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Research article – Basic and applied anatomy

Radiological anatomy of the breast

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Abstract

Breast cancer is the most frequent cancer site in women (28.8% of all cancer sites), the second most common in the world with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers) and an estimated lifetime risk of 1/9 women. It is the fifth cause of tumor death overall (7.5%) and the first in women. Diagnostic senology has the purpose of the early diagnosis of breast cancer.
The aim of this paper is to evaluate the role of all imaging techniques in studying the normal morphological anatomy of the breast. Knowing the normal anatomy of the breast is essential to integrate all available imaging techniques in order to distinguish normal from pathological structures.

Key words

Breast, normal anatomy of the breast, mammography, breast ultrasound, development of the breast, breast mri

Introduction

Diagnostic senology has the aim of the early diagnosis of breast cancer. Nowadays, breast cancer is the tumor with the highest incidence among women in western countries. As primary prevention is not possible, secondary prevention is made through mammographic screening programs to detect breast cancer at an early stage.

Diagnostic senology uses clinical examination, mammography, ultrasound and magnetic resonance imaging.

The purpose of this paper is to analyze the role played by all radiological methods in the study of the morphology of the normal breast gland.

Development of the mammary glands

Along the midclavicular-pubic lines (milk lines), during the fourth week of embryological development, two ectodermal thickening start to grow (mammary ridges). During the fifth week the mammary ridges develop into the primary buds that grow into the underlying dermis. Later, around the twelfth week of development, several secondary buds grow from the primary buds branching subsequently

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into ducts (15-24 in number) that converge towards the mammary dimple (Larsen, 2002).

From the mammary dimple both the nipple and the areola develop. The areola contains the Montgomery glands, which are considered to be rudimentary milk ducts.

Along the course of the mammary ridges one or more supernumerary nipples (polythelia) or supernumerary breasts (polymastia) may form.

At birth the gland is just a rudimentary ductal system and before puberty it simply grows with the overall body development.

During puberty the female breast gland undergoes an expansive proliferation thanks to the influence of hormones and growth factors. The pubertal breast consists an an extensive mammary tree that includes primary ducts and secondary branches that occupy the mammary fat pad. The secondary lateral ductal branches lead to terminal ducts that give rise to terminal ductal-lobular units comprising numerous blind-ended ductules, called acini that are embedded in fibroblast-rich, intralobular stroma (Williams and Daniel, 1983). On the other hand, at the onset of puberty in males, testosterone acts on the mesenchymal cells to inhibit further growth of the mammary gland upon limited development.

In females, during pregnancy, the mammary gland undergoes many changes to prepare for lactation. These changes require both gland maturation and alveologenesis and are primarily under the control of progesterone and prolactin.

Firstly, the gland shows a dramatic increase in secondary and tertiary ductal branching; secondly, it goes through the development of the alveoli, which become milk-secreting during lactation. Moreover, increased vascularization occurs and by mid-pregnancy each alveolus is surrounded by a network of capillaries.

By late pregnancy, and mainly during lactation, the alveoli occupy the majority of the fat pad and show secretory activity. All these changes are secondary to the effects of both progesterone, that is responsible for the extensive side branching and alveologenesis required to create a lactation-competent gland, and prolactin that promotes the differentiation of specialized structures, alveoli, which synthesize and secrete milk during lactation (Macias and Hinck, 2013). Alveoli are inactive and appear as acini until lactation begins.

The rapid fall in progesterone after delivery allows cortisol binding to occur and lactogenesis to proceed. Suckling stimulates sensory receptors in the nipple that activate nerve impulses; these impulses are transmitted to the hypothalamus. This permits the synthesis and release of prolactin. In the absence of prolactin, lactation does not occur.

The other specific hormone required for lactogenesis is oxytocin. Oxytocin is produced in hypothalamus and stored in the posterior lobe of the pituitary gland. It causes the myoepithelial cells to contract, which results in release of milk into the lactiferous ducts and sinuses so that it can be removed by suckling (Shiu, 1980).

After weaning the milk stagnates in the mammary ductal system initiating the process of involution that leads to apoptosis and removal of milk-producing epithelial cells and remodels the epithelial tree back to a simple ductal architecture. In menopause the breast gland architecture undergoes a dramatic change that involves the replacement of glandular epithelium and interlobular connective tissues with fat.

In the aged female breast, all that remains are a few acini and ducts embedded in thin strands of collagen.

Normal anatomy of the female breast.

The breast is a symmetrical organ located on the front of the chest on both sides of the midline.

It occupies an area that stretches from the third rib to the seventh rib and from the edge of the sternum to the armpit (Balboni et al., 2000).

The volume, shape and degree of development are very variable in relation to various factors such as age, gland development, amount of fat and relative influence of endocrine stimulation.

Before puberty, the mammary region is flat, but upon full development it assumes in females a hemispherical profile. Normal breast glands may be conical-shaped, pear-shaped or discoid (Testut and Latarjet, 1972).

At the center of the breast there are the nipple and areola. The areola is a flat hyperpigmented area of skin with a round or oval shape and of variable diameter, usually, between 3.5 and 6 cm. The nipple stays at center of the areola and has a variable size and shape (conical, cylindrical). At its apex there are several small depressions that represent the outlets of the ducts. The areolar surface is irregular due to the presence of the 8-12 tubercles of Morgagni, representing sebaceous glands.

The mammary gland is made of three components: glandular, adipose and fibrous tissues.

Functionally, it can be considered a modified apocrine sweat gland, in relation to breast-feeding.

