Unilateral Breast Edema: New Aspects of Diagnosis Using the Full Breast Ultrasonography

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Learning objectives

The knowledge of the most frequent etiologies that cause unilateral breast edema and their anatomical-sonographic appearances can aid accurate diagnosis. The benign etiologies cannot be overruled based only on the patient history, the clinical examination and the radiological-imaging methods of diagnosis in use, thus the final assessment is usually made after breast/thoracic small parts biopsy. Benign edema after conservative or radical breast cancer (BC) surgery associated with chemotherapy and radiotherapy has a controversial follow-up and no significant progress was made in the last three decades, since Ryan and Mortimer affirmed in 1986: "the post mastectomy swelling of the upper limb causes little interest until a second primary tumor develops [1]". The clinical extension of the malignant breast edema is not concordant with the real extension of the disease, and that implies corrections for according treatment; for example, the detection of malignant microcalcifications by mammography in inflammatory breast carcinoma and the axillary lymphadenopathy can be underestimated upon Tardivon [2].

This paper presents and illustrates some new descriptors useful in the positive and the differential diagnosis of the most frequent etiologies of the unilateral breast edema, using the new concept of Full Breast Ultrasonography (FBU) [3; 4].

Background

Breast edema is caused by benign or malignant diseases, following an imbalance between the input (arterial capillaries extravasation of the plasmatic fluid) and the output (lymphatic drainage obstruction or venous capillaries drainage insufficiency such as congestive heart failure, venous thrombosis). This usual definition based on the biological fluids dynamics is not sufficient for explaining all clinical-pathological cases. The diagnosis of the breast edema is still incomplete and oversimplified. In addition to the patient history and the clinical examination, the paraclinical diagnosis of breast edema is usually based on the mammographic unspecific findings: skin thickening, increased parenchymal density, and interstitial marking. Breast Ultrasonography (US) is thought a complementary tool without specific etiological findings, but allowing targeted biopsies. There is some confusion between the terms that describe various aspects and etiologies of fluid retention in specific tissues, which need to be clarified before describing unilateral breast edema.

Edema and Lymphedema: Definitions and Classification

Generally assessment defines edema as an accumulation of excessive amount of fluid in the extravascular interstitial space of the body. The intracellular edema is usually
neglected. The balance between the intravascular and the interstitial space is based on the permeability of the arterial capillaries that make the intake of fluid and of the venous capillaries and lymphatic system that reassure the drainage, in the condition of the physical dynamics of the fluids: the hydrostatic pressure pushes fluid out and the oncotic pressure pulls fluid into the respective compartments.

As regarding our purpose, there are many types of breast and trunk edema in accord with their etiologies, and many confusions and overlapping classifications in the literature, mainly based on the clinical approach and illustrated with the radiological and imaging techniques, without systematical correlation with the biological tests or the pathological data.

Most of literature does not make the differentiation between edema and lymphedema, which aren't necessarily overlapping conditions. We can affirm the lymphedema is a specific item included in the larger set of edema, which also includes others edemas such as the traumatic item, the inflammatory edema either infectious (mastitis) or non-infectious (sunburn, other burns such as thermic, chemical or post irradiation, autoimmune reaction), vascular (cardiac insufficiency, venous thrombosis), neurological (stroke, traumatic/surgical denervation) or metabolic (hypoalbuminemia found in cirrhosis, nephrotic syndrome, amyloidosis, etc.) (Fig. 1 on page 6). By the other side, the lymphedema may result after inherited (Fig. 2 on page 6) or acquired (with benign or malignant etiologies) blockage or damage of the lymphatic pathways (represented by the lymphatic vessels with blunt edge in the interstitial space, continued by the lymph nodes chains and ended by the right lymphatic duct and the thoracic duct that drains into the subclavian veins).

There are some differences between the lymphedema and the other types (items) of edema, maintained when analyzing the breast and trunk location:

- **Lymphedema** is a swelling that occurs when the lymphatic system is impaired to a given area, more or less extended, and this swelling occurs near the affected lymphatic area. In the literature it is generally accepted the lymphedema is caused by an excess of protein-rich lymph trapped within the tissues; however, there are studies that demonstrated a contrarily lower-protein content of the interstitial fluid from the swollen arm after BC treatment than in the non-swollen arm [5]. The affected tissues respond to injury with slow healing and/or a potentially serious infection; in breast lymphedema may be present in benign conditions (especially after conservative surgery of BC with axillary nodes dissection; lymphangitis; filariasis) or in malignancies: advanced stages of BC, inflammatory BC or after conservative or radical surgery. Its evolution is aggravated after radiotherapy, with small signs for improvement or with progressive aggravation whatever the treatment. In the early stages lymphedema swelling leaves a mark after a finger or closes pressing, known as pitting edema. Unlike other edemas, lymphedema leads to changes in the tissues
such as fibrosis (hardness) and an increased risk of infection. Lymphedema is harmed by treatment with diuretics, has low response to the postural treatment and is a bite improved by muscular exercise and massage. The orange peel sign ("peau d'orange") has additional signs of acute inflammation (redness and warm) and may be present in malignant or benign condition.

