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Mastologia

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CLINICAL ARTICLES

- The added value of dual - energy **contrast enhanced** digital **mammography**
- The importance of radiologic and pathologic analyses to deal with **oncoplastic surgical treatment** of locally advanced breast cancer

REVIEWS

- News from the **18th SIS world congress** on breast healthcare
- Mechanisms of **Resistance to Hormonal Treatment** in Breast Cancer and Management

CASE SERIES

- A case from Falun Central Hospital, Sweden, Laszlo Tabar and Tibor Tot

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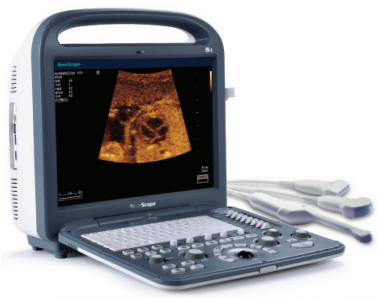

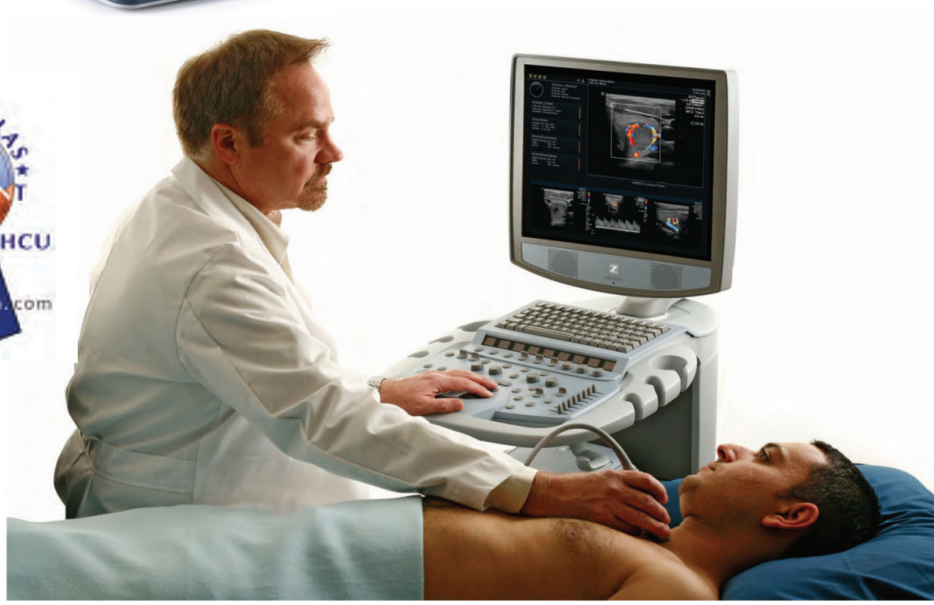

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Welcome note

Editor in Chief
Ass Pr Lydia Ioannidou - Mouzaka MD, PhD
Gynecologist-Surgeon-Breast Specialist
National Representative of Greece for Breast Centers and Breast Cancer in the European Union
President of the Hellenic Senologic Society
Delegate in European Initiative on Breast Cancer in Guidelines Development Group

The decision to issue the quarterly medical journal «Mastologia» was a wishful desire for a long time. We have not managed to do this for several reasons. Today, despite the difficult economic situation of our Country, we dare to proceed doing it, thanks to the good cooperation we have established with the Company "Zita Medical Management" of Mr. Zacharias Kaplanidis.

The timing is very good, as we, being the Hellenic Senologic Society, have just completed 35 years of fulfilled scientific activity and social contribution to the medical and social Community of Greece.

After careful consideration, we decided to issue the medical journal «Mastologia» in the belief that a journal can help in the dissemination of knowledge and the development of science. We decided to publish the «Mastologia» in English, so that its integration in international research bases such as Scopus, Embase & PubMed to be done the soonest possible.

We named the medical journal, «Mastologia» as the name "Senologia" has been registered by our French Colleagues. We gave this name in order to become conscious of the people's mind as well as in the our politicians that the recognition of the specialization in Senology is indispensable necessity if we want to consider ourselves an advanced Country.

The Senology should be officially the specialty dealing with the diagnosis and treatment of breast diseases, especially breast cancer, since the anticipation in these cases need specialized knowledge and suitable hardware. Surely, Senology should not be considered as privileged management for women, since men are affected by breast cancer as well. At the same time men can also experience all the range of the benign diseases.

Therefore, the aim of the medical journal «Mastologia» is the desire to promote Senology in Greece, the constant harmonization with the international developments and criteria, the promotion of Society's interests and also the interests of the specialised medical doctors (physicians) in the field.

As you will identify in our Editorial Board, we have being honored with the presence of prominent Colleagues from Greece and abroad, who are specialized in the field of Senology. Their participation will be an innovative energy exchange of views from different medical specialties.

We hope that our decision will satisfy the majority of those involved in Senology and will welcome this edition. We will wait for everybody's cooperation by sending original papers, announcements, interesting cases etc, suggestions, announcements for upcoming conferences and professional concerns.

Also the Journal will include evidence based Guidelines related to breast cancer diagnosis and treatment. Inside the Journal you will find the instructions for authors.

We welcome everyone who is willing to participate in the Editorial Board and eager to work.

Breast Cancer Diagnosis

The Added Value of Dual - energy Contrast Enhanced Digital Mammography

Employing a New Grading System in Breast Cancer Diagnosis

Athanasios N. Chalazonitis, Christina An. Gkali, Spyros Liopiris, Eleni Feida
Radiology Department, 'ALEXANDRA' Hospital, Athens Greece

ABSTRACT

Purpose: To determine the added value of dual - energy Contrast Enhanced Digital Mammography (CEDM) performance by means of a new grading system in breast cancer diagnosis.
Materials and Methods: 120 women, aged from 28 to 85 years (median age 56.4 years), with suspicious finding(s) in Digital Mammography, breast Ultrasonography, and breast Magnetic Resonance images, underwent dual - energy CEDM in our Radiology Department. The evaluation of the low - energy images was based on morphology of the lesion(s). High - energy images evaluation procedure utilized the differentiation of contrast enhancement intensity, based on a new qualitative grading system categorized in 4 - types: Type 0=no enhancement, Type 1=very low enhancement, Type 2=moderate enhancement, Type 3=intense enhancement. Type 0 and type 1 findings were considered to be probably benign, while type 2 and type 3 findings were considered to be probably malignant. Histopathological analysis of the suspect breast lesions was performed in all patients, after core or surgical biopsy for comparison reasons.
Results: Histopathology results confirmed 58 malignant and 62 benign lesions whereas the introduced grading system provided 68 probably malignant and 52 probably benign lesions. There was excellent correlation between proven breast malignancy and moderate or intense lesion enhancement (53 of 68), as well as between benign lesions with no, or very low enhancement (47 of 62). The positive predictive value of the CEDM contrast enhancement grading is 77.9% and the negative predictive value is 90.3% with sensitivity and specificity values of 91.3% and 75.8% respectively.
Conclusion: Dual - energy CEDM combined with the introduced grading system can be considered as a useful adjunctive tool and an evidence based classification method to conventional diagnostic mammography in every - day practice.

Corresponding author
Athanasios N. Chalazonitis
Radiology Department Director , 'ALEXANDRA' General Hospital, Athens, Greece
Email: red-rad@ath.forthnet.gr, Tel.: +30 6944 56533, Fax: +30 213 216288

Introduction

Breast cancer is considered as the most common disease in women, accounting for 27% of all female cancers. In addition it accounts for ~ 1% of all cancer cases in men. It is proven responsible for 15% of cancer deaths in women, which in turn makes it the number - two cause of cancer death worldwide[1].

Mammography mainly aims at the detection and evaluation of breast cancer and other breast diseases by differentiating breast cancer among all other breast diseases. Routine mammography has the efficiency to identify breast cancer at early and more treatable stages, but it is also associated with potential harms towards the female patient[2]. Less than 1% of women with suspicious findings on mammography actually turn out to have cancer when followed up with a tissue biopsy, whereas the vast majority of suspicious findings are considered as false positives[3]. Thorough follow - up of a suspected breast lesion on mammography exposes the patient to additional medical procedures, including redundant radiographs, breast biopsy, and possibly surgery, which typically contributes to increased patient anxiety and distress[4]. Globally, screening mammograms fail to identify up to 20% of breast cancers present at the time of screening due to false negative classification. Increased breast density is considered as the main cause of false - negative reports[5]. Dense breast tissue can shade additional abnormal lesions due to projectional overlapping. In addition, lesions seen on only one view and subtle inconspicuous architectural distortions can cause more troublesome problems towards their evaluation. Also the inter - and intra - observer variability among radiologists remains an important issue regarding the reproducibility of the classification procedure. Full Field Digital Mammography (DM) provides increased accuracy in screening pre - or peri - menopausal women, women younger than 50, and women with dense breasts[6]. Ultrasound has also become a useful complementary technique to mammography, especially for dense breasts[7].

In cases where malignant and fibroglandular tissues have similar x - ray absorption, the tumor enhancement with a contrast medium can improve the cancer detection procedure[8] due to the fact that lesions enhanced after the iodinated contrast agent are related with neoangiogenetic regions[9].

CEDM can provide angiogenesis exploration in breast carcinoma by tracking the uptake and washout of contrast agent in tissues. Thus, CEDM imaging can improve the detection of suspicious findings and their differentiation by revealing tumor angiogenesis.

Currently, two different CEDM techniques are employed: Temporal subtraction and dual - energy[10,11].Temporal subtraction CEDM utilizes a mask and a series of exposures, taken before and after injection of contrast agent. In dual - energy CEDM two separate and almost simultaneous x - ray exposures, after intravenous iodinated contrast agent administration, are employed in order to produce two mammographic images in both CC and MLO projections[10]. The low - energy image appears as a standard mammogram and the high - energy image, with a specific image processing algorithm, shows highlighted, enhanced areas of blood flow pointing to areas of potentially cancerous lesions[12].

In the proposed clinical study the dual - energy CEDM technique is employed. The study's main purpose is to determine the added value of dual - energy Contrast Enhanced Digital Mammography performance by means of a new grading system in breast cancer diagnosis. The biopsies taken from the selected clinical dataset were employed as gold standard towards the evaluation of CEDM and the proposed grading system.

Materials and Methods

Clinical Dataset

From September 2012 to December 2013, 240 women, aged from 28 to 85 years (median age 56,4 years), underwent dual - energy Contrast Enhanced Digital Mammography (CEDM) in our Radiology Department. The examination has been approved by the institutional review board and all examined women had been informed of the requirements for participation in the study and had a consent form signed.

Exclusion criteria from the study were the lack of implants and cases with any propensity of exhibiting an hypersensivity reaction to the contrast medium. In addition, pregnant, possibly pregnant, or lactating women were also excluded. Inclusion criteria were clinical find-

Table 1. Clinical findings employed as inclusion criteria for the clinical dataset employed in this study

Findings	Number of Patients	%
Single breast lesion	204	85.0%
Two or more lesions in the same breast	28	11.7%
Bilateral lesions	8	3.3%
Architectural distortions	44	18.3%
Asymmetry	58	24.2%
Calcifications	36	15.0%
Mass	52	21.7%
Mass and calcifications	14	5.8%
Architectural distortion and calcifications	4	1.7%
Asymmetry and calcifications	6	2.5%
Intramammary lymph node	2	0.8%
Breast asymmetry and cysts	4	1.7%
Cysts	6	2.5%
Postoperative scar	2	0.8%
Hematoma	2	0.8%
Paget disease of the nipple	2	0.8%
No specific findings	8	3.3%

ing(s) from digital mammography according the BIRADS score, breast ultrasonography and breast MRI. In **table 1** all inclusion criteria are depicted in detail.

All patients had undergone core or surgical biopsy in the suspicious lesions and histopathological analysis was performed.

Contrast Enhanced Digital Mammography (CEDM) Examination Protocol

All examinations were performed with a commercially available Full Field Digital Mammography system (Senographe Essential; GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom) that was modified to shape the x - ray spectrum specifically for CEDM.

Prior to the examination a catheter was inserted into the antecubital vein of the contra - lateral arm to the breast of concern. Iodinated contrast agent, Iopromide (Ultravist) 300 mg I/ml was administrated by means of an automatic power injector (CT 9000 ADV; Covidien, 20 Lower Hatch Street, Dublin 2, Ireland) at a rate of 2 - 3 ml/sec with a bolus chaser, providing a total volume of 1.5 ml/kg. Two minutes after the initiation of the contrast agent administration, the "normal" breast was compressed in a CranioCaudal (CC) view and a pair of low and high energy images was acquired. The procedure was followed by CC and Mediolaterar Oblique (MLO) views of the "suspicious" breast and finally MLO view of the "normal" breast was performed. The whole procedure is completed within 7 minutes, in order to achieve maximum contrast enhancement of the suspicious lesion[13]. Low - energy images were acquired with molybdenum (Mo) or rhodium (Rh) target and Mo or Rh filter automatically, at peak kilovoltage (kVp) values ranging from 26 to 31, ensuring that the entire x - ray spectrum was below the k - edge of iodine (33.2 keV). High - energy images were acquired with Mo target and a filter of copper, at 45 to 49 kVp, ensuring that the average energy of the x - ray spectrum was just above the k - edge of iodine. Iodine - enhanced images were generated from the combination of low and high - energy images. High - energy images revealed the enhanced lesions by canceling the non - enhanced areas of the breast[14].

Table 2. Confusion matrix of the CEDM Enhancement classification

Verified Breast Biopsies	CEDM Enhancement classification: Benign		
(Type 0 & 1)	Benign		
(Type 2 & 3)	Malignant		
Benign	94	30	PPV=77.9%
Malignant	10	106	NPV=90.3%
Sensitivity=91.3%, Specificity=75.8%			

According to the literature, for breast phantoms of 2.0 - 8.0 cm thick and 0.1 - 100% glandular fraction, CC view acquisition, from AEC settings, can result in a mean glandular dose of 0.450 ± 0.022 mGy - 2.575 ± 0.033 mGy for low energy images and 0.061 ± 0.021 mGy - 0.232 ± 0.033 mGy for high energy images. In MLO view acquisition mean glandular dose values ranged between 0.488 ± 0.007 mGy - 2.080 ± 0.021 mGy for low energy images and 0.065 ± 0.012 mGy - 0.215 ± 0.010 mGy for high energy images[12].

The low energy images interpretation was employed by means of: breast density on DM, location and type of each finding (asymmetry, calcification, mass, density, calcification ± mass, asymmetry ± calcification, architectural distortions, architectural distortions ± calcification, cysts, intramammary lymph nodes, and scars/distortions) according to BI - RADS (ACR) probability of malignancy classification.

The evaluation of Iodine - enhanced CEDM (high energy) images was based on contrast enhancement intensity and morphology of the lesions. In this study, a new lesion contrast enhancement intensity grading system has been introduced comprising 4 intermediate scales:

- no enhancement = Type 0
- very low enhancement = Type 1
- moderate enhancement = Type 2
- high/intense enhancement = Type 3

Type 0 and type 1 findings were considered to be probably benign whereas type 2 and type 3 findings were considered to be probably malignant.

Results and Discussion

According to the introduced contrast enhancement grading system, one hundred thirty six (136) women (56.7%) had type 2 or 3 of contrast enhancement (probably malignant lesions), thirty two (32) women (10.8%) had type 1 of contrast enhancement (probably benign lesions) and seventy two (72) women (30%) had type 0 enhancement (also probably benign lesions).

From the 136 type 2 & 3 patients, 106 were histopathologically proven malignancies. These cases comprised 84 invasive ductal carcinomas (79.2%), 6 ductal tubular carcinomas (5.7%), 8 Ductal Carcinoma in Situ (DCIS) (7.5%) and 8 invasive lobular carcinomas (7.5%). From the 106 patients correctly classified (True Positive cases) by the introduced grading system, 88 of the 106 malignant lesions had type 3 of enhancement (83%), whereas 18 had type 2 of enhancement (16.9%).

From the 30 patients in which all lesions were histopathologically proven benign while misclassified as malignant (False Positive cases) by means of CEDM evaluation, 8 women were identified with sclerosing adenosis (26.7%), 10 with fibroadenoma (33.3%), 2 with intramammary lymph node (6.7%), 6 with fibrosis - ductal ectasia (20%), 2 with inflammatory infiltration of the breast (6.7%) and 2 with fibroadenoma and sclerosing adenosis (6.7%). The CEDM grading on these false positive cases identified 14 lesions with type 2 of enhancement (46.7%) (4 fibroadenomas, 2 intramammary lymph nodes, 8 fibrosis - ductal ectasias), and the rest 16 had type 3 of enhancement (53.3%), (6 fibroadenomas, 6 sclerosing adenosis, 2 inflammatory infiltration of the breast and 2 fibroadenomas with sclerosing adenosis).

Regarding the 104 patients that CEDM grading classified as probably benign, 94 were histopathologically proved benign whereas 10 were turn to be malignant. The 32 cases with type 1 enhancement comprised 2 invasive ductal carcinomas (6.25%), 2 DCIS(6.25%), 4 fibroadenomas (12.5%), 2 hamartomas (6.25%), 8 fibrosis - adenosis (25%), 2 fibrosis - ductal ectasia (6.25%), 4 cysts (12.5%), 2 intraductal papilloma (6.25%) , 2 papillary in situ (6.25%) and the rest 4 sclerosing adenosis (12,5%). The 72 lesions with

type 0 enhancement, showed the following histologically results: 4 invasive ductal carcinomas (5,5%), 16 fibrosis - ductal ectasias (22,2%), 2 fibroadenomas (2,7%), 6 fibrosis - calcifications (8,3%), 26 fibrosis - adenosis (36,1%), 2 epithelial hyperplasia (2,7%), 2 papillomas (2,7%), 6 sclerosing adenosis (8,3%), 2 DIN1 (2,7%),21 postoperative scars (2,7%), 2 Paget disease (2,7%) and 2 fibrosis with fat storage (2,7%).

The overall results of the CEDM enhancement classification in terms of a confusion matrix and it's correlation with the biopsies results are depicted in **table 2**.