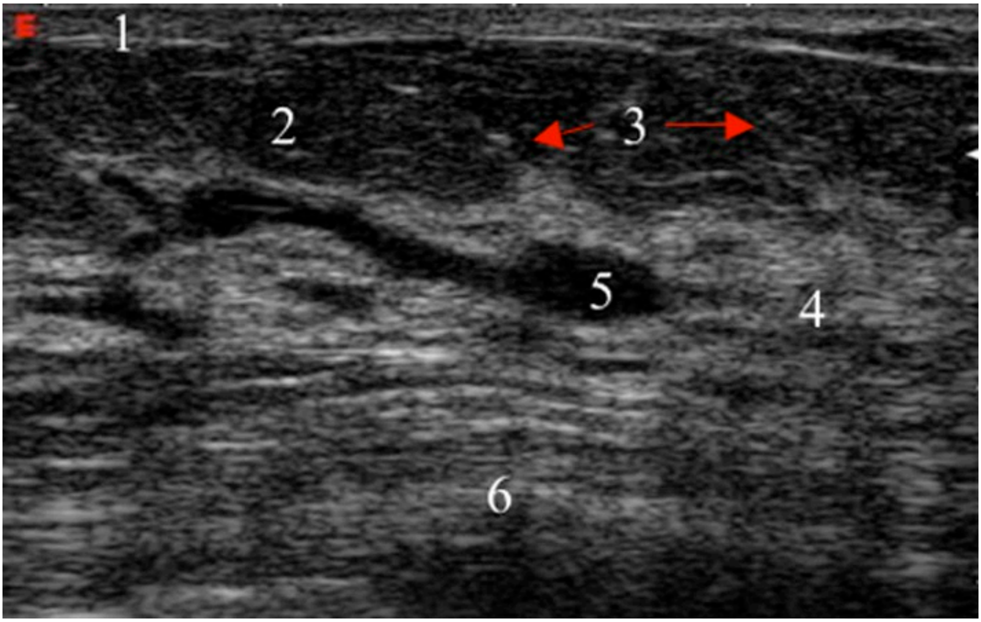

Figure 1 – Normal sonographic components of the breast gland. 1: skin; 2: subcutaneous fat tissue; 3: crests of Duret; 4: glandular parenchyma; 5: milk duct; 6: retroglandular fat tissue.

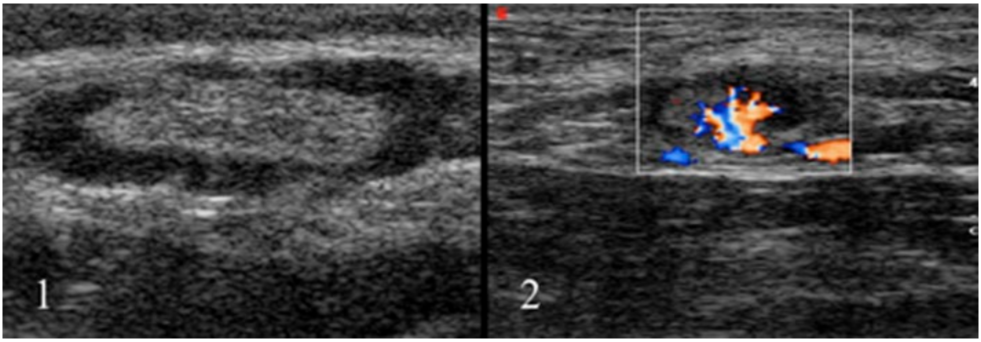

Figure 2 – Normal sonographic appearance of a lymph node; 2: normal hilar vascularization of a lymph node.

The glandular structure is composed by 15-20 lobes arranged in clusters with an irregular radial pattern around and behind the nipple (Testut and Latarjet, 1972). Each lobe is an independent glandular entity made of numerous lobules, constituted by alveoli, which are the secreting units.

The alveolar ducts converge into the lobular ducts which in turn converge into the milk ducts. The milk ducts, then, converge to the nipple with an ampullary dilatation, the lactiferous sinus.

The stroma is composed of dense fibrous and adipose tissues that surround the entire gland and penetrate between the lobes. It may be divided in three portions: a subcutaneous part, that lies between the skin and the gland, an intraparenchymal portion, located between lobes and lobules, and a retromammary portion, located behind the gland.

The breast parenchyma is contained by a two-layer fold of the subcutaneous superficial fascia, that may be divided in two parts: the superficial layer that covers the gland and contains fibrous septa, called Cooper's ligaments, which penetrate the gland and form the support structure of the parenchyma, and the deep layer, which covers the posterior portion of the gland and separates it from the underlying superficial fascia of the pectoralis major muscle. Cooper's ligaments are the suspensory ligaments of the breast gland and divide the parenchyma into lobes (Stavros, 2004).

Normal anatomy of the male breast

The male breast is located along the mid-clavicular line, at the level of the fourth intercostal space. It is anatomically comparable to the female breast but its glandular component generally does not develop, so the organ is rudimentary, and the adipose tissue is scarce.

