Correlation Between Ultrasonography and Magnetic Resonance Imaging with Pathology-Measured Tumor Size in Women with Recently Diagnosed Breast Cancer

Optimizing tumor-size estimation with imaging techniques for higher precision

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SUMMARY

The use of Breast-MRI in surgical planning of breast cancer is a field of controversy due to its high sensitivity but low specificity, alongside with overestimation of tumor-size. It has been proven many factors contribute to this overestimation. This study aims to define the extent of impact that the Clinical T-Stage, Histologic Subtype, Histologic Grade and Biologic Profile have on the correlation between MRI and ultrasonography (US) with pathology-measured tumor-size. To do so, a prospective, observational, descriptive, multicenter correlational study will be conducted in 145 women with recently diagnosed breast cancer, to whom a gadolinium-enhanced breast MRI will be performed alongside traditional triple assessment, recording largest diameter of tumor by US and MRI. This correlation will later be analyzed under the influence of the items in study individually to extract conclusions of the degree of impact, to secondly conjecture a mathematical model of optimization in tumor-size estimation.

El uso de Resonancia Magnética Mamaria (RMM) en la planificación pre-quirúrgica del cáncer de mama es controvertido dada la alta sensibilidad y baja especificidad, junto con la sobreestimación del tamaño tumoral. Ha sido demostrado que múltiples factores contribuyen a esta sobreestimación. Este estudio se centra en definir el grado de impacto que tienen la T-Clínica, Subtipo Histológico, Grado Histológico y Perfil Biológico sobre la correlación del tamaño tumoral medido por RMM o Ecografía y anatomía patológica. Se realizará un estudio prospectivo, observacional, descriptivo, correlacional y multicéntrico con 145 mujeres recientemente diagnosticadas de cáncer de mama, a las que se les realizará una MRR con gadolinio además del protocolo diagnóstico habitual, anotando el diámetro máximo de tumor observado en MRR y ecografía. Esta correlación será analizada bajo la influencia de los ítems a estudio individualmente para extraer conclusiones sobre el grado de impacto, para secundariamente desarrollar un modelo matemático de optimización en estimación de tamaño tumoral.

KEYWORDS

Magnetic Resonance Imaging. MRI. Breast Cancer. Concordance. Discordance. Tumor Size. Correlation. Ultrasonography. US. Pathology clinical.

BACKGROUND

INTRODUCTION

Breast cancer is diagnosed globally thanks to triple assessment (TA), a strategy that includes clinical examination, imaging techniques such as mammography and ultrasound (US), and pathological examination from biopsy. After diagnosis, therapeutic decisions have to be taken, and there is consensus on the use of breast conserving therapy after strong evidence of its benefits. The objective of this approach is to completely remove the tumor but affecting as least as possible aesthetics, due to the psychologic impact this can have on the patient. (1)

Since the discovery of Magnetic Resonance Imaging (MRI), many uses have been discovered for this technique. Breast MRI has shown to be highly sensitive, and can identify foci of cancer that are not evident by TA. Although it has been traditionally defended that MRI improves selection of patients for breast conserving surgery, the COMICE study recently showed no significant reduction in reoperation rate by adding MRI to TA, suggesting this technique might be unnecessary in preoperative planning(2). This may very well be due to the overestimation in tumor-size, which increases the aggressiveness of therapeutic approach, combined with the fact that old guidelines have been directly applied instead of adapting new ones to MRI technology.

Tumor size is one of the most important factors in determining disease-free and cause-specific survival rates in invasive breast cancer, particularly in cases of node-negative breast cancers where tumor size becomes of utmost importance in determining type and extent of subsequent surgical and oncological management. This is well represented by The American Joint Committee on Cancer (AJCC) for Breast Tumors, where these are classified according to size (T1 >2cm, T2 2-5cm, T3 >5cm). Therefore, accurate measurement of an invasive breast cancer is crucial for allowing the best outcome in patient management. (3)

Not many studies have been conducted studying the correlation of MRI and US with pathology-measured tumor size. The main referents in this area include the MONET(4) and the COMICE(2) studies. Since both conclude that further investigation is necessary in this field, this study aims to focus in different factors that alter the accuracy of these techniques for tumor-size estimation, to posteriorly conjecture a mathematical model for correction that can be used to optimize resources.

