Facultat de Medicina

RELIABILITY OF INTRAOPERATIVE ULTRASOUND IN MARGIN STATUS ASSESSMENT IN WOMEN UNDERGOING BREAST CONSERVING SURGERY

FINAL GRADE PROJECT

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1. ABBREVIATIONS

BCS	Breast Conserving Surgery
BCT	Breast Conserving Therapy
CT-scan	Computerized Tomography Scanner
DCIS	Ductal Carcinoma *In Situ*
ER	Oestrogen Receptor
FSA	Frozen Section Analysis
HER2	Human Epidermal Growth Factor Receptor 2
IC	Imprint Cytology
ICC	Intraclass Coefficient
IMA	Intraoperative Margin Assessment
IOUS	Intraoperative Ultrasound
LR	Local Recurrence
MRI	Magnetic Resonance Imaging
PR	Progesterone Receptor
ROLL	Radio-guided Occult Lesion Localization
SERM	Selective Oestrogen Receptor Modulator
SM	Surgical Margins
SNOLL	Sentinel Node and Occult Lesion Localization
US	Ultrasound
WGL	Wire-Guided Localization

2. ABSTRACT

Background	Effective treatment for breast cancer requires accurate preoperative planning, developing and implementing a consistent definition of margin clearance, and using tools that provide detailed real-time intraoperative information on margin status. Intraoperative ultrasound (IOUS) may fulfil these requirements and may offer few advantages that other preoperative localization and intraoperative margin assessment techniques may not.
Purpose	The goal of the present work is to determine how accurate the intraoperative ultrasound should be to acquire complete surgical excision with negative histological margins in patients undergoing Breast Conservative Surgery.
Design	A diagnostic test study with a cross-sectional design carried out in a tertiary referral hospital in Girona within a Breast Pathology Unit.
Participants	Women diagnosed with breast cancer undergoing a Breast Conservative Surgery in the Breast Pathology Unit at Hospital Universitari de Girona Dr. Josep Trueta.
Key words	Early Stage Breast Cancer; Breast Conserving Surgery; Intraoperative Ultrasound; Margin Status.

3. INTRODUCTION

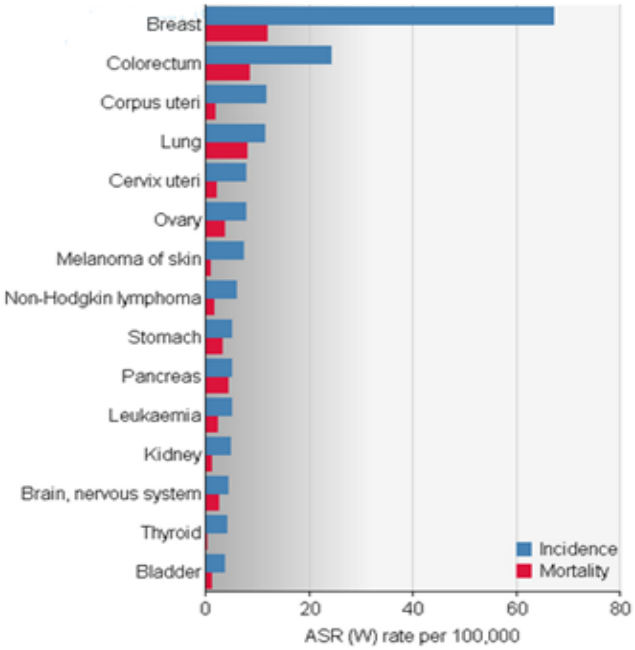
3.1. Background

Breast Cancer is the most prevalent cancer in a wide majority of countries globally, being the main type of cancer among women worldwide. Close to half of the prevalence burden is in areas of high human development although it represents only one sixth of the world's population (1).

In Europe, there were over 3.4 million new cases of cancer (excluding non- melanoma skin cancers) in 2012. The most common cancer globally was breast cancer, with an estimated incidence of 464,000 cases, representing the 13.5% of all cancer cases and the 28.8% of the cancers affecting women; moreover, breast cancer is the first cause of cancer death in European women (2). In fact, Europe carries a significant load of the global burden; with only one-ninth of the world's population, it carries one quarter of the global burden of cancer.

In 2012, as can be appreciated in the *graphic 1*, breast cancer was the most commonly diagnosed cancer among females in Spain with an incidence of 25,215 cases representing the 29% of the overall cancers in women. The five-year prevalence was 104,210 cases representing the 40% of cancers diagnosed among Spanish women. When concerning mortality, breast cancer stood for the 15.5% of cancer deaths (3).