Table 2 shows that there was excellent correlation between moderate and intense/high lesion enhancement with proven breast malignancy, as well as between no enhancement and very low enhancement with benign lesions. It must be mentioned that 4 lesions that were not visible on DM alone, even retrospectively, had positive CEDM and histopathologically were proved as malignant lesions (invasive ductal carcinomas).

A more thorough inspection in the clinical dataset employed in this study shows that in 20 patients with multifocal enhancement, 6 (33,3%) of them was histologically proved to represent multifocal cancer (invasive ductal carcinoma). Also, in 2 of 6 patients (33,3%) with multicentric enhancement histology proved multicentric cancer (invasive ductal carcinoma and DCIS). Table 2 shows that the positive predictive value (PPV) of the CEDM contrast enhancement scoring is 77,9% and the negative predictive value (NPV) is 90,3% with sensitivity and specificity values of 91,3% and 75,8% respectively.

CEDM is considered as a functional imaging technique more similar to Breast MR imaging than to unenhanced mammography. It has the ability to detect tumor angiogenesis in invasive breast cancer and have demonstrated contrast uptake and enhancement differentiation at the majority of malignant lesions independent of their size (~1 mm). The presented study presented promising results that can constitute CEDM as a useful adjunct to diagnostic mammography, ultrasonography and as an effective suspicious lesion detection and staging modality. Due to the fact that CEDM can depict solitary, multifocal and multicentric breast breast cancers that conventional mammography has not be able to, it can utilized in evaluating symptomatic women, in screening women with dense breasts (ACR 3 & 4), and in women with high breast risk cancer.

The relatively high sensitivity value of the CEDM evaluation method (introduced grading system) proves that it has the potential to increase breast cancer detection rates and to reduce biopsies in patients with no enhancement or very low enhancement (preferably of type 1) since these cases are very likely to be benign.

CEDM modality is cost - effective, faster and more patient accessible against breast MR for the most of its clinical indications. In addition, it is independent of menstrual cycle and it can be employed as an indicator for breast cancer chemotherapy response.

Despite the profound advantages of CEDM modality presented so far, in some cases increased density surrounding the periphery of the breasts was created due to radiation scattering, which in turn slightly limited the breast periphery evaluation. Moreover, the elimination of background uptake from overlying and underlying tissues in the breast should be taken into account in the near future. Even with a low level of uptake in these superimposed and adjacent tissues, the projected signal of the entire thickness of the breast could reduce the conspicuity of a lesion.

Also, the iodinated contrast agent employment is not considered completely as an out of risk procedure. The majority of adverse side effects is minor and has been decreased considerably with the use of low - osmolality contrast media. Still, life - threatening reactions, though rare, can occur in the absence of any specific risk factors and with any type of contrast media[15].

Conclusion

Dual - energy Contrast Enhanced Digital Mammography emerges as a promising and adjunctive tool in early breath cancer detection. It is easy to perform and combined with the seemingly wide future availability, it can be considered as primary modality towards every day breast cancer screening. The results provided by the introduced grading system have proven that it is highly sensitive and specific even from the beginning of its implementation. Software upgrading together with newly discovered ways (involving computerized analysis) could overcome any potential limitations and improve its diagnostic performance. ■

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The importance of radiologic and pathologic analyses to deal with oncoplastic surgical treatment of locally advanced breast cancer

Preoperative planning to deal with large tumors

Angelo Gustavo Zucca Matthes PhD, MD [1,2], Rene Aloísio da Costa Viera PhD, MD [2], Ligia Maria Kerr PHD, MD [2], Ângelo Carmo Silva Matthes PhD, MD [2], Luis Antonio Castro MD [2], Antônio Bailão Junior MD[2], Maria Aparecida Azevedo Koike Folgueira PhD, MD[3], Gilberto Uemura PhD, MD[1]

[1] Department of Gynaecology, Obstetrics and Mastology - School of Medicine of Botucatu - UNESP - Distrito de Rubião Júnior - tel 00 55 14 38116000 - Botucatu-SP - Brazil
[2] Breast Unit - Barretos Cancer Hospital - R Antenor Villela Duarte, 1331 - Barretos -SP - 14784-400 - Brazil (Breast Center Network)
[3] Department of Radiology - School of Medicine - USP - São Paulo - SP - Brazil

ABSTRACT

Introduction: Women with locally advanced breast cancer (LABC) undergoing neoadjuvant chemotherapy (NC) may have better chances of being submitted to oncoplastic surgery techniques (OST). Preoperative planning is essential to support surgical decisions.
Methods: This prospective clinical trial included women with breast cancer, clinical stage III, undergoing NC. Preoperative physical exam (PE) tumor measurement correlations with mammogram (MG), breast ultrasound (US) and magnetic resonance (MRI), as well as postoperative pathologic findings correlating with PE, MG, US and MRI were assessed. The intraclass correlation index (ricc) was used to evaluate relationships between different measurements. Correlations among the median measurements of each method were also assessed. Surgical planning has involved the whole area previously marked by the tattoo regardless of tumor response. A detailed analysis of the pathological specimen was performed.
Results: 50 patients were enrolled. PE tumor median measurement was 6.5 cm (3.0 to 14.0 cm) and pathologic median tumor was 4.0 cm (0 to 14.5cm). Pathologic response was rated as stable, progressive,

Corresponding Author
A G Zucca Mattheswww PhD, MD
R Antenor Villela Duarte, 1331- Barretos -SP - 14784-400 - Brazil, Email: anguz75@gmail.com / zucca.mamarec@hcancerbarretos.com.br, **Tel/Fax 00 55 17 33216600**

partial response, and complete response in 10%, 8%, 80% and 2% of the cases, respectively. Pathologic responses were diverse. PE tumor size before chemotherapy correlated best with MRI (ricc 0.588, p < 0.001), as well as pathologic tumor size measured after chemotherapy correlated best with MRI (ricc 0.738, p <0.001). No patient had positive margins. Skin involvement was presented in 36% of pathologic specimen. Oncoplastic surgery techniques were performed in 34% of cases.
Conclusion: Careful preoperative planning and detailed pathologic analysis are of paramount importance in the decision for using oncoplastic surgery techniques, improving the conservative surgical and reconstruction treatment rates in case of LABC. (www.clinicaltrials.gov, NCT00820690)

KEYWORDS: **breast cancer; breast conservative treatment; clinical and imaging assessment; magnetic resonance imaging; neoadjuvant chemotherapy; pathological response; prospective study.**

Introduction

In developing countries, locally advanced breast cancer (LABC) still requires special attention[1] . With the introduction of neoadjuvant chemotherapy, the focus regarding the tumor response includes not only systemic treatment, but also the possibility of conservative surgery (BCT) or immediate breast reconstruction (IBR)[2 - 4]. Different oncoplastic surgical techniques (OST) can help by reducing the impact of the surgical treatment [5 - 8]. Thus, identifying the imaging method capable of predicting tumor response will be very helpful in surgical planning.

Mammography (MG) is currently the most effective imaging method for breast cancer detection. However, it may underestimate tumor size[9] . Certain parenchymal patterns may hinder the visualization of several lesions[10]. Ultrasonography (US) is the method of choice for the detection of cysts and solid lesions. Apparently, it is more efficient in determining tumor size. More recently, magnetic resonance imaging (MRI) has been included in the group of imaging tools to be used in case of breast cancer. Further studies are necessary to determine its effectiveness[11, 12].

Comparisons of the three methods for the evaluation of breast tumors have demonstrated significant differences[13] . In LABC, assessing tumor size is important to determine the pattern of radiological response and the surgical course of action.

LABC imaging assessment requires uniform criteria for the analyses of response rates[14, 15] . Apparently, one measurement of tumor diameter is sufficient to assess changes in solid tumors[14] , but studies on this topic, especially those addressing the possibility of OST, are scarce[16, 17].

This study is required by the fact that an appropriate surgical planning can promote the use of OST for patients with LABC. In other words we can offer a choice for women who certainly should be submitted to a mastectomy without immediate breast reconstruction.

Material and methods

This prospective trial was conducted between June/2008 and December/2009, at HCB, including women with LABC, stage III, and a confirmed diagnosis of infiltrating ductal or lobular carcinoma by a previous core needle biopsy or open biopsy.

Exclusion criteria were pregnancy (abnormal βHCG), primary or secondary inflammatory carcinomas, ulcerated tumors, atypical histology, and patient unavailability to undergo all exams.

Ethics

The study was approved by the Hospital de Cancer de Barretos (HCB) Committee of Research Ethics (135/2008 and 210/2009) and registered on www.clinicaltrials.gov (NCT00820690). Written informed consent was obtained from all subjects.

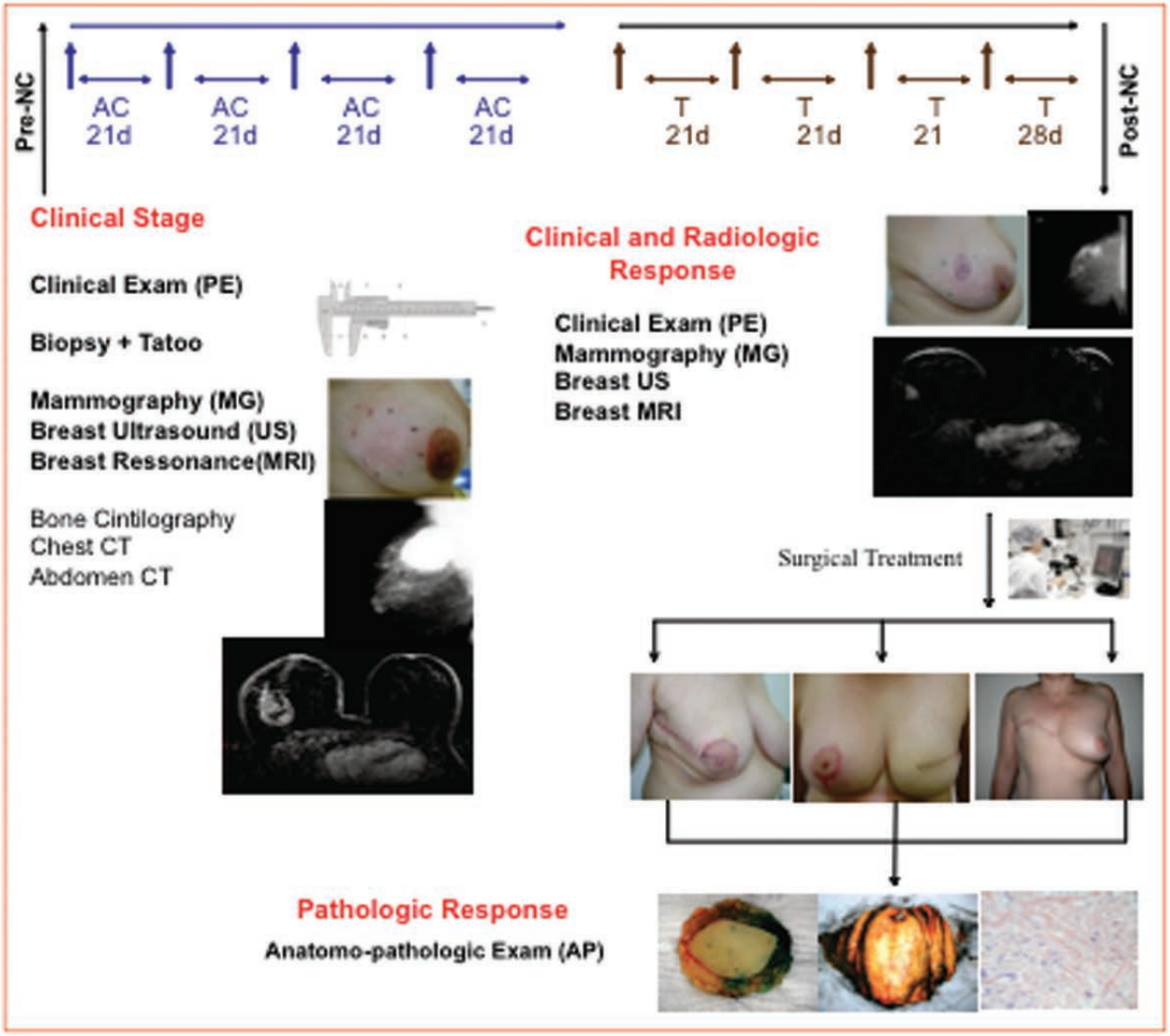


Figure 1. *Study design: clinical trial IRB 135/2008 and 210/2009 (www.clincicaltrials.gov, NCT00820690)*

Study Design

Diagnosis was confirmed by a previous biopsy. Preoperative PE tumor measurement correlations with MG, US and MRI,. Postoperative pathologic findings correlating with PE, MG, US and MRI were assessed. Tumors were measured pre - and post - operatively using a caliper. Physical examination was considered as the gold standard for comparison with the tumors pre - chemotherapy radiologic exams as well as anatomopathologic examination (AP) for post - chemotherapy ones (**Figure 1**).

Radiologic follow up exams were carried out between 22 and 28 days after the last chemotherapy cycle. Tumors were measured by members of the Department of Radiology of the Breast Radiology Division who have been blinded to the clinical pre - therapeutic examination and pathological result. US tumor assessment was undertaken in a prospective way. MRI images were obtained with Siemens® Magnetum Symphony Syngo 1.5 Tesla, using T1 and T2 weighted sequences and volume sequences (six stages) before and after paramagnetic contrast administration, and processed for kinetic behavior assessment (subtraction sequence). Tumor measurements were determined using Pixer Viewer® software.

Neoadjuvant chemotherapy, consisting of 4 cycles of doxorubicin 60mg/m^2 + cyclophosphamide 600 mg/m^2 (4AC) followed by 4 cycles of paclitaxel 175mg/m^2 (4T). All patients underwent adjuvant radiotherapy.

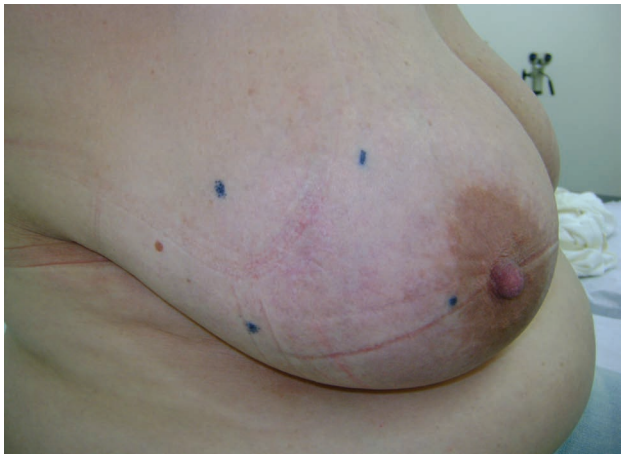


Figure 2. *Ink - marked tumor before neoadjuvant chemotherapy*

Surgical and pathological considerations

Tumor edge projection ink - marking on the skin (**Figure 2**), was performed prior the chemotherapy. The surgical drawings must include the tumor area regardless the clinical and radiological response. It is important to define the preoperative planning regardless the clinical response.

Pre - and post - therapy assessments were performed to determine whether an oncoplastic technique was possible. This study considered oncoplastic surgery treatment as a group of techniques able to provide an immediate breast remodeling and also the immediate breast reconstruction (IBR), single stage, with implants. Surgical planning was based on physical examination and imaging techniques prior and after chemotherapy, as well as on post - chemotherapy response.

The surgical choice took into account tumor size, breast volume, ability of resection of the marked area, likelihood of obtaining a surgical margin (1 cm), comorbidities, and patient desire.

Surgical specimens were identified according to their topography and spatial position. Perioperatively, an experienced pathologist examined the surgical margins by frozen section. In - depth gross and microscopic examinations were performed. All specimens including the ink - marked areas of primary neoplasia were completely sectioned for microscopic examination so that the residual tumor size could be measured even when it could not be well determined grossly. To evaluate the pathologic response we took into account the tumor area, and any fibrotic areas and presence of residual disease foci: macroscopic (residual nidus over small areas) and microscopic (residual scatter cells over original volume). Final pathologic measurement was based on total tumor size, i.e., the sum of invasive plus non - invasive disease, if present. In cases of complete pathologic response associated with in situ residual carcinoma, total tumor distribution estimates were used (**Table 1**).

Clinical, radiologic or pathologic tumor response to chemotherapy was classified according to RECIST criteria[18].

All patients were submitted to a complete axillary dissection (Levels of Berg 1, 2 and 3) .

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science - SPSS for Windows® version 17.0. The Friedman's test was used to determine whether variables were parametric or non - parametric. The study sample was characterized using descriptive statistics. MG, US and MRI results were compared with PE findings before treatment, and with anatomopathological findings after treatment. The reproducibility of diagnostic methods was assessed with the intraclass correlation coefficient (r_{icc}). The median values of the measures obtained using the diagnostic methods were compared using the Friedman's test. Wilcoxon's test was used when differences in at least one of the groups were detected. Statistical significance was set at 5%.

Results

Fifty women completed treatment. Patient mean age was 46.7 years (21 - 65 years). Infiltrating ductal carcinoma was present in 92% and infiltrating lobular carcinoma in 8% of the cases, with nuclear grades II and III in 95.7%.

Pre - and post - neoadjuvant chemotherapy (NC) tumor size was measured on PE (all cases). Before NC, tumor size could not be determined by MG, US and MRI in 19 (38%), 3 (6%), and 4 (8%) of the cases, respectively. After chemotherapy, MG, US and MRI measurements were not taken in 25 (50%), 1 (2%), and 11 (22%) of the cases, respectively. Clear MG image could not be obtained due to unfavorable or dense breast parenchymal pattern[32]. Residual tumor size was measured in 100% of the cases.

Pre - NC median tumor size was 6.5 cm (3.0 - 14.0 cm) and 4.0 cm (0 - 14.5 cm), as measured on PE and AP.