BREAST CANCER

Breast cancer is the most frequently diagnosed cancer in women, accounting for as much as 23% of all cancers, as well as the leading cause of cancer death among females, responsible of 14% of these. Furthermore, there is a global increasing incidence rate (nowadays, one in every 9-12 woman will develop a breast cancer), but fortunately followed by a decreasing annually mortality rate, partly due to the implantation of screening programs through mammographies and auto-palpation of breasts, leading to higher prevalence associated to longer survival rates.(1)

Many factors have been traditionally said to be involved in the neogenesis of these tumors, among which are: immunologic, physical, chemical, environmental, hormonal, genetic, and alimentary factors, and viral infections. In order to reduce incidence of breast cancer, these risk factors are to be aimed for.

Once the tumor has developed, secondary prevention has to take place to increase survival rates of these patients. This is where screening programs come in handy, together with clinical examinations.

BREAST LESION: ACTUATION PROTOCOL

The actual diagnostic protocol consists of the triple assessment: clinical examination, use of imaging techniques, such as mammography and ultrasound, and pathology microscopic diagnosis from biopsy. Following these, a body-CT or Gammagraphy is performed to complete extension study. The introduction of a preoperative breast-MRI to this protocol is a field of discussion among experts that is nowadays subject of controversy.

CLINICAL EXAMINATION RELEVANCE

Clinical examination has proven to be key in the early diagnosis of breast cancer. The most important aspects of clinical exploration are inspection and palpation.

Through inspection, we can search for retractions in the breast contour, nipple alterations, dilated cutaneous veins, redness of the skin, infiltration and edema, and skin ulceration.

Through a correct palpation, we can describe the tumor's size, situation, contour, and consistency. An irregular contour with irregular edges should awake suspicion, as well as a stiff consistency and a decreased mobility.

MAMMOGRAPHY AND BI-RADS CLASSIFICATION

Mammography is the most valid and widely-used radiologic technique for breast cancer screening, whose objective is to detect early stage cancer in asymptomatic women. It gives valuable information for differentiating benign and malignant lesions. When a mass lesion is detected at mammography, the lesion is first evaluated for the regularity of its margins. High density, irregular margins and speculation are important findings for malignant lesion. Also, microcalcifications in a mass lesion should be evaluated carefully. Although proven to be very sensitive, it yields a 10% of false negatives, especially in very dense breasts, were an additional ultrasonography is recommended for higher sensibility. (5)

The radiologic findings are grouped according to the BI-RADS classification (Breast Imaging Reporting And Data System), indicating how suspicious of benignancy or malignancy a lesion is.

ULTRASONOGRAPHY

Although mammography is a very effective method for detecting breast tumors, ultrasonography (US) is far more valuable in the screening of dense breasts(6). Furthermore, US is the election technique for differentiating cystic and solid masses. A cyst will appear as an anechoic lesion with regular margins, smooth walls, ovoid shape and with posterior acoustic enhancement.(5)

A study published by *W. Berg et.al* describes US yielding higher sensitivity than did mammography for the detection of specific histological subtypes, such as Invasive Ductal Carcinoma (IDC) in 94% cases, and Invasive Lobular Carcinoma (ILC) in 86% cases. However, US involves risk of overestimation of tumor extent.(6)

Moreover, *Cortadellas et.al*(7) concludes that ultrasonography is the best predictor of tumor size in breast cancer, when compared with clinical examination, mammography, and MRI, in a retrospective study just published in February 2017.

GADOLINIUM ENHANCED-MRI IN PRE-SURGICAL EVALUATION

The dynamic gadolinium-enhanced MRI is the auxiliary image technique of election of highest sensibility (88-100%) for breast cancer, although its limited specificity (22-97%) makes its use reserved for limited situations and always in combination with other imaging techniques. It is used in pre-surgical evaluation especially in the study of local extension, although its use is of big controversy, having some authors recommend its limitation to young woman with dense breasts.

Nevertheless, some studies have shown MRI has a higher sensitivity than mammography for all tumor types and higher sensitivity that US for Ductal Carcinoma In Situ (DCIS), IDC, and ILC. (8),(2),(9) This discords with the information recently published by *Cortadellas* (7), proving further investigation is necessary in this field.