Normal anatomy of the lymph node

Lymph nodes are organs that drain the lymph, located along the course of lymphatic vessels. They are made of a capsule, a reticular stroma, lymphoid tissue with

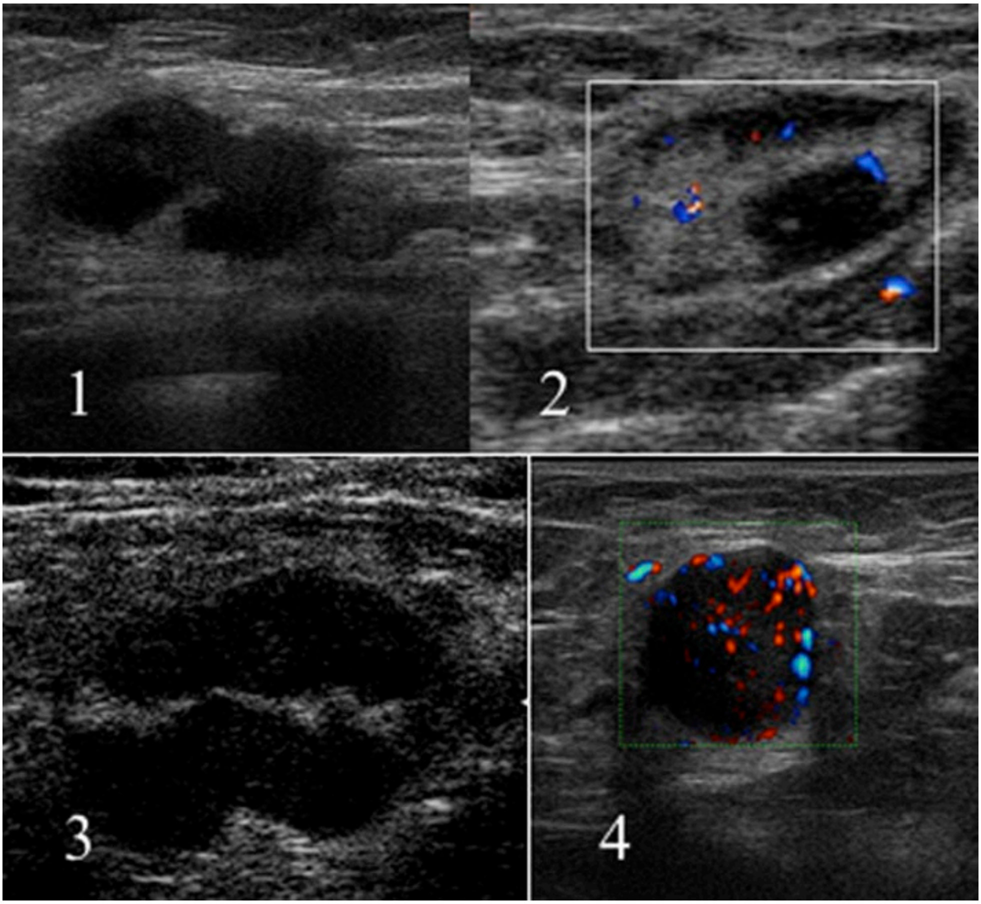

Figure 3 – Metastatic lymphoadenopathies. 1: eccentric compression or displacement of the hilum; 2: focal compression of the hilum; 3: concentric compression hilum; 4: obliteration of the medulla.

lymphocytes, blood vessels, lymph vessels and nerves.

The capsule consists of dense connective tissue that cover the entire lymph node and forms the hilum.

At the hilum the blood vessels penetrate the node and only an efferent lymph vessel leaves the organ. Afferent lymph vessels reach the organ from its surface outside the hilum.

The reticular stroma occupies the space delimited by the capsule and trabeculae and consists of reticular fibers. It contains lymphocytes and the other cells that form the lymphoid tissue.

Within the lymph node there are three regions: the cortical zone, the paracortex and the medulla.

The cortical area is occupied by aggregates of lymphocytes that constitute the primary and secondary follicles. Primary follicles contain small lymphocytes while secondary follicles show a central area called the germinal center and a peripheral portion called the mantle zone (Bassett and Kimme-Smith, 1989).

The paracortex is located deep in the cortical area, between the follicles and the medullary area. The medulla is organized into cell cords separated by large lymphatic sinuses.

The lymph nodes that are important for the breast region are the axillary, internal mammary and supraclavicular lymph nodes.

From a surgical point of view the axillary lymph nodes can be divided into three levels in relation to the pectoralis minor muscle: the first level contains the lymph nodes located outside the lower margin of the pectoralis minor muscle. At the second level there are lymph nodes located under the pectoralis minor muscle. And, finally, the third level lymph nodes lie superiorly and medially to the upper margin of the pectoralis minor muscle.

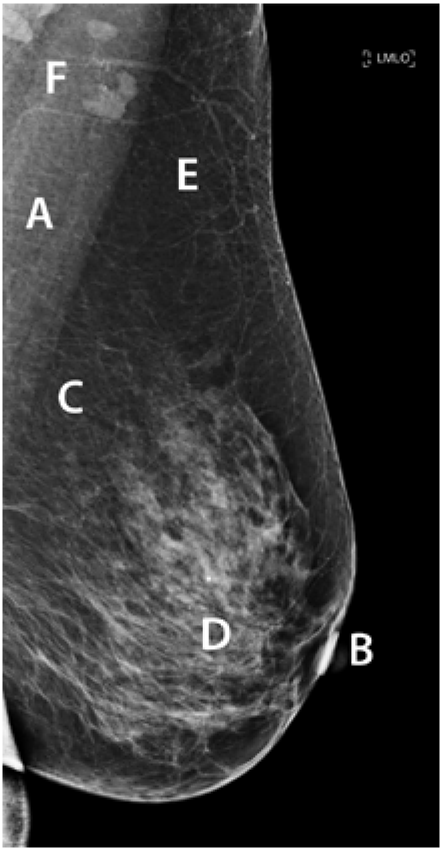

Figure 4 – Mammographic medio-lateral-oblique (MLO) projection of a normal breast. A: pectoralis muscles; B: nipple; C: fat tissue; D: glandular tissue; E: blood vessels; F: lymph nodes.

