ACTUAL ASSESSMENT, DIAGNOSIS AND MANAGEMENT OF BREAST CANCER

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ABSTRACT

Early detection is one of the best ways to combat cancer in general is catching cancer in its earliest stages which gives you the best chances of successfully treating it. Ultrasound and mammography exams may detect breast cancer at an early stage.

According to the American Cancer Society's, numerous studies show that early detection saves lives and increases treatment options. With accepted 80%-90% accuracy rate, ultrasound and especially mammography is extremely accurate, but still not in perfect level.

The American Cancer Society recommends that women age 40 and older should have a mammogram every year and should continue to do so for as long as they are in good health. Women in their 20s and 30s should have a clinical breast exam (CBE) as part of a periodic (regular) health exam by a health professional preferably every 3 years. Starting at age 40, women should have a CBE by a health professional every year.

In Albania we do use and practice the same medical protocols as in the western countries, however we face difficulties in many aspect, such as: poor patient education and information in regards to medical health, the absence of a national program covered by health insurance, and other technical matters. This article aims to bring the current assessment of early detection of breast neo-formation and its management.

Key words: *Breast cancer, early detection, ultrasound, mammography, diagnosis, management*

BACKGROUND

Up until the early 1990's, breast ultrasound examinations were primarily used to distinguish between cysts and solid breast masses and for image-guided, minimally invasive interventions [1,2,3], but the diagnostic potential of breast ultrasound has improved since then. Evolving sonographic technology with high-frequency transducers in the 7.5-10 MHz range and evolving knowledge has established breast ultrasound in the past few years as an imaging procedure to supplement mammography [4,5,6]. In order to ensure standardized evaluation criteria, the American College of Radiology (ACR) developed a Breast Imaging Reporting And Data System (BI-RADS) classification for breast ultrasound examinations in 2003 [7], which is analogous to the BI-RADS classification for mammography [8].

The classification for breast ultrasound (USBI-RADS) consists of seven categories:

- Negative
- Benign
- Probably benign
- Suspicious abnormality
- Highly suggestive of malignancy
- Known malignancy

Category 0 is assigned for results requiring additional imaging due to limited assessment. Several international comprehensive quality standards for equipment and staff performing breast ultrasound have adapted the US BI-RADS criteria [9-12].

International guidelines recommend that breast ultrasound be used as a supplemental examination but not as a primary method for screening of breast cancer [13-17]. Screening for breast cancer focuses on detecting occult cancer at an early stage with tumor size preferably smaller than 1 cm, negative lymph node status and with no evidence of distant spread [18].

Mammography has been established as the primary method for screening. Some 35%-45% of non-palpable cancers are detected as microcalcifications in mammographic studies [19]. These microcalcifications can sometimes be visualized by modern ultrasound equipment, but cannot be reliably identified as such without knowledge of mammography [20,21].

However, not every carcinoma is detected in breast cancer screening. Breast density is one of the factors leading to false-negative findings in mammography [22-25]. Furthermore, mammographically dense breast tissue has been identified as an independent marker strongly associated with breast cancer risk and in particular with higher risk of interval cancer, i.e. cancer detected between screening tests [26-28].

Epidemiological studies have confirmed that individuals at varying risks according to the appearance of dense breast tissue in mammograms can be identified, and there is strong evidence for influence by genetic variants [29,30].

Risk Factors

Age, family history and genetics, late first pregnancy and obesity are well-established risk factors for breast cancer. Most women with breast cancer are postmenopausal although breast cancer is not uncommon in premenopausal women and is often more aggressive in this group. The recognition of gene mutations in the germ cell line (for example, in the BRCA1 gene) is a major advance in understanding the basis of inherited disease; in this regard, the genetic profile is now being increasingly incorporated in breast cancer risk assessments, particularly for families prone to breast cancer at an early age.

DIAGNISTIC APPROACH

Screening and Diagnosis of Breast Cancer

Imaging plays a crucial role for breast cancer screening, for classifying and sampling non-palpable breast abnormalities, as well as for defining the extent of breast tumours, both locally, loco-regionally, and at distant sites. Evaluating response to therapy constitutes an additional important role of imaging. Therefore, imaging via different modalities represents an essential, life-long component for patients with breast cancer, from initial diagnosis throughout the evolution of the disease. However, most breast cancers are detected by physical examination or via a mammography as part of a screening programme.