In nonfatty breasts, US and MRI have proven to be more sensitive than mammography for breast cancer detection, but both MR and US involve risk of overestimation of tumor extent. Finally, *Berg* concludes that combined mammography, clinical examination and MRI are more sensitive than any other individual test or combination of tests. (6)

PATHOLOGY CLASSIFICATION

According to pathological findings in the biopsy, and for the purpose of this investigation, we subdivide breast cancer into:

IDC: INVASIVE DUCTAL CARCINOMA

EIC: IDC WITH EXTENSIVE INTRADUCTAL CARCINOMA

ILC: INVASIVE LOBULAR CARCINOMA

DCIS: DUCTAL CARCINOMA IN SITU

"OTHER HISTOLOGY": Mucinous, papillary, medullar, tubular and apocrine breast cancer

BREAST MRI: CURRENT USE AND CONTROVERSY

It is well established that MRI is by far superior to mammography in the detection of breast cancer. Due to its very high negative predictive value, MRI can be used to confidently exclude the presence of breast cancer, and, this, avoid unnecessary surgery. Furthermore, due to its high sensitivity, MRI can detect cancer in the ipsilateral and contralateral breast that is missed by mammography and clinical examination. For all these reasons, MRI is considered an integral part of the work up of patients who undergo breast-conserving treatment for breast cancer. However, MRI has only been adopted in clinical practice slowly. Reasons for this include high costs of MRI, frequency of false positives, and fear of overtreatment because of overestimation. (1)(10)(11) (12)

Because MRI is so sensitive, it was assumed that preoperative MRI would estimate the extent of disease more accurately than conventional imaging, thereby improving surgical planning. However, data available has shown that preoperative MRI has not improved outcomes, overestimates the extent of disease, and has overall limited value. The COMICE trial showed no difference in the reoperation rate with or without the use of preoperative MRI. In addition, many women had mastectomies (27.6%) later proven not necessary in pathology. Furthermore, in a review of 1558 consecutive patients with invasive breast cancer and/or noninvasive breast cancer, MRI was not associated with an advantage to lower re-excision rate, improve the rate of breast conservation surgery achievement, or lower recurrence rate. (1)(8) (2)(12) (13)(4)(14)

Mennella describes that the type of biopsy procedure and the time interval between biopsy and preoperative MRI are not independently associated to MRI-Pathology discordance. However, size, histology and margins of tumors do have an impact. It is still a matter of discussion up to what extent do these have an influence, as well as what other factors lead to discordance in tumor-size estimation. (8)

Grimsby describes that breast MRI is concordant with pathologic tumor size within .5cm among 53% of patients. Among tumors overestimated by MRI, 65% had additional significant findings in the breast tissue around the main lesion: satellite lesions, ductal carcinoma in situ, and/or lymphovascular invasion(15)

In a study conducted by *Onesti*, he describes that MRI and pathology tumor size were positively correlated (R=.650), but with an average overestimation by MRI of .63 cm (P <.0001). When stratified by MRI tumor size (<2.0 cm and >2.0 cm), a significant difference

was found only in tumors greater than 2.0 cm (average overestimation = 1.06 cm; P <.0001). This trend continued for the histological subtypes of ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and invasive lobular carcinoma (ILC).(16)

Therefore, we can see how tumor size and histologic subtype are indeed factors affecting the accuracy of MRI in tumor-size estimation, but further investigation in this area is needed.

On a separate subject, it has been well-established in several studies that MRI is a highly-recommended diagnostic tool for high-risk patients. These include: being a BRCA1 or BRCA2 mutation carrier or having a first-degree relative with these, receiving previous radiotherapy on the chest-wall, personal history of Li-Fraumeni or Cowden disease, or having an estimated lifetime risk of breast cancer of 20 percent or higher calculated with the BRCA-PRO model. It is in order to mention that these patients are not the subject of this study and thus these will be included in the exclusion criteria for selection of patients.(1)'(17)

Also, this investigation aims to focus on Breast-MRI as part of the pre-surgical examination by analyzing factors that influence tumor-size appearance. This has to not be mistaken with the full body CT-Scan that patients undergo during the extension study.

JUSTIFICATION OF STUDY AND OBJECTIVES

Because MRI is so sensitive, it was assumed that preoperative MRI would estimate the extent of disease more accurately than conventional imaging, thereby improving surgical planning. However, available data has shown that preoperative MRI has not improved outcomes, overestimates the extent of disease and has overall limited value(1)

It is thereby this study's main objective to examine the correlation of MRI and US with Pathology-measured tumor size according to histologic subtype, histologic grade, clinical T-stage, and Biologic profile (Estrogen receptors, Progesterone receptors, and Her2/Neu) in order to secondly conjecture a mathematical model of approximation to maximize precision of tumor-size estimation in breast-cancer.