Diagnostic techniques

Mammography is the main diagnostic technique for the radiological study of the breast. It shows, however, some limitations, such as a low sensitivity in case of dense breast, in which the presence of a rich mammary gland tissue with high radiopacity, prevents a proper study and makes the recognition of radiological signs of malignancy difficult.

Ductal galactography is a special mammogram indicated in cases of nipple discharge. It allows the study of the ducts showing eventual filling defects after injecting iodinated contrast material.

Tomosynthesis is a relatively new technique that allows the study of the breast in pseudo-threedimensional way. Its advantage is to overcome the so-called anatomical noise due to the superimposition of the breast tissues.

Ultrasonography is the other standard examination of the breast, it allows the differentiation of solid and liquid-filled nodules and is less influenced than mammography from breast density. It is useful especially in the study of the breast in young patients and in pregnant or lactating women.

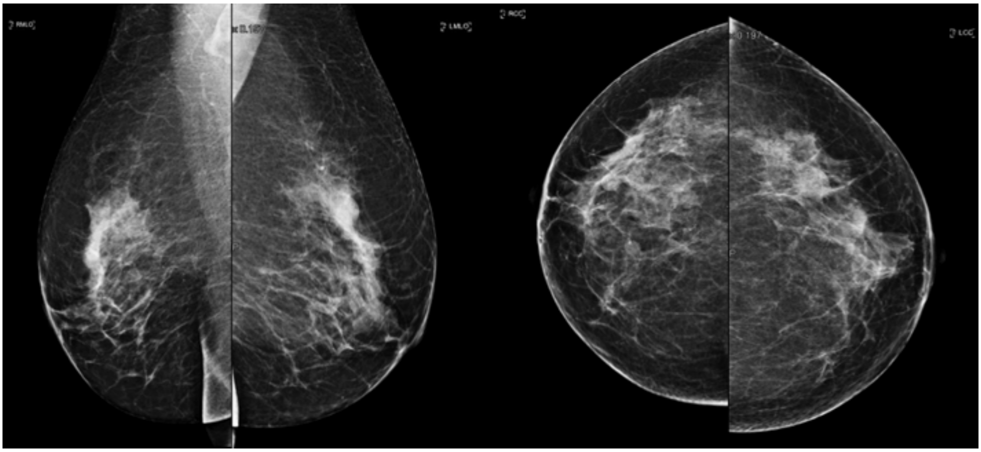

Figure 5 – Standard mammographic medio-lateral-oblique (MLO) and cranio-caudal (CC) projections.

Magnetic resonance imaging (MRI) of the breast provides a multiplanar representation of the breast. It allows a full anatomical study of the gland and, using a contrast media, also a functional analysis. Breast MRI is performed using intravenous paramagnetic contrast agents that show vascularized tissues such as tumors, which are characterized by neoangiogenetic phenomena.

In addition, MRI without contrast is useful for the study of breast implants. On the other hand, breast MRI can not be proposed as a screening technique but it is, usually, a third-level examination performed at the end of a diagnostic process.

Normal ultrasound anatomy of the breast

All anatomic structures of the breast can be detected by ultrasound.

Starting from the cutaneous surface going deep, four different regions may be identified:

1) the region of the skin, nipple and areola;
2) the subcutaneous (pre-mammary) region;
3) the glandular region;
4) the retro-mammary region.

The skin can be seen as two hyperechoic lines separated by a hypoechoic line representing the dermis and has a variable thickness between 0.5 and 2 mm. The areola and nipple generally determine an attenuation of the acoustic signal and are hypoechoic.

The nipple produces a strong attenuation of the acoustic signal that partially mask the underlying structures. Under the nipple, the lactiferous ducts branch, they are anechoic or moderately echogenic tubular structures, depending on the content. They have a diameter of 2-3 mm, which gradually decreases going towards the periphery.

The subcutaneous region or pre-mammary region is located between the skin and the mammary fascia and it contains mostly adipose tissue, which is less echogenic than the glandular tissue. The thickness of this fatty region can vary up to 2-3 cm. The subcutaneous fat tissue is crossed by thin hyperechoic lines, Cooper's ligaments which extend from the skin to the glandular region.

The glandular region, located between the pre-mammary region and the retro-mammary region, has a triangular shape with the apex towards the areolar region and the base towards the pectoral muscle and is enfolded by the mammary fascia that appears as a thin echogenic line. The echogenicity of this region varies in relation to the percentages of glandular and adipose tissues. Fat tissue is hypoechoic, while the glandular tissue and stroma are echogenic. The most superficial part of this region shows some hyperechoic "pyramids" from which the Cooper ligaments, or ridges of Duret, branch.

Sonographically, breasts having larger quantity of fibroglandular component are more echogenic, while predominantly adipose breasts are diffusely hypoechoic (Blend et al., 1995; Gordenne, 1995; Balboni et al., 2000]. The breast gland shows constant changes in echogenicity due to factors such as age, menstrual cycle, pregnancy and lactation.

The region of Chassaignac is located behind the gland, it is made from the retro-mammary fat that is hypoechoic. The pectoralis major muscle is slightly more echogenic than the retromammary fat.

More deeply, the ribs show attenuation of the acoustic signal and appear as hypoechoic structures, and the parietal pleura can be displayed as a hyperechoic line.

The intramammary vascular network is made of arterial vessels proceeding from the deep portion of the gland to the ligaments of Cooper. The venous network follows the arterial network. Doppler techniques can be used in order to show the vessels.

Normal ultrasound anatomy of the lymph node

Ultrasonography can be used to study axillary lymph nodes, the internal mammary chain, located along the parasternal line from the second to the fifth intercostal space (Gordon and Gilks, 1988), and the supra e infraclavicular lymph nodes.