In Albania, unfortunately, we do not have a national screening program by the state health care system, thus the screening programs are mostly temporary, short term initiatives that do not address the need of Albanian population in long prospective and appropriate care for breast tumors. On the other hand, the technology and trained physician namely radiologist are an asset of the same level as in the developed countries. However, as per clinical protocols we do use and follow the most up to date principles of assessment, diagnostic criteria and management as of the same standard of western countries clinical practice.

X-ray mammography

Mammography uses low-energy X-rays (usually around 30 kVp) to examine the breast and is the primary imaging modality for breast cancer screening, detection and diagnosis. The goal of a screening mammography programme is to detect small (<1 cm) tumours, typically through identification of characteristic masses and/or microcalcification, fig.1.

Mammographic screening is generally suggested to the asymptomatic 40–45-year-old female population at 2-year intervals, while the American Cancer Society and the American College of Radiology recommend yearly mammograms beginning at the age of 40 years [6,7,14]. In case of a normal screening mammogram, the woman is simply invited to the next round of screening. Successful mammographic screening leads to cancer detection at average earlier stage and with smaller size of the lesions which in turn reduced breast cancer mortality.

Fig. 1. Fig.2

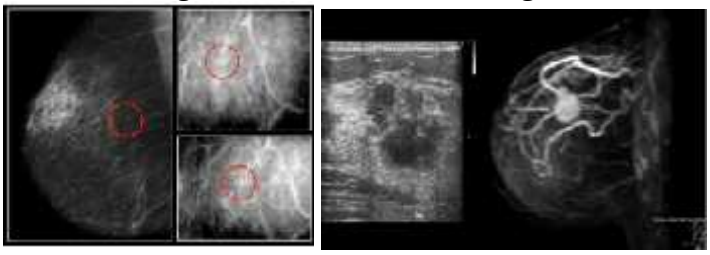

Fig.1. *Example of early, in-situ breast cancer detected by screening mammography in a 52-year old woman. Suspicion of cancer is raised by detecting an area with microcalcifications (indicated by red circles) in the breast; images in the right panels represent enlarged details of the same area in two different projections.* ***Fig.2.*** *Imaging results obtained in a 40-year old woman in the regular screening for mammography show a mass with irregular margins in the upper inner quadrant of the left breast (maximum diameter 25 mm; image not available because performed in another centre). The patient was then referred for further characterization. Left panel: US imaging confirms the inhomogeneous mass with irregular margins in the left breast. Right panel: MRI with gadolinium contrast shows that the mass has ductal-type contrast enhancement, suggesting breast cancer (confirmed by needle core biopsy as infiltrating ductal carcinoma).*

While excisional biopsy has been for some time commonly employed to ascertain the histological nature of suspicious lesions detected during mammography, this practice has now been largely replaced by stereotactic core needle biopsy. Mammography is also used to guide placement of hookwire needles for intraoperatively localizing non-palpable tumours (e.g. a breast cancer detected by microcalcifications); nevertheless, this procedure is now being increasingly replaced by a procedure called 'radio-guided occult lesion localization' (or ROLL) based on the intralesional injection of radiolabelled particles (99mTc-macroaggregates of human albumin, or 99mTc-MAA) that do not migrate from the site of interstitial administration and on subsequent use of a hand-held gamma probe for intraoperative guidance.

Moreover, mammography is used to define the extent of malignancy before definitive breast-conserving surgery as well as to monitor the breast after surgery and external beam radiation therapy. Both ultrasound examination and magnetic resonance imaging (MRI) are important complementary modalities to X-ray mammography for diagnosing, characterizing and determining the extent of breast cancer, fig.2, while ultrasound is routinely utilized in these roles, the routine use of MRI is still limited by local logistical and availability constraints, fig.4.

Ultrasound

Breast ultrasound is an important, cost-effective, and quick imaging tool for staging patients with breast cancer [1,2,3,4,5,6]. Disease is assessed for unifocality versus multifocality versus multicentricity and histological confirmation of additional sites of disease via ultrasound-guided biopsy at the time of ultrasound evaluation is possible, fig 3. Regional lymph nodes are assessed to include the ipsilateral axillary, infraclavicular, internal mammary, and supraclavicular nodal basins.

Sonographic features that suggest lymph node abnormality include the absence of a central echogenic “fatty hilus,” and subtle eccentric cortical hypertrophy that can be hypoechoic relative to the rest of the nodal cortex53. Because afferent lymphatic channels enter a node through the periphery of the cortex, abnormalities of the cortex can indicate early metastatic involvement. It is therefore critical to direct the needle tip to the hypoechoic abnormal cortex and not the central hilus or the normal cortical regions during biopsy to ensure the highest possible yield of metastases.