HYPOTHESIS

Histologic subtype, Histologic grade, clinical T-stage and Biologic Profile are factors influencing US-Pathology and MRI-Pathology tumor-size correlation, thereby leading to an unnecessary amount of mastectomies (non-conservative breast therapies) in breast cancer management. Therefore, a correction of the impact of these factors by a mathematical model should lead to higher precision in tumor-size estimation with imaging techniques.

METHODS AND MATERIALS

DESIGN

This is an observational, descriptive, prospective, multi-centric, correlational study with 145 women with newly diagnosed, biopsy-proven, primary breast cancer who will be offered to enter the study, following a consecutive sampling, by undergoing a Breast Gadolinium Enhanced MRI before surgical treatment. Tumor-size measurements, excluding those obtained by MRI, will be obtained from the traditional triple assessment. In both cases, only the largest diameter of lesion size will be used to determine tumor size. Patients without a clear and precise measurement of the largest diameter of tumor size due to any reason will be excluded from the study. Cases in which neoadjuvant chemotherapy can't be delayed to after the MRI has been performed will also be excluded, as this factor is a demonstrated source of discordance(15).

SAMPLE SIZE NEEDED: CALCULATING N

Calculating sample size needed for a bilateral mean contrast: $N = \frac{2(Z\alpha+Z\beta)^2 \cdot s^2}{d^2}$

Zα: Z-value for Risk α; if α= 0.05, Zα= 1.960

Zβ: Z-value for Risk β; if β = 0.01, Zβ= 2.326

s^2: known variance in control group → from Mennella: $\bar{x}$=24.8 mm +/- 19.4 mm with CI95% (thus, s = 9.7mm, s^2 = 94.09mm^2) (13)

d^2: minimum difference to detect as relevant. We define d= 5mm → d^2= 25mm^2

Thereby:

$N = \frac{2(1.960+2.326)^2 \cdot 94.09}{25} = 138.27.$

If we assume a possible 5% loss (7 people), we can optimize for an **N = 145**

INCLUSION CRITERIA RECENTLY DIAGNOSED BREAST CANCER

- >18 years old
- No metastasis
- Possibility to perform US and MRI

EXCLUSION CRITERIA

- Contraindications of MRI: including but not limited to
  - Patients with severe claustrophobia
  - Patients who have a Heart Pacemaker or an Implantable Cardioverter Defibrillator
  - Patients who have a metallic foreign body such as projectiles form firearms
  - Patient who have an aneurysm clip in their brain
  - Patients who have had metallic devices placed in their back (such as pedicle screws or anterior interbody cages)
  - Patients with cochlear implants
  - Patients with an Intrauterine Device (IUD)
  - Patients with orthopedic devices
- Previous radiotherapy in chest-wall
- Previous breast cancer in ipsilateral or contralateral breast
- High-Risk Patient: including, but no limited to
  - BRCA1 or BRCA2 carrier
  - BRCA1 or BRCA2 1st degree case
  - Li-Fraumeni Syndrome
  - Cowden Syndrome
  - Peutz-Jegher Syndrome
- Lynch Syndrome Patients with an active neoplasia other than the breast cancer
- Patients with metastasis of unknown origin
- Patients that are pregnant
- Patients <18 years old
- Renal Insufficiency or Nephrogenic Systemic Fibrosis, or Gadolinium allergy
- Patients who need neoadjuvant chemotherapy that can't be delayed until after the MRI has been performed
- Patients without a clear and precise measurement of the largest diameter of tumor size due to any reason

DATA COLLECTION

Since the purpose of this investigation is to analyze correlation of tumor-size according to multiple factors, the recollection of the following data is of crucial importance:

- **Size measured by Ultrasound** (in mm)
  - Largest tumor diameter measured in US, recorded in millimeters.
- **Size measured by MRI** (in mm)
  - Largest tumor diameter measured in MRI, recorded in millimeters.
- **Size calculated by Pathology** (in mm)
  - Largest tumor diameter measured in pathology, recorded in millimeters.
- **Clinical T-Stage**(18) (T1-T2-T3-T4): As defined by the American Joint Committee on Cancer. Pre-Surgical Evaluation. Record pertaining category
  - T1: Tumor ≤20 mm in its biggest dimension
    - T1a: 1mm ≤ tumor ≤ 5mm
    - T1b: 5mm < tumor ≤ 10mm
    - T1c: 10mm< tumor ≤ 20mm
  - T2: 20mm < tumor ≤ 50mm
  - T3: tumor > 50mm
  - T4: any tumor-size with one of the followings:
    - T4a: extension to thoracic-wall, not including pectoral muscle
    - T4b: edema (including orange-skin) or breast skin ulceration, or satellite lymph nodes of the skin limited to the same breast
    - T4c: both T4a and T4b combined
    - T4d: Inflammatory carcinoma
- **Histologic Subtype**(13) (IDC, EIC, ILC, DCIS, Other): Record pertaining category. For the purpose of this investigation, classification is as follows:
  - IDC: INVASIVE DUCTAL CARCINOMA
  - EIC: IDC WITH EXTENSIVE INTRADUCTAL CARCINOMA
  - ILC: INVASIVE LOBULAR CARCINOMA
  - DCIS: DUCTAL CARCINOMA IN SITU
  - "OTHER HISTOLOGY": Mucinous, papillary, medullary, tubular and apocrine breast cancer; or any histology that doesn't fit the previous categories.

- **Histologic Grade/ Nottingham Score** (18) (19) (G1/G2/G3): Post-Surgical Evaluation. Record pertaining category. In this scoring system, three factors are taken into consideration by pathologists:
    - Glandular (Acinar) / Tubular Differentiation
        - Score 1: >75% of tumor area forming glandular/tubular structures
        - Score 2: 10% to 75% of tumor area forming glandular/tubular structures
        - Score 3: <10 of tumor area forming glandular/tubular structures
    - Nuclear Pleomorphism
        - Score 1: Nuclei small with little increase in size in comparison with normal breast epithelial cells, regular outlines, uniform nuclear chromatin, little variation in size
        - Score 2: Cells larger than normal with open vesicular nuclei, visible nucleoli, and moderate variability in both size and shape.
        - Score 3: Vesicular nuclei, of the with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms
    - Mitotic Count: using a high power filed diameter of 0.50mm
        - Score 1: ≤7 mitoses per 10 high power fields
        - Score 2: 8-14 mitoses per 10 high power fields
        - Score 3: ≥15 mitoses per 10 high power fields

    Each of these features is scored from 1-3, and then each score is added to give a final score, which is classified as:

    - Grade 1 (G1): score of 3, 4 or 5
    - Grade 2 (G2): score of 6 or 7
    - Grade 3 (G3): score of 8 or 9

- **Biologic Profile (**E, Pg, Her2/Neu, Ki67): Record if positive or negative
    - **Estrogen Receptors (E):** Positive if result shows >10%. Negative otherwise. Record the % in the comment box.
    - **Progesterone Receptors (P):** Positive if result shows >10%. Negative otherwise. Record the % in the comment box.
    - **Her2/Neu:** Record if positive or negative result.
    - **Ki67:** Record if positive or negative result.

Nevertheless, the following information shall also be recorded for possible further analysis:

- **Age** of patient (in years old)
- **Reproductive age versus Menopause**
- Presence of **microcalcifications** (yes/no)
- **Lymph Node Invasion** (20): Number and localization of lymph nodes affected (N-factor of TNM) as defined by the American Joint Committee on Cancer (pNX, pN0, pN0(i-), pN0 (i+), pN1mi, pN1a, pN2a, pN3a).

All of these data will be collected into a predefined table that can be found as an attachment to this investigation protocol. (See Attachment 1 in page 24)

CHRONOLOGY

1. Informative meeting with professionals willing to participate in the investigation. This meeting will serve as an opportunity to explain the study, thoroughly go through every step of the investigation and resolve any doubts rising from the protocol.
2. Patient recently diagnosed with breast cancer thanks to Triple Assessment. In this step, the patient is identified as suitable for the investigation and proposed to enter the study. Check for inclusion and exclusion criteria. If met, explain study and give "information to the patient document" (see attachment 3 in page 26). If the patient accepts, signal of informed consent document. Record filiation data, and submit information to project manager. If all criteria is met, an identification number will be assigned to the patient.
3. Collection of data: Start to collect the data as indicated in Table 1 (see attachment 1 in page 24). In this step, the following should be collected: Age, Reproductive Stage, Size by Ultrasound (obtain information from medical history, as this is part of triple assessment. In case this information is not available, another US is necessary), Clinical T-Stage, Histologic Subtype, Biologic Profile, Histologic Grade, Presence of microcalcifications, Lymph Node Invasion.
4. Patient receives Breast-MRI with Gadolinium contrast. The tumor-size in MRI is recorded in the patient's collection data table.
5. Patient undergoes surgery as part of the normal treatment (independently of Breast MRI result)
6. Biologic specimen analyzed in pathology lab. Once results are available, record: tumor-size measured by pathology.
7. Once there is information collected for 145 patients, researchers perform statistical analysis of data.
8. Extracting conclusions, and attempting to conjecture the mathematical model through the inclusion of correcting factors leading to tumor-size discordance between techniques.