Lymph nodes are oval with a normal echogenic hilum and a hypoechoic cortex. Normal lymph nodes are oval or elongated, with a clear differentiation between the cortex, that is hypoechoic, and the hyperechoic medullary zone. In elderly patients the cortex reduces its thickness, while there is an increase of fat tissue within the lymph node. In case of cortical atrophy and fatty replacement the lymph node may appear completely isoechoic and be difficult to recognise.

Neoplastic and metastatic lymph nodes are usually globular in shape, round, they do not show the normal cortico-medullary differentiation and may be completely hypoechoic.

The parameters to consider when studying lymph nodes are: size, morphology and echogenicity.

Size does not seem to be a reliable criterion for the differentiation between a benign or a malignant behaviour. It is useful to calculate the ratio between the longitudinal and transverse diameter of the lymph node, defined as "roundness index". When this ratio exceeds the value of 1 the lymph node can usually be considered benign. However, beside morphology, it is important to analyze the profile of the cortex and medullary zone, as well as the vascularization. A hyperplastic lymph node is characterized by vascular signals distributed harmoniously from the hilum to the periphery. Inflammatory lymph nodes grow proportionately and maintain the original shape, while neoplastic lymph nodes increase disproportionately the short axis and appear spherical.

Regarding echogenicity, the cortex of the abnormal lymph node tends to become markedly hypoechoic and even anechoic. In this case it is useful to use color Doppler to distinguish it from a cyst. This modification is typical for neoplastic infiltration, but may also occur in cases of severe inflammation. The reduction of echogenicity is a reflection of the high number of cells inside the lymph node. Other suspicious features of malignant lymph nodes are compression or eccentric displacement of the hilum, focal hilum compression, concentric compression of the hilum and complete absence of the hilum (Stavros, 2004; Tschammler et al., 1998; Vasallo et al., 1992).

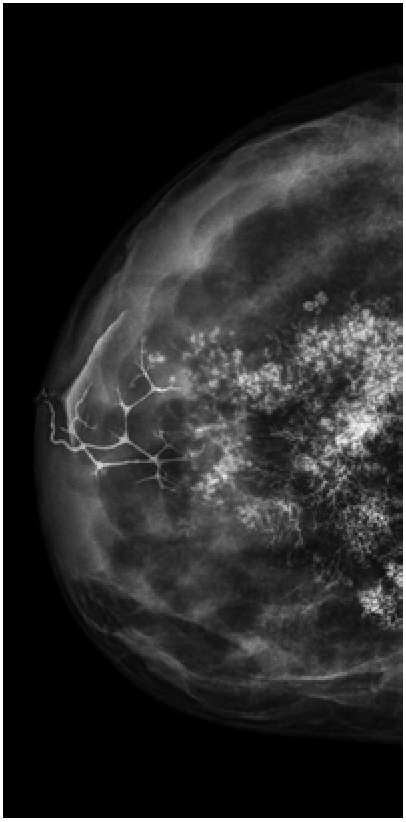

Figure 6 – Galactography, entire ductal tree.

Normal mammographic anatomy

The mammographic appearance of the normal breast depends on the amount of the main components: the fat tissue appears radiolucent, the stroma and the gland appear radiopaque.

The sensitivity of mammography strongly depends on the density of the breast.

A mammogram is usually performed in two projections, the MLO (medio-lateral - oblique) and CC (cranio-caudal) after compression.

The skin appears as a thin, continuous, radiopaque rim of homogeneous density, of about 1 mm well distinguishable from the radiolucency of the underlying subcutaneous fat tissue.

The areola usually has a thickness of 3-5 mm with a central opacity of cylindrical shape corresponding to the nipple.

Posteriorly there is the retroareolar region, that is a triangular-shaped area which is of particular interest because it may hide focal anomalies such as breast tumors (Lattanzio and Simonetti, 2005).

In normal conditions the milk ducts are not detectable. In case of ducts dilatation they might be visible as linear opacity of various thickness. Galactography is an

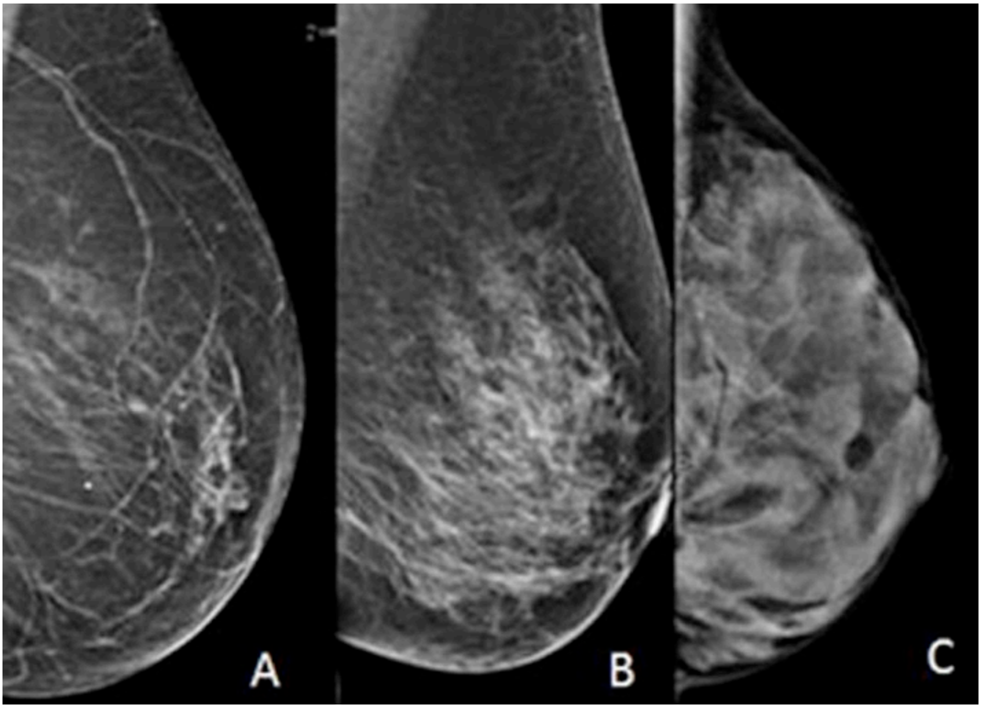

Figure 7 – A; fibroadipose pattern; B: fibroglandular pattern; C: dense pattern.