Any suspicious lymph nodes identified at the time of staging ultrasound are subjected to ultrasound-guided needle biopsy with immediate on-site evaluation by a dedicated breast cytopathologist, allowing for accurate nodal staging [American Joint Committee on Cancer (AJCC) criteria] and comprehensive care for the breast cancer patient. The highest-order suspicious node detected is subjected to biopsy, as the N stage impacts overall staging, determines eligibility for various chemotherapy protocols, and also contributes to adjuvant radiation therapy planning. Additionally, these sites of disease can also be used to assess response in patients undergoing neoadjuvant chemotherapy.

Fig. 3.

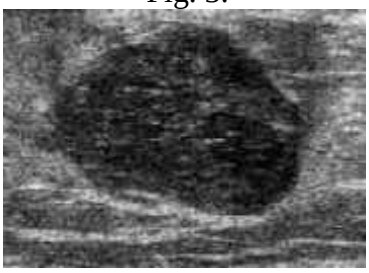

Fig.4.

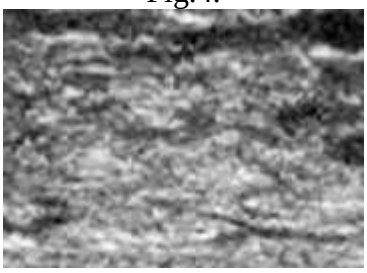

Fig.3. *A breast mass detected by ultrasound examination.* ***Fig.4.*** *A suspicion mass assessed by ultrasound missed by mammography but detected by MRI*

Radio-guided occult lesion localization (ROLL)

In general with the widespread availability of breast cancer screening programmes, breast cancer is being increasingly detected at an earlier stage, and some of the lesions may not be palpable. Several techniques have been developed to assist the surgeon in exactly locating these small cancer foci to facilitate excision during surgery, such as percutaneous introduction of a marker (a needle or wire) during a stereotactic or ultrasound-guided biopsy.

Recently, a radio-guided technique based on direct intra-lesional injection of a radiopharmaceutical constituted by relatively large particles that do not appreciably move from the site of interstitial injection (such as 9mTc-macroaggregates of albumin, with a size range of 10–150 μm) has been developed and largely validated.

In the operating theatre, the exact location of the tumour is identified with the help of a gamma probe, which is introduced through the surgical incision and thus helps to easily localize the focal deposition of the radiopharmaceutical (and the tumour). This technique is now being increasingly performed for non-palpable breast lesions, and in several centres around the world it is now considered the routine standard procedure for such clinical condition.

Overall staging

The introduction and diffusion of advanced cancer imaging with hybrid PET/CT equipment is having an increasing impact on the clinical management of patients with breast cancer (as well as in patients with a variety of other malignancies). In fact, this technique yields crucial information on the loco-regional and whole-body burden of metabolically active disease, and therefore leads to treatment strategies tailored to the individual patient's conditions, from the phase of initial staging after diagnosis (see above) to the phase of assessing response to anti-tumour therapy.

Besides its use for initial staging of the axilla (see above), FGD PET/CT is now being recommended for systemic staging in patients with locally advanced breast cancer, i.e. either a primary tumour larger than 5 cm, and/or skin or chest wall tumoral involvement, fixed axillary nodes, positive supraclavicular/infraclavicular and/or internal mammary chain lymph nodes, and inflammatory cancer. Currently, the standard curative approach with these patients consists of neoadjuvant chemotherapy followed by surgery with axillary nodal dissection and external beam radiation therapy [30,31].

Assessment of the efficacy of anti-tumour therapy

FDG PET/CT has been shown to be particularly useful for restaging breast cancer both in patientswith rising tumour markers and negative/equivocal findings at conventional imaging, and for evaluating response to therapy. In fact, there is increasing clinical evidence for breast cancer and other tumours that post-treatment FDG PET/CT is the most accurate procedure for assessing response to therapy, both in the neoadjuvant setting and in case of tumour recurrence after primary treatment. The concept of using FDG PET/CT for predicting a therapeutic response is based on an early decrease in glucose metabolism (instead of changes in size, that generally occur later when evaluated by other conventional imaging modalities); such reduction in glucose consumption is closely correlated with the efficacy of therapy. In particular, FDG PET/CT has been shown capable of discriminating patients as responders from non-responders earlier than CT and/or MRI [30,31].