Radiologic and pathologic examinations did not confirm 20% of the clinical complete responses. Pathologic responses were classified as stable disease, progressive disease, partial response and complete response in 10%,

Table 1. Correlation among the different pathologic response types and surgical assessement

Pathological Findings		Radical Mastectomy	Oncoplastic Techniques	Total N (%)
Partial response	Concentric diminution	14(42,4%)	9(52,9%)	23 (46%)
	Macro and microscopic (invasive plus *in situ*)	2(6,1%)	2(11,8%)	4 (8%)
	M icroscopic disease	4(12,1%)	3(17,6%)	7 (14%)
	Macroscopic disease	5(15,2%)	1(5,9%)	6 (12%)
Stable disease		4(12,1%)	1 (5,9%)	5 (10%)
Complete response		0	1 (2%)	1 (2%)
Progressive disease		4(12,1%)	0	4 (8%)
Total		33(100%)	17(100%)	50(100%)

Table 2. Pre - and post-NC tumor size

Tumor size	PE		MG		US		MRI		AP
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Post
Number of patients	50	50	33	25	47	49	46	39	50
Mean	7.07	3.54	4.43	3.53	3.93	2.75	5.95	3.87	4.51
Median	6.50	3.30	4.40	3.50	3.80	2.00	5.95	3.50	4.00
Standard deviation	2.02	2.53	1.42	2.34	1.67	2.04	1.83	2.78	3.04
Minimum	3.00	0	1.30	0	0.50	0	3.00	0	0
Maximum	14.0	10.00	7.90	10.00	8.00	10.00	10.20	12.90	14.50
Percentile 25	6.00	2.00	4.00	2.10	2.80	1.55	4.57	2.00	1.97
Percentile 50	6.50	3.30	4.40	3.50	3.80	2.00	5.95	3.50	4.00
Percentile 75	8.00	5.00	5.00	4.65	5.00	3.40	7.00	5.60	6.85

Pre-NC correlation - Friedman's test p<0.001 and Wilcoxon's test p<0.008;
Post-NC correlation - Friedman's test p=0.613

8%, 80% and 2% of cases, respectively. A great variety of pathologic responses was observed (**Table 1**).

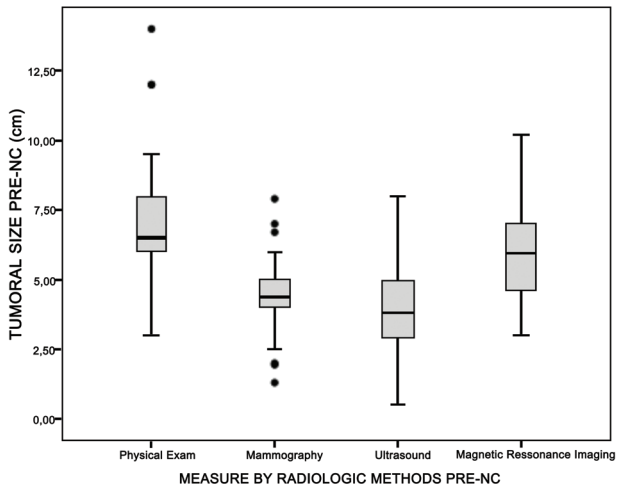
Pre - chemotherapy PE tumor size best correlated with MRI (r_{icc} 0.588, p<0.001) (Figure 3), followed by US (r_{icc} 0.408, p = 0.002) and MG (r_{icc} 0.016, p = 0.46) measurements.

The comparison of pathologic tumor size with post - chemotherapy PE and radiologic measurements revealed that MRI showed the best correlation (r_{icc} 0.738, p <0.001) (Figure 4), followed by MG (r_{icc} 0.681, p < 0.001), PE (r_{icc} 0.381, p = 0.003) and US (r_{icc} 0.371, p = 0.004).

Given that variables were nonparametric and the groups were paired in these cases, mean tumor size values were compared in order to validate the results (**Table 2**).

After chemotherapy 20 patients were supposed to be submitted a BCT. However during surgery it was reduced to only 17 (34%) patients who were operated upon and actually received some kind of OST. Most part of patients underwent OST were submitted to MRI pre - CN (15 cases, 88%) and post - CN (12 cases, 77%). In some cases, MRI was not performed due to technical problems, patient claustrophobia, or patient no - show.

The post - QN intraclass correlation related to PE, MG, US and MRI for the mastectomy cases were respectively 0.555 (p= 0.012), 0.827 (p=0.001), 0.571 (p=0.11) and 0.838 (p<0.001). The same correlation for the OST cases was respectively 0.181 (p=0.347), 0.605 (p=0.091), 0.257 (p=0.280) and 0.455 (p=0.165).



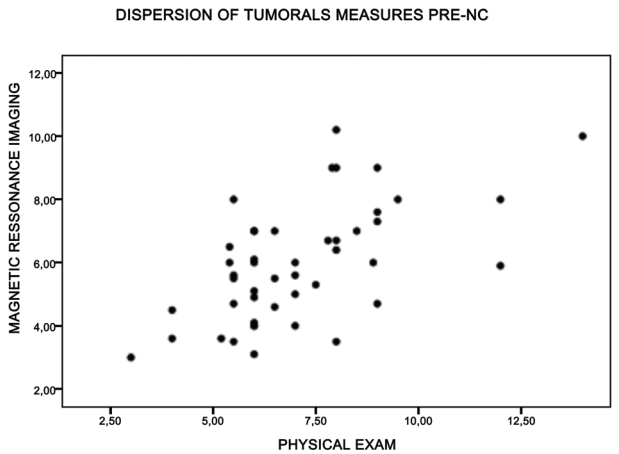
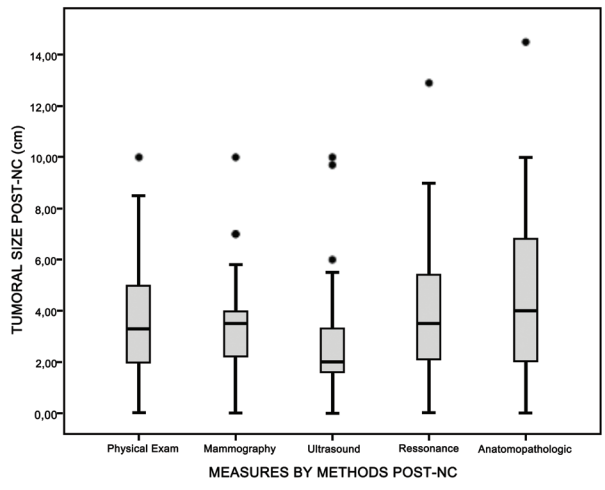


Figure 3. *(a) Box Plot of pre - chemotherapy measures; (b) correlation between pre - NC PE and MRI tumor measures.* r_{iic} *0.588, p<0.001*



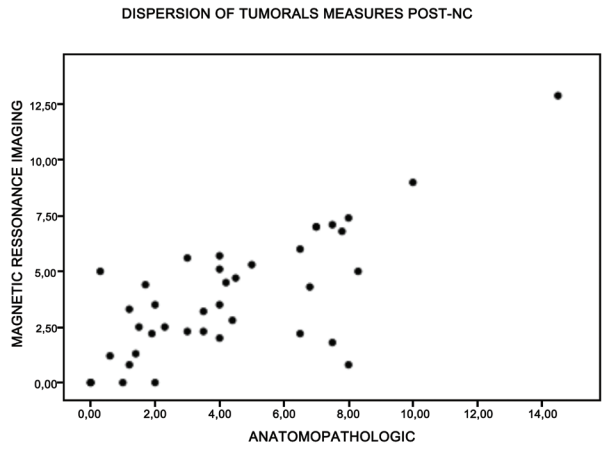


Figure 4.*(a) Box plot of post - chemotherapy measures; (b) correlation between post - NC PE and MRI tumor measures.* r_{icc} *0.738, p<0.001*

Discussion

Initially inoperable LABC has been associated with high rates of mastectomy and poor survival[19] . Neoadjuvant therapy, initially used in patients with operable tumors, particularly candidates for breast conservation treatment, has become more widespread [3, 20, 21]. Within this framework, preoperative planning is essential. Optimal planning of surgical treatment relies on the use of imaging techniques to detect tumor response. Histological studies have shown that pathologic response to NC may be diverse[22 - 24]. Therefore, accuracy in predicting the extent of residual lesions that may influence surgical decisions is of paramount importance, especially in breast - conservation surgery[13] . OST allows a wide and safe approach with minimal aesthetic impairment[5]. Accurate tumor size estimation is critical in guiding OST, and some authors advocate the use of a combination of methods for tumor assessment[13] . Weatherall et al[25] demonstrated that the tumor size correlation coefficient between MRI and pathologic analysis was the highest at 0.93, while PE and MG produced correlation coefficients of 0.72 and 0.63, respectively, compared to histologic measurement. MRI increases the accuracy of the radiologic evaluation of the response to chemotherapy, being therefore relevant when a conservative surgery is contemplated[16, 26]. In this study, both MG and US showed no important correlation before surgery. MRI correlation, in turn, was significant and showed a moderate - to - strong correlation rate (r_{icc} 0.738, p <0.001). This suggests that MRI

measurements are more reliable than those obtained on PE. A graphic analysis of the results (**Figures 3 and 4**) reveals the correlations obtained. MRI does not expand the number of conservative surgery but allows better conditions for the surgeon to expand its trial of the surgical planning.

MRI has been more and more used for the preoperative assessment of patients with LABC after NC. Bhattacharyya et al [27] found that MRI correlation with pathologic size was r=0.71, consistently with others who reported correlations of r= 0.75 [42], and r=0.72[28] . Despite the diverse pathologic responses observed, our findings (r=0.73 correlation) are in line with those reported in the literature. In four of our cases, MRI had complete radiologic response while in three others there was tumor microfragmentation. It is noteworthy that in the series mentioned above there were few stage III cases and the median tumor size was smaller than in our study. Cheung et al[29], with equipment similar to ours, demonstrated that in tumors larger than 4cm MRI correlation was close to ideal (r =0.98) while palpation showed only a moderate correlation (r=0.68). Although examinations were supposedly performed under the same conditions, palpation correlation was weak (r=0.38), and MRI correlation did not exceed r=0.73 in our study. It is possible that the tumors assessed were so large that radiologic analysis and physical examination were hampered.

Several trials have showed that preoperative MRI in breast cancer patients, non - LABC, with tumors that would have met the criteria for treatment with lumpectomy may increase the number of unnecessary surgical procedures[30]. All aimed at small lesions of breast cancer. The COMICE trial [31, 32] studied the impact of increased detection rate of additional disease foci with MRI in clinical practice. They reported that the addition of MRI to conventional triple assessment (MG, US and cytology) was not significantly associated with reduced operation rate. They concluded that MRI might be unnecessary. The Monet Trial [33] was a randomized controlled trial that indicated that the addition of MRI to the usual care in patients with nonpalpable breast cancer does not reduce the number of surgical procedures and appears to be associated with a significantly increased reexcision rate. Obviously the MRI indication for surgical planning has been misunderstood and sometimes exagerated. There is a need for time and further studies for more conclusions as recently exposed by Dr Fisher[34]. Those points might be different for patients who underwent to NC, although they must be mentioned. Prospective trials should also be considered after NC to assess the MRI for that particular indication and taking into account the surgical use of oncoplastic techniques.

After NC anatomopathologic responses are quite variable. With oncoplastic surgery and favorable breasts, tumors can be safely removed regardless of their size[5, 35,36]. Even though MRI correlation with pathologic findings was found to be high in this study as well as in others reported in the literature, it cannot accurately identify residual tumors in all cases that justifies the preoperative marking of the area to be resected, particularly when the patient has LABC and the possibility of conservative management is being considered.

Another point which is worth noticing in our series was the low rate of complete pathologic response to the chemotherapy regimen used. In the National Surgical Adjuvant Breast and Bowel Project (NASPB - 27), the rate of complete pathologic response to the same chemotherapy regimen was 25.6%[37], whereas in this study the rate of complete response to the same chemotherapy regimen was 2%. This is likely to be due to the large size of the tumors in our series (median of 6.5cm, range 3.0 - 14.0cm), or to the method used for anatomopathologic analysis - total resection of the tumor area before chemotherapy and systematized serial sectioning of the entire area. This is worth noticing because resection of the total tumor area prior to chemotherapy and removal of potential tumoral deposits not detectable with imaging techniques have not been performed in any of the controlled studies available.

In general, the reported proportions of LABC patients undergoing breast conservation surgery after NC (as opposed to adjuvant chemotherapy) have increased. In this study we have discussed how a preoperative planning could help to treat large tumors by an oncoplastic approach. These techniques provide tools to remove the whole tumor area previous to NC and allow immediate breast reconstruction or glandular remodeling. The ink - marked tumor[38] was completely resected irrespective of clinical - pathologic response. Post - chemotherapy radiologic tumor measurements were compared with those obtained through AP. This allowed controlling the quality of both measurement and pathologic response type assessment of the tumor resection.

Conclusions

LABC usually presents with large tumor extension. This

facilitates the surgeon's choice to treat radical. On the other hand a careful preoperative planning and detailed pathologic analysis are of paramount importance in the decision for using oncoplastic surgery techniques. The radiological exams do not provide a well - established correlation. The MRI seemed to be the best correlation exam however the pathological complete response after NC showed very low rates probably due to the systematic pathological analysis focused on the pre - NC tumoral ink - marked area. The proper use of oncoplastic techniques helps on this dissection and allows to increase rates of BCT and IBR in case of LABC.

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Conflict of interests

The authors declare that they have no commercial competing interests or financial support for this study.

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ABBREVIATIONS

NC: neoadjuvant chemotherapy
OST: oncoplastic surgery techniques
BCT: breast conservative treatment
IBR: immediate breast reconstruction
PE: physical examination
MG: mammography
US: breast ultrasound
MRI: breast magnetic resonance imaging
LABC: locally advanced breast cancer
BCH: Barretos' Cancer Hospital
AP: anatomopathologic examination
A: doxorubicin
C: ciclofosfamide
T: paclitaxel

18th SIS World Congress

News from the 18th SIS World Congress on breast healthcare

Apostolos Zavos [1], Ioannis Papadopoulos [2], Lydia Ioannidou - Mouzaka [3]

[1] Surgeon Gynecologist Obstetrician. Subspecialty Breast Diagnostic and Surgery, Board member of Hellenic Senologic Society, Deputy Editor of Mastologia Journal. Larisa, Greece
[2] Resident - Radiologist Sismanoglio Hospital, Athens
[3] Gynecologist, Surgeon - Breast Specailist, President of the Hellenic Senologic Society

The **Senologic International Society (SIS)** is organizing a World Breast Congress every two years in a different continent. The 18th World Congress was hosted jointly by the **SIS** and by the American Society of Breast Disease **(ASBD)** and associated with 100 entities from 50 countries. It was one of the biggest global educational forums that aimed to provide to participants access to the latest achievements in research, clinical practice and techniques in breast healthcare.

This time the **18th SIS Congress** took place in Orlando, Florida, USA, October 16 - 19, 2014, at Walt Disney World Swan Hotel. It was an exciting meeting in Senology, with distinguishes invited speakers and numerous participants leading professionals who came from all around the world united by a passion to improve the quality of services provided in the diagnosis and treatment of breast diseases and the quality of life of those fighting with breast cancer and breast related diseases.

SIS is the first and one of the biggest International Societies for breast diseases and breast cancer, founded in 1976 in Strasbourg - France, by the late **Charles - Marie Gros** (1910 - 1984). He was Professor of Medicine from 1950 - 975, and Head of the Department of Radiotherapy and Radiology at University of Strasbourg, France). He was the father of the modern breast imaging and forger of the concept of Senology.

He structured Senology step by step towards as to fulfill its main role, which was to represent the true alliance between all the Senologic entities in the various affiliated countries. In 1963, he created a new multidisciplinary medical specialty for the care of breast diseases, allowing scientific strictness and humanism, proposing to identify it with the term **"Sénologie"**. Other important SIS members, such as the **Honorary Presidents**, **Prs Hans Joachim Frischbier**, **Miguel Prats - Esteve** and **Umberto Veronesi** contributed in making SIS one of the biggest Senology Societies.

Since 1976, **SIS** aims on bringing together the National Societies of Senology around the world and improving the knowledge and the quality of breast health assistance worldwide. Since then promotes educational activities as it was the "Certificate of Senology" in Strasbourg and then through courses of International School of Senology, Seminars, National Congresses, International Congresses. He has implemented the accreditation program for Breast Cancer Centers and engages in collaborative activities with more than 100 affiliated Institutions.

On the other hand **ASBD** is a non - profit professional Medical Society in the United States that serves all healthcare professionals and advocates involved in the fight against breast cancer.

The mission of the Organization, which was founded

Corresponding author
Dr Apostolos Zavos MD
Surgeon Gynecologist Obstetrician. Deputy Editor of Mastologia Journal. Larisa, Greece, E - mail: zavosa@gmail.com

at 1976 at the Annual Congress of the American College of Obstetricians and Gynecologists, is to advance the multidisciplinary team approach to breast healthcare through professional education, consensus development and training programs.

This year the **ASBD** celebrates it's 38th Anniversary, and the Society is privileged to have an active leadership and membership composed of expert clinicians in all disciplines of breast healthcare. The **ASBD** provides an opportunity for clinicians to stay current with new findings in prevention, screening, diagnosis, and treatment including exposure to numerous new pharmaceutical and technological advances.

As co - hosts, **SIS** and **ASBD** managed to succeed a well - organized Congress, which held a very high scientific level.

The Congress

During the four days of the Congress, world internationaly recognized speakers delivered informative, thought provoking talks that both stimulated and challenged the audience. Participants and speakers engaged in robust debates and stimulating discussions on hot topics and controversial issues including epidemiology, prevention, screening, diagnosis, treatment, education, rehabilitation, and nursing. Free papers and posters reflected recent work and provided a forum for exchange ideas, open discussion and collaboration.

In addition to the main program, there were unique opportunities for industry leaders to showcase their products and offer workshops to clinicians from all around the globe. One of the greatest events of the Congress was the **Global Summit on Oncoplastic Surgery**.

Beside that, a lot of hot and controversial topics about the sentinel lymph node, the high risk not malignant lesions, the evolutions in breast radiations, the diagnostic challenges, DCIS and lobular lesions, triple negative cancers were discussed.