- **Other-types edemas** represent the body’s normal response to an injury such as a trauma (contusion, sprain), inflammation, irradiation, stroke, venous insufficiency. The mechanisms are complex and incomplete explained. The excess of interstitial fluid is part of the healing process and leaves the area spontaneously or following anti-inflammatory drugs. Edema due to some injuries may associate additional intracellular fluid and bloody suffusions that help with healing. When edema is caused by circulatory system problems, such as chronic venous insufficiency, results a swelling in the lower areas of the body segment and may have postural improvement; in breast unilateral edema was described after arteriovenous fistula with subclavian or innominate vein thrombosis secondary to hemodialysis [6; 7]. There is a large opinion usually these cases do not leave a mark when a finger is pressed into it (it is known as nonpitting edema). Metabolic edema secondary to hypoalbuminemia is usually generalized and may have etiological treatment; non-lymphatic edema usually can be relieved with diuretics.

According to the International Society of Lymphology, the (clinical) stages of the lymphedema are [8]:

- **Stage 0 (subclinical or latent):** There are no visible changes to the arm, hand, or upper body, but there is a subjective difference in feeling, such as a mild tingling, unusual tiredness, or slight heaviness. The stage 0 lymphedema may be stationary for months or years before obvious symptoms develop.
- **Stage 1 (mild):** The arm, hand, trunk, breast, or other area appears mildly swollen, with "pitting edema." This early-stage lymphedema is considered reversible and clinically it responds to the postural drainage (when elevating the arm, the swelling resolves).
- **Stage 2 (moderate):** The affected area is even more swollen, the postural drainage does not help, and there is a sign of non-pitting edema. Subcutaneous tissues present inflammation, hardening, or thickening. Any treatment has not completely results.
- **Stage 3 (severe):** This is relatively rare in people with breast cancer; the affected limb or area of the body becomes very large and misshapen, and the skin takes on a leathery, wrinkled appearance.

The "peau d'orange" syndrome
Despite its high incidence and frequent use in the clinical practice and in the literature, there is not a clear definition of this term; we prefer to consider the *peau d'orange* (fr.) a syndrome with various locations involving the skin and the subjacent small parts with multiple etiologies.

The orange peel skin represents a particular type of edema that is not included in the above classification; when it is developed in the breast, it may be present both in benign conditions (chronic abscess, folliculitis, postsurgical conservative therapy) or in malignant conditions, the most frequent and by far the most severe being the inflammatory BC (carcinomatous mastitis).

The pathogenesis of the *peau d'orange* is simplistic explained by the lymphatic edema that develops the swollen skin, with thickening of the dermal layer without swelling of the sweat ducts, which are tethering the skin at the sweet pores level, resulting an orange peel appearance [9]; stromal invasion with lymphatic obstruction is affirmed. However, this "stroma" is not defined in the literature: what region of the breast? And how the lymphatic obstruction realizes the skin (epidermis and derma) thickening? The lymphatic network has anastomoses, then what level is obstructed? And why the discoloration of the skin, usually in breast with pale/dark nipple and reddish, warm affected periareolar skin of various extension (Fig. 3 on page 7)? Why usual nipple retraction /inversion?

In fact, the skin thickening could be explained by an intracellular edema of the epidermis and increasing of the dermal interstitial lymphatic fluid with increasing of the activity of the macrophages and lymphocytes; moreover the arterial hyperemia in the dermal papillae realizes the heat and redness of the skin, and the consecutive rise of the strain in the dermal collagenous, elastic, and reticular fibers add the hardening of the skin and complete the clinical picture. This explanation is concordant with the findings of the high resolution US, completed with Doppler and SE, as we will further illustrate, and with the anatomical and functional bases of the skin that were described from the beginning of the 20th century but were neglected upon Ryan [1] and are still misunderstood [10].