Graphic 1. *Estimated age-standardised incidence and mortality rates of breast cancer in Spanish women*



Resource*: GLOBOCAN 2012: Estimated Cancer Incidence, Prevalence and Mortality Worldwide in 2012. [Internet]. Lyon: Internation Agency for Research on Cancer (IARC); 2014. p. 1–7. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx*

With reference to a local level, in the Sanitary Region of Girona, according to the CanGir 2007-9 report submitted by el Registre del Càncer de Girona, by the time of 2013-2014, it is estimated an incidence of breast cancer of approximately 389 cases, being the most common diagnosed cancer among women in Girona (4). All in all, breast cancer has become the leading cause of cancer in terms of new cases according to the latest official reports.

Updated data regarding cancer incidence and mortality in Europe is a crucial resource in both planning and assessing the impact of cancer control programmes at a global and regional level (2).

Due to the fact that breast cancer is the most common cancer in women, Health Care Services from high developed countries have targeted this disease as an important issue to be focused on. As a consequence of its high prevalence and incidence, lots of funds have been invested in improving the medical approaches to diagnose and treat effectively patients affected by this cancer. During the last decades, important screening programmes have been designed to detect early stage breast cancer. The direct consequence of this measure is the detection of a large amount of stage I-II breast cancers, currently representing more than 80% of diagnosed cancers (5).

In fact, and, as a consequence of the early detection of breast cancer, its surgical treatment has been in considerable evolution over the past decades. Previously, the radical mastectomy introduced by Halsted, an American surgeon, was the standard treatment for breast cancer of any size or type, regardless of the patient's age. This surgical technique cuts out the breast, axillary nodes and chest muscles including pectoralis major and minor. Radical mastectomy was the surgical treatment choice for most of the 20th century and the option of attempting a surgical procedure that would conserve the breast was not widely considered during those years (6). It was during the 70s, when important clinical trials were performed in order to update the management of early diagnosed breast cancers with the aim of reducing the physical and psychological morbidity associated with this aggressive procedure (7).

These randomized clinical trials concluded that there was no significant difference in the disease-free survival, long-term survival and overall survival among women with early stage breast cancer who underwent mastectomy and those who had gone through Breast Conserving Therapy (BCT), which is the removal of the primary tumour and a margin of surrounding tissue (lumpectomy) plus adjuvant radiotherapy; the surgical part is also called Breast Conserving Surgery (BCS). The results of these studies showed that there

was no decrease in overall survival after BCT (6,7). New less aggressive, safe and effective standards of care in loco-regional and adjuvant systemic therapy were accepted in order to reduce the extent of surgical procedures and to improve the outcome of patients with early-stage breast cancer. Thus, surgical treatment shifted from mastectomy to breast conserving surgery in conjunction with adjuvant therapies as first choice treatment for early stage breast cancer (8).

Even though BCS has proved to be equivalent in terms of long-term survival when compared to mastectomy (9), this surgical approach is not exempt from disadvantages. BCS faces some limitations:

1. Localizing non-palpable tumours
2. The possibility of inadequate resection of the tumour during the initial operation
3. Potential risk of local recurrence (LR)

1. Localizing non-palpable tumours

Regarding the first issue, that is the localization of non-palpable lesions, several preoperative localization techniques have been developed (10,11):

- **Carbon Marking**

  Inert charcoal powder diluted with saline solution introduced through the skin, marking the way to reach the lesion. It is introduced under image guidance such as stereotactic or sonographic localization. The following surgical excision is guided by the presence of the carbon in suspension. Due to charcoal stability, surgery can be performed with delay. A potential disadvantage is the obstruction of needle tip as a consequence of carbon powder particles precipitation.

- **Wire-Guided Localization (WGL)**

  It consists in the placement of one or more needle or flexible wire into the centre of the lesion in order to guide the surgeon in excision. It can be guided through mammographic, sonographic or CT image techniques. Despite the fact that WGL is relatively simple and cost-effective, it may have some disadvantages such as wire dislodgment leading to a difficult excision-guided surgery. Nowadays, it is considered to be the *gold standard* approach for clinically non-palpable tumours.