In order to make this information more clear visually, Table 2 is available in the attachments. (See Attachment 2 in page 25)

STATISTICAL ANALYSIS

Categorical data will be expressed as number and percentage, while continuous data as mean and standard deviation. The normal distribution of MRI, US and pathology measurements will be assessed using D'Agostino-Pearson test in each factor examined (histologic subtype, clinical T, histologic grade and biologic Profile), comparing separately MRI vs Pathology and US vs Pathology for each category examined. Since some data-sets don't follow normal distribution (e.g. tumor size in the different histologic subgroups), non-parametric tests will be used instead of parametric ones. The degree of relationship between two independent variables will be determined by using the Sperman's rank correlation.

Concordance between MRI or US and Pathology tumor-size is defined as a difference of ≤5mm.

Mann-Whitney test will be used to assess the difference between the medians of two independent groups, and Kruskal-Wallis test to verify the presence of a statistically significant difference between the medians of more than two different groups. After a positive Kruskal-Wallis test ($p<0.05$), a post-hoc analysis will be conducted performing pairwise comparison of subgroups.

Bland-Altman analysis will be used to determine to what extent the MRI or US tumor size correlates with the four main factors.

In addition, the absolute difference between MRI and Pathology measurements will be calculated, and the presence (or absence) of MRI-pathology discordance (difference >5mm) will be put as a dichotomous dependent variable in a multivariate logistic regression model, using the four main variables and the pathology size as independent variables.

ESTIMATED BUDGET

In order to calculate the estimated budget for this investigation, the following are considered:

	Price/Unit (€)	Number of Units	Total Price (€)
Gadolinium Enhanced Breast-MRI	175	145	25.375
Materials (Paper, Binders, Staplers, Printer Ink…)	10	145	1450
Statistics Consulting	300	-	300
Extra Emergency Burden	500	-	500
TOTAL			27.625

It is in order to mention that the following are not considered direct costs of this investigation: Monetary compensation for participants or researchers, economic cost derived from triple assessment (as this is performed independently to the investigation), and transportation costs.

EXPECTED RESULTS AND PRACTIC APPLICATIONS

With this correlational study we aim to define the amount of impact the factors investigated have on the correlation between MRI and US with Pathology-measured tumor size. We have therefore chosen the factors based on strong believe that these yield real alteration on the response variable, thus expecting to find the actual extent of influence they have. The four main variables we expect to see as influencers are clinical T-stage, Histologic subtype, Histologic Grade and Biologic Profile. The secondary variables collected (age, reproductive stage, lymph node invasion) we believe will have a smaller impact on the distortion of correlation. Furthermore, US and MRI-measured size will both have to be taken into consideration when pursuing the secondary objective of this investigation, which is to conjecture a mathematical model of approximation to optimize size estimation. This model will then have to be tested in future studies to verify for reliability. If proven to be reliable, we believe this model should be implemented into clinical practice in order to achieve the maximum level of accuracy, and thus indicate conserving breast therapy with less margin of error.

LIMITATIONS OF STUDY

As in any scientific investigation, this study presents several limitations.

The first limitation is common to all kinds of studies: aleatory error. This is defined as the lack of precision caused by arbitrariness. This error doesn't affect the internal validity but decreases the precision of the investigation. A solution to minimize this error is to increase the sample size studied, but this also derives in an increases budget.

Secondly, it is a correlating investigation, and thus is encumbered by all the limitations of such design. These include, but are not limited to, the lack of temporal sequence, the inability to control confounding factors, and the fact that a lack of correlation might not mean a lack of association.