In breast, the lymphatic vessels are surrounding but do not penetrate the mammary lobules. In the skin, there are two lymphatic plexuses covered by the arterial-venous ones: the deeper ones at the interface derma-hypoderm, parallel with the skin, above the superficial fascia and communicating by thin vertical vessels with the superficial plexus located in the deep derma, which ends by loops of thin lymphatic vessels in the core of dermal papillae, behind the arterial-venous capillaries junction [10; 11; 12]. The flux of the lymph is directed from the superficial to the deep plexus, because except the lymphatic loops the rest of vessels contain valves similar to the veins. In some pathological conditions, the retrograde/dermal back flow may contribute to the breast skin edema, as proved some lymphangiographic studies [13] and illustrated by the high resolution US (Fig. 4 on page 8).
Unilateral breast edema is important in the clinical and imaging diagnosis in the aim to discriminate a benign or malignant etiology. It may be present as primary lesion or secondary to a surgical and radiotherapeutic interventions and many combinations may be found. Conventional radiological and imaging features are non-specific for the large majority of cases and the final diagnosis is made by biopsy or complementary examinations with increasing of the cost-benefit ratio and of the patient discomfort. However, the engineering development of the ultrasonographic machines offers the possibility to develop the technique of scanning and the diagnostic descriptors in breast US (Fig. 5 on page 9, Fig. 6 on page 10).

Images for this section:

Fig. 1: Pathophysiological classification of edema

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Fig. 2: Congenital lymphedema in a 2-month-old male infant

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**Fig. 3:** Breast with unspecific "peau d'orange" (orange-peel skin)

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Fig. 4: US comparative radial scans at 6:00 o’clock: right breast edema illustrates skin thickening, enlarged lymphatic plexuses without Doppler signal, global hyper-echogenicity (nipple in the upper-left corner of the screen)

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Fig. 5: SE of benign-type breast edema in a patient of 62-year-old following conservatory surgery of left breast cancer: the lobar area with the galactophorous ducts (arrows) has low strain and the lymphedema is limited to the superficial premammary tissues

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Fig. 6: Radial panoramic view in L: 6:00 breast with lymphedema: thickening of the nipple-areolar complex (arrows), thickening of the skin and of the premammary fatty tissue with increased echogenicity, salient lymphatic vessels (thick arrow) and normal atrophic glandular lobar area with proportional atrophy of the glandular stroma and of the galactophorous ducts (dashed arrow), in a menopausal patient of 51-year-old

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Findings and procedure details

Technique of examination: We used the FBU, an anatomical radial and antiradial ultrasound scanning completed by the Doppler and Sonoelastography. This technique is based on the Ductal breast Echography (US) illustrated by Teboul and Halliwell since 1995 [14] and developed by Teboul in 2003 [15] and its promoters simultaneously with the development of the engineering of the machines used in the US; it has the advantage of the anatomical scanning and of standardization [16]. The radial and antiradial scanning centered by the main galactophorous ducts’ axes, using long linear probes eventually provided with water-bag adaptors, offers reproducible anatomical views similar to the gross section of breast pathology described by Tot and col [17]. The benefit of the high resolution of the last years’ transducers offered a better magnification of the breast tissues similar to a Magnifier 3X to 5X. When adding the new development of Doppler and the SE with the scoring upon Ueno (Tsukuba), the characterization of the whole volume of the targeted tissues (breast, axilla, surrounding small parts, large and small vessels, and local lymphatic system) becomes more "intelligible" [15], accurate and reproducible. This non-invasive comprehensive technique and interpreting of breast was named FBU and has the advantage to illustrate the breast lesions both benign and malignant with the same performances, with a detailed anatomy allowing accurate measurements over 0.5mm with the actual transducers in use.

The examination was performed by a trained radiologist, with long experience in Doppler Ductal US, completed by practice in the Real-Time SE for 7-9 years including this study; some follow-up examinations and some second-opinions were demanded to other radiologists trained in FBU. All cases were assessed upon the US BI-RADS 2013. The Ultrasound platforms were various, but provided with good quality of Doppler, with a high resolution linear transducer and with SE; the best examination was considered when we used a couple of a long transducer (7MHz) provided with a water-bag device for the general, quick radial scanning and an additional usual shorter, but of higher resolution transducer (10-14MHz) for the measuring, Doppler and SE (Hitachi machine). Some machines had a multi-frequency linear transducer with trapezoidal field-of-view, type virtual-convex scanning (Voluson) that combined the advantages of the first two. When a long transducer was not available (Aloka), the radial scanning was performed by using a double-screen composed image, with the respect of nipple position in the left-upper corner of the screen, and the right screen adding the peripheral area of the mammary lobe visualized by slipping the transducer in the radial axis. Sometimes the same patient had follow-up exam with different machines without imaging changes with implications in the diagnosis accuracy.