- **Radio-Guided Occult Lesion Localization (ROLL)**

  It is based on the preoperative injection of radioactive isotope ^{99m}Tc (radioactive technetium) into the tumour under mammographic or sonographic guidance followed by a scintigraphy scan of the breast in order to check the correct inoculation of the tracer. The surgeon detects the tumour with the help of a gamma probe and checks the adequacy of excision. Moreover, the tracer can be injected near to the tumour to be drained in the sentinel node, which can be easily identified by the gamma probe. This additional technique is called "sentinel node and occult lesion localization" (SNOLL). A complication of this approach is the risk of dispersion of the tracer among the breast tissue hindering the localization of the lesion.

- **Intraoperative Ultrasound (IOUS)**

  It consists in the intraoperative ultrasound assessment of the lesion immediately previous to the surgery. The tumour must be visualized by sonography for this technique to be successful. It allows to plan the incision and reassess orientation in real-time. Additionally, it may help in positioning the wire, injecting the dye or marking on the skin. This approach avoids the requirement of the preoperative localization of the tumour. In addition, the IOUS may guide the resection of the tumour and assess the margin status.

Despite the fact that WGL is considered to be the *gold standard* approach for preoperative localization, it has technical and scheduling drawbacks. This has led to the development of alternative localization techniques. Among these techniques, intraoperative sonographic localization has proved to be an accurate and simple method of ensuring adequate excision of screen detected palpable and non-palpable lesions. It is comparable to WGL, but avoids painful preoperative localization and saves both radiology and theatre time. It may become the new *gold standard* for image-guided surgery in BCS (12,13).

Many lesions are clearly visible on ultrasound, therefore allowing the localization of the tumour and its limits; however, on the one hand, there are other breast tumours that are scarcely visible on ultrasound such as DCIS, and on the other hand, there are others owning image features that are not well detected through the ultrasound and may not exhibit the typical criteria for malignancy; for instance, invasive lobular carcinoma may not show posterior acoustic enhancement, simulating a benign lesion

when, in fact, the real underlying character of the lesion is malignant (14). In these cases, other preoperative localization techniques might be suitable.

As BCT has been established as the choice treatment for early stage breast cancers and for those cancers with a satisfactory clinical response to post-neoadjuvant therapy, a new challenge has arisen. That challenge is the adequacy of margin resection when BCS is performed; a positive margin results in additional surgery. Over the last years, the advances on the new preoperative localization techniques and methods of intraoperative margin assessment have resulted in a reduction of positive margin rates, reporting acceptable rates as low as 15-20% (15); however, BCS is still associated to high re-excision rates ranging from 20 to 60% (16).

2. **Possibility of inadequate resection of the tumour during the initial operation**

Regarding the second downside of BCS, the probability of inadequate resection of the tumour during the initial operation leads to a major risk of a positive margin in the excised tumour; several intraoperative margin assessment (IMA) techniques have been developed in order to avoid inadequate margins in BCS (11,17):

- **Standard Cavity Shaving**

  It consists in the resection of breast tissue from all 6 margins (anterior, posterior, superior, inferior, medial and lateral) after the excision of the primary specimen, in the same procedure. It allows to precisely asses which margin is involved in order to calibrate the resection of the tumour.

- **Intraoperative Specimen Radiography**

  Once the specimen is excised, a digital mammography on the specimen is applied to ensure that the entire lesion is removed. If abnormal tissue is detected close to the surgical margin, the corresponding region of the cavity can be shaved.

- **Ultrasound-guided excision**

  Use of intraoperative US-guided excision consists in placing the ultrasound-probe while BCS is undergone, hence allowing to reassess orientation in real-time and confirm complete excision of the tumour. Its purpose is to obtain accurate margins.

- **Novel surgical techniques**

  Emerging technologies such as spectroscopy or optical coherence tomography (OCT) may have limited clinical applicability and may require further research to prove their reliability.

- **Intraoperative Pathological Assessment:**
  - *Frozen Section Analysis (FSA)*

    Once the specimen is excised, orientated with sutures, margins are inked and it is thinly sliced; samples from any area of concern are cut, frozen with embedding medium, and processed in less than 30 minutes.

  - *Imprint cytology (IC)*

    It consists in placing each of the six margins in contact with a glass slide to determine if they are tumour-free. Cancer cells will adhere to the glass whereas normal adipose cells will not. Once all the margins are imprinted, each slide is fixed and stained. The process lasts for approximately 15 minutes.

The ideal technique for removing non-palpable and palpable invasive breast cancers should be performed in a single intervention and should be simple, accurate and cost-effective, and it should provide a good cosmetic result and be comfortable for the patient. The ultrasound technique seems to be a suitable approach due to the fact that can be used in both localizing palpable and non-palpable lesions and in guiding the excision in BCS.

