period. Real pain occurs with breast cancer only rarely and usually in its advanced stages. Even though the symptoms might be very obscure, they should not be underestimated or dismissed as simple mastopathy.

**Inspection.** Breast asymmetry alone is a common finding and does not necessarily point to malignancy; however, neither does it mean it should be ignored, especially in cases of dynamic change. Apparent changes in breast shape or skin color (inflammatory breast carcinoma) must lead the clinician to perform further examinations. Changes in breast shape and size often become significant with lateral elevation of the arms; during this part of the elevation, nipple inversion and skin become marked, representing one of the most suspicious signs. The *mamillae inverteratae* (inverted nipples) which occur from puberty and are bilateral, should also be recognized. The sign of orange-like skin should be further clarified, as well as all eczematous changes of the nipple. The bilateral nipple discharge called galactorrhea is often associated with hyperprolactinemia and is a topic of gynecologic endocrinology. All bloody nipple discharge samples must be examined by imprint cytology and galactography (ductography). Ninety-five percent of findings consist of benign changes (most often intraductal papillomas); bloody nipple discharge is only associated with malignant disease in 5% of cases. One should also look for bloody discharges from an eczematous nipple associated with Paget carcinoma.

**Palpation.** Breast palpation may be done in a standing, sitting, or lying position with the arms pressed against the hips, arms at the sides or arms raised. It is very difficult to provide universal instruction for the correct breast examination technique, since different findings are palpable in different positions. Clinicians should always palpate with the entire flattened surface of the stretched finger pads pressed against the chest wall. The entire breast and all of the breast quadrants are palpated in a circular motion. At the end of the examination, the axilla, cervical, supra- and infraclavicular lymph nodes are palpated. All palpable tumors and nodes should be carefully characterized based on their size, consistency, shape, movability against the surrounding tissue, particularly skin (plateau phenomenon), and chest wall. Nipple
discharge should be examined by pressing the nipple. Every suspicious palpable finding should be further examined; this is most commonly performed by imaging methods.

A significant portion of carcinomas may be identified by clinical examination and history taking. The remaining tumors (clinically occult tumors) cannot be discovered through inspection or palpation and can only be detected by paraclinical examination methods.

**Imaging techniques** for breast lesion diagnosis are described above within interventional methods.

On X-ray mammography, breast tumors typically present as ill-defined masses with radiating lines ("spiculae", Fig. 26), but may also present with a focal distortion of tissue, a cluster of ductal-type microcalcifications, or other suspicious X-ray signs. Evaluation of the mammography images requires great experience on the part of the examiner. On breast ultrasound, a typical image of breast carcinoma is characterized by an ill-defined hypoechoic lesion with ill-defined borders and posterior acoustic shadowing (Fig. 27). As with mammography, an experienced examiner is required for breast ultrasound interpretation. Every suspicious breast lesion should be examined by some form of percutaneous breast biopsy (see above).

![Fig. 26 X-ray mammography of breast carcinoma. Characteristic suspicious ductal microcalcification (on the left) and a stellate lesion with "spiculae" (on the right).](image)
Surgical removal of the primary tumor (tumor extirpation, lumpectomy)

The final option for defining a breast lesion is its surgical extirpation and definitive histological examination. The procedure is easier in cases of palpable tumors. A semicircular incision is made directly above the tumor or, in cases of periareolar localization, along the lower border of the areola, between the areolar and breast skin. If the lesion leads to skin changes (retraction, fixation), the affected skin region should also be excised (a sickle-shaped incision). Dissection is performed carefully in order to excise the entire tumor / affected tissue.

The tissue sample is marked by suture material according to its orientation within the breast, in order to aid the pathologist with tumor orientation. The tumor surface is then stained with ink so the pathologist can identify its margins in paraffin-embedded slides (this is important in cases of malignancy). The procedure continues with hemostasis, drainage, and skin suturing.

If impalpable lesions are present, they must be localized preoperatively. A needle biopsy, either ultrasound-guided or stereotaxic, in case of pure mammographic manifestation (e.g. microcalcifications), is performed. A dye (e.g. methylene blue) or (even better) a hook wire, is inserted into the breast via a needle in such a way that the tip of the wire and its hook lie at the site of the lesion. Afterward, the surgeon makes a semicircular incision just next to the wire and dissects the tissue along the wire up to its end. Extirpation is performed together with a margin of healthy tissue. In cases with microcalcifications, an X-ray image is obtained to verify their presence in the extirpated tissue.
11.1.9 **BREAST CANCER TREATMENT**

Even though breast cancer has garnered more attention from scientists and clinicians than many other diseases, the most appropriate therapy has not been clearly delineated yet. Treatment strategies stem from the results of observational studies of different therapeutic regimes and has rapidly changed in recent years. Surgical treatment was previously regarded as a maximum radical procedure, but limited surgery is now the preferred strategy in an effort to maintain the mental and physical integrity of the patient. This is possible thanks to early disease stage detection and new methods of postoperative adjuvant therapy. New prognostic markers for tumor tissue, and grouping patients according to risk, enable individualized treatment planning. Therefore, it is difficult to provide universal recommendations and guidelines for breast cancer treatment.