Finally, of great interest and importance were the Tumor Board sessions that were presented and discussed by a panel of expert pathologists, surgeons, radiologists, radiotherapists and medical oncologists. For everyone being there, it was a great opportunity to build on a valid opinion among the evidenced based practice and gain access to the latest research.

During the first day of the Congress a lot of interesting workshops took place, such as the management of **HR** (high risk) patients, large format histopathology, the interventional breast ultrasound workshop and an expert panel meeting about how we practice Senology in 2014.

Nevertheless, the great event of the day was the Global Summit on Oncoplastic Surgery. It was a unique opportunity for breast surgeons interested in oncoplastic surgical management and treatment of breast cancer and breast disease to meet some of the experts in the field, talk with them and get used with specific techniques that can be used in day to day practice.

It was a great opportunity to learn ways to begin integrating Oncoplastic techniques into our practice from others who have accomplished this. Participants met Internationally famous specialists, true pioneers in the field of the Oncoplastic Surgery, as well as general breast surgeons who have successfully adopted new techniques into their practice to improve patient care.

Important topics that were discussed were the importance of the multidisciplinary approach and risk assessment of the patients pre - operatively, recognized factors that impact decision making process when considering breast conservation vs mastectomy, as well as how to determine suitable candidates and appropriateness for prophylactic mastectomy.

Special consideration was given in the understanding of how to integrate augmentation; reduction and mastopexy when performing breast surgery as also skin and/or nipple sparing mastectomy with immediate reconstruction.

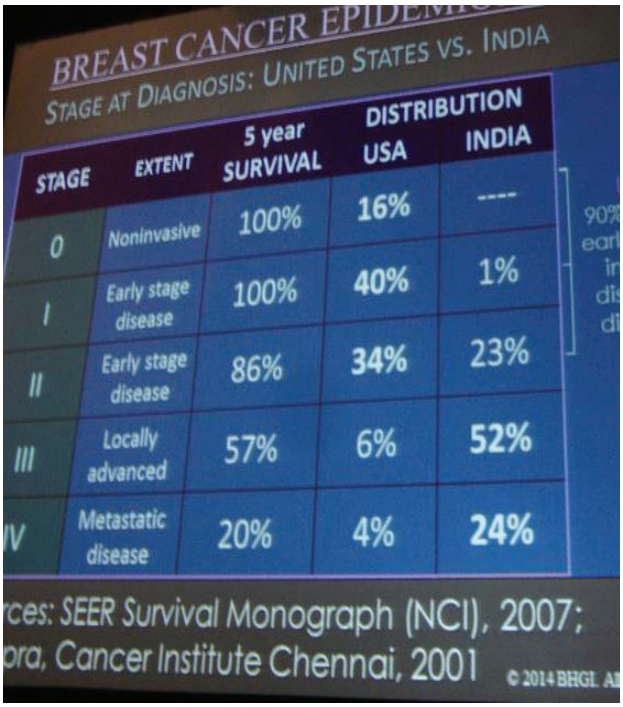
Participants were finally, enlightened on how to discuss with patients aesthetic approaches to breast cancer management and on the impact of methods of radiation therapy in the management of breast cancer patients.

Special interest was paid to the breast irradiation methods, especially the new ones, like partial breast irradiation, intraoperative radiotherapy, used to save time with focus on the final breast appearance, as well as the prophylaxis of future lung, heart problems and also the angiosarcoma (not so often seen in now days).

One of the pioneers in Oncoplastic surgery, **Dr Gail Lebovic**, MD was the winner of the 2014 Pathfinder Award. The **ASBD** Board of Directors established the Pathfinder Award as part of the Society's 30th Anniversary celebration to recognize the innovators who have combined research and clinical practice with an interdisciplinary understanding to advance the fight against breast disease and breast cancer.

After the announcement of the winner an inspiring 2014 Pathfinder Lecture followed namely "The Blessings of On-

Picture 1. *Conference Hall: The Congress Welcome Reception followed the Key lecture*



Picture 2 *from presentation (with permission). Table, showing the great difference, between USA and India, in the stage of cancer during diagnosis. (2014 BHGI)*

coplastic Surgery". We were able to go through the "surgical life" of one blessed person **"Dr Lebovic"** the establishment of a new type of surgeon, the breast surgeon who is a much more than just a person performing a mastectomy. Everyone in the audience felt moved with the efforts of these people to make breast surgery and oncoplastic surgery a reality for everyone today.

During the Opening Ceremony, the **SIS** President and Board of Directors awarded **Professor Ruben Orda** and **Dr Carlos Garbino** with "Medals of Excellence".

During the four days of the Congress there was a successful medical equipment and pharmaceutical products Exhibition where participants could enjoy their time with coffee and soft drinks while getting familiar with new technological equipment. There was also a separate room for posters were a lot of interesting topics were presented and discussed.

The 2nd day was very important with a lot of conflicting issues discussed and important conclusions made. The first "meet the experts" sections were about the surgical managements of BRCA carriers, for which annually mammography and MRI and clinical breast examination 2 to 4 times a year were proposed. Chemoprevention should be proposed for consideration for women after the age of 35 and childbearing and risk reduction mastectomy as an option.

For this special population the role of MRI was discussed. Special considerations were mentioned concerning the cost and the difficulty of making biopsies through MRI. Another issue mentioned was the detection of atypia in patient's family history and the increase of breast cancer risk.

At the same time, the difficulties in diagnosis and treatment of lobular neoplasia were also discussed at a "meet the experts" session. Special consideration was given in the pleomorphic LCIS and the margins difference between this neoplasia type and the invasive carcinoma.

One of the next sessions was the dense breast and the significant role of the ultrasound in such kind of breasts. At the same time, a very important problem was discussed, namely the management of breast cancer in the developing Countries. The first presentation started, with the statement of Seffrin that "every patient regardless of where he or she is born deserves an equal chance at a long life and good health". Something like this does not stand in these countries, since in contrast with the USA where 90% of the tumors are at diagnosis at an early stage, in India 80% are either locally advanced (52%) or metastatic

Friday, October 17, 2014					
07:30-08:30	Meet the Experts: Surgical Management of BRCA Carriers	Meet the Experts: Lobular Neoplasia. Where are we today with Diagnosis and Treatment	Meet the Experts: Radioactive Localization of Non-Palpable Lesions		
08:30-10:00	The Dense Breast	Management of Breast Cancer in Developing Countries		SIS Board of Directors Meeting 2	
10:00-10:30	Coffee Break, Exhibition and Poster Viewing			ASBD Board meeting (10:15 - 11:45)	Poster Viewing Session 1
10:30-12:00	Is Breast Cancer Prevention Possible in 2014?	Breast Ultrasound: Important Updates in 2014	Oral Communications - Session 1	ASBD Business meeting (11:45 - 12:15)	
12:00	Lunch Break, Exhibition and Poster Viewing				Poster Viewing Session 1
12:15-13:15	Industy Symposium *(Non-CME Promotional Session organized by Agendia)*				
13:30-15:00	Effective Use Of Breast Imaging Modalities	High Risk Lesions			
15:00 – 15:30	Coffee Break, Exhibition and Poster Viewing				Poster Viewing Session 1
15:30 -17:00	Controversies and Challenges with DCIS: A Multidisciplinary Perspective	Nurse Navigation: A Must in 2014	Oral Communications - Session 2		
17:00 – 18:30	Tumor Board Session: Multidisciplinary Approach to Rare Breast Lesions				Poster Viewing Session 1 (until 19:00)

Table 1. *Short schedule of the Scientific Program*

at diagnosis (24%). The importance of the Clinical breast examination was highlighted as also everyday problems such as the lack of post - surgical irradiation therapy and inadequate adjuvant systematic therapy. There are areas where only one Pathologist exists for a 1.000 bed hospital and the Pathologist report takes 4 - 6 months. **Dr.B.Anderson** from the U.S.A. referred to International Collaboration and implementation of research for developing cancer control strategies in developing Countries.

One of the next sessions was about Breast Ultrasounds and the important updates in 2014 with a panel of well known radiologists. **E.B.Mendelson** discussed the new changes in BIRAD's criteria for ultrasounds. **A. Munding-er** (the present President of the **S.I.S.)** presented the importance of defining small lesions stiffness, since the same characteristics have also small cysts or cancers.

The importance of elastography and the two types, strain and seer - wave were analyzed. Other issues regarding ultrasounds such as a screening tool and management of benign masses were also discussed.

At noon, a very interesting Industry Symposium was organized by Agentia, about the development and the validation of new recurrence assays. The new Blue Print Test, which evaluates 80 genes, was presented. There are steel many unresolved issues about these tests, the cost remains high and in many Countries the only available test from the Insurance Companies is the DX Oncotype test. The controversies about the usefulness of the test in clinical practice steel exist and further studies are needed.

During the afternoon the "High Risk lesions" session held the biggest interest with a crowded audience attending the problems occurring with scleroelastic lesions like Radial Scars, in diagnosis and management.

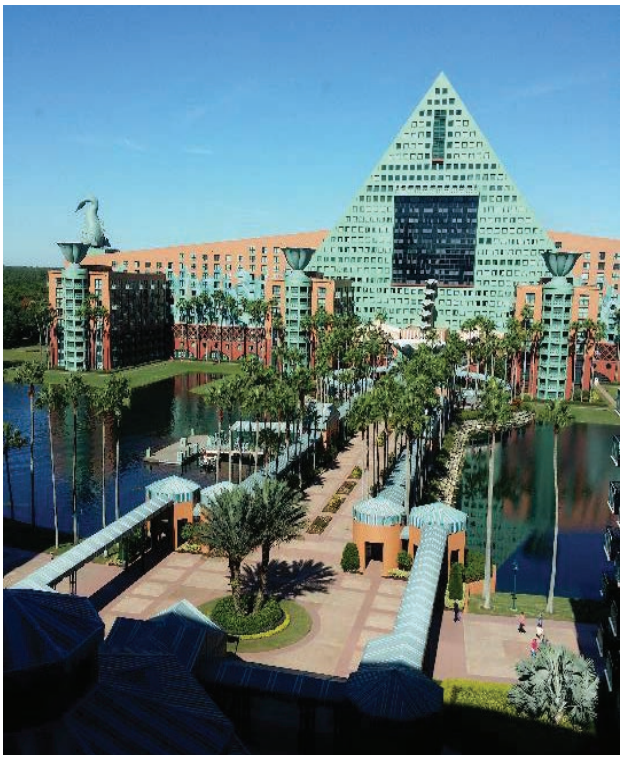
From 1979 it was recognized as a pathological finding characterized by **Azzopardi** as infiltrating epitheliosis.

For all these benign lesions the problem is the increased risk for cancer development in the future. According to the risk is based the decision of the management. Big discussion was made on atypical hyperplastic lesions, papillomas and LCIS.

T.Tod analyzed the role and the benefits of large format histopathology. This technic is the best way to evaluate atypical lesion, their margins and to correlate them with the imaging.

S.C.Willey discussed about the management of the above lesions, concluding that indication for the excision of them is the discordance between clinical, radiographic and pathologic findings, the inadequately sampling, the existence of atypia in core needle sampling and a palpable papilloma. Special interest was given to the expected upgrade rate of this lesions and their expected risk for breast cancer developing in 20 years.

On the contrary, only selected cases should be left without excision and should be monitored closely. For these



Picture 3. *Orlando, Florida, USA, at Walt Disney World Swan Hotel*

cases chemoprevention is an option that should be considered for the reduction of cancer developing.

The Greek origin, **K.P.Siziopikou** working in the USA, was the Pathologist that impressed during the DCIS session. She was also one of the basic panelists in the Tumor Board session that attempted a multidisciplinary approach for rare breast lesions such as metaplastic breast cancer, pleomorphic lobular carcinoma in situ and partial breast irradiation.

The next day, very important issues were discussed with the most interesting for Breast Surgeon in the personalizing approach of surgery in breast cancer, with special considerations for the multiple roles of the breast surgeon and his important position in organization and management of breast cancer patients from diagnosis through the therapy, treatment and the follow up.

Special surgical considerations were the nipple sparing mastectomy, approaches to minimize the risk for positive margins and issues concerning axillary surgery.

The sessions "Sentinel Lymph Node and Multidisciplinary Management, 2014" held great interest. Based on the new guidelines and the Z0011 trial a lot of discussions took place and stimulated disagreements. Special issues that were analyzed were the preoperative imaging of axilla lymph nodes, the optimal management of the patients when the lymph nodes prove positive, whether sentinel lymph node procedure should be used after Neoadjuvant Chemotherapy and especially how should we treat patients that were lymph node positive before Neoadjuvant Chemotherapy.

Last but not least, the importance of Neoadjuvant Chemotherapy was discussed, as also the prevention and treatment of breast cancer related lymphedema. The role of Genomics nowdays in breast cancer was also a matter of debate.

On the last day of the Congress less surgical but really important issues were discussed, concerning psychological, psychosocial and psychosexual topics, global health issues.

Screening and treatment problems in the World were discussed as well as educating and empowering patients regarding emotional, psychosocial and sexual recovery after breast cancer.

Closing this review of the SIS Congress it would be a mistake not to mention the important role of some people like Laszlo Tabar who as an invited speaker presented "hot topics" like the "Update and the current view on the mammography screening debate" basically questioning the Canadians trial results, as also the role of automated breast ultrasound combined with digital mammography as a better approach to examine women with dense breast tissue, and a really revolution proposal to unify the classification of breast and prostate cancers based on the anatomic site of cancer origin and on long - term patient outcome.

It was really a blessing to listen him talking with such enthusiasm there, as we also have the priviledge to hear him here in Athens in November 2014, invited by the President of the Hellenic Senologic Society Pr Lydia Ioannidou - Mouzaka, in an Advanced Course on multimodality detection and diagnosis of breast diseases.

Another great effort that was made during that Congress was the successful claiming of the 2020 SIS World Congress on Breast Diseases to be held in Athens Greece. This Congress we believe it can be one of the biggest International events on breast, as in 1992 was the Congress of Rodos Island's, confirming the high medical standards of our Country. But of course, such a success always is combined with the participation and assistance of the Members of all the National Societies on Senology Worldwide. ■

Mechanisms and Management of Resistance to Hormonal Treatment in Breast Cancer

Andreas V. Koulouris[1], Panagiota Economopoulou[2], Nikolaos Kentepozidis[1]

[1]251 Airforce General Hospital, Department of Medical Oncology, Athens, Greece

[2]Medical Oncology Unit, 2nd Department of Internal Medicine, Attikon University Hospital, Haidari, Athens, Greece

Introduction

Breast cancer is among the leading causes of cancer - related death in women. It is unanimously considered a highly heterogeneous disease that is divided into at least five subtypes. Several studies have indicated that there are three major factors that contribute to this heterogeneity in breast cancer: a) the differential expression of estrogen receptors, b) the proliferation of cancer cells and c) the ERBB2/HER2/neu amplification. The identification of two most common subtypes is based on the expression of estrogen receptors. Approximately 70% of human breast tumors show high ER expression and can be classified as "luminal". This term indicates that this tumor arises from the inner (luminal) cells lining the apical surface of the mammary ducts. Luminal tumors can be further subdivided into "Luminal A" and "Luminal B" according to HER2 expression and the ki67 proliferation index. Particularly, Luminal B tumors are distinguished by either expression of HER2 or high proliferation rates.

As far as anti - estrogen treatment is concerned, it aims either to decrease estrogen levels or to inhibit signal transduction through estrogen receptors. Anti - estrogen therapy consists of three components: a) the Selective Estrogen Receptor Modulators - SERMs, such as tamoxifen, that blocks estrogen receptors, b) the Selective Estrogen Receptor Modulators - SERMs, like fulvestrant, which accelerates the proteasomal degradation of the estrogen receptor and c) the aromatase inhibitors such as letrozole, anastrozole and exemestane, which block either the production of estrogen or the action of estrogen on receptors (**Table 1**).

Tamoxifen has been the gold standard endocrine therapy for postmenopausal, hormone - sensitive breast cancer for over 20 years. However, approximately 50% of patients with metastatic disease do not respond to first - line treatment with tamoxifen (de novo resistance). Furthermore, a considerable proportion of patients, who initially respond to treatment with tamoxifen, eventually develop recurrence after completing tamoxifen treatment (acquired resistance). This different response may emerge from the expression of specific agents involved in signal transduction pathways, which could be identified as potential predictive biomarkers for resistance to the aforementioned therapy in breast cancer. Finally, these biomarkers may be useful to identify the patients who may benefit from further targeted therapies.

Tamoxifen resistance is the main factor that influences the treatment effectiveness. Aromatase inhibitors either as initial adjuvant therapy or sequentially after tamoxifen may be beneficial to patients whose tumors are resistant to tamoxifen. However, when it comes to advanced breast can-

Corresponding author

Panagiota Economopoulou

Oncology Unit, 2nd Department of Internal Medicine Attikon University Hospital,
National Kapodistrian University of Athens, 1st Rimini St, 12462, Haidari, Athens, Greece, Tel: +30-210-5831655,
Fax:+30-210-5831690, Email: panagiota_oiko@hotmail.com

Table 1. Mechanism of action according to different types of hormonal trerapy		
Hormonal therapy	Pharmacodynamics	Drugs
Selective Estrogen Receptor Modulators-SERMs	Estrogen Receptor Inhibitors, mixed agonist/antagonist activity	Tamoxifen, Raloxifene
Selective Estrogen Downregulators-SERDs	Acceleration the proteasomal degradation of the estrogen receptor	Fulvestrant
Aromatase inhibitors	Decreased estrogen production	Letrozole, Anastrozole, Exemestane

cer, the response rate to aromatase inhibitors seems to be slightly higher than that of tamoxifen and both *de novo* and acquired resistance to this treatment may also be noticed. Finally, fulvestrant has been proven to have clinical efficacy in breast cancers with second recurrence occurred following the initial response to tamoxifen and aromatase inhibitors[1-3].