In the following table are shown the advantages and disadvantages of IMA techniques:

	ADVANTAGES	DISADVANTAGES
Frozen Sections	- Results within 30 minutes - Decreases cost of treatment	- Requires an on-site breast pathologist - Labour intensive - Tissue lost for permanent section - Technically difficult - Not suitable for DCIS and non-palpable lesions
Imprint Cytology	- Results within 15 minutes. - Tissue not lost for permanent section - Decreases cost of treatment	- Requires an on-site breast pathologist - Does not distinguish between *in situ* and invasive carcinoma - Artefacts are common
Ultrasound-guided excision	- Dynamic 3D assessment of margin status - Probe differentiates invasive carcinoma, benign pathologies, and normal tissue - Suitable for palpable and non-palpable tumours. - Lower volume excised relative to palpation-guided surgery - Quick performance time	- Not suitable for DCIS, multifocal disease, or tumour with large areas of microcalcifications - Operator dependant - Learning curve
Standard Cavity Shaving	- Does not prolong operation time - Systematic surgical procedure - May overcome false positives of lumpectomy margin	- Depends on volume of surgical specimen compared to the volume of tumour - May affect cosmetics - Lengthens the operating time
Intraoperative Specimen Radiography	- Detects DCIS - Reduces volume of tissue excised	- Two dimensional image - Surgery delay - Incapable of detecting small, non-calcified lesions - High rate of non-specific findings - Margins may be distorted - Requires second method for the detection of the lesion

Adapted from: *Angarita FA, Nadler A, Zerhouni S, Escallon J. Perioperative measures to optimize margin clearance in breast conserving surgery. Surg Oncol. 2014 Jun;23(2):81–91.*

Even if IOUS presents significant advantages as a margin assessment technique, limited data is available regarding the role of specimen US in the assessment of surgical margins. However, it is reported that specimen sonography may be restricted by both false-positive and false-negative results (18). Related to false-positive results, IOUS may overestimate margin involvement, a possible reason that may explain this is the "pancake phenomenon" described as the compression applied during sonography causing a flattening of the specimen contributing to underestimation of the normal-appearing tissue volume located between the transducer superficially and the tumour margin deeply, and might cause the tumour to appear falsely close to the specimen surface (15). When concerning to false-negative rates, understood as underestimation of the involved margins, a possible cause that might explain these results could be the presence of intraductal component which is poorly visible on ultrasound.

In spite of IOUS limitations, especially the ones regarding its validity, in the present study it will be assumed that a correction coefficient may be applied in order to rectify these observed differences. Certainly, IOUS may correctly identify margins, but the surgeon should be preoperatively aware of the presence of possible histological or biological factors that may contribute to major false-positive or false-negative rates (19).

3. Potential risk of local recurrence

Regarding the third drawback related to BCS, there is no doubt that acquiring negative margins decreases the risk of local recurrence, for that reason, the priority of the surgeons is to achieve the complete excision of the tumour with negative margins (11). Actually, one of the most important predictors of local recurrence, as reported in the literature, is margin status (20).

Positive margin rates after BCS for breast cancer and DCIS are 15-47% and 20-81%, respectively. Nonetheless, re-excision rates range from 23-59% with a reported mean of 26% depending on the treatment centre and the surgeons practice (11,21–23). The fact that up to 60% of patients undergoing breast conserving surgery require re-excision highlights the importance of optimizing margin clearance. However, patients should not systematically undergo unexpected additional operations when there is a positive margin due to poor cosmetic results, increased medical costs and patients' anxiety (15,24). Hence, preoperative prediction of surgical margins status has recently gained a key role in planning BCS.

According to the reviewed literature, the most important factors that influence and predict a positive margin status are: (a) presence of DCIS, (b) multifocal disease, (c) large tumour size, (d) lobular histology, (e) microcalcifications on mammography, (f) high grade breast cancer (10,25,26). Additionally, there are other factors that may influence margin status, even though less evidence on them is found. These are: younger age at diagnose and presence of limfovascular invasion (27).

The importance of accurately identify predictors of a positive margin after BCT is that they may guide surgery. Surgical planning should be designed individually according to patient and tumour characteristics, offering a wider excision or mastectomy to avoid re-excision surgery in those patients at high risk of involved margins (26).