The selection of cases used for illustration implied a retrospective analyze of 76 (5.4%) patients with unilateral breast edema from a total of 1420 patients examined between Jan.
2014–Sept. 2016. The FBU findings were compared with the final diagnosis (biological, other radiological-imaging exams and pathological data). Some patients were recalled supplementary for the therapeutic survey, especially in primary benign breast edema (posttraumatic, mastitis, folliculitis) after the first 1-2 months interval and in secondary benign breast edema (postsurgical breast cancer therapy, post radiotherapy), usually after each 3 month interval in the first year. The cases with breast edema associated with primary breast malignancy or with suspect recurrence were referred to the oncological services and had pathological positive reports. All cases with suspect malignant edema were subject of anterior thoracic US for the assessment of the pleural and sub pleural lung integrity, with checking of the eventually presence of the sub pleural metastatic nodules, pleural effusions [18] and of the pulmonary interstitial edema associated to the mediastinal lymphadenopathy, expressed by the replacement of the "lines A" parallel with the pleura by the "lines B" or "comet-tail artifact" of Lichtenstein [19] (Fig. 7 on page 18; Fig. 8 on page 19).

**Results:** The unilateral breast edema was present either in patients without previous mammary treatment, as a primary lesion of unknown etiology, or after conservative surgery for benign lesions (rarely) or for malignancies (frequently, usually the edema being considered secondary to the armpit lymphadenectomy and to the radiotherapy), classified as secondary breast edema. The radical surgery of BC is nowadays represented by mammectomy with axillary nodes excision, preserving the pectoral muscles; the follow-up examination in edema demonstrated various involvement of the skin, pectoral muscles, axillary small parts, upper limb and sometimes changes in the contralateral breast (thoracoappendicular edema).

The FBU specific findings for benign breast edema were: skin thickening, lymphatic subcutaneous spaces, hyper echogenicity of the premammary fatty tissue, vascular superficial hyperemia and increased strain of the premammary fat continuing the skin strain as compared with the glandular lobar structure. Fluid collections were found according to the etiology. The satellite lymph nodes were either surgical removed or with inflammatory changes.

The malignant breast edema was characterized by skin thickening, lymphatic subcutaneous spaces, diffuse hyperemia including the lobar anatomy and increased strain ratio of the mammary glandular structures; some malignant masses were discovered usual in relationship with the nipple, and some presented skin and costal-muscular extensions. There was no correlation with the presence and extension of the lymphadenopathy, but all cases presented an abnormal nipple-areolar complex.

The benign features of the unilateral edema were found in 65/76 (85.5%) cases, from which 28 cases (43% of the benign edema) represented benign conditions after complex treatment of BC (surgical therapy, radiotherapy and polychemotherapy); the follow-up
FBU interval was recommended according to the secondary findings (seroma, associated pathology) and no biopsy was necessary.

The malignant features of edema were demonstrated in 11/76 (14.5%), from which almost 2/3 cases as a primary malignancy and 1/3 as recurrences; all primary or secondary malignancies with edema represented 38/76 cases (1/2), but only 11/38 had a real-type malignant edema (28.9%), meaning less 1/3 cases; that results 2/3 cases with breast edema and history of BC do not need breast biopsy. In the literature, the malignant breast edema such as inflammatory BC had positive biopsy in the area of peau d’orange in only 38% cases, resulting almost 2/3 biopsies results false-negative [20].

The peau d’orange was frequently present in this series, 41/76 (85.4%), because it represented the most alarming clinical sign either in benign or malignant etiologies; the stage 0 of the lymphedema is either rarely presented because of non-alarming symptoms, or may be misdiagnosed as false-negative; it is not routine to perform comparative skin thickness of both breasts and it is not possible for all ultrasound platforms to acquire comparative SE for both breasts using the double screen imaging.

Some examples of the most frequent types of breast edema are illustrated in the followings:

- **Traumatic edema** (Fig. 9 on page 20, Fig. 10 on page 21, Fig. 11 on page 22) was rarely found in this series (2/76 cases), because on the one hand not all breast trauma with skin marks are referred to imaging investigation, and on the other not all breast trauma develop skin edema. The marked skin ecchymosis with edema may suggest breast dilacerations with hematomas, while skin focal hardness and thickening with subtle ecchymosis may be found in the subacute or chronic stage of posttraumatic fat necrosis.

- **Benign localized edema secondary to a skin and subcutaneous infection**, without extension to the subjacent mammary lobe(s); it occupies less 1/3 skin surface and was identified in 5/76 cases, secondary to folliculitis (Fig. 12 on page 23), insect bite infection, cat scratch and infection after removal of the periareolar hair.