In spite of the increasing number of new endocrine agents introduced in the last few years, resistance to hormonal therapy remains a major obstacle to successful breast cancer treatment. The in - depth investigation of molecular mechanisms underlying this resistance will lead to the development of new promising therapeutic strategies. This chapter initially reviews the function of the estrogen receptor and subsequently focuses on the analysis of resistance mechanisms to hormonal therapy in breast cancer and their impact on treatment strategies.

The Function of Estrogen Receptors Alpha and Beta

Estrogens play a major role in the growth, differentiation and function of a plethora of tissues including normal breast tissue, endometrium, bones, the cardiovascular system and brain. The actions of estrogen are mediated by two dimeric nuclear proteins ERα and ERβ, each encoded by a separate gene, ESR1 and ESR2 on the sixth and fourteenth chromosome (6q25.1 and 14q23.2), respectively. Both receptors have been documented in normal breast tissue, but only ERα expression has been demonstrated to be implicated in tumorigenesis. On the other hand, although several aspects of ER β's role remain unclear, it seems to exert beneficial effects on tumor progression through the inhibition of estrogen - induced proliferation of cancer cells. Furthermore, there are indications that ER - β deficiency contributes to tumorigenesis with its over - expression to a better prognosis for breast cancer patients.

Estrogen receptors alpha and beta show significant overall sequence homology, and both are composed of six domains. The N - terminal A/B domain (also called AF1) is able to transactivate gene transcription in the absence of bound ligand (e.g., the estrogen hormone). The C domain, also known as the DNA - binding domain, plays a crucial role in receptor dimerization and, also, binds to estrogen response elements in DNA. The D domain is a hinge region that connects the C and E domains. The E domain which also referred to as "Ligand Binding Domain" (LBD) contains a site which is responsible for receptor dimerization and the ligand binding cavity AF2 as well as binding sites for co - activator and co - repressor proteins. The E - domain in the presence of bound ligand is able to activate gene transcription. The C - terminal F domain seems to have a coordinating function between AF1 and AF2 domains, although this function is not of paramount importance when it comes to transcription activation. Finally, it is noteworthy to mention that the aforementioned receptors show a high degree of homology between the DBD and LBD domains (**Figure 1**).

Estrogen receptor - α mediates cells proliferation and survival via two pathways, namely the classical and the non - classical pathway. The classical pathway is triggered when the estrogen receptor binds estrogens, which leads to its dimerization as well as transcription initiation. The estrogen - receptor complex, which is formed, binds a DNA sequence, which is called Estrogen - Response Element (ERE) either directly or through protein - protein interactions. This results in recruitment of regulatory proteins, which amplify or suppress transcriptional activity of the receptor according to the ligand specificity. On the contrary, as far as the non - classical pathway is concerned, the response to estrogens is mediated by estrogen receptors, which are embedded in the cytoplasmic membrane. Estrogen receptors interact

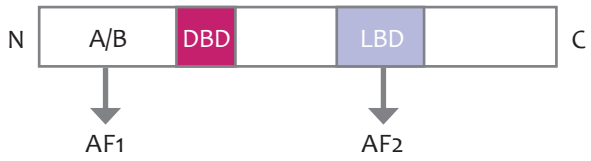


Figure 1. *The domain structures of estrogen receptor*

with a plethora of proteins included G - proteins, growth factors receptors (EGFR, IGFR1, HER2) and cytoplasmic kinases (MAPKs, P13K, AKT) activate independent gene - regulatory pathways. Recent studies provide evidence that G - Protein - Coupled Estrogen Receptor 1 (GPER) may be implicated in the non - classical pathway of response to estrogens. To sum it all up, there are interactions between these two pathways, which can lead to the development and progression of breast cancer[4-6].

Hormonal Therapy

Hormonal therapy in hormone - dependent breast cancer entails the manipulation of the endocrine system through exogenous administration of drugs that inhibit the production or function of estrogens. Drugs included in the SERMs and SERDs categories interact with ER directly. Firstly, the SERM inhibitor binds to the estrogen receptor, but the altered receptor structure prevents transcription from initiating, although the transcription factor is able to bind to DNA. Particularly, tamoxifen, which belongs to this drug category, silences AF - 2 in ERα to produce antiestrogenic action; however AF - 1 is not fully silenced. On the other hand, drugs included in the SERDs group, such as fulvestrant, bind to the LBD domain and subsequently inhibit the receptor dimerization, which results in impaired transcriptional regulatory activity and in proteasomal degradation of the receptor.

Different molecular mechanisms underlie the activity of aromatase inhibitors. It has been demonstrated that most estradiol in women during the reproductive years, is produced by the granulosa cells of the ovaries by the aromatization of androstenedione to estrone. When it comes to post - menopausal women, the decline in estradiol levels is attributed to a decrease in its production by ovaries. But estradiol is not only produced in the gonads; in particular, fat cells produce active precursors to estradiol, and will continue to do so even after menopause. Moreover, estradiol biosynthesis in these women is mostly observed in peripheral tissues, where aromatase catalyzes the last steps of estrogen biosynthesis from androgens and specifically, it transforms androstenedione to estrone and testosterone to estradiol. That illustrates why estradiol levels remain within the 10% of the pre - menopausal reference range. Estrogens, which are produced by peripheral tissues of post - menopausal women, are considered to stimulate breast cancer cells in which estrogen receptors are expressed. Finally, irreversible steroidal inhibitors, such as exemestane, compete with potential endogenous substrates and irreversibly bind to aromatase leading to its deactivation. On the contrary, non - steroidal inhibitors, such as letrozole, inhibit the synthesis of estrogen via reversible competition for the aromatase enzyme[7-10].

Response to Hormonal Therapy in Breast Cancer

As far as the response to Hormonal Therapy is concerned, the evaluation of tumor cell estrogen receptor (ER) expression status by immunohistochemical analysis is of paramount importance. Particularly, the absence of the expression of estrogens receptors is equivalent to treatment failure. It has been investigated that the majority of cancer cells, which exhibit intrinsic resistance to endocrine therapy, are associated with insufficient expression of estrogen receptors. However in a few cases, intrinsic resistance has also been encountered in ER positive tumors. But is the immunohistochemical evaluation of hormone receptor status enough to predict hormone responsiveness in breast cancer?

There are some considerations that need to be taken into account before this can be answered. To begin with, ER positive tumors: a) do not respond at all to endocrine therapy, b) present differential responses to endocrine disrupting compounds c) show heterogeneous resistance among hormonal therapy categories and, finally, d) often convert their drug sensitive phenotype to drug resistance even if their estrogen receptors status remains relatively constant. It is blatantly obvious that ER tumors represent a heterogeneous subgroup, especially when it comes to sensitivity to hormonal therapy. To sum up, it all boils down to the fact that further research is needed to select individual biomarkers which would be useful to evaluate the effectiveness of hormonal therapy in breast cancer.

Regarding the response to hormonal treatment, a significant degree of heterogeneity is attributed to the estrogen receptors level of expression, which can be considered a quantitative predictive biomarker of hormonal treatment response. It has been investigated that both adjuvant treatment with tamoxifen and hormonal therapy

for metastatic breast cancer contribute to reduced recurrence and mortality rates when it comes to tumors with a high estrogen receptors expression. According to St. Gallen 2009 recommendations on the primary treatment of early breast cancer, tumors with immunohistochemical ER expressions of more than 50% should be considered highly responsive to hormonal therapy. On the contrary, results of clinical trials (ATAC and BIG 1 - 98) demonstrate that there is no statistically significant correlation between levels of ER expression and the effectiveness of aromatase inhibitors compared with tamoxifen. Consequently, when it comes to the benefit of hormonal therapy, the rates of the receptors positivity seem to be a poor predictive biomarker in comparison with receptors positivity itself. However, patients with ER positive tumors seem to be in dire need of reliable predictive biomarkers correlated with the *de novo* resistance to hormonal therapy. Furthermore, this heterogeneous response to hormonal therapy may be partially attributed to ER interactions with several regulatory factors as well as signal transduction pathways. HER - 2 positive tumors are a striking example of poor response to hormonal therapy, although high levels of ER expression are observed. From a molecular perspective, diverse response among drug categories can be explained by molecular differences. Particularly, clinical trials evaluating letrozole reveal that its efficacy is higher regarding HER - 2 and EGFR positive tumors.

In conclusion, the aforementioned heterogeneity of the ER positive tumors, when it comes to their therapeutic response, poses a challenge for research. The identification of biomarkers correlated with *de novo* resistance to these drug categories seems to be of supreme importance, regarding the screening of patients who will benefit from the timely initiation of additional therapies [11 - 13].

Mechanisms of Resistance to Hormonal Treatment and Management

As far as endocrine therapy in breast cancer is concerned, several mechanisms of resistance have been investigated, such as loss of estrogen receptor, regulation of signal transduction pathways, changes in microRNAs expression and modification of the tamoxifen metabolism. Furthermore, both the interactions between classical and non - classical pathways of estrogen response and the correlation between ER subgroups and growth factors contribute to the resistance to hormonal therapy. The major mechanisms responsible for this resistance are described below.

1. Loss or Modification of ER Expression

As highlighted in previous paragraphs, estrogen receptors positivity is considered the fundamental predictive biomarker of response to hormonal therapy, whereas the loss of ER expression seems to be the major mechanism of *de novo* resistance. This loss of ER expression can be explained by several mechanisms. Initially, epigenetic changes, such as the methylation of CpG domains of ER gene promoter and the modification of histones lead to nucleosome arrays in their most compact form, thus preventing transcription of the genes into messenger RNA. *In vitro* experiments have shown that combination therapy with DNA methyltransferase - 1 inhibitors (DNMT, such as 5 - aza - 2' - deoxycytidine, which are enzymes that catalyze methylation) and histone deacetylase inhibitors (HDAC inhibitors, for example trichostatin A, which are enzymes that can result in the hyperacetylation of histones, thereby affecting gene expression) promotes the activation of ER expression in breast cancer cells and increases their sensitivity to antiestrogens. Moreover, *in vitro and in vivo studies* have demonstrated that treatment with entinostat, belongs to HDAC inhibitors contributed to increased aromatase and ER expression and, subsequently, to sensitization of cancer cells to estrogens and letrozole. Furthermore, Scriptaid, which is another HDAC inhibitor has proven that it promotes the re - expression of functional estrogen receptors, thus blocking cell proliferation and resensitizing hormone - resistant cancer cells to tamoxifen.

On the other hand, it is supported that the loss of ER expression may be responsible for acquired resistance to hormonal therapy. However, only 17 - 28% of patients with acquired resistance to hormonal therapy lack of ER positivity and, moreover, ER positive tumors, which initially respond to tamoxifen, often continue to express estrogen receptors even after developing resistance to the treatment. Needless to say, that, approximately 20% of these patients responded to second - line treatment with aromatase inhibitors or fulvestrant, which provides additional evidence that these tumors continue to express estrogen receptors.

Hypoxia, EGFR or HER2 over - expression (upregulation), MAK kinases activation, expression of genes, such as p53 and pRb2/p130 are posed to be additional mechanisms involved in loss of ER expression. Particularly, hypoxia induces proteasome - dependent degradation of estrogen receptor alpha in cancer cells. It has also been documented that a high expression of EGFR and HER2 in ER negative cells may unveil that the activation of signaling pathways of growth

factors and the subsequent activation of MAP kinase may contribute to transcription repression of ER gene, which results in resistance to hormonal therapy. Moreover, recent research has indicated that p53 mutations deregulate the ER gene expression. Needless to say that significant portion of breast cancer with p53 mutations are classified as ER negative tumors. Finally, given that pRb2/p130 - complexes bind to the ER - alpha promoter and play a crucial role in the transcriptional regulation of the ER - alpha gene, the pRb2/p130 gene emerges as the promising target molecule for the management of ER negative breast cancer.

ER expression is also modified by gene mutations, which influence the response to anti - estrogens. A striking example of these mutations is an aspartate to tyrosine substitution at position 537 in the ligand - binding domain, which entails ER activation in the absence of ligand. Furthermore, a lysine to arginine substitution at position 303, leads to increased sensitivity to estrogens, but may modify ER function. However, these mutations are estimated to account for only 1% of all breast cancer cases.

Finally, resistance to tamoxifen has been demonstrated in altered ERβ expression. Particularly, high levels of ERβ have been found to correlate with pre - invasive breast tumors, which show resistance to tamoxifen. On the contrary, a number of studies have investigated that low ERβ levels contribute to resistance to hormonal therapy. Consequently, controversy surrounds the role of estrogen receptor beta in resistance to hormonal therapy [14 - 17].

2. Epigenetic Regulation of ER Expression

Several epigenetic mechanisms regulate the expression of estrogens receptors. Loss of ERα expression is often related to the hyper - methylation of the ERα gene promoter. Similarly, PR methylation is observed in tumors that proved resistant to hormonal treatment. In addition, the expression of the HOXB13 protein is placed under epigenetic surveillance. Particularly, HOXB13 expression has been linked to the recurrence of lymph node - negative, ER - positive tumors of patients, who received tamoxifen. Moreover, methylation of the CDK10 (cyclin - dependent kinase 10) promoter has been indicated to lead to decreased levels of CDK10. Low levels of CDK10 are associated with more rapidly progressive recurrence following tamoxifen treatment. The methylation of selected candidate genes DNA and its relation to the patients' prognosis who have received tamoxifen can be challenging for intensive research. Last but not least, enzyme inhibitors, which are under epigenetic surveillance, such as the aforementioned DMNT and HDACs inhibitors, show evidence of promising antitumor activity. Providing that these epigenetic changes are reversible, the inhibition of these mechanisms (either directly or through combination therapy) is considered an appropriate therapeutic strategy for hormone - refractory tumors. Conclusively, research on epigenetics is bound to allow the identification of new epigenetic biomarkers, which can predict and diagnose the acquired resistance to hormonal therapy.

3. Regulation of Signal Transduction Pathways

Signaling pathways related to receptors of growth factors are able to stimulate cancer development either in coordination with the ER pathway or without its involvement and there is evidence of their contribution to the resistance to hormonal therapy. The signal amplification through these pathways activates both classical and non - classical pathways of ER activity, whereas the majority of anti - estrogen drugs solely activate the classical pathway. There are interactions between these pathways and ER pathway, which not only do they result in activation of signaling via growth factors, but they also promote the phosphorylation of ER and regulatory proteins. The reduced ER α phosphorylation at serine 118 (pER α - S118) and the increased ER α phosphorylation at serine 167 (pER α - S167) in the activation function - 1 (AF1) domain of ER α appear to recruit co - activators, resulting in enhanced ERα - mediated transcription, and also affect the cellular response to tamoxifen. Indeed, the over - expression of the AIB1 molecule has been correlated significantly with resistance to tamoxifen and also seems to be responsible for the resistance to this compound in MCF - 7 (Michigan Cancer Foundation - 7) cell line, which over - expresses HER2.

Furthermore, when it comes to hormone - resistant tumors, over - expression and activation of receptors, such as EGFR, HER2 and IGF1R, lead to activation of MAPK and PI3K/AKT signaling pathways, which subsequently promotes cell proliferation. Experimental investigations have indicated that the HER2 gene transfection to ER positive cancer cells results in decreased ER levels and, consequently, in increased resistance to tamoxifen. Several studies have documented that the HER2 expression plays a crucial role in the aforementioned resistance to hormonal therapy. Particularly, a meta - analysis of clinical trials has demonstrated that tamoxifen was administered to patients with metastatic ER/HER2 positive breast cancer earlier than those with HER2 negative tumors. In addition, the mechanism

that bears the responsibility of development of resistance to fulvestrant seems to be the HER2 and MAPK over - expression of these tumors. Finally, when it comes to examestane, the suggested mechanism includes the activation of the EGFR pathway through a protein, namely amphiregulin, which, subsequently, induces MAPK activation and cell proliferation. As previously mentioned, the IGF1R pathway interacts strongly with the ER pathway. Particularly, IGF1R stimulates the activation of kinases, which induces phosphorylation of ER. Reversibly, estrogens increase the activity of IGF2, which lead to signal amplification through IGF1R. It has been reported that ER positive MC7 cells with ectopic IGF1R expression exhibit resistance to treatment with tamoxifen and fulvestrant, but should IGF1 ligand be bound, activation of MAPK and PI3K pathways occurs independently of the expression of ER. Moreover, recent evidence highlighting delayed resistance to tamoxifen in tumors with high levels of IGF1 and ER expression unveil a synergistic interaction between the two pathways.

Finally, recent studies have revealed that MED1 (Mediator of RNA polymerase II transcription subunit 1), which belongs to ER co - activators, may be responsible for resistance to tamoxifen in HER2 positive, ER positive tumors. Specifically, lesser levels of MED1 lead to sensitization of HER2 positive cancer cells to tamoxifen [20 - 25] .

4. PI3K Pathway

The PI3K Pathway has been extensively investigated when it comes to its role in carcinogenesis. The AKT (Protein Kinase B), which is an important signaling molecule in this pathway, is involved in cellular survival, by inhibiting apoptotic processes. It has been indicated that inactivation of PTEN (AKT inhibitor) leads to increased AKT phosphorylation in ER positive cancer cells leading to increased cell proliferation, reduced cell death and resistance to tamoxifen and fulvestrant. In addition, resistant cells to hormonal therapy present elevated levels of IGF - 1R, HER2 and EGFR expression, as well as increased activation of PI3K/AKT/mTOR pathway. It is worth mentioning that, although PI3K activation via HER2 or FGFR2 expression entails resistance to hormonal therapy in ER positive tumors, mutations within the catalytic domain of PI3K (PI3KCA), which account for approximately 30% of hormone - sensitive breast tumors, seem to contribute to a better prognosis of these tumors.

Experimental studies on breast cancer cells have demonstrated that long - term estrogen deprivation initially confers hypersensitive of these cells to low concentrations of estrogen and, eventually, these cells become independent of estrogen; therefore they are resistant to hormonal therapy. Increased MAPK and mTOR expression seem to be major players in this phenomenon. Indeed, MCF - 7 cells exposed in long - term administration of tamoxifen expressed increased MAPK levels in the presence of the acquired tamoxifen resistance. These cells pass through three stages: a) tamoxifen functions as an antagonist of estrogen, b) the cells gradually become sensitive to the agonistic effect of tamoxifen and γ) the cells become hyper - sensitive to tamoxifen [26 - 28].