11.1.10 **SURGICAL TREATMENT**

**Breast-conserving (saving) surgery**

If the rule in the Halsted era was to operate as much as possible, the rule for surgeons today would be to operate as much as needed. Long-term observations of patients after breast-conserving surgeries showed that, in comparison to mastectomy, breast-saving surgeries do not mean poorer results regarding either recurrences or long-term survival. Nowadays, conservative surgery has become standard treatment in breast cancer patients. It includes following procedures:

- **Lumpectomy** (“local excision”): simple excision of the tumor without respect to the margins;

- **Segmentectomy** (“wide excision” and “limited, partial, segmental resection”): excision of tumor with 1 – 2 cm margins of healthy tissue, “in sano”;

- **Quadrantectomy** – excision of the tumor with breast quadrant and overlaying skin.

Limited breast surgery includes the complete resection of the tumor within healthy tissue, axillary lymph nodes dissection and postoperative irradiation of the breast. Although not the tumor size itself, but rather its relative size in relation to breast size, is important for the surgery type, most candidates for limited surgery are those in stage I of the disease. Larger breasts seem to be appropriate for limited surgery even if larger tumors are present, but they make postoperative irradiation more difficult. Limited surgery may be performed in all cases
where an acceptable cosmetic result is expected, in cases with good irradiation tolerance, and if there is no contraindication to the surgery. Contraindications may be divided into:

Absolute contraindications:
- Multicentric carcinoma or extensive multifocality,
- Diffuse microcalcifications on mammography,
- Poor cosmetic effect,
- Postoperative breast irradiation is contraindicated or denied by patient.

Relative contraindications:
- Extensive intraductal component in tumor surrounding,
- Extensive lymphangiosis carcinomatosa,
- Age < 35 years (especially in cases of BRCA1 and BRCA2 mutations),
- Active disease of connective tissue (lupus, scleroderma, etc.).

Some absolute contraindications have become relative as experience has been gained with limited surgery (e.g. infiltrating lobular carcinoma, EIC, retro-mamillary tumor location and others).

**Surgical procedures in the axilla** can be divided into:
- **Radical axillary dissection** – systematic removal of the lymph nodes up to at least level II, with removal of axillary adipose tissue up to the axillary vein. It represents a standard surgical procedure performed within the field of breast-conserving surgery; at least 10 – 12 lymph nodes should be removed and histologically examined.
- **Subradical axillary dissection** – removal of level I lymph nodes in (sometimes in DCIS)
- **Axillary revision** – removal of the lymph nodes only according to their macroscopic appearance (e.g. in cases of recurrence in the axilla)
- **Sentinel lymph node biopsy** (sentinel lymphadenectomy)

**Lymphatic mapping** with subsequent removal of the axillary sentinel lymph nodes probably represents the most significant progress in breast surgery over the last decade. The **sentinel lymph node** is the first lymph node or group of lymph nodes draining the area of the primary breast tumor. The concept of sentinel lymph node biopsy consists of preoperative marking of the lymph node (using isosulfan blue dye, radiocolloid or nanoparticles), intraoperative detection (visual detection or detection using a special probe) and a thorough histological
examination. In cases with negative results (i.e. absence of metastatic cells), further axillary dissection is not performed. This procedure has become dominant in lymph node staging in patients with cT1 tumors with clinically negative axilla (cN0). In these cases, the risk of axilla metastases is low and axillary dissection would unnecessarily burden the patient. It requires an experienced surgeon with expertise in axillary dissection. Its primary benefits are minimal damage of lymph vessels and a significant reduction in postoperative axillary morbidity. A detailed histological examination of sentinel lymph node micrometastases creates new issues with regard to adjuvant therapy (Fig. 28).

An integral part of conservative surgery is irradiation of the remainder of the breast with an overall dosage of 55 – 60 Gy (see Postoperative irradiation of the breast).

**Modified radical mastectomy**

Modified radical mastectomy is the removal of the breast gland with axillary dissection, and with conservation of the major and the minor pectoralis muscle. The breast gland should be removed together with the fascia of the chest muscles and thoroughly dissected from the subcutaneous tissue in order to reduce the risk of recurrences to a minimum. Previously, this procedure was a standard treatment method of breast cancer, and many patients continue to undergo this procedure today in cases of contraindication to breast saving surgery.