- **Benign localized edema following periareolar lumpectomy or segmentectomy for benign lesions** was frequently visualized (16/76 cases), with reversible evolution (Fig. 13 on page 25, Fig. 14 on page 26); the water-bag transducers are more useful in the examination of the nipple-areolar area without distortions or acoustic shadowing, and in the absence an amount of Ultrasound gel should aid better scanning [4]. In our experience, associated duct ectasia with chronic over infection, usually Staphylococcus aureus or haemolyticus or Streptococcus, may increase the risk of post operatory inflammation both after benign or malignant lesion
removal. Sometimes, the presence of a suture granuloma may be found associated to the local edema (Fig. 15 on page 27).

- **Benign breast edema following the axillary or innominate vein thrombosis** was found in 7/76 cases following hemodialysis after arterial-venous fistula thrombosis extended cranially or associated to a central venous catheter inserted in the superior vena cava by the subclavicular vein or the internal jugular vein (Fig. 16 on page 29); we found venous thrombosis after chemotherapy using a central venous line, usually on the opposite site to mammectomy, with edema issued in the homolateral breast. Breast edema represented a collateral finding for the Doppler examination as main recommendation in arterial-venous fistula malfunction; however, a FBU should be performed as a quick complementary screening test to eliminate associated breast pathology.

- **Benign edema in cardiac insufficiency** was performed as screening test in 3/76 cases of high risk for BC; unless to be unilateral, breast edema was mostly bilateral asymmetric, more salient according to the dominant decubitus; in all cases it was associated with previous enlarged menopausal breasts; skin color with cyanosis and subcutaneous salient venectasias changed during the examination in dorsal decubitus; some cases with orthopnea need to be examined in standing position and the Ultrasound scanning may be incomplete in the largest breasts; however these cases are more difficult/impossible to visualize in mammography or MRI and the US rests the first intention examination.

- **Mastitis in non-feeding breast secondary to acute infection of fibro-cystic dysplasia** was rarely associated with breast edema (3/76 patients); most infected mammary cysts had a chronic evolution, the acute mastitis occurs rarely and when present the breast edema is limited to the lobar projection and the nipple-areolar complex. FBU was useful in the differential diagnosis of the infected inspissated cysts with isoechoic/hypoechoic appearances and peripheral salient vasculature, which are mimicking solid tumors, but the SE demonstrated a Blue-Green-Red scoring (BGR); the associated breast edema was not a frequent finding, even in large cysts of 50-84 ml volume, with positive biological tests. The infected fibro-micro-cystic dysplasia is the best mimicker of BC, clinical, mammographic or at MRI examination; it was associated with edema at presentation or after puncture-biopsy, and FBU allowed the differential diagnosis based mainly on the SE with a BGR-summation score [3].

- **Tumoral localized edema** was identified in 2/76 patients with pseudo-infected aspect, one after puncture-biopsy (Fig. 17 on page 29, Fig. 18 on page 30) and another in a male breast cancer; the central location with the nipple-areolar involvement may explain the presence of the edema.

- **Primary malignant extended unilateral breast edema** was examined by FBU in 6/76 cases, from which 2 cases with an advanced BC, with extension to the pectoral fascia and satellite axillary, supraclavicular and homolateral deep cervical lymph nodes involvement; in a case there were identified skin metastases extended to the premammary area, without development of
the peau d'orange (Fig. 19 on page 31, Fig. 20 on page 31, Fig. 21 on page 32). The inflammatory BC present in 4 patients illustrated
diffuse changes in more than 1/3 breast surface, from which 2 patients with
diffuse parenchymal changes without mass detectable at mammography or
MRI examination; SE presented malignant-type edema without localization
of the malignant nucleus, but the salient new formation vasculature better
demonstrated by the 3D Doppler technique was the best technique to
guide the biopsy (Fig. 22 on page 33, Fig. 23 on page 34, Fig. 24 on page 35, Fig. 25 on page 36). The FBU was superior
to the mammography in the inflammatory BC associated with a mass,
demonstrating the malignant descriptors upon Stavros, completed by the
new-formation vasculature with an incident angle of the plunging artery,
almost pathognomonic for malignancy [21], and by the SE that delineated
the extension of the lesion and the nipple-areolar complex involvement. A
rare case of inflammatory breast cancer with mass-forming tumor presented
a severe paraneoplastic nephrotic syndrome, but without lymphadenopathy;
the importance of the early detection and treatment of the malignancy
consists in simultaneously improvement/healing of the renal disease,
represented by the membranous glomerulopathy, an autoimmune process
determined by the malignant antigen [18].