5. Stress - Activated Protein Kinase/ c - junNH2 Kinase Pathway

Interactions between the Stress - Activated Protein Kinase/ c - junNH2 kinase pathway and the ER pathway are mediated by either the AP - 1 (activating protein - 1) transcription complex or the direct MAPK activation. According to a study, the development of resistance to tamoxifen was related to increased AP - 1 DNA binding, whereas data derived from xenografts support that tamoxifen resistant tumors present increased transcriptional activity of AP - 1. Moreover, there are indications that tamoxifen resistant cancer cells are characterized by high p38 MAPK levels. This protein is activated in response to ionizing radiation, oxidative stress and tissue ischemia. Providing that p58 phosphorylation enhances the agonistic activity of tamoxifen in endometrial cells, it may also bear the responsibility for the agonistic activity of tamoxifen *per se* [29 - 31] .

6. Additional Signaling Pathways

Nuclear factor - κB (NFκB), Notch, keratinocyte growth factor - KGF and Platelet - derived growth factor (PDGF) are included in additional signaling pathways. As far as NFκB is concerned, it stimulates the cell proliferation and the activation of proteins, such as cyclin D1 and plasminogen activator (uPA). The latter has been associated with disease progression in hormone - refractory tumors. When it comes to ER - positive tumors with low NFκB levels, it has been indicated that tamoxifen - induced NFκB activation leads to cell proliferation, which contributes to resistance to hormonal therapy.

KGF pathway significantly stimulate normal human breast and human breast cancer epithelial cell proliferation in a dose - dependent manner; therefore, leading to conversion of androgens to estrogens in these cells. KGF may also, play an inhibitory role in the induction of breast cancer cell

apoptosis via a reduction of ER and PR levels, conferring resistance against anticancer drugs on breast cancer cells. On the other hand, Notch pathway is involved in the regulation of Cancer Stem Cells (CSCs) in breast cancer. Particularly, ligand proteins binding to the extracellular domain of notch proteins induce proteolytic cleavage and release of the intracellular domain, which enters the cell nucleus to modify gene expression; therefore regulating adhesion and migration of cancer cells. Estrasdiole inhibits this activity. Tamoxifen, in contrast, re - activates Notch signaling. The combination therapy with γ - secretase inhibitors and tamoxifen seems to be a more effective approach to suppression of Notch expression, as it blocks the agonistic activity of tamoxifen via NOTCH; thus enabling the antagonist activity of tamoxifen, which eventually contributes to overcoming the aforementioned resistance. As far as PDGFRs are concerned, they belong to cell surface tyrosine kinase receptors for members of the platelet - derived growth factor (PDGF) family and their activation plays vital role in the transduction of several intracellular pathways as well as in the cell proliferation. Abelson murine leukemia viral oncogene homolog 1, also known as ABL1, is a protein which has been implicated in processes of cell differentiation, cell division, cell adhesion, apoptosis and stress response. In vitro and in vivo evaluation of the interactions between ER and PDGF/Abl pathways provide evidence that they potentially promote the hormone - resistant phenotype [32 - 33] .

7. Altered Expression of Specific microRNAs

MicroRNAs constitute a class of regulatory molecules which contain 19 - 24 nucleotides. Their function is mediated via base - pairing with complementary sequences within the target mRNA molecules. Gene silencing eventually occur either via mRNA degradation or preventing mRNA from being translated. Besides regulating a plethora of cell processes, such as cell proliferation and cell death, these molecules can also be involved in carcinogenesis. Providing that miRNAs different expression patterns of miRNAs have been identified in hormone - resistant and hormone responsive breast cancer cell lines, altered expression of miRNAs seems to be implicated in conferring tamoxifen resistance. Particularly, elevated miR221/22 levels observed in HER2 positive tumors are associated with resistance to tamoxifen regarding hormone responsive breast cancer cells, which is mediated by the reduction in levels of a cell - cycle inhibitor. Furthermore, disordered expression of this miRNA appears to entail resistance to fulvestrant through the activation of BETA - catenin. MiR - 342, miR - 451 and miR - 210 are also implicated in comfering hormone resistance. Finally, miR - 128a, which targets the TGFβ receptor, has been associated with resistance to letrozole [34 - 35] .

8. Regulatory Proteins

Regulatory proteins are involved in the regulation of the transcriptional activity of ER; therefore leading to its agonistic effect on normal tissues, in comparison with its antagonistic effect on breast cancer cells. However, increased levels of ER co - activators, such as AIB1, amplify the agonistic effect of tamoxifen and may contribute to resistance to tamoxifen. Reversibly, it has been documented that the AIB dissociation from estrogen receptors leads to restoration of the sensitivity to tamoxifen. It is worth mentioning that recent studies have revealed that AIB1 is associated with resistance to tamoxifen in HER2 positive tumors. Pax2 is another molecule, which constitutes a crucial mediator of HER2 suppression in HER2 tumors. Particularly, Pax2 inhibition entails elevated levels of HER2 and affects the activity of tamoxifen. Finally, the nuclear receptor corepressor (NCoR) constitutes a major predictive marker for response to tamoxifen. Specifically, high rate of ER - NCoR binding is observed in hormone responsive cells. Reduced NCoR levels, in contrast, are associated with acquired resistance to tamoxifen [36 - 37] .

9. Tamoxifen Metabolism and Resistance Linked to Genetic Background

Tamoxifen is extensively metabolized predominantly by the cytochrome P450 (CYP) system to several primary and secondary metabolites, some of which exhibit more antiestrogenic effects in breast cancer cells than tamoxifen itself]. Tamoxifen metabolism mostly occurs via two pathways, 4 - hydroxylation and N - demethylation, both of which result in the very potent secondary metabolite, endoxifen. Originally, the 4 - hydroxylation path, which is catalyzed by multiple CYPs including CYP2D6, was given much attention because the immediately resulting metabolite, 4 - hydroxy - tamoxifen, had been shown to be approximately 30 - to 100 - fold more potent as an antiestrogen than tamoxifen. Consequently, polymorphisms in cytochrome CYP2D6 may affect its enzymatic activity. Because CYP2D6 is responsible for the hydroxylation of N - desmethyltamoxifen to endoxifen, genetic variations, which cause differences in CYP2D6 metabolizer status may play an important role in individual therapeutic benefit. This has led to research into the possi-

Table 2. Mechanisms of resistance to hormonal therapy

Factors affecting tumor growth	Pharmacodynamics	Targets	Treatment
Growth factors and protein kinases	Estrogen receptor and post-translational regulatory protein modifications, activation of non-classical estrogen triggered pathways	EGFR/HER2,IGFR-1, MAPK, PI3K/AKT/mTOR PDGF, KG-F,CDK4/6, Notch	Gefitinib, lapatinib, Pan/PI3K and AKT inhibitors, everolimus, palbociclib, γ-secretase inhibitors
Epigenetics	Primers methylation, histones deacetylation, loss of ERa expression	Histones, HOXB13, CDK10	HDAC inhibitors (erinostat) and DMNT
Transcriptional factors	Estrogen-independent tumorigenicity	ERβ, NFκB, AP-1	NFκB inhibitors
Regulatory proteins	Regulation of relative agonist or antagonist activity of selective ER modulators	AIB1, NCOR	
microRNAs	Modified gene expression	miR221/222, miR-342, miR-451, miR-210, miR-128a	
Genetic abnormalities	Mutations in cytochrome CYP450 block the metabolic activation of tamoxifen to endoxifen	CYP3A4, CYP2D6	Gene therapy

AIB1: amplified in breast 1, AP1: activator protein 1, CYP450: cytochrome p450, EGFR: epidermal growth factor receptor, ER:estrogen receptor, IGF1-R: insulin-like growth factor-1 receptor, MAPK: mitogen-activated protein kinase, NCOR1: co-repressor of estrogen receptor, PI3K: phosphatidylinositol-3 kinase.

ble association between CYP2D6 genotype and maximum benefit from tamoxifen therapy. For example, the genetic identification of CYP2D6 would be beneficial to clinical practitioners in order to calculate the optimal individual dose of tamoxifen. Furthermore, although tamoxifen metabolism is carried out predominantly by the liver, cancer cells may be involved in this process via the expression of a functional cytochrome P450. Consequently, the altered tumor metabolism of tamoxifen may contribute to resistance to hormonal therapy. Current developments in *P*450 - directed gene therapy, where an exogenous *P*450 gene and a prodrug activated by that *P*450 are delivered to the site of the tumor open a promising perspective for the management of the aforementioned resistance. To sum up, it all boils down to the fact that this theraputic strategy possesses a plethora of potential benefits, such as superior efficacy, selectivity and reduced toxicity [38-39].

Finally, it is worth taking into consideration that the co - administration of tamoxifen with drugs, such as some antidepressants, which inhibit the cytochrome CYP2D6 activity, lessen the production of endoxifen; thus, the activity of tamoxifen . The mechanisms of resistance to hormonal therapy and their management are illustrated in the **Table 2.**

Approach to the Patient with Hormonal Therapy Resistance

Resistance to hormonal therapy leads to the development of therapeutic approaches aiming to: 1) Compete the ER without focusing on the hormonal dependent activity abolition, and 2) Target the growth factors pathways, as well as their interaction with the ER on hormonal resistance development.

1. Combined Therapy Using Fulvestrant

The aromatase inhibitors therapy does not totally prevent the tumor targeting mediated by estrogens; therefore, the tumors can still express ER and PR. The optimization of the anti - estrogen therapy could be achieved using combination of therapies focused on the unbound ER receptor (non - classical mechanism). The different categories of endocrinic therapies partially present mutually adjusted underlying biological mechanisms, increasing thus the possibility of improved effectiveness, when a combination of them is used. Specifically, a combination including fulvestrant could impact on the total inhibition of estrogen targeting. A randomized trial, however, in uncured patients with ER(+) tumors, comparing the administration of anastrazole,

fulvestrant or the combination of both of them, has not reported any statistically significant differences concerning the PR, ER and Ki67 expression.

Conflicting are also the results of published studies regarding the more appropriate therapy following the progression on non - steroid aromatase inhibitors. Indeed, in the randomized EFECT study (Evaluation of Faslodex and Examestane Clinical Trial), both fulvestrant and examestane showed similar efficacy, whereas the randomized phase II SOFEA study (Study of Faslodex With or Without concomitant Arimidex vs. Examestane following progression on non - steroidal Aromatase inhibitors) was performed in menopausal women being relapsed after induction therapy with non - steroid aromatase inhibitor; no difference in overall survival or event - free survival was noted, however, in this study, after the administration of examestane, fulvestrant or the combination of anastrazole and fulvestrant. Moreover, in FACT (Fulvestrant and Anastrazole Combination therapy) study, women with ER positive tumors were randomized and anastrazole or combination of anastrazole and fulvestrant was administrated after first relapse, with the latter resulting in better outcomes.

The combination with fulvestrant has been also tested in the metastatic breast cancer. In a randomized study, menopausal women with no previous therapy presented better overall survival with the combination of fulvestrant and anastrazole, highlighting the significance of targeting ER activity through the non - classical pathway, namely irrespectively of the bounding to receptor [40 - 43].

2. Combination of Therapy with Inhibitors of Signaling Growth Factors Pathways

As the signaling via growth factors affects the ER activity, the combined hormonal therapy using inhibitors of signaling growth factors pathways aims to increase the response to hormonal therapy, delay or even prevent the resistance, as well as, in cases of already resistant disease, to restore hormonal sensitivity. Experimental studies showed primarily promising results using inhibitors of tyrosine kinase, followed by phase II studies, as this by Smith et al., showing that preoperative combined therapy with the EGFR inhibitor, gefitinib, and anastrazole, did not overcome resistance in hormone - dependent breast cancer. In metastatic HER2/ER positive breast cancer, however, the combination of lapatinib, a tyrosine kinase inhibitor blocking EGFR , with letrozol, seemed to be effective; it should be noted, though, that patients with HER2 negative ER positive tumors were not benefited by the aforementioned therapy.

Moreover, mutations of thePIK3CA gene, which participates in the PI3K/AKT/mTOR pathway, are observed in 30% of breast cancer cases and lead to lesser activation of PI3K-pathway and a better outcome. Translational primary studies revealed the significance of this pathway, whereas the TAMRAD phase II study (Tamoxifen Plus Everolimus) evaluating the combination of everolimus (mTOR inhibitor) with tamoxifen in menopausal patients with HER2 negative ER positive metastatic tumors following progression on aromatase inhibitor therapy showed clinical benefit. In the same context, the respective phase III BOLERO - 2 study (BreastCancerTrialsofOralEverolimus - 2) reported that the combination of examestane and everolimus is superior to single therapy with examestane in relapsed patients after non - steroid aromatase inhibitor therapy, with the latter combination being approved by the European Medicine Agency (EMA). Lastly, in a phase II study the combination of letrozol with everolimus ad preoperative therapy during four months before surgery, resulted in increase of clinical response. The aforementioned results point to potential better outcomes deriving from the administration of combined therapies using inhibitors of growth factors pathways in patients with initially hormone - sensitive and then hormone - resistant disease; a possible explanation is the installation of diverging function of pathways, whereas their ability to overthrow the ER signaling could be used as therapeutic approach. By contrast, the combined therapies have not been proven beneficial in patients not having received hormonal induction therapy. Indeed, the combined therapy with letrozol and temsirolimus was not superior to letrozol as induction therapy on hormone - sensitive tumors in a phase II study.

3. Other Targeting Molecules

The HDAC inhibitors seem to be promising therapy in pre - clinical studies. In the ENCORE 301 study, the combination of HDAC entinostat inhibitor with examestane resulted in increase both in progression - free survival (PFS4,3 months vs. 2,3 months) and overall survival (26, 9 vs. 19,9 months).

The cyclin - dependent kinase (CDK) 4/6 plays an important role in the regulation of cellular cycle and its inhibition results in the termination of the cycle in phase G1. The combined therapy of a specific CDK 4/6 inhibitor (palbociclib) with letrozol has been found to result in considerable increase of PFS (26 vs. 7,5 months) as induction therapy in patients with ER positive aggressive breast cancer. As prog-

nostic biomarkers the amplification of cyclin D1 gene and loss of p16 are used. Moreover, current studies evaluate the clinical response to the combination of aromatase inhibitors with dasatinib, a tyrosine kinase inhibitor BCR/Abl, as well as the effectiveness of pan/PI3Kand AKT inhibitors. As expected, the abundance of multiple targeted therapies allows the adjustment of the therapeutic approach using different drug combinations, as well as individualizing the hormonal therapy resistance approach [44-49].

Conclusion

In conclusion, hormonal therapy resistance is a multi - factorial issue and given the heterogeneity of breast cancer in both clinical and molecular basis, therapeutic approaches need to be individualized. Combined hormonal therapy with drugs targeting proteins implicated in the endocrine therapy resistance is a promising approach aiming to overcome or prevent resistance, with the ultimate goal being to defend patients' clinical benefit. ■

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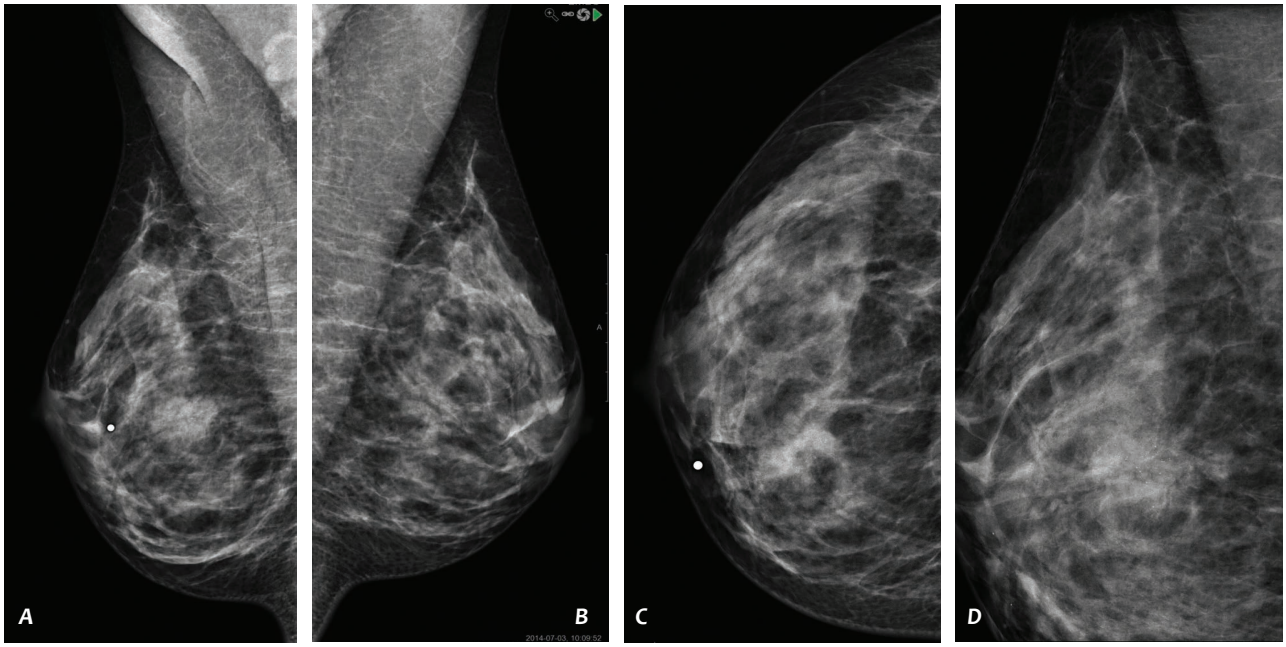
Educational case presentation

A case from the Departments of Mammography, Clinical Pathology and Surgery, Falun Central Hospital, Sweden

Laszlo Tabar, Tibor Tot
Department of Radiology, Department of Pathology / Cytology

24 YEAR OLD WOMAN with self-detected hard tumor in the upper-outer quadrant of her right breast. Her father's mother had BC at age 34 and died from BC at the age of 54. Clinical breast examination confirmed the presence of a freely movable hard tumor with irregular borders. No skin changes, no discharge were present. The axillary lymph nodes were normal at palpation.