Even so, the definition on what constitutes the optimal margin width remains controversial. Despite the long-term prognostic implications of margin status, no consensus is established on what should be considered an adequate negative margin in breast oncology. There is a higher risk of local recurrence when positive margins are obtained; nevertheless, there are not significant differences in local recurrence rates with margins of 1mm, 2mm, or 5mm (25,28). In an attempt to standardize the adequate extent of tumour-free margins in BCS, the Annual Meeting of the American Society of Breast Surgeons that took place in May 2014, concluded that an acceptable margin for invasive breast cancer is *'no ink on tumour'* when assessed by pathologists (29,30). When regarding DCIS due to its difficulty on preoperatively localize lesions, a wider margin width should be reckoned. A margin distance of 2mm or less is associated to a higher risk of local recurrence (31).

The definitions about positive and negative margin status are summarized in the following table:

	For invasive carcinoma	**For *in situ* carcinoma**
Positive margin	Presence of ink on any cancer cells (>0mm at the transected or inked surgical margin)	Presence of tumour within less than 2 mm of the resection margin
Negative margin	No ink on tumour	Absence of tumour within less than 2 mm of the resection margin

Beyond discussing on what should be an adequate margin width such as close or narrow, we should be adopting negative margins as the standard definition of an

adequate margin. The subjectivity that implies the terms close or narrow should be replaced with the measurement of the distance of the tumour cells from the inked specimen surface, without further qualification or judgement (32).

Although margin status is considered to be a significant predictor of LR, there is a new tendency reassessing the importance of margin width on the incidence of LR, in favour of other prognostic factors such as the biological behaviour of the tumour (10,25,33). The likelihood of LR is less related to the surgical margin width than to the underlying tumour biology and to the availability of effective adjuvant therapy. With regards to systemic treatment, the combination of chemotherapy and tamoxifen (a SERM that acts as an oestrogen antagonist in the breast) is associated to a reduction in the LR rate; concerning to tumour biology, triple negative tumours (lack of expression of the oestrogen and progesterone receptors (ER and PR), as well as non-amplified HER2 status) are associated to a highest risk of LR. Another factor that should be taken into account is the histological type; the likelihood of margin involvement of DCIS is considerably higher when compared to invasive carcinoma.

To sum up, effective treatment requires accurate preoperative planning, developing and implementing a consistent definition of margin clearance, and using tools that provide detailed real-time intraoperative information on margin status. In this sense, intraoperative ultrasound (IOUS) may fulfil these requirements and may offer few advantages that other preoperative localization and intraoperative margin assessment techniques may not:

- Direct location avoiding the need of a preoperative localization of both palpable and non-palpable lesions (34).
- Acquisition of the three axes of the tumour resulting in a more accurate surgical planning technique leading to a less extirpation of healthy breast tissue (35).
- Awareness of the exact location of the lesion in relation to the overlying skin and underlying fascia at all times during the operation
- Patients will not have to undergo the unpleasant wire placement before surgery, moreover, the specimen radiographs after excision are not required.
- The adequacy of surgical margins is allowed by the ultrasound-guided excision.
- When used in guiding surgery, it produces results immediately, therefore allowing the decision to take further shaving with minimal impact on operating times.
- The preoperative and intraoperative care processes are less complex, which saves time and money due to a reduced use of radiology and nuclear medicine.

3.2. Justification

As can be appreciated, the management of breast cancer remains an up-to-date issue in hospitals' breast pathology units; in spite of being the most common cancer among women worldwide (1), it still generates discrepancies among physicians, especially with reference to early stage breast cancers treated with BCT. The *gold standard* for localizing non-palpable lesions, which is WGL, is currently being shifted by other diagnostic methods much more valid and reliable (12). Additionally, the increasing use of intraoperative margin assessment techniques indicates the significance of attaining negative margins in a one-time intervention. Obtaining adequate margins is a crucial issue for adjusting the volume of excision, for avoiding unnecessary resection of healthy breast tissue, and for good cosmetic outcome (36). Nonetheless, the lack of standardization on what should be an adequate margin width reflects that the matter in question is still controversial.

The need to develop this project lies on the fact that up to 26% of patients require a second operation to ensure clear margins (23); a method capable of accurately assessing intraoperative margins would potentially reduce the number of second operations as well as the recurrence rate. Although the consequences of the additional re-excision lumpectomy probably do not affect overall survival (33), it can potentially increase the patients' postoperative anxiety, resulting in worse cosmetic outcomes, delay in the initiation of adjuvant chemotherapy and radiation therapy, increase the wound infection risk and would suppose an additional expenditure for health care services (37).