![Fig. 28 Patient after breast-conserving therapy with good cosmetic results. Arrows indicate scars on the skin after quadrantectomy and axillary dissection.](image)

**Radical mastectomy (sec. Rotter-Halsted)**

This procedure involves the removal of the entire breast gland together with the major and minor pectoralis muscles, and axillary dissection and is performed in cases of muscle infiltration; sometimes, partial resection of the muscle is sufficient.
Skin-sparing (nipple-sparing) mastectomy

A new surgical procedure developed during the last decade is the skin-sparing (or nipple-sparing) mastectomy. This technique allows for the removal of the breast with preservation of the skin and/or nipple, enabling better cosmetic results of subsequent breast reconstruction. In some cases, a skin-sparing mastectomy with immediate breast reconstruction (e.g. breast implants) can be provided with one-step surgery. Several studies on skin-sparing mastectomies showed that the incidence of local recurrence is similar to the incidence following simple mastectomies. Proper patient selection is of great importance. Contraindications to these approaches include inflammatory breast cancer and skin involvement associated with the tumor. Preoperative and postoperative radiotherapy are not contraindications to skin-sparing mastectomy.

Fig. 29 Sentinel lymphadenectomy after lymphatic mapping with blue dye.

Surgical treatment of advanced metastatic breast cancer

If the disease is in an advanced stage with apparent distant metastases at the time of diagnosis, the complex health state of the patient and disease prognosis should be evaluated before the indication of treatment. Surgical procedures do not affect the future course of disease at this stage, and have a variably palliative character in the context of tumor reduction. In most cases a simple mastectomy is performed. In cases of organ metastases, surgical treatment should be consulted with competent specialists (chest surgeon, abdominal surgeon, orthopedist, etc.).
11.1.11 Adjuvant (Postoperative) Breast Cancer Therapy

As mentioned above, the median size of breast tumors at the time of their detection is still about 2 – 3 cm, which usually means that the carcinoma has already spread, forming metastases, and becoming a systemic disease. Metastases can be clinically occult and detectable only under microscope. If metastases of the lymph nodes are verified by histological examination, distal metastases should always be taken into account. This means local surgical treatment is not sufficient at this stage, and the patient needs systemic treatment. It is already known that adjuvant treatment can prolong not only the overall survival of the patient, but also the recurrence-free period.

Adjuvant chemotherapy

Adjuvant therapy for breast cancer is designed to treat micrometastatic disease throughout the body of the patient. Unfortunately, it represents an aggressive cytotoxic treatment affecting the whole organism, not only the malignant cells; therefore, patient selection is important and should be done with respect to their overall health condition. On the other hand, based upon the results of meta-analyses, it is known that adjuvant chemotherapy can significantly prolong both overall survival and recurrence-free survival in breast cancer patients; therefore, this treatment should be recommended in certain cases.

The following are determining factors for patient selection: age, overall health state, TNM-stage, premenopause / postmenopause, and risk group. Risk grouping is an assessment of important morphological clinical data that helps to estimate disease prognosis and the need for adjuvant treatment. The principles and regimes of chemotherapy are regularly re-evaluated and updated at “consensus-conferences.” Specific courses of adjuvant therapy for each individual patient should be carefully evaluated by a team of medical specialists.

In most cases, combinations of more than one cytostatic drug are used for adjuvant chemotherapy (polychemotherapy). The most common drugs include 5-fluorouracil, adriamycin, cyclophosphamide, methotrexates, and taxanes. Recently, a new, targeted therapy using specific molecules has been established in the field of breast cancer adjuvant treatment. The molecules are monoclonal antibodies that interfere with the extracellular part of the tumor’s HER2 receptor (see above). The most widely known treatment is called trastuzumab (Herceptin®), and it is used in adjuvant treatment for breast carcinoma with HER2 receptor overexpression. It is often combined with anthracyclines and taxanes. Additional molecules are also used in anti-tumor treatment, such as angiogenesis inhibitors.
and others. Side effects of chemotherapy are reduced by supportive drugs (antiemetics, corticoids and others). In cases with good tolerance to treatment, the entire course of chemotherapy may be carried out in an outpatient clinic.

Adjuvant hormonal treatment
Hormonal therapy is by no means the least significant part of adjuvant therapy for breast cancer. In some cases (e.g. postmenopausal patients with positive hormonal status tumor), hormonal therapy is the primary adjuvant treatment and reduces the burden of chemotherapy. Again, prior to the indication of hormonal therapy, the “overall patient” risk should be estimated. Tamoxifen (an anti-estrogen drug) started a revolution in the field of hormonal treatment. It is able to stop the growth of tumor cells, both in primary tumors and metastases, through blockage of the estrogen receptors. There are wide ranges of selective estrogen receptor modulators (SERMs), which affect metabolism in cancerous cells, not by merely blocking the superficial steroid receptors, but through other complex mechanisms. A different mechanism is used by selective estrogen enzyme modulators (SEEMs). SEEMs inhibit the aromatase transforming androstenedione into estrogen and estrogen-related intermediates, so its blockage has an anti-estrogenic effect. Therapy using high doses of progesterone, particularly medroxyprogesterone acetate, is used in advanced cases of breast carcinoma and bone metastases. The treatment also includes chemical oophorectomy by GnRH-analogues in premenopausal women. It is applied in the form of depot subcutaneous implants and is preferred over surgical or radiation oophorectomy.