invasive examination that uses the injection of contrast media into the ductal tree and may be performed if a papillary lesion is suspected (Fig. 6) (Lamont et al., 2000).

The subcutaneous fat appears as a thick radiolucent layer, crossed by fibrous linear structures that correspond to the crests of Duret and Cooper's ligaments.

The breast gland has a triangular shape with the apex towards the nipple. The shape and density vary from individual to individual and are also influenced by hormonal stimuli. The breasts are classified according to their density and the amount of fibroglandular tissue (Fig. 7-8).

Behind the breast gland the fat tissue outlines the retromammary space, which separates the breast from the pre-pectoral fascia overlying the pectoralis major muscle.

The pectoral muscle is homogeneously radiopaque. It is important to check the presence of the pectoralis major muscle in both projections as a quality control of the mammogram (Kopans, 2007; Sechopoulos, 2013).

The blood vessels are more easily visible in breasts that contain abundant fat and appear as thin, tortuous, linear opacities, sometimes showing parietal calcifications especially in elderly or diabetic patients.

An innovative imaging technology derived from digital mammography is tomosynthesis which allows a pseudo- three-dimensional reconstruction of the breast.
This technique is based on the movement of the X-ray tube in a given arc between

15° and 45°. From a series of two-dimensional projections at low dose, volumetric images are obtained, which subsequently can be displayed as a series of pictures or in a video sequence.

The advantage of tomosynthesis is to overcome the limits of mammography represented by the high density of the mammary gland, due to the overlap of anatomical structures (the so-called "anatomical noise"). It has been shown by many large studies that tomosynthesis can reduce the number of false negatives and the re-call rate of women with breasts difficult to analyse on mammogram (Fig. 9) (Hendrick, 2010).

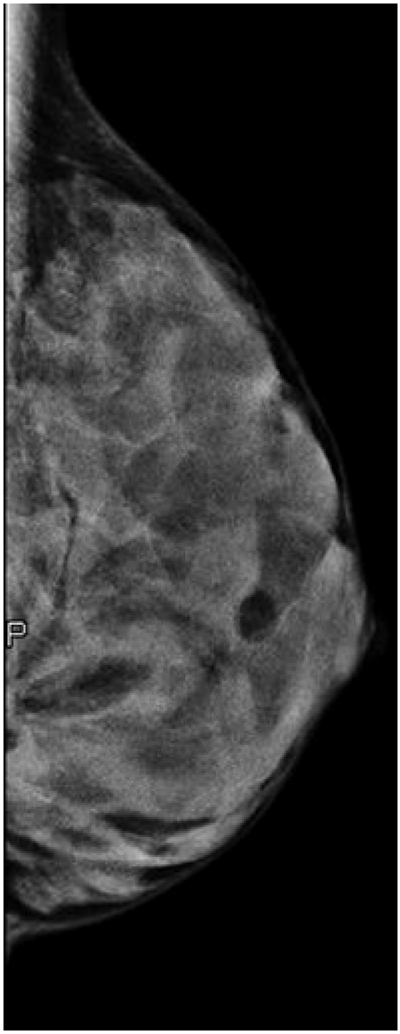

Figure 8 – Dense breast in cranio-caudal projection.

Mammographic anatomy of the normal lymph node

The parameters that characterize a lymph node can not be studied electively in mammography, in contrast to what happens with ultrasound examination.

In general, any mammographic opacity should be explored for shape, margins, density, location, association with microcalcifications, number, mono- or bilaterality, and should be correlated with the clinical history and physical examination.

The normal lymph nodes may appear as well-defined, circumscribed opacities with usually low density and a central radiolucent portion corresponding to the fat hilum. They can be round, oval or lobulated and are usually not larger than 1 cm. They may be in any part of the gland, although they are preferentially in the upper quadrants of the breast or in the axillary area.

In case of normal or reactive lymph nodes, their size may increase but the other features do not vary significantly on mammography.

Metastatic lymph nodes show usually a globular shape and lose the normal cortico-medullary differentiation. The size of a lymph node does not appear to be a reliable criterion for differentiation between a benign and malignant behaviour. A malignant lymph node sometimes shows a denser center than the surrounding tissue and is relatively homogeneous; in addition it may have spiculated edges. Moreover, it may be accompanied by architectural distortion of the structure of the breast.