Specifically linked to this investigation, the following are sources of limitation:

· Measurement of the larget tumor diameter by different radiologists might leed to small diferences. This is one of the points to discuss in the staff meeting prior to starting the study. Also, a Kappa Test could be perfomed to analyze the magnitude of impact of this error. This error is tried to combat by excluding from the study those cases with significant controversy

· There is technical complexity in obtaining an accurate measurement of DCIS lesions at pathological analysis of surgical specimens (as previously reported by other studies"

· Investigator influence during the malignancy assesment of the results due to previous knowledge of the results with other imaging techniques cannot be excluded.

· There is always a selection bias, as woman are subjectively selected for the investigation.

· Pathology is defined in this study as the gold standard. Thus, our study includes all the limitations inherent to today's standards for pathology

· The low prevalence of certain hystologic subtypes leads to a smaller precision estimation of the impact this factor has on tumor-size correlation.

· There are many items that could be playing as confounding factors, that are not taken into consideration by this investigation.

· Due to the high quantity of exclusion criteria, external validity might be compromised.

However, it is important to mention that in order to reassure the highest level of quality, and in order to reduce confusion, previous to publishing this investigation, a thorough

reevaluation will be carried out using the 22-item check-list defined in the STROBE Declaration for Observational Studies.

CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

ETHICAL STATEMENT

The study will have to go through the ethical committee of all centers participating in the investigation, although no denials are assumed due to the safety associated with magnetic resonance, and especially due to the exclusion of patients who could detriment from gadolinium use.

DIFFUSION MECHANISMS

The main diffusion mechanism planned for this investigation is the publication of the study in **Acta Radiologica (SAGE Journals)**, the leading journal in the ambit of imaging techniques. It is also the journal that holds most of the previous articles linked to this investigation, thus contributing to the development of knowledge in this field.

Publication in other scientific journals may also be contemplated, especially those concerning specifically breast cancer, and radiologic journals. These include:

· *Advances in Breast Cancer Research* (ISSN: 2168-1597)

· *Global Journal of Breast Cancer Research* (ISSN: 2309-4419)

·*Nature Partner Journals (NPJ) Breast Cancer* (ISSN: 2374-4677)

·*International Journal of Breast Cancer* (ISSN: 2090-3189)

·*The Breast Journal* (ISSN: 1524-4741)

·*The Breast: Official Journal of the European Society of Mastology* (ISSN: 1532-3080)

· *Breast Cancer Research and Treatment* (ISSN: 1573-7217)

· *The Lancet* (ISSN: 0140-6736)

· *European Journal of Cancer* (ISSN: 0959-8049)

· *The New England Journal of Medicine* (ISSN: 0028-4793)

· *European Journal of Radiology* (ISSN: 0720-048X)

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ATTACHMENTS

ATTACHMENT 1: TABLE FOR COLLECTION OF DATA

TABLE 1: DATA COLLECTION

AGE	(years old)					
REPRODUCTIVE STAGE	Premenopausia		Menopause			
SIZE IN ULTRASOUND	(mm)					
SIZE IN MRI	(mm)					
SIZE IN PATHOLOGY	(mm)					
CLINICAL T STAGE	T1	T2	T3	T4		
HISTOLOGIC SUBTYPE	IDC	EIC	ILC	DCIS		OTHER
HISTOLOGIC GRADE	G1	G2	G3			
BIOLOGIC PROFILE	**E**	(+)	(-)	**Pg**	(+)	(-)
	Her2/Neu	(+)	(-)	**Ki67**	(+)	(-)
MICROCALCIFICATIONS	YES	NO				
LYMPH-NODE INVASION	pNX	pN0	pN0 (i-)	pN0(i+)		pN1mi
	pN1a	pN2a	pN3a			
ADDITIONAL COMMENTS						

Insert number for AGE, SIZE IN ULTRASOUND, SIZE IN MRI and SIZE IN PATHOLOGY. Circle the best-fitting option for all the others. Write percentages of biologic profile and any additional comments if necessary in the box available.

ATTACHMENT 2: TABLE OF CHRONOLOGY FOR DATA COLLECTION

TABLE 2. Chronogram of Data Collection			
	DATA COLLECTION #1: Once the patient is assigned an ID number for the study	DATA COLLECTION #2: Once the Breast-MRI has been conducted	DATA COLLECTION #3: After pathology has examined the surgical specimen
AGE	X		
REPRODUCTIVE STAGE	X		
SIZE IN US	X		
SIZE IN MRI		X	
SIZE IN PATHOLOGY			X
CLINICAL T-STAGE	X		
HISTOLOGIC SUBTYPE	X		
HISTOLOGIC GRADE	X		
BIOLOGIC PROFILE	X		
MICROCALCIFICATIONS	X		
LYMPH-NODE INVASION	X		

ATTACHMENT 3: INFORMED DOCUMENT FOR THE PATIENT & INFORMED CONSENT

INFORMATION DOCUMENT FOR THE PATIENT

Correlation between Ultrasonography and Magnetic Resonance Imaging with Pathology-Measured Tumor Size in Women with Recently Diagnosed Breast Cancer: Optimizing tumor-size estimation with imaging techniques for higher precision.