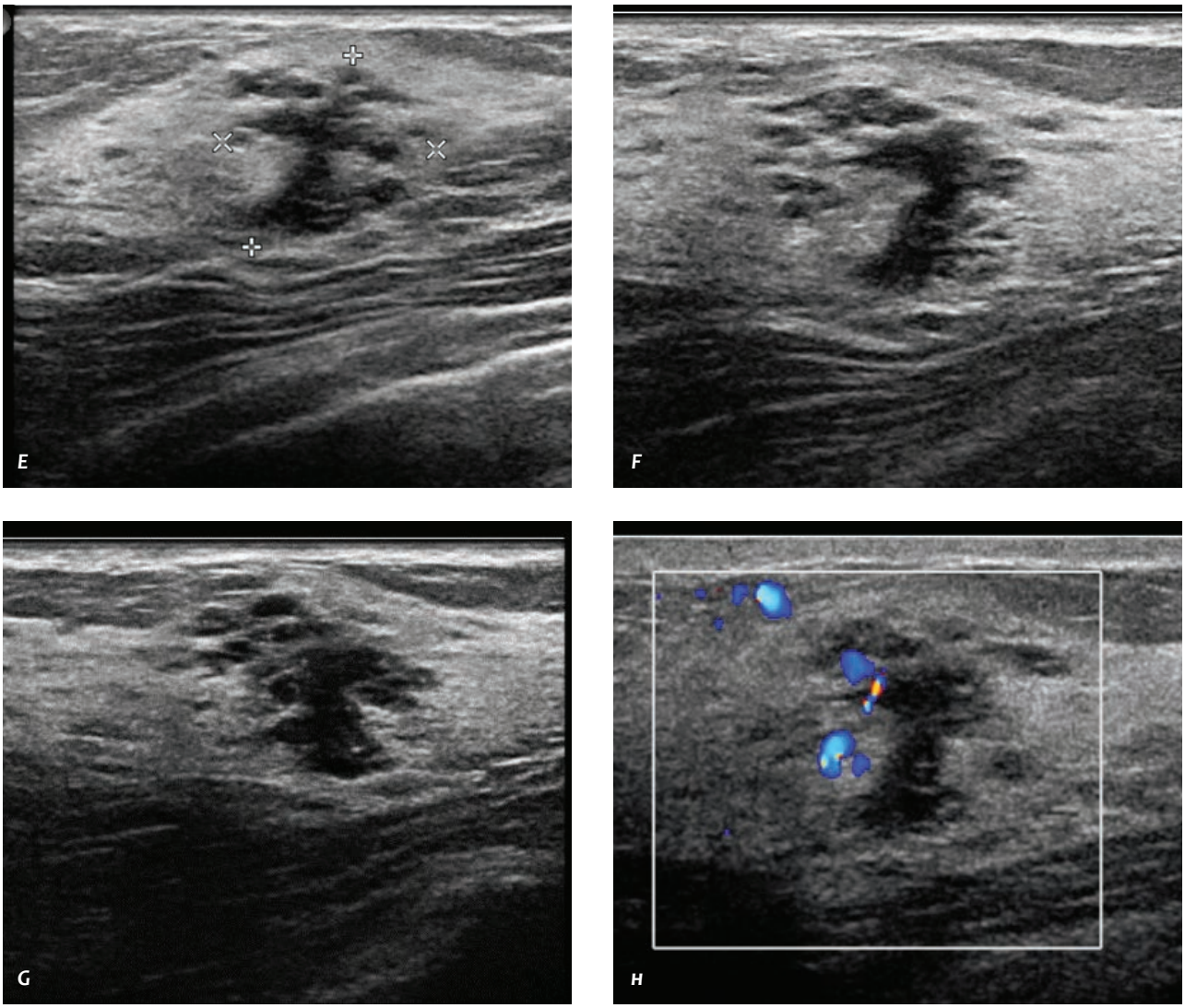


Right and left MLO (a,b) and CC (c) projections. The palpable, hard tumor is encircled. The solitary lesion is lobulated and ill-defined

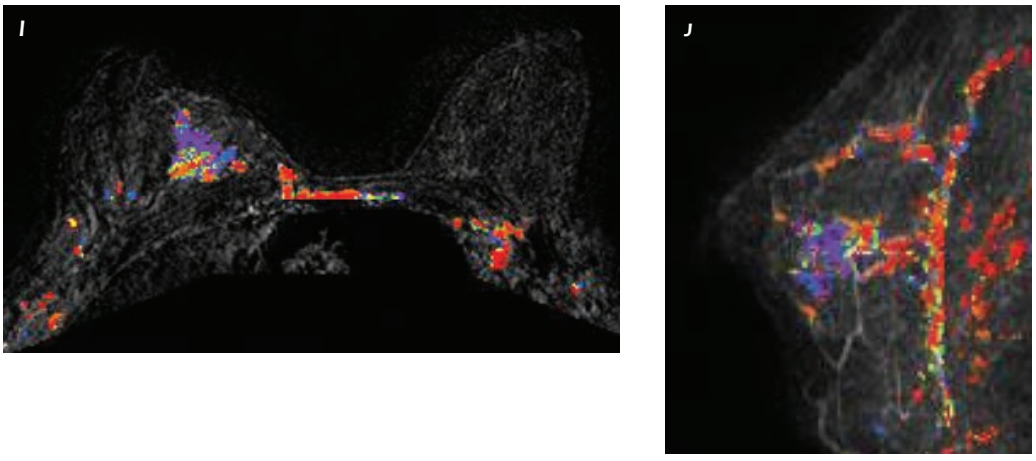
Fig. D. *Microfocus magnification, MLO projection. Both the palpatory finding and mammograms suggest malignancy*

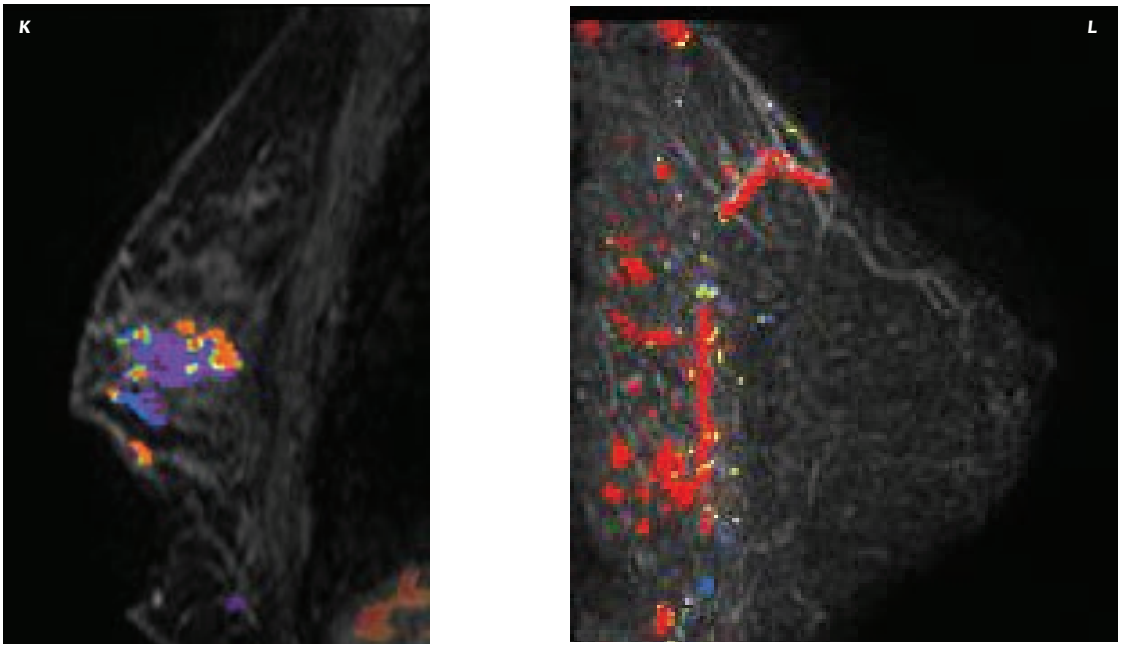
Corresponding author

Prof. Laszlo Tabar
Professor of Radiology at University of Uppsala School of Medicine, Sweden, Medical Director of the Department of Mammography, Falun Central Hospital, Sweden, and Consultant Radiologist for numerous Comprehensive Breast Centers in the United States



Figs. E-H. *Hand-held ultrasound: the lesion consists of dilated ducts and cystic lesions. No ultrasound signs of malignancy demonstrable. The finding suggests juvenile papillomatosis ("Swiss cheese disease")*





Figs. I-L. *Breast MRI. Normal left breast (i, l). Right breast (i, j, k): 4 cm deep to the nipple, in the direction of 2 o'clock, there is a 22x18 mm triangle shaped heterogeneous non-mass enhancement, suspicious for in situ or/and small invasive cancer foci. No pathologic lymph nodes are seen in the axilla*

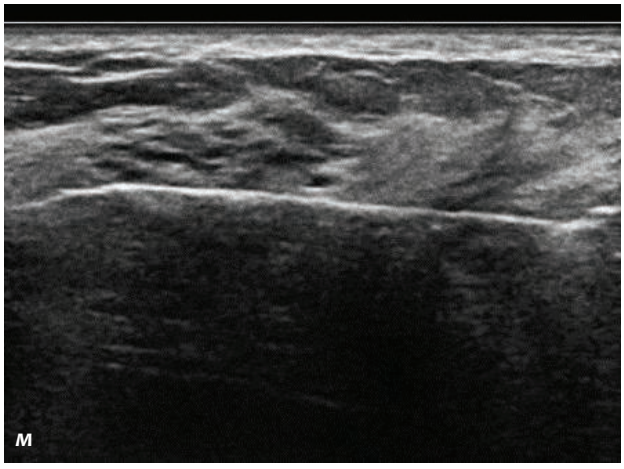
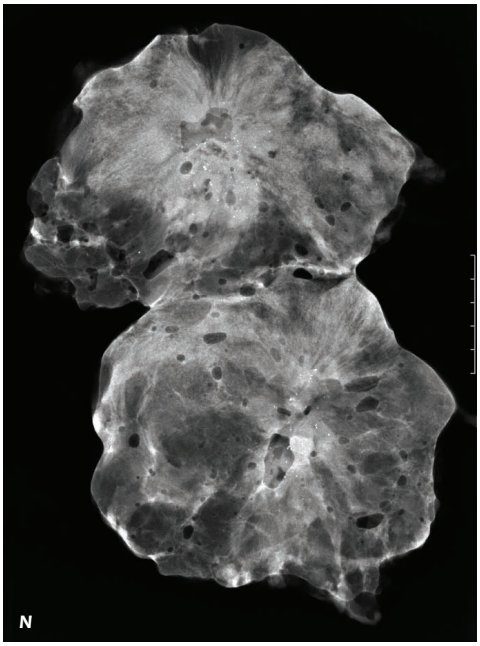
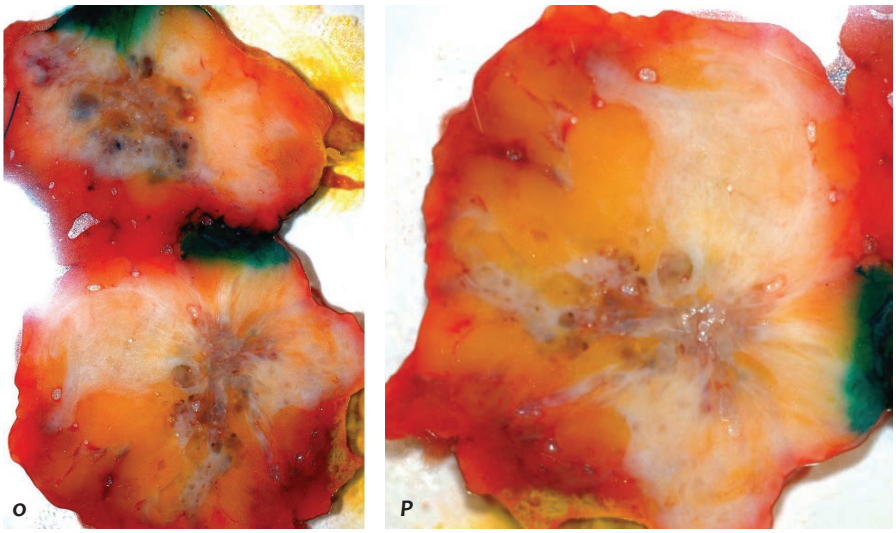
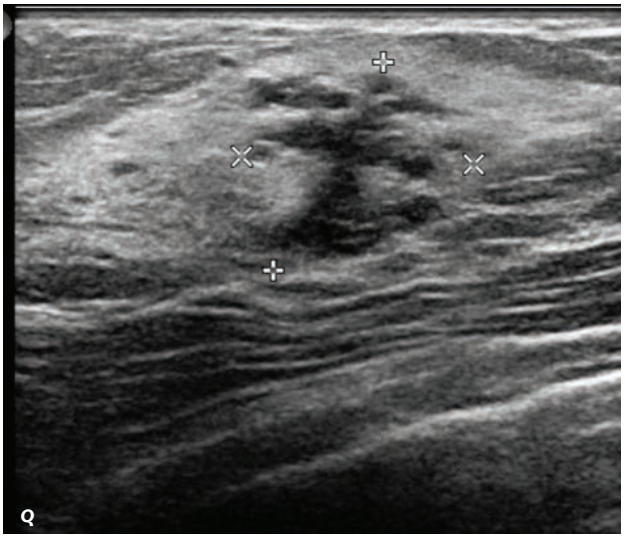


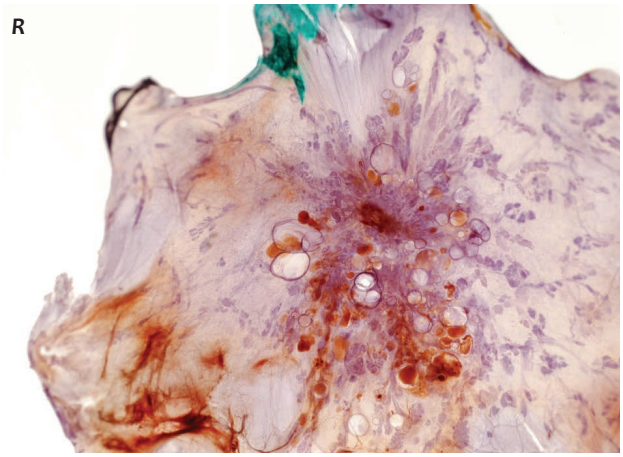
Fig. M: *Ultrasound guided 14-g core biopsy. The histologic examination showed no signs of malignancy. The most probable diagnosis is Swiss cheese disease*

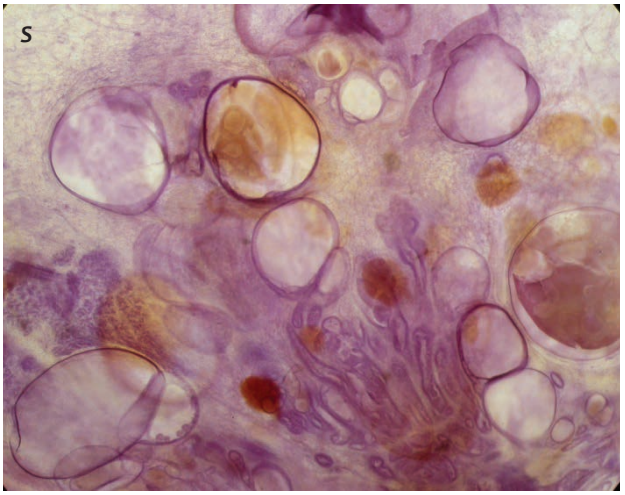


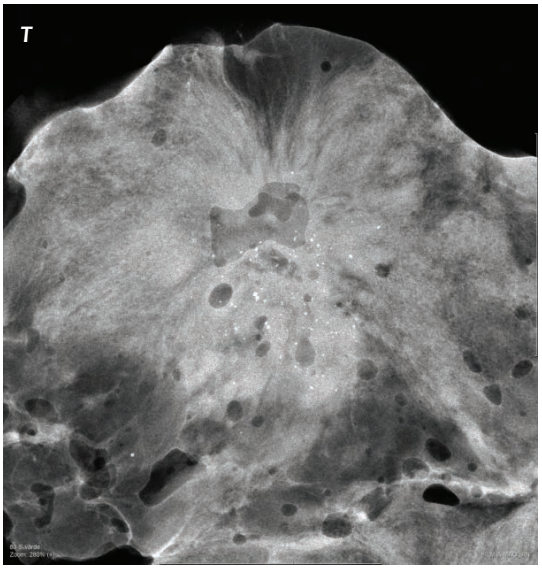


Figs. N-Q: *Specimen slice radiograph (N) correlated to the operative specimen slice photographs (O, P) and the preoperative ultrasound image (Q).*