Postoperative irradiation of the breast
Radiation therapy is an important part of adjuvant breast cancer therapy. It is a standard part of treatment in cases of breast-conserving treatment and consists of the homogenous irradiation of the remainder of the breast in tangential fields of gamma-rays with an overall dosage of 45 – 50 Gy, and an additional 10 – 20 Gy targeted specifically on the lumpectomy cavity. A standard method is the use of gamma radiation from a radioactive cobalt Co\textsuperscript{60} source. The overall dosage is divided into smaller daily doses of about 1.8 – 2 Gy (which last for approximately 2 minutes) for better toleration, and is administered at an outpatient clinic. The entire treatment lasts for about 5 – 6 weeks. Prior to the irradiation itself, CT simulation is performed. CT simulation is a process to determine the exact location and size of the area to be treated in order to reduce the radiation load of the heart and lungs. Nowadays, routine postoperative irradiation of the chest wall following mastectomy is not performed. It is indicated in special cases (carcinomatous projections on the dorsal part of the mastectomy
sample, pectoralis muscle infiltration and others). Some authors recommend it in all pT3-pT4
tumors without respect to the nodal status, in cases of multicentricity or extensive intraductal
components. Further, irradiation of the axilla and supraclavicular lymph nodes is not routinely
used unless an axillary dissection has not been performed, or in cases of macroscopic
infiltration of the surrounding adipose tissue. The number of retrosternal lymph node
irradiations has been reduced; it can be considered in cases of excentric, medial localization of
primary breast tumors.

Another therapeutic method is **interstitial, postoperative irradiation** of the tumor bed after
breast-conserving therapy with the “after-loading” technique, where a dose of 20 – 25 Gy may
be used without local skin damage. A system of plastic or metal conductors are placed into the
tumor site in two planes while the patient is under general anesthesia. Small particles from the
radioactive source are applied through this system by a special pulsatile technology in exact
time intervals. It enables the use of higher doses and achieves better radiation homogeneity.
This method is used in special radiation centers and in certain cases. In cases where both
irradiation and chemotherapy are indicated, a “sandwich” method can be used; i.e. the patient
receives the first cycles of chemotherapy, followed by irradiation, followed by the final cycles
of chemotherapy. The simultaneous application of both therapeutic methods is possible.

A new radiation approach involving intraoperative irradiation of the tumor bed has recently
been developed in the field of radiation oncology. Targeted intraoperative radiotherapy is
performed with electron beams or X-rays. A mobile linear accelerator is used to deliver
radiation while the patient is in the operation room. **Intraoperative radiation therapy** in
select patients is equivalent to several weeks of whole breast radiation therapy after breast-
saving surgery.

**Adjuvant immunotherapy**
The issue of host immune response to cancer tissue is not fully understood. Complicated
immune mechanisms may eliminate malignant cells and avoid the metastasizing process. On
the other hand, the selection of genetically modified malignant cells of the primary tumor may
lead to loss of immune surveillance, and further to the uncontrolled proliferation and
dissemination of tumor cells. Inflammatory immune cells present in the area of tumor, such as
macrophages and T-lymphocytes, represent cell-mediated immune response to the tumor.
Several studies have shown that the presence of infiltrating T-lymphocytes in cancer tissue is
associated with an improved outcome, and that the immune system participates in the control
and elimination of tumor cells. Many recently published clinical studies have shown that
tumor-infiltrating CD8+ lymphocytes have antitumor activity. One option in active specific immunotherapy is the preparation of analogue vaccines from tumor cells that are modified by viruses. These should activate the immune system and lead to the destruction of the cancer cells. The vaccine should be prepared from the patient’s own tumor and should be administered at certain time intervals. Therapeutic interventions in immune mechanisms bring new possibilities to anti-cancer treatment and are the center of attention in clinical trials.

11.1.12 NEOADJUVANT (PREOPERATIVE, PRIMARY) CHEMOTHERAPY OF BREAST CANCER

Neoadjuvant treatment is a new, modern strategy with the objective of decreasing tumor size using cytostatic (“down-staging”) drugs. It is used in order to enable breast-conserving therapy in cases where tumor size would contraindicate breast-saving surgery. Before neoadjuvant treatment is applied, tumor tissue must be histologically verified by percutaneous biopsy. The same substances used in adjuvant treatment are applied. Tumor size is measured via an imaging examination before every treatment cycle, so the patient undergoes a kind of “in vivo test” of tumor sensitivity to the cytostatics, which is advantage in comparison to adjuvant chemotherapy. Current experience shows that tumor size can be reduced by up to half of its previous size in 80% of cases. After breast-conserving surgery, standard postoperative irradiation is administered, together with the remaining chemotherapy cycles. Some centers also have experience with primary tumor irradiation in conjunction with primary chemotherapy. Another indication for neoadjuvant chemotherapy is inflammatory breast carcinoma.