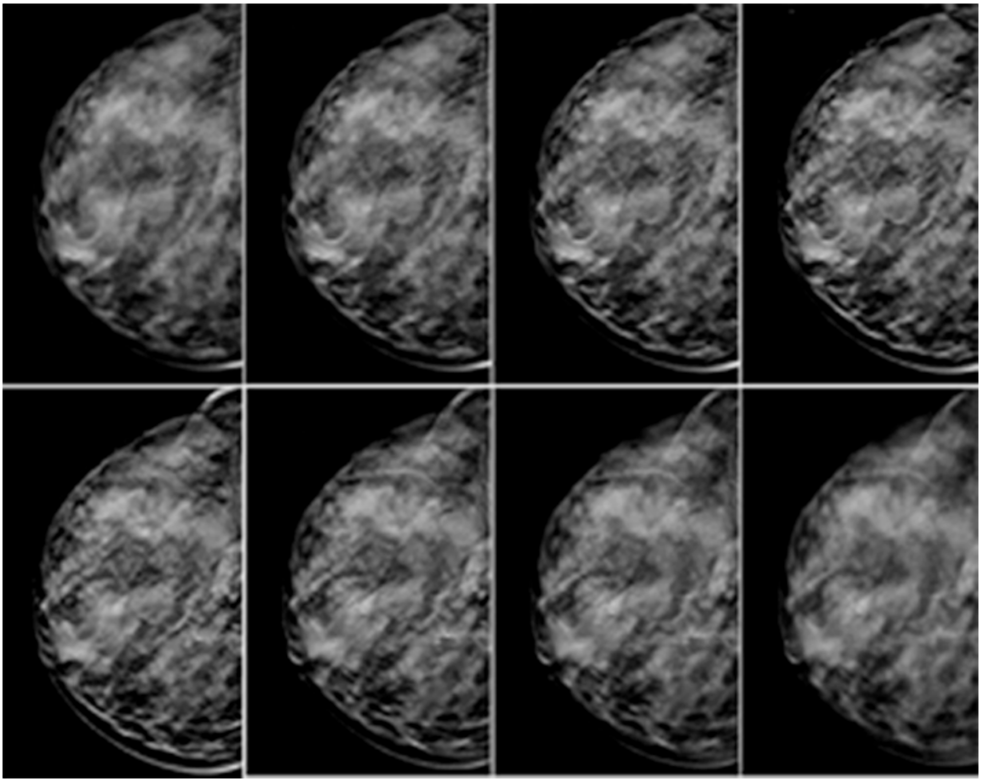

Figure 9 – Tomosynthesis of cranio-caudal examination of a breast.

Dosimetry

The mammographic dose is related to many factors, including the performance of the generator and the X-ray tube, the degree of compression and the number of repeated exposures. Modern systems are equipped with automatic exposure meters (AEC) which, depending on the breast density, automatically select the voltage and the type of anode.

The radiation dose for a tomosynthesis procedure in CC and MLO projections is generally comparable to the dose observed in a standard examination in two projections: 1-2 mGy of average glandular dose (AGD) (Mann et al., 2008). The beam quality is similar to that of mammography; European guidelines suggest that the AGD for a mammogram in a normal breast of 4-5 cm thickness should be kept below 2-5 mGy.

In a screening setting, some women will be recalled for further mammographic investigations such as different projections or magnification views; all these additional mammograms increase the dose to a patient.

The data from the literature suggest that tomosynthesis can not only reduce the recall reate of patients for further investigation, but that a single projection has a diagnostic performance equivalent to a dual-projection digital mammography.

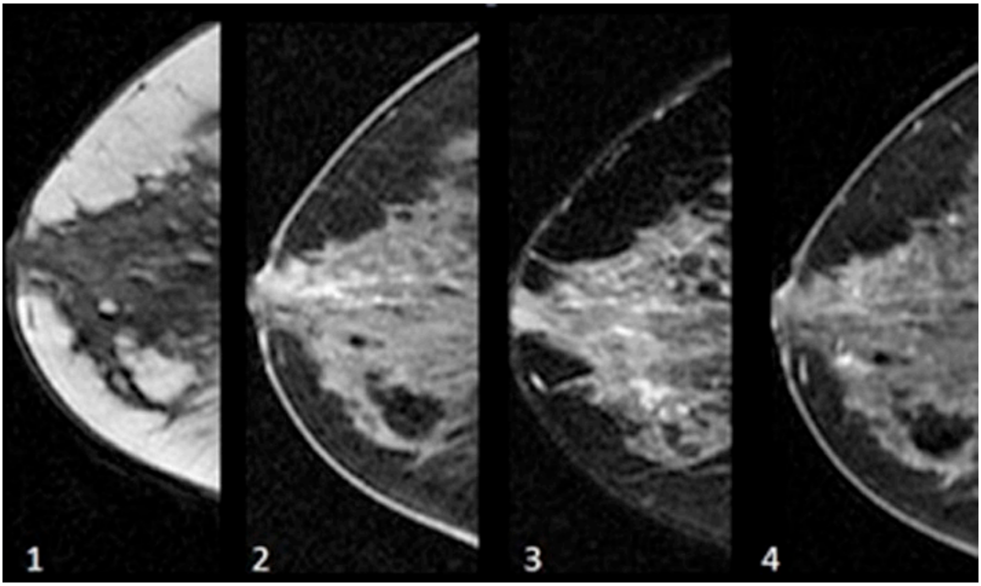

Figure 10 – 1: T1-weighted turbo spin-echo image; 2: T1-weighted turbo spin-echo image with fat suppression, 3: T2-weighted turbo spin-echo image with fat suppression: 4: contrast-enhanced T1-weighted image.

From the available literature the LAR (Lifetime Attribuable Risk) of tomosynthesis does not seem to be significantly superior to standard 2D digital mammography.

Normal anatomy of the breast on magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is the most sensitive technique for the study of the breast. It allows the study of areas that are not clearly visible on conventional techniques such as the posterior part of the breast and the chest muscles. The study of the breast with MRI needs the use of paramagnetic contrast media.