• The most cases of benign breast edema were associated with conservatory
surgery of BC associated with/without radiotherapy, in 24/76 patients. The
main value of the FBU in the positive and differential diagnosis was the
illustration of the ductal-lobular tree changes, of the type of new-formation
vasculature and of the SE; only the correlation of all these descriptors
could be concordant with the pathological reports (Fig. 26 on page 37).
From this group, benign breast edema was associated with an infected
seroma with prolonged evolution after puncture-drainage and antibiotherapy
in 4 patients (Fig. 27 on page 37, Fig. 28 on page 38); the high
incidence of the conservatory surgical complications may be explained
by the non-anatomical excision, type "segmentectomy", "sectorectomy",
with remnants from the involved mammary lobes and associated with large
axillary lymphadenectomy. The new anatomical technique of breast surgery
based on the sentinel node excision followed by the completely removal of
the involved mammary lobe in accord with "the sick lobe theory", leads to
nearly complete avoiding of the postoperative complications and of the risk
of recidivism upon Dolphin, 2014 [22].

• The follow-up FBU of breast edema after conservative surgery associated
with radiotherapy was useful in detecting the recidivism of a ductal
carcinoma in situ in the first 2 years interval in the adjacent quadrant in 2
patients (Fig. 29 on page 39), explained by the incomplete excision of a
mammary lobe extended over the arbitrarily limits of the quadrants.

• Late metastases after 14 years interval in a patient with conservative
BC surgery (Fig. 31 on page 41, Fig. 32 on page 41, Fig. 30 on
page 42) were detected by US in the opposite suprascapular skin,
in the homolateral parasternal small parts and in the pleural space; the
homolateral persistent breast edema was considered of combined surgical and radiotherapeutic etiology, while the contralateral breast presented small lesion suspect on contrast MRI.

- The thoracic and upper limb edema after mammectomy completed with radiotherapy was more rarely present between all the patients with radical surgery, with benign aspect in 4 cases and reversible outcome and with malignant evolution in a single case.

Observations about FBU findings in breast edema:

1. Unexpected normal thickness of the Cooper ligaments or loss of delineation;
2. Hyperemia with present Doppler flow of the subcutaneous arteries and veins contrarily to the assumption of venous thrombosis or insufficiency;
3. Edema not correlated with the volume of the nodular BC, or with the extension of the disease (may be absent in the multifocal or in the lobar cancer);
4. Edema either benign or malignant may be associated with normal / benign inflammatory satellite lymph nodes;
5. Inflammatory BC with edema is associated with malignant cells thrombi in the lymphatic vessels in up to 38% cases [20], that means the obstruction of the lymphatic vessels is not the main etiology for edema; moreover the satellite lymph nodes may be macroscopically non-invaded; the local hyperemia and the breast stromal reaction demonstrated in the last years in behalf of the malignancy may better explain the peau d'orange formation;
6. Not all regional skin metastases were associated with local edema (Fig. 33 on page 42);
7. All breast edema included the nipple-areolar complex; the anatomy of breast vasculature with the periareolar circle functioning similar to the Willis circle in brain may explain this involvement of the central breast structures, whatever could be located the inflammatory or malignant lesion of the breast or of the skin and hypodermis surrounding the periareolar region. In the Fig. 34 on page 43 (gynecomastia), breast edema was significantly developed between the surgical scar and the nipple, in a male after cutaneous spinocellular epithelioma at R:11:00 location, treated by repeated surgical excision without satellite lymphadenectomy and 46Gy local Radiotherapy;
8. Radiation-induced breast edema is difficult to discriminate from the surgical etiology, usually they overlap; however, the radiodermatitis is strictly located on the exposure area and in the most severe cases it is usually associated with the clinical occult subpleural pulmonary fibrosis under the same thoracic area, that can be easily demonstrated by the US when the lines "B" Lichtenstein are present (Fig. 7 on page 18);
9. All breast edema were gravitationally more developed in the inferior quadrants; in systemic diseases, the unilateral breast involvement was
depended on the side of the prolonged decubitus (cardiac failure, nephrotic syndrome, systemic amyloidosis);

10. There is a physiological early stage edema in the postovulatory/secretory stage of the menstrual period, demonstrated by FBU as increasing strain in the stromal area, with changes in the FLR domain; this physiological edema is related to the mastodynia and depends of the high level of progesterone, paradoxically associated with increased mitosis of the lactocytes, reversible after the hormonal decay; the use of the Progesterone as local or oral treatment of the mastodynia in not justified and may aggravate the eventual dysplasia with increasing risk of developing BC with PR receptors.