In this sense, giving medical evidence of a reliable and accurate approach that provides adequate information on what concerns margin status is the endpoint of this project. As mentioned above, in our study we will consider the intraoperative ultrasound as a safe, useful and efficient technique that will allow us to achieve a complete status of resection (35). Furthermore, we aim to address how large US-measured margin should be to achieve an adequate pathological margin. The exact distance in millimetres between the tumour edges and the resection margin obtained through US will be compared with the pathologically assessed margins. The confirmation that IOUS is a reliable and accurate method for achieving adequate margin status will have a relevant positive impact on breast pathology units and, above all, on patients' management with the advantages that it entails.

Hence, this project could be used as a basis for clinical practice and further research projects on this topic. We have to insist in the need of warranting the reliability of the measurement tools used in the daily clinical practice and research so that inexact and not dependable information is not acquired.

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5. QUESTION

Is the intraoperative ultrasound technique a reliable and accurate approach in assessing the surgical margins in Breast Conservative Surgery when compared to histological analysis?

6. HYPOTHESIS

Main hypothesis:

The intraoperative ultrasound is a reliable technique in guiding the gross status margins in patients undergoing Breast Conservative Surgery in order to obtain negative margins.

Secondary hypothesis:

- The intraoperative ultrasound will overestimate the gross tumour margins when compared to microscopic margin assessment.
- There may be possible confusion factors that may influence the expected findings between the studied variables.

7. OBJECTIVES

Main objective:

The goal of the present work is to determine how accurate the intraoperative ultrasound should be to acquire complete surgical excision with negative histological margins in patients undergoing Breast Conservative Surgery. We aim to compare the measured distance to the margin by the pathologist and the same margin by intraoperative ultrasound.

Secondary objectives:

- To determine how and in what cases intraoperative ultrasound overestimate status margins in patients undergoing breast conserving surgery when compared to microscopic margin assessment.
- To evaluate if the relationship between intraoperative ultrasound margin assessment and negative status margin is due to possible interactions of other covariables.

8. MATERIAL AND METHODS

8.1. Study Design

A diagnostic test study with a cross-sectional design carried out in a tertiary referral hospital in Girona within the Breast Pathology Unit which integrates a multidisciplinary team formed by gynaecologists, general surgeons, radiologists, pathologists, oncologists and radiotherapists.

8.2. Participants

The study population is based on women diagnosed with breast cancer undergoing a Breast Conservative Surgery in the Breast Pathology Unit at Hospital Universitari de Girona Dr. Josep Trueta. A core needle biopsy will be used for preoperative diagnosis and all patients will undergo preoperative evaluations using mammography, ultrasound (US) and magnetic resonance imaging (MRI) according to the established protocol.

8.3. Inclusion criteria

- Patients undergoing Breast Conservative Surgery (BCS)
- Early stage Breast Cancer: stages I-II (see ANNEX I)
- Palpable and non-palpable lesions
- Ultrasound screen detectable lesions

8.4. Exclusion criteria

- Multicentric lesions tributary to mastectomy
- Tumour with large amount of calcifications and/or microcalcifications without an associated mass
- Preoperatively diagnosed primary or associated DCIS (Ductal Carcinoma *In Situ*)
- Extensive intraductal component or exclusive DCIS
- History of neo-adjuvant therapy (chemotherapy)
- History of external radiotherapy on the chest wall

8.5. Sample selection

A consecutive non-probabilistic sampling will be performed as women are diagnosed of breast cancer tributary to BCS. The sample recruitment will take place in Hospital Universitari Dr. Josep Trueta throughout a year and a half.

8.6. Sample size

Sample size calculations are based on software R 3.1.1 Library Sample Size. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 155 subjects are necessary to recognize as statistically significant a difference greater than 1%. It is estimated that at Dr. Josep Trueta's Hospital approximately 90 breast conserving surgeries might take place within a year. A dropout rate of 15% has been predicted.

8.7. Variables

Having into consideration the aim of the study, the variables are defined as it follows:

8.7.1. Independent variables:

The independent variables are represented by the two compared approaches used for assessing margin status of breast tumours:

- **Intraoperative ultrasound**

  Margin distance in millimetres obtained within IOUS corresponds to a continuous quantitative variable. The process that entails the acquisition of the margin distance by the intraoperative ultrasound is detailed below.