11.1.13 TREATMENT OF LOCAL BREAST CANCER RECURRENCE

Local recurrences of breast cancer occur in about 10 – 15% of patients after primary surgery. These can be surgically removed in cases of early detection. Most locoregional recurrences after breast-conserving surgery occur within 2 years after surgery. In cases of previous limited surgery, repeated conserving surgery is possible; however, a secondary mastectomy is preferred in most cases. Recurrence in the chest wall area is surgically excised (wide excision) and irradiated by electrons from a linear accelerator. The importance of recurrence onset in prognostic evaluation is not clear. In cases of locoregional recurrence, new staging examinations must be performed and focused on distant metastases. It seems the prognosis is worse if the recurrence occurs soon after primary surgery.
11.1.14 TREATMENT OF ADVANCED BREAST CANCER

At this point, it should be said that patients with distant metastases at the time of breast cancer diagnosis cannot survive, as the metastasizing breast carcinoma is incurable. In some cases, treatment can prolong the patient’s life and increase its quality. The median survival time for these patients is two years. Therapy should be selected on a strictly individual basis, in accordance with the extent and size of the metastases. Surgical treatment is only possible in a few cases and must be consulted with specialists. The tumor should be histologically examined either by simple mastectomy or palliative extirpation of the tumor. Aggressive chemotherapy is only an option for a small group of patients, especially where visceral metastases are present (liver, lungs). After induction of remission, the patient continues with some type of palliative chemotherapy regimens. Some centers have had positive experiences with intra-arterial chemotherapy applied through intra-arterial catheters (e.g. liver metastases). Hormonal therapy with either tamoxifen or aromatase inhibitors is beneficial in postmenopausal women. Bone metastases respond well to irradiation and treatment with bisphosphonates. Supportive surgical intervention might be beneficial in cases of imminent fractures. CNS metastases respond to radiation therapy.

The treatment of advanced breast cancer is an extremely demanding part of oncology, requiring cooperation between experienced chemotherapists and other specialists. The therapeutic advances are so individual, that it is impossible to mention them all in this text.

11.1.15 BREAST CANCER PATIENT FOLLOW-UP

In comparison to some other oncologic diseases, in breast cancer, the idea of the “basically cured” patient after a 5-year-period of recurrence-free survival cannot be accepted. They may relapse even 10 – 20 years after primary treatment. Surveillance and regular patient check-ups (follow-ups) are necessary in breast cancer. The main objective of the follow-up is early recognition and treatment of side effects of primary treatment (postoperative complications such as lymphedema of the arm, chemotherapy effects, radiation etc.); early detection and treatment of recurrences and metastases (tertiary prevention); rehabilitation support; wellness-center treatment; psychological support; and detection of other malignancies. About 80 % of all metastases and recurrences occur during the first three years after primary treatment. Breast carcinoma metastasizes predominantly into bones (ribs, pelvic bone, spine), lungs (and pleura), the liver, and CNS. Regular check-ups should be done every 3 months during the first year (or first 2 years, in high-risk patients) after primary treatment; later, they should be done
every 6 months. Follow-ups should last for at least 5 (10 is preferable) years after primary treatment.

A diagnosis of breast cancer means great trauma in woman’s life. The mental integrity can be further compromised by a mastectomy, which markedly affects self-confidence. Fear of death, concerns about children (in younger patients), fear of family disintegration or sexual dysfunction – all of these fears demand a high degree of moral and empathic qualities in health care personnel responsible for treatment. In ideal cases, the follow-up is carried out by one particular doctor, to facilitate the development of a confidential relationship between the patient and doctor. An appropriate psychological attitude is often more important than any examination process.

11.1.16 PROGNOSIS OF WOMEN WITH BREAST CARCINOMA

Breast cancer prognoses vary among different groups of patients and are related to the pathological-anatomical extent of the tumor at the time of primary therapy. Tumor size and the number of affected lymph nodes remain the most important prognostic factors. Among other prognostic factors, histological grading, the status of hormonal receptors and HER2 receptors are of the greatest value. Time intervals between primary treatment and the onset of recurrence or metastases also influence the prognosis. A shorter interval means a worse prognosis. Almost all patients with carcinoma in situ (pTis pN0 pM0 and about 95 % of patients with breast carcinoma < 1 cm (pT1a-b pN0 pM0)) survive for 10 years after the primary diagnosis. Among patients in stage II of the disease, the 10-year survival rate is about 50 %. The mean overall survival time in patients with metastatic breast cancer does not exceed 2 years. Inflammatory carcinoma has an even poorer prognosis. The proportional reduction in recurrence and mortality as a result of adjuvant treatment is the same for each patient, but the absolute benefits depend on a patient’s risk. Unfortunately, nearly 30 % of women with cancer confined to the breast and 75 % of women with nodal involvement will ultimately relapse.