Images for this section:
Fig. 7: US aspect of an anterior pleural metastasis in the homolateral hemithorax, frequent in advanced stages of breast carcinoma with unilateral edema (upper image); the "comet-tail sign" of Lichtenstein in chest US [19], pathognomonic for the pulmonary interstitial syndrome, demonstrating the "lines B" (lower image)

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Fig. 8: US assessment of a pleural effusion in a patient of 39-year-old with paraneoplastic nephrotic syndrome secondary to a right breast cancer with "peau d'orange" sign; associated HCV positive test may be involved too, in the immune complexes that built-up in the kidney; the US represents the most harmless technique of diagnosis and monitoring the therapeutic response [18]

Fig. 9: Extended breast ecchymosis and non-pitting edema following a blunt trauma in a patient of 77-year-old

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Fig. 10: The same patient: The FBU represents the less harmful first-intention examination and the anatomical radial scanning with the water-bag long probe allows the global breast evaluation

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Fig. 11: The same patient: Dual screen SE in a patient of 77-year-old, with breast edema and ecchymosis following a blunt trauma, illustrates a complex BGR score that is depicting a multiloculated hematoma.

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Fig. 12: FBU aspect of a localised breast inflammatory edema associated to a folliculitis

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Fig. 13: Radial Doppler US in a 67-year-old patient with benign localized edema following periareolar lumpectomy for fibroadenoma demonstrates the nipple-areolar complex involvement, associated ectasia and increased flow in both the periareolar arterial and venous ring
**Fig. 14:** The same case: The SE demonstrates benign-type breast edema with increased strain of the skin and of the premammary fat, but normal elasticity of the mammary lobar area and of the sentinel node.
**Fig. 15:** FBU in unilateral breast edema in a 29-year-old patient with benign aspect associated to a suture granuloma

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**Fig. 16:** Color Doppler absent signal in an axillary vein thrombosis secondary to a malfunctioning arterial-venous fistula, in a dialyzed patient of 48-year-old, with benign-type breast edema; the US represents the first-intention technique of examination

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**Fig. 17:** Localized unilateral breast edema in a 34-year-old patient with R: 6:00 periareolar infected tumor after puncture-biopsy; the radial Doppler scanning using a long-probe with water-bag demonstrates the lobar anatomy

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**Fig. 18:** The same case: The FBU demonstrates a benign-type peritumoral vasculature upon Kujiraoka and col., 2005 [21], concordant with a score 2 Ueno for the breast mass (upper images) and with the benign features of the sentinel node (behind images); the breast puncture-biopsy, performed as a routine in other service, would be not mandatory
Fig. 19: Primary malignant extended unilateral breast edema in an advanced BC, with extension to the pectoral fascia and satellite axillary, supraclavicular and homolateral deep cervical lymph nodes involvement, without development of the peau d'orange sign in a patient of 66-year-old
**Fig. 20:** The same case: Malignant unilateral breast edema in a patient of 66-year-old: the radial scanning with dual-screen SE demonstrates a tumor with score 5 Ueno connected to the nipple-areolar complex and the extension to the pectoral fascia; the tumor-nipple connection is essential in the developing of the breast edema in our experience, while the satellite nodes involvement may be absent.

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Fig. 21: The same case: FBU demonstrates skin metastasis by the lymphatic way (permeation nodule) in the subclavicular region additional to the malignant breast edema

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Fig. 22: Inflammatory BC in a patient of 51-year-old with asymmetrical macromastia demonstrates the "peau d'orange" with diffuse changes of more than 1/3 breast surface, without mass detectable at mammography or MRI examination

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Fig. 23: The same case: SE presented malignant-type edema without localisation of the malignant nucleus, with diffuse increase of the strain in the skin and hypodermis, preserved elasticity of the premammary fat between the body’s fascia superficialis and the glandular deeper region that had inhomogeneous lower elasticity; the macromastia may be difficult to examine with accuracy in all techniques mammography, US, and MRI

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Fig. 24: The same case: Inflammatory BC without mass forming usually presents a salient new formation vasculature illustrated by contrast-enhanced MRI, difficult to perform on such large breasts; the easier technique to detect the most suspect region would be the Doppler US with long transducer

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Fig. 25: The same case: The 3D Doppler technique better demonstrated the nucleus of the diffuse malignancy and was the best technique to guide the biopsy; however,
there are not available linear transducers to allow 3D Doppler acquisitions, and future engineering achievements are needed to improve the overall accuracy.

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Fig. 26: FBU aspect in a benign scar and breast edema following conservatory surgery of BC in a 62-year-old patient; the non-anatomical surgical breast section is frequently the most important etiological factor of the post operatory unilateral breast edema, while the complete excision of the mammary lobe (considered as an anatomical-functional unit), after the dissection of the sentinel node, results 0.3% relapses after Dolphin et al [22]

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**Fig. 27:** Conservatory surgery for BC in a 71-year-old patient, followed by a benign breast edema associated with an infected seroma near the armpit extremity of the scar, with prolonged evolution after puncture-drainage and antibiotherapy; multidetector CT allowed multiplanar reconstructions that demonstrated the breast edema, the chronic seroma and absence of any metastasis in the thorax.