  Once the patient is diagnosed and she is considered to be a potential candidate for the present study (fulfilling the inclusion criteria), she will be assessed by the surgeon before undergoing the breast conserving surgery. Indeed, previously to the surgical intervention, the lesion will be sonographically assessed at the outpatient consulting room in order to verify whether the lesion is visible on ultrasound or not, therefore, ensuring if the patient is a definitive candidate for the study. Finally, patients will be scheduled for surgery.

  At the operating room, an intraoperative ultrasound technique will be used. The procedure is performed under general anaesthesia. The intraoperative ultrasound-scanning will be performed using a portable 13.5MHz probe (Siemens VFX 13-5, Multi-D) that is coupled to a mobile US unit (ACUSON Antares™ Premium Edition, Siemens AG).

  Firstly, the tumour is going to be preoperatively localized and scanned by an ultrasound probe covered by a sterile plastic sleeve and conductive gel in patients

undergoing BCS. After sterile preparation and draping, the lesion will be carefully localized in the breast by US before incision. The tumour size, the lesion-to-skin distance, and the lesion-to fascia distance will be measured in millimetres by US. After the localization of the tumour in the transverse and craniocaudal directions, the tumour size and excision margins will be marked on the skin, then the incision will be made straight down toward the chest wall.

After the incision, the skin overlying the lesion will be dissected from the subcutaneous tissues, and the US probe will be positioned in the wound to reassess the position of the lesion. The surgeon repeatedly will perform US, placing the ultrasound probe in different positions in order to obtain clear surgical margins.

Once the specimen is removed, an *ex vivo* US will be carried out by the surgeon in order to determine the accuracy of the complete tumour resection. To orient surgical specimen sutures or staples will be placed at the cut edge to mark two or more of the six surfaces.

Then, the excised specimen will be placed into a bowl where it will be submerged under saline serum in order to achieve better image quality. The resection margins will be orientated in all six surfaces (anterior, posterior, superior, inferior, external and internal). The distance between the hypoechoic tumour edge and the resection margin will be measured by the surgeon in millimetres. The obtained sonographic images will be printed along with the measured distances (in millimetres); such information will be saved in the study file, which will only be accessible for the research team. Furthermore, all data obtained during the procedure will be recorded in the study database for the subsequent data analysis. If margin involvement is detected through US, immediate cavity re-excision will take place.

Once the process is completed, the surgical specimen will be carefully orientated on a polystyrene basement where a schematic drawing of the breast is represented. The specimen will be attached to the support with needles and it will be sent to the pathology department in order to be analysed.

- **Pathology assessment**

  Margins in millimetres assessed by pathologists correspond to a continuous quantitative variable.

  Once the margin status from the excised specimen is assessed by the IOUS at the operating room, it is send to the pathology service where it is evaluated and processed by the pathologist. Nowadays, the pathologist evaluation of the excised specimen is considered to be the *gold standard* for margin status assessment.

  Firstly, the status of surgical margin will be assessed by applying ink to all six surfaces of the lumpectomy specimen; each one will be inked in different colours. Afterwards, the surgical specimen will be cut in 3-mm-thick slices.

  Following that, the pathologist will assess the macroscopic margins of the sliced specimen using an adapted ruler. Whether clearly affected margins are observed, it will be reported at the operating room while the surgery is still being performed and, in consequence re-excision of the involved margin will take place. Whether macroscopic affection of any margins is observed, the microscopic assessment of the margins will be effectuated.

  Subsequently, the material will be fixed in neutral buffered formaldehyde and processed in paraffin blocks according to standard procedure. Section 4 μm thick will be cut and stained with haematoxylin-eosin. These samples will be analysed through the microscope with the aim of assessing the microscopic margin width, which is the closest distance of an inked surface to any tumour cells. Certainly, the presence of cancer cells at a fixed distance will be the determining factor to establish whether a positive or negative margin is observed.

8.7.2. Dependant variable:

The dependant variable in this study is the assessment of the margin status which is defined as the distance measured in millimetres between the edge cut and the tumour in the excised specimen. The dependant variable is considered to be a continuous quantitative variable.

According to the reviewed literature, and as specified in the background of the project, there is some controversy on what it should be an adequate margin status, especially when it is positive. The present study will take as reference the following definitions for invasive carcinoma:

- *Positive margin* will be considered as the presence of invasive cancer at any distance detected at the inked surgical margin.
- *Negative margin* will be considered when there is 'no ink on the tumour', defined as the absence of tumour within the inked surgical margin.