The above-mentioned facts emphasize the importance of early breast cancer diagnoses. Mammographic screening can enhance the overall survival rate by 20 – 30 %. New prognostic factors that could help in the planning of treatment strategies are still being sought. Current research is also dedicated to chemoprevention for breast cancer in high-risk patients with studies involving selective estrogen receptor modulators, retinoids, and other substances.
11.2 **BREAST SARCOMAS**

Sarcoma is a rare form of breast disease comprising about 0.5 – 1% of breast malignancies. Breast sarcomas include stoma sarcomas, osteosarcomas, leiomyosarcomas, liposarcomas, or angiosarcomas. It is a heterogeneous group of different tumors with different levels of malignancy. They are usually clinically rapidly growing tumors, and this is what usually brings women to the doctor. Some angiosarcomas may occur as a postradiation complication. Treatment consists of a surgical simple mastectomy without lymphadenectomy, since sarcomas are typical of hematogenous (not lymphatic) metastases. The real value of chemotherapy and radiation therapy is not clear and they are only successful in some cases.
12 SURVEILLANCE OF PATIENTS WITH GENETIC RISK OF BREAST CANCER

It is estimated that about 5–10% of breast cancers are due to a familial, genetic predisposition. As has already been mentioned above: 1) genes with high penetrance, and 2) the pathogenic mutations of genes that are normally primarily responsible for i) the regulation of various phases of the cell cycle and ii) DNA damage correction mechanisms, are responsible for the formation of hereditary breast cancer. In the end, they lead to genomic instability and the accumulation of other genetic alterations (e.g. various oncogenes, inactivation of tumor suppressor genes, amplification of cell cycle regulators, apoptosis, drug resistance, etc.). Hereditary breast and ovarian cancer (HBOC) may also be part of associated syndromes associated with multiple tumors (e.g. Li-Fraumeni, Lynch, Fanconi anemia, familial diffuse gastric cancer, Cowden syndrome, etc.).

The best known (and most extensively studied, thus far) molecular genetic substrates for HBOC are the BRCA1 / BRCA2 gene mutations, which are responsible for about 15% of all cases. These are relatively "large" tumor suppressor genes with autosomal dominant inheritance. Women with HBOC have a high lifetime risk of breast and ovarian cancer (BRCA1 mutation carriers, about 85% and 60%, respectively; BRCA2 mutation carriers, 85% and 35%, respectively). Men with hereditary (germ-line) BRCA1 mutations are associated with a more frequent incidence of prostate cancer; BRCA2 mutations are associated with the risk of male breast cancer (lifetime risk of about 40%). In both sexes, HBOC is also more closely linked to a variety of other tumors, such as melanoma and carcinoma of the larynx, esophagus, stomach, intestine, etc. Unfortunately, a clinically relevant predictor of cancer risk in particular carriers of germ-line mutations is not available. Even within high-risk families with specific mutations of BRCA1 / BRCA2 genes, some individuals never develop the disease throughout their entire lives. Descendants of persons with HBOC have a 50% chance of inheriting the defective gene. If both parents are carriers, it is theoretically possible to transfer both pathogenic mutations. The prevalence of BRCA1 and BRCA2 mutations in the general population is approximately 1: 500 – 1000 and 1 – 2: 1000, respectively. BRCA1 / 2 are relatively large genes and consist of 24 and 27 exons, respectively. In both genes, about 800 mutations have been previously identified, including five large specific gene reshufflings in the BRCA1 gene. Not all represent pathogenic
alterations, approximately half of them are estimated to be a form of polymorphism without risk of cancer, and (as of yet) unclear clinical significance.

It is recommended that genetic counseling of patients with multiple occurrences of cancer in the family, or the occurrence of cancer in young (premenopausal) age, be provided by a specialist (gynecologist, surgeon, gastroenterologist, etc.). Suspicion of HBOC occurs primarily in women with occurrences of: breast cancer and / or ovarian cancer in several family members; cancer in women younger than 30 years; or bilateral breast cancer prior to 50 years of age. The doctor (a genetic counseling specialist) assesses the personal and family medical history and, if the patient meets the criteria, recommends molecular DNA testing. A molecular genetic analysis in the laboratory will follow. After completion of the DNA analysis, the patient is invited to the specialist for another consultation, during which the doctor interprets the results of the molecular analysis. The genetic examination looks for the presence of changes (mutations) in genes BRCA1 (24 exons) and BRCA2 (27 exons), and in certain regions of the CHEK2 gene (exon 9 and 10). Mutations in BRCA1 / 2 genes impact the function of proteins that are important in cell processes, such as the repair of damaged DNA, etc. Genetic testing primarily begins with an analysis of the BRCA1 gene. In cases with negative BRCA1 analysis outcomes, an analysis of the BRCA2 gene, followed by an analysis of the long gene deletions (in the genes mentioned above) will be performed. When a germline mutation is found in a patient with cancer, other relatives can also be evaluated for the mutation to determine who has inherited this mutation (predisposition to disease). Accordingly, it is then possible to calculate the risk of cancerous diseases within a family.