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Fig. 28: The same case: The volumic US analyse by orthogonal scans was useful in the estimation of the punctured fluid and in the follow-up of the seroma, while the 3D-4D acquisitions were useful for the clinicians (upper images); the dynamic volumic measurements and the SE are useful tools in the assessment of the benign edema and in predicting the healing evolution (lower scans, after 6 months interval)

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Fig. 29: FBU usefulness in detecting the recidivism of a ductal carcinoma in situ in the first year-interval in the adjacent quadrant in a 52-year-old patient; the breast edema developed lately and the Doppler and SE secondary changes may be explained by the incomplete excision of a mammary lobe extended over the arbitrarily limits of the quadrants maintained still by the 2013 US BI-RADS assessment
Fig. 31: The same case: In malignant breast edema US is recommended as first-intention examination of the thorax, useful for the detection of changes in the small parts and in the pleural and subpleural regions. In this picture, US aspect of a contralateral suprascapular skin metastasis (left scans) and evaluation of the asymptomatic pleural effusion (right images)
**Fig. 32:** The same case: Sternal metastasis extended to the small parts around the second homolateral sternocostal joint, detected by FBU (upper images) that illustrates the new formation vasculature and a malignant-type SE; breast MRI (lower left and middle images) and multidetector CT demonstrated the generalised metastasis (bones, muscles, skin, lung) and targeted biopsy confirmed the late breast ductal carcinoma.

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![Fig. 32 Images]

**Fig. 30:** Chronic late unilateral breast edema at 17-years-interval following conservatory surgery and complex oncological treatment, in patient of 70-year-old with regular medical examinations, required more imaging examinations; the multidetector CT (upper reconstructions) and the breast MRI (below images) offered specific information and a global assessment of the disease.

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Fig. 33: FBU illustrates infracentimetrecl skin metastases in a patient of 57-year-old after conservative surgery for lobular carcinoma in situ, without breast edema

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Fig. 34: Breast edema significantly developed between the surgical antiradial scar and the right nipple, in a male after cutaneous spinocellular epithelioma at R:11:00 location, treated by repeated surgical excision without satellite lymphadenectomy and 46Gy local Radiotherapy; there is an asymmetrical gynecomastia, more developed on the right side. Note the skin discoloration on the exposure area, significant for radiodermatitis, extended above the surgical scar, but without subjacent edema.

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Conclusion

The use of the integrative concept FBU, which correlates the Doppler and the SE, was useful in the diagnosis and the follow-up of the benign breast edema, avoiding unnecessary biopsies; the malignant cases were better evaluated by detection of the location of the increased strain and vasculature in the glandular area, with easier detection of the tumor masses obscured on Mammography, of the local invasion of the surrounding tissues and better evaluation of the satellite lymph nodes.

Mammography was still recommended by the clinicians as first method of investigation of the patients older than 40 year-old, but it was followed by FBU and rarely by breast MRI in all cases of our series (protocol useless and with increasing costs, because of the poor sensibility of the mammography in densified edematous breast). FBU allowed the detection and localization of the primary tumors or of the metastases in the small parts, with selection of the pathway for targeted biopsies; the benign collections were localized, evaluated and treated by echo guided puncture.

Malignant-type edema diagnosed by FBU could miss satellite adenopathies, but was usually associated with increased level of the tumoral markers and could imply distant metastases, and a Multidetector CT scan (thorax, abdomen and pelvis) was useful in the global evaluation.

The reduced number of cases in this series and the various pathology sometimes with overlapping benign edema and malign history, did not allow a detailed statistical analysis; however, our observations based on the complex sonographic examinations of the cases, aided by the follow-up FBU especially for benign findings, and confirmed by the other radiological-imaging techniques and by the biological tests, were encouraging to perform more detailed future studies. The main advantage of this technique as comparing with the classical ultrasonographic approach is represented by a better correlation with the breast pathology, as a magnifier drawing a non-invasive gross section. In the meantime, the correlation of the descriptors "vasculature-strain" is useful in reducing of the false-diagnosis in the classical US and especially in the solitary SE.

By conclusion, FBU is a fast, standardized, cheap and non-invasive technique feasible with the most ultrasonographic machines in use and we recommend it as first-intention method of imaging diagnosis of (unilateral) breast edema.
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References