The breast gland is studied using mainly fat-saturated sequences (T1 and T2 with or without fat suppression, pre- and post-contrast) (Morris and Liberman, 2005). Thanks to the multiparametric nature of MRI, it is in fact possible to saturate the signal of the fat tissue by increasing the contrast of the contrast-enhanced structures, such as breast tumors. Fat saturation techniques are commonly used in magnetic resonance imaging to suppress the signal from adipose tissue and allow reliable acquisition of contrast–enhanced images.

Magnetic resonance imaging allows the study of all components of the breast: the skin appears smooth and has a thickness of around 2 mm; the nipple-areola complex shows an enhancement with variable intensity after the administration of contrast media, while the intensity of the pectoral muscle increases to a lesser extent. The intensity of the enhancement of the breast gland highly depends on the menstrual cycle and the hormonal stimulation (Fig. 10). In pre-menopausal

Figure 11 – Normal appearance of a lymph node in a magnetic resonance imaging (MRI) examination in a T1-weighted image.

women, a breast MRI should be performed only during the II to the III week of the menstrual cycle to avoid false positive results due to so-called background enhancement.

The milk ducts may be visible if there is ductal ectasia; the MRI signal depends on the type of content: if the ducts contain serum, the content will be hypointense on T1 and hyperintense on T2, if they contain blood, the lumen will be hyperintense in both sequences T1 and T2 (Dhillon et al., 2011).

Considering the wash-in of the contrast media inside a nodule and the subsequent wash-out, it is possibile to draw a intensity/time curve that can be used to differenti-

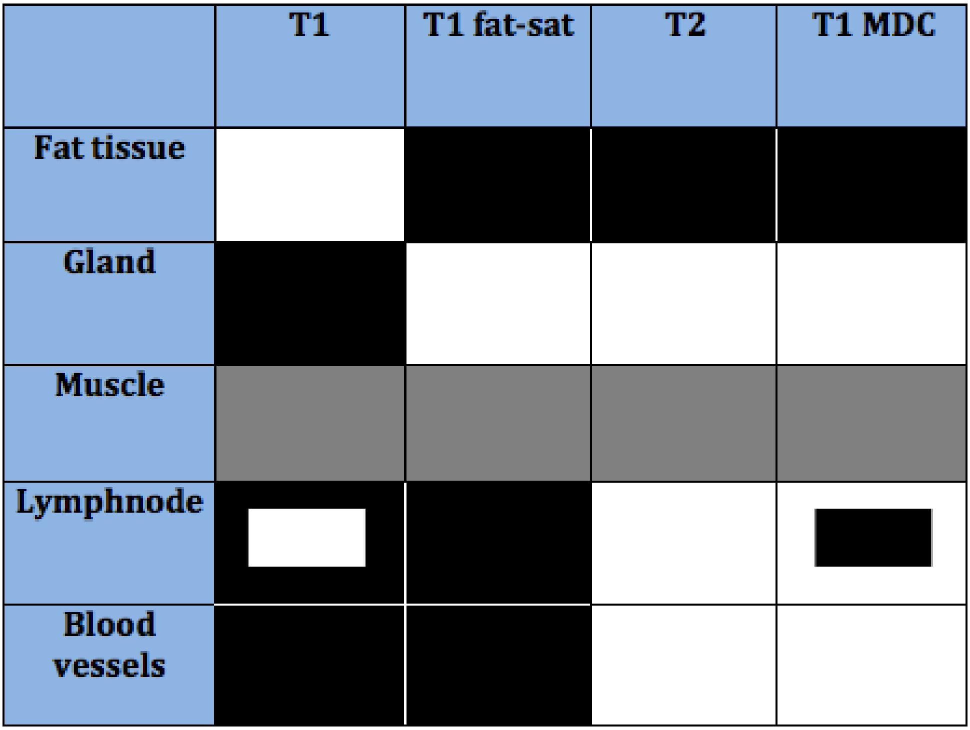

Figure 12 – Revision of the MRI signal of the normal structures of the breast.

ate lesions that have a slow, continous wash-in, such as benign lesions, from nodules that have a fast wash-in and a fast wash-out such as breast tumors.

Anatomy of lymph node on MRI

Magnetic resonance imaging allows the study of lymph nodes showing their kidney-shaped appearance, the fatty hilum and their signal before and after the administration of contrast media.

After the injection of contrast media, lymph nodes become hyperintense due to their rich vascularization (Dhillon et al., 2011) (Fig.11). Regarding the MRI apperance of lymph nodes, T1 sequence without fat-saturation are useful to show the fatty hilum of an enhancing lymph node that might simulate a breast lesion.

Considering all the information that can be gathered using all the availabile magnetic resonance sequences for the morphological study of the breast, we propose a summary table regarding the semiotics of normal structures, in order to obtain more information and to integrate them with the other available methods (Table 1).

Table 1 – Magnetic resonance imaging (MRI) signal of the normal structures of the breast on T1-weighted images with and without fat saturation, T2-weighted images and on contrast-enhanced T1-weighted images.

	T1 pre-c.a.	T1 F.S. pre-c.a.	T2 pre-c.a.	T1 post-c.a.
Fat tissue	bright	dark	dark	dark
Breast gland	dark	bright	bright	bright
Muscle	isointense	isointense	isointense	isointense
Lymphnode	bright with a dark rim	dark	bright	dark with a bright rim
Blood vessels	dark	dark	bright	bright

Abbreviations: c.a.: contrast agent; F.S.: fat-saturated.

Conclusions

The modern diagnostic senology has different methods available to study the breast: mammography, ultrasound, MRI and, brand new, tomosynthesis. By integrating all imaging modalities we can perform a complete morphological study of the breast, which allows to differentiate normal from pathological structure. The final purpose is to diagnose malignant lesions precisely and in early stages, improving the prognosis of patients with breast cancer.

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