Currently, it is not possible (mainly due to financial reasons) to investigate the presence of BRCA1 / 2 mutations in the whole population. When testing for the presence of BRCA1 / 2 mutations, we include individuals with a significantly increased risk of mutations compared to the general population (Tab. 16).
Tab. 16 Criteria for selecting patients for genetic testing (Slovak Republic)

**Individuals with verified breast / ovarian cancer are referred** for testing if at least one of the following criteria is fulfilled:

- There are three or more relatives with breast / ovarian cancer on one side of the family (bilateral carcinoma is considered, and counted, as two tumors)
- Two first-degree relatives (second-degree relatives through the father, as well) with breast / ovarian cancer, if at least one tumor was diagnosed before 50 years of age
- One relative with breast / ovarian cancer, and another first-degree relative with an HBOC-associated tumor (colorectal, pancreatic, prostate, uterine cancer, malignant melanoma), and at least one of them was diagnosed before 50 years of age

**Individuals with verified breast / ovarian cancer without a family history are referred if at least one of the following criteria is fulfilled:**

- Bilateral breast / ovarian carcinoma or their combination, primary diagnosis of the disease before 50 years of age
- Breast / ovarian carcinoma, primary diagnosis before 40 years of age
- Medullary or atypical medullary breast carcinoma, or
- Triple negative breast carcinoma, primary diagnosis before 50 years of age
- Breast carcinoma in a male

It is also possible to examine **asymptomatic individuals** when it is not possible to investigate a family member (due to their death, unavailability, refusal to undergo examination, etc.) and the patient comes from a family in which:

- A first-degree relative had bilateral breast / ovarian cancer
- 2 first-degree relatives (second-degree relatives through the father, as well) have / had ovarian cancer
- The patient’s father or brother, plus another first- or second-degree relative, had breast cancer

Patients with indications of HBCO are monitored through the breast care department and receive preventive examinations at different time intervals than normally recommended for the general population of women (Tab. 17). Patients requiring special care do not need to fear a poor outcome. After completion of family planning, patients learn about prophylactic surgery possibilities (bilateral mastectomy and salpingo-oophorectomy) and decide for themselves if any of these options are acceptable. Additional appropriate prophylactic measures are changes in lifestyle and / or chemoprevention with selective estrogen receptor
modulators (tamoxifen, raloxifene, etc.). Male carriers of BRCA1 / BRCA2 gene mutations also have their own observation schedule (Tab. 18).

**Tab. 17 Preventive care program for women with evidence of HBOC (Slovak Republic)**

- Monthly breast self-examination
- Physical breast examination every 6 months from 25 years of age
- Annual X-ray mammography from 30 years of age
- Annual magnetic resonance breast imaging from 25 years of age
- Annual breast ultrasound from 25 years of age
- Annual abdominal ultrasound examination from 21 years of age
- Gynecologic examination (including transvaginal ultrasound) every 6 months from 21 years of age
- Annual CA-125 serum tumor marker testing from 21 years of age
- Colonoscopy (coloscopy) every three years from 45 years of age
- Annual fecal occult blood testing from 40 years of age
- Annual ophthalmology and dermatology exams from 30 years of age (especially in BRCA 2 mutation carriers)

**Tab. 18 Preventive care program for male carriers of BRCA1 / 2 gene mutations**

- Monthly breast self-examination
- Monthly testicle self-examination
- Annual breast ultrasound from 30 years of age
- Annual urological examination (including serum PSA) from 45 years of age
- Annual fecal occult blood testing from 40 years of age
- Colonoscopy (coloscopy) every 3 years from 45 years of age
- Annual abdominal ultrasound examination from 30 years of age
- Annual ophthalmology and dermatology exams from 30 years of age (especially in BRCA 2 mutation carriers)
13 THE MALE BREAST

Many of the patients seeking medical advice in breast care departments are men. The most common problems in male patients are breast enlargement (either symmetrical or asymmetrical) or palpable "lumps" in the breast. Patients are often referred from other specialists (general practitioner, pediatrician, surgeon, endocrinologist, etc.). Ignorance of these problems often causes patients to be sent for many unnecessary tests until they are finally referred to a breast disease specialist.