Dear patient,

The objective of this document is to briefly and clearly explain the purpose of the study in which we offer you to participate. This document might contain words you don't understand, in which case we strongly urge you to not hesitate to ask the specialists involved in the study for explanations. When you have completely understood all the information presented, and if you are willing to participate, we will kindly ask you to sign an informed consent document.

The study we are conducting has as main objective analyze the correlation existing between real tumor-size calculated in pathology after surgical extraction and preoperative estimation by means of imaging techniques such as ultrasound (US) and magnetic resonance (MRI), and to what extent different factors contribute to an increasing discordance. This way, we pretend to later conjecture a mathematical model that takes into consideration these factors and helps in the decision process of therapeutic approximation to breast cancer, hoping always for breast conservation therapy, meaning surgery that is minimally invasive without compromising security. This is why we kindly ask you to participate in the study, which only means that you will undergo a MRI scan previous to any possible surgery.

Leaving the study

Your participation in this study is completely voluntary, meaning you are free to leave the study at any moment of the investigation, without having to give any particular reason. Also, leaving the study will not compromise your treatment or future medical attention in any way.

Your doctor can also dismiss you from the study at any given time if he/she considers it best for you, or if you don't meet the requisites to participate. You could be dismissed from the study if it is considered that you could be harmed in any way, if you need any treatment not allowed by this study, if you don't follow the instructions given for the study, if you get pregnant during the study or if the study is canceled.

Possible Risks and Inconveniences

The possible risks associated with this study are those associated with the practice of an MRI Scan, none of which are different of those associated to MRI in common practice.

Confidentiality

Your medical history and biologic data will be accessed keeping the most precautious and strict confidentiality in a way that does not violate personal privacy. Your data will be codified so that the information obtained won't identify you directly. This way you will not be able to be identified during the analysis and presentation of the results in publications related to this study. You are guaranteed the strictest compliance with the Law of Protection of Personal Data (Spain: Ley 15/1999 de Diciembre de Protección de Datos Personales)

If you accept to participate in this study, you authorize the access to your medical history not only by your doctor and team, but also by the staff involved in the development of this study (Study promoter) and the Regulatory Health Authorities

Monetary Compensation

There is no monetary compensation for the possible expenses incurred in the fulfillment of requisites of the study, such as transportation, nor for participating in this study.

Results

Once the study is completed and the results are available, your doctor can inform you if you wish. If the study results are published and you are interested in getting to know them, you will be given a copy of the publication or you will be given access to the results.

Acknowledgment:

We would like to thank you for taking the time to read this document. Please take the time you need before deciding whether to participate in this study. If you finally decide to take part in the study, you are kindly asked to sign two copies of the informed consent and keep one of them. The other will remain on file in your medical record. If any doubts appear during the course of this investigation, or in case of any emergency, please don't hesitate to contact the staff in charge.

INFORMED CONSENT DOCUMENT

Correlation between Ultrasonography and Magnetic Resonance Imaging with Pathology-Measured Tumor Size in Women with Recently Diagnosed Breast Cancer: Optimizing tumor-size estimation with imaging techniques for higher precision.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

I authorize the performance of a Magnetic Resonance in addition to the traditional triple assessment of breast cancer (including clinical examination, ultrasound imaging and/or mammography, and pathologic examination from biopsy-obtained tissue).

Regarding the use of clinical information available in my medical history and of any biologic material left-over by the study:

· I authorize the use of biologic materials and the clinical data associated with these for any further investigation, knowing this information will be treated anonymously.

YES □ NO □

· I wish to be informed of important information derived from the investigation

YES □ NO □

· I authorize to be contacted in the case of need of more information or biological samples.

YES □ NO □

Print Name of Participant: _____

Date (DD/MM/YY): _____

Signature of Participant:

Print Name of Researcher: _____

Date (DD/MM/YY): _____

Signature of Researcher: