

University of Medicine and Pharmacy of Craiova
DOCTORAL SCHOOL

THESIS
IMAGING ALGORITHM SCREENING BREAST TUMORS
EXECUTIVE SUMMARY

PhD supervisor : Professor Doctor Ion Georgescu
PhD Student : DAN SILVIU CRAINIC
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The objective of this work consists in studying cases of malignant breast tumors, in order to develop strategies as accurate diagnostic imaging , required the adoption of appropriate therapeutic attitude. We started from the hypothesis that classical triad - mammography, breast ultrasound , breast puncture with cytology - enables the diagnosis in most cases .

Breast cancer is the most common malignancy in women and the leading cause of cancer death in them. The constant increase in the incidence and mortality from this disease redirecting efforts reasons for adopting effective secondary prevention strategies. Imaging investigations play an undeniable in detecting malignant breast lesions and post- therapy. The importance of early diagnosis in controlling breast cancer is well established.

We studied the cases diagnosed with malignant mammary tumors , which were investigated by mammography, breast ultrasound and magnetic resonance in order to determine the contribution of each imaging investigation methods in order to achieve an accurate diagnosis as assessing the benefits and possible limitations either of the methods. Diagnostic strategies are primarily differentiated depending on the situation, namely , the diagnosis of malignant breast tumors and post- therapy in patients with breast cancer.

The research was conducted in three directions:

- Evaluation of females investigated in breast screening program;*
- Patients with symptomatic breast imaging investigated, from which we selected the malignant breast tumors ;*
- Patients with breast cancer imaging posttherapeutic investigated .*

INTRODUCTION

Mammary tumors, especially breast cancer is a major public health problem worldwide, the first frequency in cancer in females, due to their high frequency . Earlier this decade, Romania breast cancer was the most common form of cancer diagnosed in women and the leading cause of death by malignant tumors them. The disease can occur any age. It has been shown through studies that early detection and treatment of breast cancer the chance of survival for patients with this condition and reduce the number of mutilating operations. An important role in the detection of benign and malignant tumor lesions of the breast, and in pursuing their post therapeutic they hold imaging investigations. This allows detection of breast tumors sometimes several years before the change can feel . It is widely accepted that sectional imaging - ultrasonography , computed tomography , magnetic resonance - the possibility of characterizing breast lesions. Knowledge substrate histopathological lesions is essential radiologist who interprets the information based on the physical properties of tissues and absorbing ionizing radiation, ultrasound reflection , emission of electromagnetic signals . Mammographic examination still has a very important role in the diagnosis of breast cancer. It has become so as a method for screening and diagnosis of abnormalities in tangible for their characterization. Ultrasonographic examination of the breasts, originally used only for differentiating cystic

lesions of the solid is today thanks to new technologies (elastography , Doppler ultrasound, contrast ultrasound) an imaging method used to evaluate breast lesions . MRI is an important imaging technique that allows more accurate differential diagnosis between benign and malignant lesions .

In the first part of the paper we presented data from the literature on the anatomy of the mammary gland , mammary tumor types , especially breast cancer - epidemiology, clinical, imaging methods and their use in investigating these pathological changes , and special part I presented the material and methods used and the results arising from the study of significant groups of patients .

KNOWLEDGE

Breast development starts in the womb life, breast sketch derived from ectoderm . Development during intrauterine life takes place in several stages. Between the 4th and 6th week there is a thickening of the ectoderm of the breast along the line extending from the root of the upper member to the lower leg . Between weeks 6 and 7 appears mammary ridge portion located in the middle third of the thoracic mammary line . This outbreak of 4-6 cells form body breast primitive sketch . Mainder regressing mammary any incomplete involution leading to formation of breast tissue or gland and / or nipple , supernumerary . In parallel epithelial and mesenchymal cells differentiate and form primitive vessels . At this stage breast primitive body changes shape on several occasions . The nipple and areola are clearly outlined . From the 13th week of 15-20 appear mesenchymal cords that are future major lactiferous channels . Between weeks 20 and 32, placental steroid hormones produced channeling epithelial cords . Between weeks 32nd and 40 develops lobulo - alveolar structures , breast tissue grows in volume and complex forms areolo - streak . At birth , the mammary gland is a disc of 1cm diameter with a thickness of about 3 mm. This gland secretion shows a transitional milk (, witch " milk) due to the collapse of placental and maternal steroid hormones . Classically, after genital crisis, it is recognized that breast enters a quiet period until puberty but in fact, it seems that the mammary gland differentiation continues, producing lobular branches of secondary channels and lobes structure. At puberty, breast development is one of the main phenomena that occur at puberty; it occurs before the occurrence of menarche . At puberty , breast development occurs in five stages before the occurrence of menarche and menstrual cycles after installing the emergence of progesterone allows the formation of acini and curbing the galactophore proliferation.

NORMAL BREAST - mammary gland is an pair and symmetrical organ attached to reproductive system, with the woman milk secretion function . The female breast is breast region that is located on both sides of the sternal region , having the following boundaries : the upper: coast II, or III , lower: coast VI or VII, medial: lateral edge of the sternum and anterior axillary line . In depth extends to the pectoralis major fascia . The breast tissue contains glandular and adipose tissue for cell - glandular lobules arranged between the lobes and with blood vessels , lymphatics and nerves . Its structures are supported by ligaments Cooper fixing skin , areola and nipple to the underlying. The stratigraphic succession plans is as follows: skin coating layer premamar for cell - fat, ammma body and and retromammary fat for cell layer .

MAMMARY GLAND STRUCTURE - mammary gland consists of parenchyma and stroma. Glandular parenchyma consists of a variable number of 15 to 20 elementary glands or lobes . Each lobe consists of a single tubular gland - acini formed from a highly branched canalicular system . Canalicular system of an entire lobe is reminiscent of sewer main duct lactifer. Stroma is likely conjunctival breast adipose and nonpregnant women is more abundant than canalicular system (parenchyma) . Breasts are hormone organs , characterized by morphological and functional dynamism . Breast arteries arise from

internal thoracic artery, breast veins arise from capillary network and breast lymphatics are superficial and deep lymphatics between the two networks there are wide anastomosis .

BREAST TUMOR PATHOLOGY - BREAST CANCER

Breast lesions are extremely diverse, particularly in benign or malignant tumor pathology. In a recent paper of breast pathology, were described no less than 130 different injuries . Of these only 10% are inflammatory . The rest corresponding to hyperplastic or neoplastic processes are characterized by a proliferation more or less important to the breast structure. The exhaustive classifications, almost three quarters of tumor processes mentioned are rare lesions; some of them correspond to histologic variants whose identification is frequently no practical interest currently recognized.

BREAST CANCER EPIDEMIOLOGY

Cancer is statistically both worldwide and in Romania the second cause of death . For women breast cancer ranks first in the incidence of disease. Due to its high frequency of this neoplasia is a major public health problem worldwide . At the beginning of the last decade in most countries in Western Europe and in North America has been a decrease in breast cancer mortality , coupled with the widespread use of screening mammography , while in countries of Central and Eastern Europe is persistent upward trend recorded mortality of this malignancy . In Romania , breast cancer is the most frequently diagnosed cancer in women and the leading cause of death by malignant tumors them. Breast cancer can occur at any age, but rarely before 30 years.

BREAST CANCER RISK FACTORS - history may identify certain personal characteristics or demographics that can give a woman a higher risk of developing breast cancer, namely: age over 40 years; degree relatives with breast or ovarian cancer; a history of breast cancer; benign breast pathology; history of endometrial cancer, ovarian cancer or colon cancer; prolonged therapy with exogenous estrogen; obesity; early menarche; late menopause; nulliparity; first pregnancy to term after 30 years; obesity; mutations in genes BRCA1 and BRCA2; urban environment, socio - economic level; exposure to ionizing radiation.

CLASSIFICATION OF BREAST TUMORS :

Benign lesions - adenosis and adenomas, sclerosing adenosis, papillomas, ductal epithelial hyperplasia .

Injury border - atypical ductal epithelial hyperplasi , lobular neoplasia .

Noninvasive neoplasia (carcinoma in situ) - intraductal carcinoma .

Infiltrating carcinomas – micro - invasive carcinoma , infiltrating carcinoma .

Other mammary tumors

TNM STAGING OF BREAST CANCER

The purpose of the staging is to evaluate whether the disease is curable or known therapeutic methods, where it is curable, to enable the prediction of the evolution of the need for the use of adjunctive therapies and therapeutic response. TNM classification takes into account the primary tumor (T), regional lymph nodes (N) and distant metastasis (M) .

METHODS IMAGING IN BREAST TUMORS

Mammography, ultrasound, magnetic resonance imaging, galactografia, pneumochistografia, biopsy, computed tomography, positron emission tomography, breast scintigraphy . Mammography is X -ray examination of the breast and still has a strategic role in the diagnosis of breast cancer. It has about 90 % sensitivity; specificity of the

method is reduced. Ultrasonography is a fast and non-invasive diagnostic morphological irradiated providing information relating to the structures examined, the examination technique in real time. Magnetic resonance imaging is a technique complementary to mammography and ultrasound, which allows the identification of malignant lesions by studying their behavior after intravenous paramagnetic contrast injection.

OWN CONTRIBUTIONS

STUDY OBJECTIVE AND WORKING HYPOTHESIS

The objective of this work consists in studying cases of malignant breast tumors, in order to develop strategies as accurate diagnostic imaging, required the adoption of appropriate therapeutic attitude. We started from the hypothesis that classical triad - mammograph, breast ultrasound, breast puncture with cytology - enables the diagnosis in most cases. Breast cancer is the most common malignancy in women and the leading cause of cancer death in them. The constant increase in the incidence and mortality from this disease redirecting efforts reasons for adopting effective secondary prevention strategies. Imaging investigations play an undeniable in detecting malignant breast lesions and post- therapy. The importance of early diagnosis in controlling breast cancer is well established. Part of the arsenal of modern imaging methods more or mammography, ultrasound, magnetic resonance, computed tomography, positron emission tomography, breast scintigraphy, thermography, mono - photonic transmitters, needle biopsy of palpable mammary lesions, imaging guided percutaneous biopsy of lesions, preoperative localization imaging - guided needle biopsy and excision of impalpable breast abnormalities, galactografi , pneumochistografia . We studied the cases diagnosed with malignant mammary tumors, which were investigated by mammography, breast ultrasound and magnetic resonance in order to determine the contribution of each imaging investigation methods in order to achieve an accurate diagnosis as assessing the benefits and possible limitations either of the methods. Diagnostic strategies are primarily differentiated depending on the situation, namely, the diagnosis of malignant breast tumors and post - therapy in patients with breast cancer. If malignant mammary neoplasia diagnosis and diagnostic stages are established according to the existing anomaly: palpable tumor , unilateral nipple discharge, breast skin changes, breast and others. The research was conducted in three directions. The first direction is to evaluate females, investigated in breast screening program, part of PN2.2. - Prevention and control in cancer pathology, Imaging Department of Emergency County Hospital Craiova being involved in this program. The criterion for inclusion in the program is the one belonging to risk groups for breast cancer. The results were reported standardized classification using BI - RADS (Breast Imaging - Reporting and Data System) American College of Radiology (ACR) . We aimed to determine the optimal diagnostic steps subsequent detection of abnormalities suspicious of malignancy (categories 4 and 5) and attitude toward optimal with high probability of benign lesions (category 3) . Screening for breast cancer meets the criteria set by the World Health Organization or disease is an important health issue as measured by morbidity, mortality and other variables related to the spread of the disease, the disease is detectable preclinical phase, treatment of detected before the appearance clinical symptoms is cheaper than disease treatment after the onset of symptoms, screening test meets acceptable levels of accuracy and cost and followed the screening test and conduct must be acceptable for individuals at risk for professionals in the health system. Another group consists of people with symptomatic breast imaging investigated, of which we selected those diagnosed with breast malignancies . These patients seeking to establish optimal imaging investigations algorithm based and presenting symptom that prompted the doctor. We compared the results obtained by performing a single imaging investigations

that provided by the combination of several methods, taking into account the order made. The third group consists of females with breast cancer imaging investigated after treatment. In this group we compared the results obtained by performing a single imaging investigations that provided by the combination of several methods. The purpose of the analysis stages of investigation in these patients is to optimize early diagnosis of recurrence.

MATERIAL AND METHODS

Material: In the period January 2002 - December 2011 we conducted a retrospective study several groups of patients who were evaluated by imaging methods in the Laboratory of Radiology and Medical Imaging of Alba Iulia County Emergency Hospital, Bucharest Fundeni Hospital, Center „PRIMA MEDICAL” Craiova. The study was conducted in collaboration with the Department of Medical Oncology Hospital Emergency County Alba Iulia. In this study we established three groups: group I - included 4503 female persons. They were examined by either mammography or breast ultrasound. Patients were examined were presented at the doctor's or specialist or family doctor tells you or on its own initiative. Group I was divided into three subgroups : Subgroup I 1 - 3856 subjects who bilateral mammograms were performed in two planes; Sub-group I 2 - 628 subjects who breast ultrasound have been performed; Subgroup I 3 - 527 subjects that were performed bilateral mammography and breast ultrasound in two planes . GROUP II - made up of 847 patients examined for diagnostic imaging in those centers. They were selected from all patients examined. The criteria underlying the inclusion of patients in this group were: detection of lesions in the breast; highlighting a suspicious abnormality or imprecisely determined by imaging methods used with greater or lesser probability of malignancy. Were excluded from this group cases with breast lesions that did not allow a correct diagnosis of suspected abnormalities detected by understatement . This group was divided into six groups: Subgroup II 1 - consisting of 247 patients undergoing mammograms were performed; subgroup II 2 - composed of 68 patients undergoing breast ultrasound were performed; subgroup II 3 - consisting of 457 patients that were performed mammograms and ultrasounds breast ; subgroup II 4 - composed of 32 patients that were performed mammograms and magnetic resonance examination and / or CT; subgroup II 5 - composed of 26 patients that were performed breast ultrasound and magnetic resonance examinations and/or computed tomography ; subgroup II 6 - composed of 17 patients that were performed mammography, breast ultrasound and magnetic resonance examination and/or CT. GROUP III - it consisted of 412 patients who were examined post - treatment by imaging methods. The criterion that led to the inclusion of patients in this group was performing at least one therapeutic modalities : chemotherapy, surgery and radiotherapy .

People in this group imaging examinations were performed rhythmic measure of treatment and thus have conducted several examinations (periodic) within the time period studied. This group was divided into six subgroups. This division was made by type of imaging investigations performed, regardless of when they are made. These subgroups are: subgroup III 1-178 patients undergoing mammograms were performed; Subgroup III 2 - 24 patients undergoing breast ultrasound have been performed; Subgroup III 3 - 135 patients that were performed mammograms and breast ultrasound; Subgroup III 4-41 patients that have been performed mammography examination and magnetic resonance and/or CT, subgroup III 5-7 patients that have been performed breast ultrasound and magnetic resonance examination and/or CT; Sub-group III 6-27 patients that have been performed mammography , ultrasound examination and magnetic resonance breast and/or CT .

METHODS OF BREAST CANCER DIAGNOSTIC IMAGING

Mammograms were performed with mammography Senographe DMR +, manufactured by GENERAL ELECTRIC, with bucky 18/24 cm, automatic exposure system with standard compressor with Stereotaxis system. Ultrasound examinations were performed on two devices: Siemens Adara, and ESAOTE allowing adaptation to breast thickness, thus optimizing spatial resolution and contrast. Conventional ultrasound examinations were performed with the patient supine or oblique arm (arms) high overhead clearances upper outer quadrant, extending axillary and submammary sulcus . Were made longitudinal and transverse sections. To ensure intimate contact between the skin and transducer was used ecogel of quality. Under ultrasound were evaluated axillary lymph node groups , internal mammary and subclavian. Also used color Doppler and power Doppler examination to evaluate vascular lesions. Magnetic resonance examinations were performed with an apparatus GENERAL ELECTRIC HORIZON SIGNA LX with a 1.5 Tesla magnet . Magnetic resonance imaging examinations were performed on females between days 7-14 of the menstrual cycle, with dedicated antenna for breast study, patients were positioned prone with ensuring adequate compression and reduce motion artifacts by immobilizing breasts between two plates for each breast. The investigations were performed with computed tomography apparatus Siemens SOMATOM EMOTION multislice (16) . The examinations were performed intravenous iodinated contrast native arterial phase, venous and parenchymal. CT examinations were conducted generally in breast cancer patients undergoing therapy (chemotherapy, radio, hormone) to assess the extent of the lesion and response to treatment (initial and follow-up examination) in collaboration with the physician (oncologist) .

RESULTS IN ACTIVE SCREENING PROGRAMS FOR BREAST CANCER.

Distribution persons imagistic investigated under this program during the time the investigation was conducted, there was a fluctuating distribution of the number of cases, consisting of the downward trend in 2009 and their significant reduction in the last year . Patients included in the active detection of breast cancer in 3411 were spread over many years and age. A survey was taken and the issue of age of patients investigated. Addressability was found higher in the age groups between 41-50 and 51-60 years respectively. The distribution of patients by age groups was as follows: under 20 years - 9 persons; 21-30 years - 81 persons; 31-40 years - 483 persons; 41-50 years - 676 persons; 51-60 years - 603 persons; 61-70 years - 374 persons; 71-80 years - 128 persons; 80 years - 14 people. Another criteria analyzed was the environment from which they originated patients investigated in the program of early detection of breast cancer. He found such a clear allocation for urban, probably due to easier access to the information provided in the promotional campaigns and the program itself of these patients compared with those in rural areas. Of the patients examined imaging in the screening program for breast cancer were selected cases with indeterminate or suspicious abnormalities or high probability of malignancy. The number of cases was 205. A percentage of 4.52 % of cases with indeterminate or suspicious lesions or high probability of malignancy is a significant percentage considering the fact that the program to detect breast tumors were included patients undergoing there was no clinical suspicion of malignancy.

RESULTS IN DIAGNOSIS IMAGING.

The second group was composed of 687 patients examined for diagnostic imaging, the presence of a malignant breast lesions and abnormalities evidence of suspicious or indeterminate or with high probability of malignancy by one or more of the

imaging methods used, selected from all patients examined. This group includes six subgroups based on imaging investigations performed: Subgroup II - 134 patients undergoing mammograms were performed; Subgroup II B - 42 patients undergoing breast ultrasound have been performed; Subgroup II C - 412 patients that were performed mammograms and breast ultrasound; Subgroup II D - 34 patients which were performed mammography examination and magnetic resonance; Subgroup II E - 36 patients which were performed breast ultrasound and magnetic resonance examinations; Subgroup II F - 29 patients that were performed mammograms, breast ultrasound and magnetic resonance examinations. The first aspect studied was related to their background imagicistic investigated patients with malignant lesion. It was found prevalence of patients from urban areas (412 cases) compared with those from rural areas (256 cases). It was shown that the most affected age groups were, in decreasing order, 51-60 years, 61-70 years and 71-80 years. The small number of cases in the category 21-30 years is justified by the low incidence of these lesions in young women. There is however a large number of patients in the age group 31- 40 years.

We then studied patients presenting reasons for imaging investigations. In these patients, the reasons were: palpable mass in the breast or breasts; breast pain; nipple discharg ; axillary lymph nodes or distant metastases unspecified starting point; hormone replacement therapy; inflammatory phenomena; changes in nipple (retraction , suspicion of Paget's disease) ; + breast pain palpable mass; + nipple discharge palpable mass; + breast pain Nipple discharge; formations palpable + nipple changes ; formations palpable + skin changes; + palpable axillary lymphadenopathy formations; + palpable formations inflammatory phenomena; breast pain palpable mass + nipple discharge; hormone replacement therapy + palpable mass . The most common signs and symptoms that led presentation doctor formations were the tangible, palpable formations association with breast pain, breast pain, presence of axillary lymph nodes or distant metastases unspecified starting point, inflammatory phenomena. The order in which investigations were carried out for reasons sometimes depended imaging referral to specialist consultation .

THERAPEUTIC RESULTS IN POST IMAGING.

Group III consisted of 480 patients examined post- treatment imaging. The criterion for inclusion in the squad was to perform at least one therapeutic modalities - chemotherapy, surgery and/or radiotherapy for breast cancer. We divided this group into six subgroups based on imaging tests performed, regardless of the time of their concurrent or successive : Subgroup III A - 199 patients undergoing mammograms were performed; Subgroup III B - 20 patients undergoing breast ultrasound have been performed; Subgroup III C - 220 patients that were performed mammograms and breast ultrasound; Subgroup IIID - 16 patients which were performed mammography examination and magnetic resonance; Subgroup III E - 4 patients that have been performed breast ultrasound and magnetic resonance examinations; Subgroup III F - 21 patients which were performed mammograms , breast ultrasound and magnetic resonance examinations. It was found predominance of patients from urban areas. Response to neoadjuvant chemotherapy, preoperative, was evaluated in 138 of the patients, by performing mammograms at the beginning and end of treatment. They were followed parameters: tumor volume, taking into account spiculiforme lesions, only dense center, change in tumor density, contour, appearance microcalcifications, skin thickening, swelling and lymphadenopathy. The main criterion that the basis for assessing response to chemotherapy was the tumor volume . The response was considered complete if not viewed the original tumor mass and partly mammographic control where tumor volume decreased by 50 %. The study revealed a favorable response to 49 cases.

DISCUSSIONS

BREAST TUMOR IMAGING DETECTION.

The patients investigated in the screening program and the time in which it was conducted investigations were distributed aligning their downward trend in 2007. There was a high addressability age groups 41-50 years and 51-60 years, and clear distribution for the urban environment, probably justified easy access to the information provided in the promotional campaigns and the program itself of such persons, compared with those in rural areas. 4.52 percentage of cases with indeterminate or suspicious lesions or high probability of malignancy is significant given the fact that breast cancer screening program were included people that there was no clinical suspicion of malignancy.

IMAGING METHODS.

The imaging diagnostic imaging play a major role in detecting malignant breast lesions. After studying the epidemiological data was found predominance of patients from urban areas. The results are consistent with those of the literature. It highlights a parallel between the age distribution resulting from this study and studies on the epidemiology of breast cancer . The reports on the distributions backgrounds, age groups at each of the 6 subgroups formed and the whole group are also proportionate.

POST THERAPEUTIC IMAGING METHODS.

Constant increase in the incidence and mortality from this disease redirecting efforts reasons for adopting effective secondary prevention strategies. Response to chemotherapy, which can be quantified imaging is essential, being a very important prognostic factor. The assessment also allows the detection of early postoperative complications and residual lesions and the possible late recurrence. It aims at early detection of recurrence and significantly reducing the number of surgical biopsies for benign lesions for diagnostic imaging in evaluating therapeutic post with as much accuracy.

CONCLUSIONS

1. Patients were investigated by imaging methods in the screening program and the time frame within which the study was conducted showed relatively oscillating distribution. There was a high addressability age groups 41 - 50 years and 51 - 60 years. Also there was a clear distribution for patients in rural urban. 2.The percentage 4.52 % of cases with indeterminate or suspicious lesions or high probability of malignancy discovered through the screening of mammary tumors is significant given the fact that therein were included patients in which there was no clinical malignancy suspicion. 3. Most cases with lesions of this type were found in age groups 71 - 80 years, 51-60 years and 61 - 70. By comparing the percentage of the total number of patients examined by imaging methods to the percentage of the number of cases with suspicious lesions with high probability of malignancy in each of the age groups studied showed that there is a parallelism between these categories. However, increased frequency in the age group 51 - 60 years can be justified only in part by the greater number of patients examined in this age group imaging. 4. In terms of the distribution of patients according to the degree of suspicion of malignancy was found in favor of the distribution of cases with suspicious abnormalities, which emphasizes the importance of early detection of breast tumors screening programs. Conditions for inclusion in the screening program which consisted of no clinical signs of malignant mammary determined the presence of a larger number of cases falling with suspicious lesions compared to those with high probability malignitate.5 injuries.

Comparing the percentages represented by patients investigated by mammography, those that were investigated by ultrasound breast and those that were investigated by both methods the total number of patients investigated with the same categories percentages of the number of cases detected suspicious lesions and with high probability of malignancy was concluded that there is a significant increase in detections of mammary tumors by combination of the two methods allowed detection of mammographic imagistic. 6. The mamographic examinations allow the greatest number of suspicious lesions and the probability of malignancy. This is because, on the one hand, the majority of patients who were investigated by this method was due to the increased percentage of patients over 40 who were present and on the other hand due to the increased performance of this method of imaging exploration the anomaly detection architectural focal outbreaks of microcalcifications and density asymmetries. 7. Young patients with dense breasts, making breast ultrasound is indispensable, is extremely useful for further characterization of lesions detected mamografic. 8. Algorithm imaging investigation in the screening program include performing mammography breast tumors in both breasts incidences cranio - caudal and oblique medio - laterale patients over 40 years and performing breast ultrasound in patients under 40 years and one of the association other methods of investigation as complementary method in all cases where the limits imposed by the method performed by first intention .