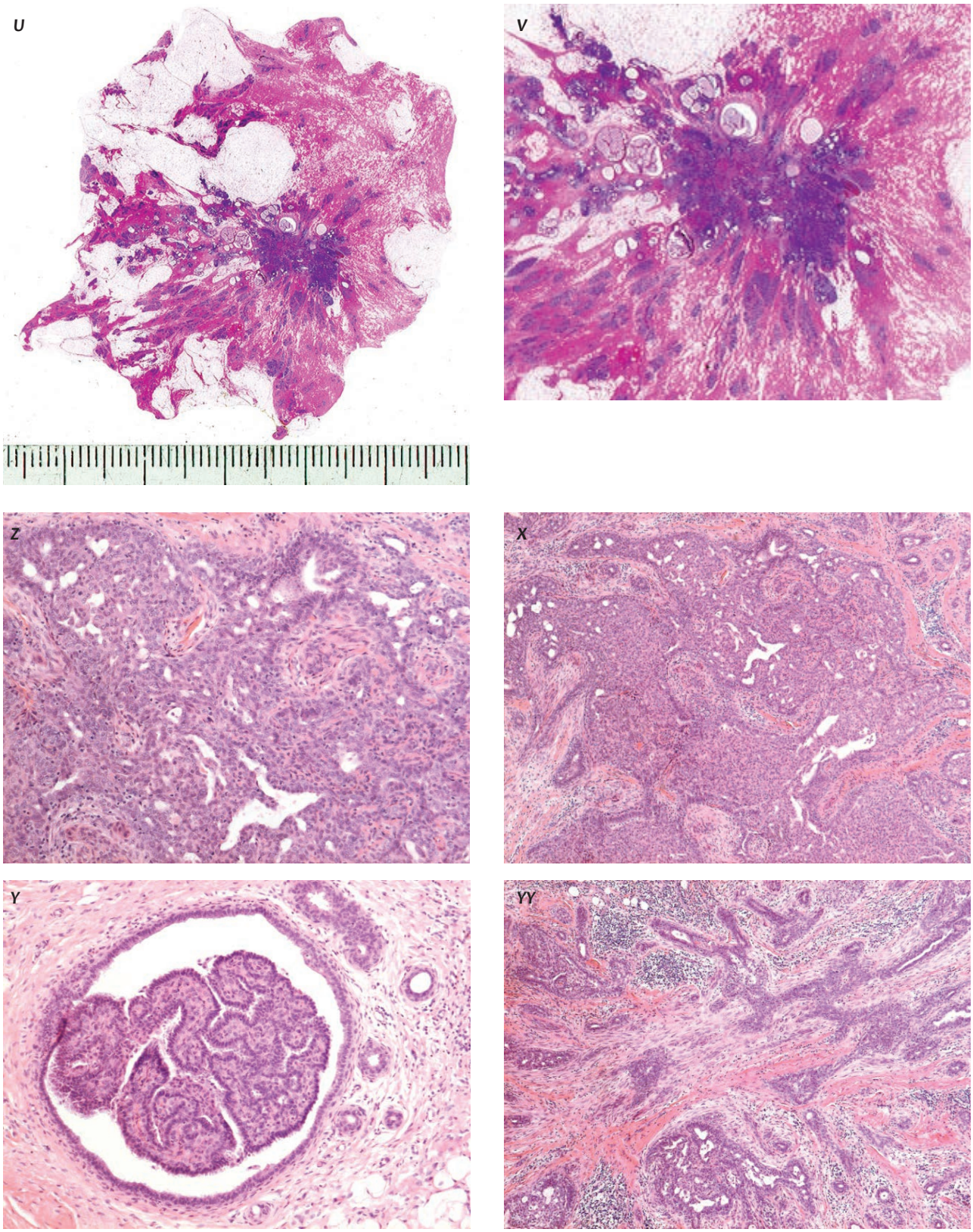




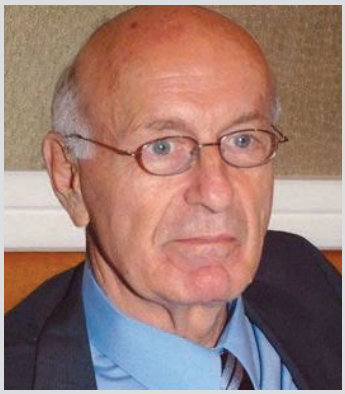




Figs. R-T. *Subgross (3D) histologic (r,s) correlation with the specimen slice radiograph*



Figs. U-YY. *Low and intermediate power histology images showing the characteristic microscopic image of juvenile papillomatosis / Swiss cheese disease, an extreme form of localized, tumor forming fibrocystic change. 25 x 20 mm Swiss cheese disease. Multiple benign papillomas with florid epithelial hyperplasia. Central papilloma with sclerotic stroma gives the impression of a stellate mass. Multiple benign cysts. No histologic signs of malignancy*



Dimitrios Trichopoulos
(1938-2014)

Greece became poorer

For those who knew and appreciated Dimitris Trichopoulos, these 6 words will be very well understood. Dimitris Trichopoulos was a human being, a scientist, a researcher, a point of reference, a point of inspiration and a never ending traveller. I had the fortune and privilege to meet him during my 4th year at the Medical University of Athens. He was an Associate Professor, at that time, teaching the lessons of Hygiene and Epidemiology at the University of Athens. Since he had distinguished me among my fellow students, I had the ability to ask him for a Doctorate Dissertation theme, during my training in Obstetrics and Gynecology. Straightaway he gave me an experimental theme on mice. My Doctorate Dissertation was of great success, since I managed to save the mice's life and my thesis finished in shorter time than planned.
Some years later, while I was working on my PhD Thesis with Dr Niki Agnantis, -at that time she was the Director of the Pathology Department of the Oncological Hospital of Athens " St Savvas"- I went to find late Prof. Trichopoulos to ask for his contribution concerning the statistical analysis of my PhD Thesis which he gladly accepted.

Dimitrios Trichopoulos was a charismatic scientist; he studied Medicine at the University of Athens with specialization in Internal Medicine, Microbiology, Public Health and Epidemiology at the Universities of Athens, London, Harvard and Oxford. He served as Professor and Chairman of the Department of Hygiene and Epidemiology, University of Athens Medical School, Chairman of the Department of Epidemiology, Harvard School of Public Health, Director of the Harvard Center for Cancer Prevention and as Adjunct Professor of Medical Epidemiology at Karolinska Institutet, Sweden. He was Vincent L. Gregory Professor of Cancer Prevention and Professor of Epidemiology at the Harvard School of Public Health, Regular Member of the Academy of Athens and President of the non-profit Hellenic Health Foundation.

Recipient of the "Eleanor Roosevelt" Fellowship; "Cutter Lecturer" at the Harvard School of Public Health (1982), "Ipsen Lecturer" at the Institute of Social Medicine of Aarhus University (1987) and Cassel Memorial Lecturer, Society for Epidemiologic Research (1999); Member of the Delta Omega Honorary Public Health Society, U.S.A.; Officier de l'Ordre des Palmes Académiques, France; Corresponding Member of the National Academy of Medicine of France and of the Royal Academy

of Medicine of Belgium; Chairman of the European Union Health Group during the Greek Presidency (1988) of the European Union; Distinguished Lecturer in the Japan Cancer Research Center (1992) and the National University of Singapore (2007); Honorary Doctor of Medicine, Universities of Uppsala (1994), Thessaly (2007) and Democritus (2009); recipient of a Smoke-Free America Award for demonstrating the role of passive smoking in the development of lung cancer (1996); Commander of Honor of the Greek Republic (1996); Listing by the Editor of the Lancet of a paper by DT among 27 papers deserving to form a Canon for Reading Medicine from antiquity to now (1997); Distinguished Physician, Hellenic Medical Society of New York (1999); Brinker International Award for Breast Cancer Research (2000); Hygeia Award for Contribution to Medicine, New England Hellenic Medical and Dental Society (2001); Grande Covian Award for studies on the Mediterranean diet, Spain (2002); Julius Richmond Award for demonstrating the role of passive smoking in the development of lung cancer (2004); Medal of Honor, International Agency for Research on Cancer, World Health Organization (2007); Honorary Fellow, Royal College of Physicians, London, UK (2008); National Delegate for Greece, Federation of the European Academies of Medicine (2008); Fellow, European Academy of Cancer Sciences (2009); Award of Merit, Harvard School of Public Health (2009); Award for Significant Contributions, City of Athens, Greece (2010); Herald of the Hippocratic Spirit, Society of Hippocratic Spirit, Greece (2013); Honorary Award, Hatzigakeion Cultural Foundation, Greece (2013); Xanthopoulos and Pnevmatikos Award for Outstanding Academic Teaching (2014).

Dimitrios Trichopoulos had authored or co-authored over 1,000 publications (mainly research papers, but also he wrote books, monographs, reports, reviews, commentaries, etc.), of which more than 900 are listed in international databases. He had done extensive original work concerning breast cancer etiology, mainly focusing on the early life origins of this disease. He had published the original paper implicating passive smoking in the causation of lung cancer. He had contributed to the elucidation of the etiology of hepatocellular carcinoma, the quantification of the association between psychological stress and coronary heart disease and the identification of several dietary and other important risk factors in the etiology of a number of cancers and other diseases.

Dimitrios Trichopoulos was Professor of Cancer Prevention at Vincent L. Gregory, Professor of Epidemiology at Harvard University, Member of the Academy of Athens and President of the non-profit Hellenic Health Foundation. He's very good partner, as in the Scientific field as well as during his adult life who stood on his side was his lovely wife Antonia Trichopoulou.

GREECE HAS LOST ONE OF THE MOST OUTSTANDING SCIENTIST AND BECAME POORER.

With all my gratidude to him,

Pr Lydia Ioannidou - Mouzaka MD, PhD
Editor in Chief of the Journal
Gynecologist-Surgeon-Breast Specialist
National Representative of Greece for Breast Centers and Breast Cancer in the European Union
President of the Hellenic Senologic Society
Delegate in European Initiative on Breast Cancer in Guidelines Development Group

Meetings, Conferences & Congresses

29 May - 2 June 2015	**51st Annual Meeting of American Society of Clinical Oncology** McCormick Place. Chicago, Illinois *Info: ascoregistration@jspargo.com*
7 Ιουνίου 2015	**International Seminar in Oncoplasty** Organised by the Hellenic Senologic Society (SHS) Athens - Greece *Info: Mrs Nikoletta Tsiamba, Communication Manager SHS, www.mastologia.gr* *tel. +30 210 74 70 257, fax +30 21077 16 834, E-mail: reception@mastologia.gr*
10-13 Ιουνίου 2015	**41ο Ετήσιο Πανελλήνιο Ιατρικό Συνέδριο** Ξενοδοχείο Hilton, Αθήνα *Διοργάνωση: Ιατρική Εταιρεία Αθηνών www.mednet.gr*
18 - 20 June 2015	**Breast Cancer Screening Conference - Learning from the Past, Planning for the Future (BCS1)** Dublin, Ireland *Info: Francesca Marangoni - e-ESO Managing Coordinator, www.e-ESO.net* *Tel +39 02 85464525, E- Mail: fmarangoni@eso.net*
18 - 20 Ιουνίου 2015	**13ο Ευρωπαϊκό Σεμινάριο Κολποσκόπησης & Παθολογίας του Τραχήλου** Πρακτικό Μέρος: 18/6 ΜαιευτήριοΙΑΣΩ & Θεωρητικό Μέρος: 19 & 20/6 Ξενοδοχείο Hilton *Πληροφορίες: MD Congress www.athensefc2015.mdcongress.gr* *Τηλ: 210 6074205 Φαξ: 210 6074222 E-Mail: s.diakopoulou@mdcongress.gr* *Διοργάνωση: Γυναικολογικό Ινστιτούτο Αθηνών*
16-18 July 2015	**14th Annual International Congress on the Future of Breast Cancer®** Hyatt Regency Huntington Beach, Huntington Beach, CA *Info: www.gotoper.com/conferences/ibc/meetings/14th-Annual-International-Congress-on-the-Future-of- Breast-Cancer,* *Tel: ++ (609) 378-3701, Fax ++ (609) 257-0705, E-Mail: Info@gotoper.com*
18- 19 Σεπτεμ. 2015	**2ο Σεμινάριο Παιδικής και Εφηβικής Γυναικολογίας** Θες/νίκη, Ολυμπιακό χωριό *Info: MD Congress Τηλ: 210 6074 200 Φαξ: 210 60 74 222, E-Mail : md@mdcongress.gr*
22 - 25 October 2015	**SIS European Congress on Breast Diseases- 6th** Congress of the Croatian Senologic Society, Opatija, Croatia *Info: www.novacon.hr/senology2015,* *E-Mail: lidija.vucic@zg.t-com.hr*
22-24 October, 2015	**Controversies in Breast Cancer International Congress** Melbourne - Australia *Info: www.congressmed.com/cobra*
25 Οκτωβρίου 2015	**2ο Forum + Εκθεση "Εναλλακτικές Προσεγγίσεις στην Υγεία"** Imperial Hotel, Λάρισα *Περισσότερες πληροφορίες: www.pharmamanage.gr*
24 - 27 October 2015	**ESCO19, International Meeting of the European** Society of Gynaecological Oncology (ESGO), Nice - France *Info: www.esgo2015.esgo.org*

5-7 November 2015	**Advanced Breast Cancer. Third International Consensus Conference** Lisbon, Portugal *Info: Helder Carvalho, Viagens Abreu SA, Linda-a-Velha, Portugal.* *Tel. +351 21 415 6120, E-Mail: helder.carvalho@abreu.pt*
6 - 8 Νοεμβρίου 2015	**Πανελλήνιο Συνέδριο Ιατρικής Φυσικής & Ακτινοθεραπευτικής Ογκολογίας** Ξενοδοχείο Porto Rio, Πάτρα Οργάνωση Ελληνική Εταιρεία Ακτινοθεραπευτικής Ογκολογίας & Ενωση Φυσικών Ιατρικής Ελλάδας Ε.Φ.Ι.Ε. *Γραμματεία: PRC Congress & Travel (Κέντρο Δημοσίων Σχέσεων)* *Τηλ. 210 77 11 673, Fax: 210 77 11 289, www. Prctravel.gr, E-Mail: congress2@prctravel.gr*
20 -21 Νοέμβ. 2015	**Χειρουργικές εξελίξεις στην Γυναικολογική Ογκολογία και στην ποιότητα ζωής** Αθήνα - Πολεμικό Μουσείο *Γραμματεία: MD Congress* *Τηλ: 210 6074205 Φαξ: 210 6074222 , E-Mail: md@mdcongress.gr*
29 Nov.- 4 Dec.2015	**Annual Meeting RSNA, South, North & Lakeside Center** 2015, McCormick Place, Chicago, USA. *Info: www.rsna.w org, Tel: 1-312-791-7000*
8 - 12 Decem. 2015	**2015 San Antonio Breast Cancer Symposium** Organization: San Antonio Breast Cancer Symposium Location: 200, E. Market Street, San Antonio, USA *Info: www.2015sanantoniobreastcancersymposium* *Tel: +210-450-1550 Fax: 210-450-1560, E-Mail: sabcs@uthscsa.edu*
9 - 11 March 2016	**10th European Breast Cancer Conference (EBCC- 10)** Amsterdam RAI, The Netherlands. *Info: ECCO - the European CanCer Organisation, Avenue E. Mounier 83, B-1200 Brussels, Belgium, www.ecco-org.eu/EBCC, Tel: +32 2 775 02 01, Fax:+32 2 775 02 00* *E- Mail: ebcc10@ecco-org.eu*
5 - 8 May 2016	**19th SIS World Congress on Breast Healthcare** Warsaw, Poland *Info: www.sisbreast.org/19th-sis-worldcongressonbreasthealthcare*
3 - 7 June 2016	**2016 ASCO Annual Meeting- American Society of Clinical Oncology** Chicago, ILLINOIS *Tel: (571) 483-1300 E- Mail :ascoregistration@jspargo.com*
16-18 June 2016	**11th Duesseldorf Breast Cancer Conference.** Dusseldorf - Germany
3 - 5 July 2016	**Symposium Mammographicum 2016.** Arena & Convention Centre (ACC) Liverpool, *Website: http://conferencesympmamm.org.uk/* *Tel: + 44 (0) 20 8977 7997, E-Mail: sympmamm@conferencecollective.co.uk*
15-18 March 2017	**15th St. Gallen Breast Cancer Conference.** Austria Convention Centre in Vienna / Austria

"MASTOLOGIA" is the official scientific journal of the Hellenic Senologic Society (HSS). Its main objective is to publish original articles, reviews and case reports on breast diseases. The journal "Mastologia" is also concerned in the continuous education of the Senologists and aims at promoting the science of Senology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations, basic applied laboratory research as well as new data and recent developments of senological interest. Papers published in other Journals are not accepted.

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Figure legends: Ensure that each illustration has a legend. Supply legends separately, not attached to the figure. A legend should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used. Legends should be sent separately.

Tables: Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables above the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

References

Citation in text: Please ensure that every reference cited in the text is also present in the reference list. Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'impress' implies that the item has been accepted for publication.

Web references: As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given. However, for more than one author, only the first should be listed followed by „et al".

List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2000;163:51–9.

Reference to a book:

2. Strunk Jr W, White EB. The elements of style. 3rd ed. New York: Macmillan; 1979.

Reference to a chapter in an edited book:

3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York:

E-Publishing

Inc; 1999, p. 281–304.

Note shortened form for last page number. e.g., 51–9, and that for more than 6 authors the first 6 should be listed followed by „et al."

CENTRE OF PSYCHOSOCIAL SUPPORT FOR WOMEN WITH BREAST CANCER "ELLI LAMBETI"

Tel: +30 210 77 73 112, Fax: +30 210 77 16 834
E-Mail: reception@mastologia.gr

The Centre "ELLI LAMBETI"- Background:

The Centre of Psychosocial Support for Women with Breast Cancer "Elli Lambeti" was founded in April 2002 by the Hellenic Senologic Society with the aim to improve the quality of life of women with breast cancer and at the same time support the members of their families. It is an independent non-governmental Centre which is sponsored by public and private entities.

Since its creation until today, the Centre has offered its services to over 4500 people, who either visited it, or asked support via phone conversations either because they live in rural areas, or because they are not able to move, or even due to their wish to remain anonymous.

In the friendly and pleasant environment of the Centre, trained psychologists provide psychological services and social support by appointment for FREE, following the principles of medical confidentiality.

To whom the Center refers to

- All women with a recent diagnosis of breast cancer
- All women diagnosed with breast cancer and who follow medical treatment
- All women who are in the process of recovery
- All close family members as well those persons who are close to their work and social environment
- All women with carcinophobia

Services offered by the Centre.

The Center offers the following services free of charge:

- Information in relation to the disease
- Individual psychological and counseling support to women with breast cancer
- Psychological and counseling support to their family members, both during and after treatment
- Support the process of reintegration into the family and the work environment
- Ability to meet and contact other women facing the same problem
- Participation in cultural events and other activities (meetings, celebrations, bazaars, concerts,drawing exhibitions etc.)
- Group therapy
- Beauty therapeutic groups
- Dietary therapeutic groups
- Provision of specialised brochures

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