During the course of their disease, about 30% to 85% of patients with recurring and/or metastatic breast cancer develop bone metastases, mostly to the spine and pelvis, followed by ribs, skull and femur. Although bone scanning with 99mTc-labelled phosphonates is the most commonly used method for staging bone metastases, the high sensitivity of this technique is counter-balanced by low specificity, since false positive findings can be due to trauma, degenerative changes, and other benign conditions; on the other hand, false negatives can occur in the presence of metastases with predominantly osteolytic patterns and low bone turnover. The availability of a bone-seeking PET agent such as 18F-fluoride (that accumulates by chemio-adsorption at sites of

increased bone turnover) has increased the potential clinical applications of PET/CT imaging also for evaluating bone involvement, e.g. by metastasis. This imaging technique is much more sensitive (and also more specific) than conventional bone scintigraphy with 99mTc-labelled bone-seeking agents. Nevertheless, several cost and availability issues must be adequately addressed before this imaging technique can be recommended for patients with breast cancer, especially considering that bone metastases from this tumour tend to be osteolytic or intramedullary and are therefore likely to be better detected by FDG PET/CT than are osteoblastic lesions.

CONCLUSIONS

Although the incidence of breast cancer (expressed as age-standardized rate) is almost three-fold higher in developed than in developing parts of the world, this is the most common female cancer in both developed and developing countries. On the other hand, mortality is growing especially in those regions of the world without early detection programmes. Age, family history and genetics, late first pregnancy, and obesity are well-established risk factors for breast cancer. Imaging plays a crucial role for breast cancer screening, for classifying and for defining the extent of breast tumours locally, locoregionally, and at distant sites. Most breast cancers are detected by X-ray mammography, usually as part of nationwide screening programmes. Ultrasound (US) examination is routinely used as an essential complement to physical examination and mammography in the evaluation of suspicious/equivocal breast masses; US has also become the modality of choice for guiding percutaneous interventional procedures on breast masses, from needle core biopsy to ablation. Magnetic resonance imaging (MRI) with a contrast agent has an important role for identifying mammographically equivocal breast masses as malignant or benign, as well as for defining the local extent of malignant disease.

Besides radiological imaging (mammography, US, MRI), nuclear medicine imaging techniques are playing an increasingly complementary role in the diagnostic characterization of breast lesions, especially when breast-dedicated devices are employed, both for conventional scintimammography and above all for positron emission tomography (PET). Radionuclide procedures play crucial roles for radio-guided surgery in patients with breast cancer, either as radio-guided occult lesion localization (ROLL) or as radio-guided sentinel lymph node biopsy in the phase of primary treatment. Whole-body PET is also of paramount importance for systemic staging, for restaging after neoadjuvant therapy of locally advanced breast cancer, and for assessing the efficacy of anti-tumour therapy.

REFERENCES

1. Bassett L, Kimme-Smith C: Breast sonography. *Am J Radiol* 1991, 156:449.
2. Jackson VP: The role of US in breast imaging. *Radiology* 1990,177.
3. Parker SH, Jobe WE, Dennis MA, Stavros AT, Johnson KK, Yakes WF,Truell JE, Price JG, Korzt AB, Clark DG: US-guided automated large core breast biopsy. *Radiology* 1993, 187:507.
4. Stavros A, Thickman D, Rapp C, Dennis M, Parker S, Sisney G: Solid breast nodules:use of sonography to distinguish between benign and malignant lesions. *Radiology* 1995, 196:123.