Gynecomastia (benign swelling of the male breast) may appear at any age. In newborns, this happens due to the physiological transplacental transport of estrogens from the mother to the child's circulation, and usually subsides within a short time. During pre-adolescence and adolescence, it may also occur transiently (often asymetrically) due to the onset of hormonal changes during this age period. It is probably associated with an increased conversion of androgens-to-estrogens in peripheral tissues, via the enzyme aromatase. Constitutional gynecomastia is frequent in obese boys and some syndromes (e.g. Klinefelter syndrome), but does not exclude the alimentary origin of gynecomastia in otherwise appropriately developed children (e.g. artificial presence of estrogens in chicken meat, etc.). During a physical examination, evident resistance in the breast is usually not detected; only the diffuse enlargement of mammary gland tissue (Fig. 30). Palpation of the locoregional lymph nodes should always be a routine part of the physical examination. During an ultrasound examination, hypoechoic areas with no apparent focal changes in the retromamillary region can be found. It is recommended to measure the breast tissue mass in two perpendicular planes. Documenting the findings thoroughly will help immensely in cases involving repeated examinations. Pubertal gynecomastia subsides spontaneously in most cases, often after 2 – 3 years. When examining adolescent boys and young men with gynecomastia, one should always specifically inquire about the use of anabolics and other bodybuilding-related supplements.

In most cases, physical and ultrasound examinations are sufficient for the differential diagnosis of gynecomastia. In select cases, the following additional evaluations may help: testicular examination including an ultrasound and hormone profile (T3, T4, SHBG, E2, FSH, LH, testosterone, prolactin) and eventual genetic testing. Gynecomastia in adults and older men is usually caused by age-constitutive physical changes and / or hormonal changes in the
presenium and senium, such as hypogonadism, hormonally active tumors, liver disorders and the use of certain drugs. When we detect a resistance (lump) during the physical examination of men in this category, we have to consider the possibility of primary or secondary breast cancer. Clinical and ultrasound examinations should, therefore, be associated with X-ray mammography (Fig. 31).

Surgical treatment of gynecomastia depends on the stage of gynecomastia and consists of the simple removal of glandular tissue with eventual liposuction, or subcutaneous mastectomy with eventual repositioning of the areolar-mamillary complex. During conservative treatment of gynecomastia, we administer tamoxifen or testolactone (a peripheral aromatase inhibitor).

**Malignant tumors** in males represent about 1% of all breast cancers. The relative incidence of male breast cancer increases with age, but occasionally malignancy also occurs in young men (Fig. 32). In the USA, incidence of male breast cancer is higher in African-Americans than in Caucasians; overall incidence is approximately 1,400 new cases per year. In Europe, the prevalence of male breast cancer is 1 in 100,000 men. Given that the majority of male breast cancers are estrogen receptor-positive, hormonal context is considered, although the exact etiology is still unclear. One of the proven risk factors is Klinefelter syndrome. As a result of testicular insufficiency, these individuals have low levels of androstenedione, resulting in an increased ratio of estrogens to androgens. It is reported that about 4% of men with breast cancer have Klinefelter syndrome. The risk of developing breast cancer in these patients is 20 to 50 times higher than the risk in men with a normal karyotype. Another important risk factor is a positive family history, especially in families with mutations in the BRCA2 gene (see above). Chronic liver disease is also a risk factor in view of the relative hyperestrogenism resulting from disturbances in hormone metabolism. A positive correlation was also observed in men with prostate cancer and colon cancer.

The clinical and surgical management of men with breast cancer is similar to that for women. In most cases, the triple-test (physical examination, breast imaging and percutaneous breast biopsy) confirms the diagnosis. X-ray mammography is primarily only performed in mediolateral views based on the relative volume of the organ. The standard procedure is a modified radical mastectomy (Fig. 32); lymphatic mapping and sentinel lymph node biopsy techniques are also established in the field of male breast surgery. Lymph node status is the most important prognostic factor in men. Adjuvant therapy is administered according to principles similar to those in cases of female breast cancer. Prognosis depends on the disease
stage at the time of primary diagnosis: 5-year survival in stage I ranges from 75 to 100%; in stage II, it ranges from 50 to 80%; and in stage III, it ranges from 30 to 60%.

**Fig. 30** Pubertal gynecomastia in a 15-year-old boy

**Tab. 19 Possible etiological causes of gynecomastia**

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<tr>
<td>- hypothalamic-pituitary</td>
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<td>- primary testicular failure: congenital anorchism or cryptorchidism, trauma, castration, orchitis, Klinefelter syndrome (47 XXY)</td>
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<td>- testosterone, anabolic steroids, HCG, aldosterone antagonists, digoxin, ketoconazole, reserpine, histamine receptor antagonists (cimetidine, ranitidine), chemotherapeutic agents, some psychotropic drugs, some antibiotics etc.</td>
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Fig. 32 X-ray mammography of an asymmetrical breast tissue area with a suspicious stellate lesion with microcalcifications in the right breast of a 26-year-old man (above). Biopsy-proven infiltrating ductal carcinoma resulted in a modified radical mastectomy with axilla dissection (below).
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