5. Skaane P, Engedal K: Analysis of sonographic features in the differentiation of fibroadenomas and invasive ductal carcinoma. *AJR* 1998, 170:109.
6. Rahbar G, Sie A, Hansen G, Prince J, Melany M, Reynolds H, Jackson V, Syre J, Bassett L: Benign versus malignant solid breast masses: us differentiation. *Radiology* 1999, 213:889.
7. Mendelson EB, Baum JK, Berg W, Merritt C, Rubin E: *Breast ImagingReporting and Data System* BIRADS: Ultrasound. Reston VA: AmericanCollege of Radiology; 2003.
8. D'Orsi D, Bassett L, Berg W, *et al.*: *Breast Imaging Reporting and Data System, BI-RADS:Mammography* Reston VA: American College of Radiology; 2003.
9. Madjar H, Mundinger A, Degenhardt F, Duda V, Hackelöer B, Osmers R: Qualitätskontrolle in der Mamma-Sonographie. *Ultraschall in Med* 2003, 24:190.
10. Madjar H, Ohlinger R, Mundinger A, Watermann D, Frenz J, Bader W, Schulz-Wendlandt R, Degenhardt F: BI-RADS analoge DEGUM Kriterien von Ultraschallbefunden der Brust - Konsensus des Arbeitskreises Mammosonographie der DEGUM. *Ultraschall in Med* 2006, 27:374.
11. Amercan College of Radiology: ACR Practice guideline for the performance of breast ultrasound examination. American College of Radiology. ACR practice guideline Res. 34; 2007:569.
12. Quality Determinants Working Group: *Quality determinants of organized breast cancer screening programs* Minister of Public Works and Government Services Canada, Ottawa, Ontario; 2003.
13. Albert US, Schulz K, German Agency for Quality in Medcine. *J Cancer Res Clin Oncol* 2004, 130:527.
14. Smith R, Saslow D, Sawyer K, Burke W, Costanza M, Evans W, Foster R, Hendrick E Jr, Eyre H, Sener S: American Cancer Society guidelines for breast cancer screening. Update 2003. *CA Cancer Journal of Clinicans* 2003, 53:141.
15. SIGN Scottish Intecollegiate Guideline Network: *SIGN Scottish Intecollegiate Guideline Network. Management of breast cancer in women* Edinburgh: SIGN; 2005.
16. NCCN National Comprehensive Cancer Network: *Breast cancer screening and diagnosis guidelines* USA: NCCN Clinical Practice Guidelines in Oncology; 2007.
17. Albert US, Altland H, Duda V, Engel J, Geraedts M, Heywang-Köbrunner S, Hölzel D, Kalbheim E, Koller M, König K, *et al.*: 2008 update of the guideline early detection of breast cancer in Germany. *J Cancer Res Clin Oncol* 2009, 135:339.
18. Michaelson J, Silverstein M, Sgroi D, Cheongsiatmy J, Taghian A, Powell S, Hughes K, Comegno A, Tanabe K, Smith B: The effect of tumor size and lymph node status on breast cancer lethality. *Cancer* 2003, 98
19. Sickles E: Mammographic detectability of breast mircrocalcification. *AJR* 1982, 139:913.
20. Soo M, Baker J, Rosen E: Sonographic detection and sonographically guided biopsy of breast calcification. *AJR* 2003, 180:941.
21. Cheung Y, Wan Y, Chen S, Lui K, Ng S, Yeow K, Lee K, Hsueh S: Sonographic evaluation of mammographic detected microcalcification without a mass prior to stereotactic core needle biopsy. *J Clin Ultrasound* 2003, 30:323.
22. Ma I, Fishell F, Wright B, Hanna W, Allan S, Boyd N: Case-control study of factors associated with failure to detect breast cancer by mammography. *J Natl Cancer Inst* 1992.
23. Mandelson MT, Oestreicher N, Porter PL: Breast density as a predictor of mammographic detection: comparison of intervaland screen-detected cancers. *J Natl Cancer Inst* 2000

24. Roubidoux M, Bailey J, Wray L, Helvie M: Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. *Radiology* 2004, 230
25. Porter G, Evans A, Cornford E, Burrell H, James J, Lee A, Chakrabarti J: Influence of mammographic parenchym pattern in screening -detected and interval invasive breast cancers on pathologic features, mammographic features and patient survival. *Am J Roentgenol* 2007.
26. McCormack V, dos Santos Silva I: Breast density and parenchymal patterns as markers of breast cancer risk: a meta analysis. *Cancer Epidemiology Biomarkers and Prevention* 2006.
27. Boyd N, Gua H, Martin I, Sun L, Stone J, Fishell E, Jong R, Hislop G, Chiarelli A, Minkin S, *et al.*: Mammographic density and the risk and detection of breast cancer. *N Eng J Med* 2007.
28. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J Natl Cancer Inst* 2007.
29. Vachon C, Sellers T, Carlson E, Cunningham J, Hilker C, Smalley R, Schais D, Kelemen L, Couch F, Pankratz V: Strong evidence of a genetic determinant for mammographic density, a major risk factor of breast cancer. *Cancer Research* 2007, 67:84
30. Aebi S, Davidson T, Gruber G, Cardoso F, Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 22 (2011) 12–24. 14
31. Keam B, et al. Early metabolic response using FDG PET/CT and molecular phenotypes of breast cancer treated with neoadjuvant chemotherapy. BMC Cancer. 20 (2011) 452.