8.7.3. Covariables

These variables are included because we want to describe our population. We are also going to use them to make a multivariate analysis and its influence on the correct diagnosis:

- Age: in years
- Histology: lobular or ductal carcinoma, presence of DCIS and LCIS. Based on the WHO classification of breast tumours (see ANNEX I)
- Grade: stages 1,2 and 3 from Nottingham Histologic Score System (see ANNEX II)
- Tumour size: measured in millimetres
- Microcalcifications detected on mammography
- Multifocal disease detected through image techniques priors to surgery

8.8. Methods of data collection

For data collection, the surgeons of the breast pathology unit will inform the rest of the members of the unit about the study that is being carried out. Special requirement will be asked to pathology department due to the fact that they represent one of the most important parts of the study concerning the microscopic margin status assessment.

Most of the data will be collected from the electronic medical records of the participating women and will be reflected in the study database. Homogeneity in data collection must be ensured. The information will be obtained from:

- Radiologist report: the image techniques MRI, mammography and US will be used for obtaining information about tumour size, nodal status, presence of microcalcifications and multicentric lesions.
- Pathologist report: the needle core biopsy will provide information about histological type, grade and tumour biology (receptor expression and molecular type). Additionally, the microscopic margin width (distance in mm) will be calculated.
- Surgeon report: intraoperative ultrasound will be used at the operating room in order to localize the lesion and guide the surgery. Once the specimen is excised, its margins will be measured in millimetres with the IOUS.

The following table summarizes the data collection process:

REPORT	DATA RESOURCE	COLLECTION PERIOD		
		PRIOR TO SURGERY	DURING SURGERY	AFTER SURGERY
Radiologist	MRI Mammography US	Tumour size, nodal status, presence of microcalcifications and multicentric lesions		
Pathologist	Needle Core Biopsy	Histological type, grade and tumour biology		
	Excised specimen			Margin width in mm (microscopic)
Surgeon	IOUS	Localization of the lesion	Margins width in mm (sonographic)	

9. STATISTICAL ANALYSIS

Descriptive analysis:

For quantitative continuous variables, assuming a normal distribution, the mean and the typical deviation will be estimated. If not possible to assume a normal distribution, the median and the quartiles will be estimated.

Bivariate analysis:

Considering that intraoperative ultrasound and microscopic analysis measure systematically different, we aim to determine the grade of concordance between these two tests. The appropriate test for this purpose is to calculate the Intraclass Correlation Coefficient (ICC). A variance analysis model ANOVA with repeated measures will be used to calculate the ICC. Nevertheless, if it is a non-parametric variable a Kuskal-Wallis test will be performed. A 95% confidence interval will be assumed. Moreover, each covariate will be fitted with a stratified analysis univariately and jointly with margin status and distance.

In order to accomplish the second endpoint, sensitivity, specificity and positive and negative predictive values will be calculated for predicting positive histological margins. In addition, positive and negative likelihood ratios will be calculated and a ROC curve will be designed for the tested study variables.

Multivariate analysis:

For attaining the third endpoint, a multivariate analysis will be performed adjusting covariables in order to detect possible confusion caused by the specified covariables that may explain the relationship found between the independent and dependent variables. Considering that our study variables are both quantitative, a multiple lineal regression will be carried out. However, taking into consideration that we have repeated measures, an aligned mixed model with Gaussian response and controlling for the dependence of measures will be performed as well.

A *p* value of less than 0.05 will be used to determine statistical significance. A *p* value over 0.1 will be considered as weak evidence of association.

Statistical calculations will be performed using IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

10. ETHICAL ASPECTS

This study will be evaluated by the Clinical Research Ethical Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of Hospital Universitari Dr. Josep Trueta in Girona. It will assess if the study fulfils the required criteria for being approved; moreover, the recommendations given by the committee will be taken into account.

Related to the participants, they will be given the participant information sheet (see ANNEX III) and they will be asked to sign the informed consent in order to be included in the study (see ANNEX IV).

The project will be carried out according to the principles of the Helsinki Declaration and in accordance with the Medical Research Involving Human Subjects Act (last revision in 64th WMA General Assembly, Fortaleza, Brazil, October 2013). Besides, we will take into consideration the Spanish Organic Law *14/2007, de Investigación Biomédica,* that regulates biomedical investigation involving human beings in Spain.

Confidential rules will be respected and all study participants will be informed according to article 5 from Spanish Organic Law *15/1999, de 13 de diciembre, de Regulación del Tratamiento Automatizado de los Datos de Carácter Personal*. The right of accessing to any kind of information concerning the patient is guaranteed as well as the participants' right of consulting, modifying or erasing the personal data from their personal file. All data will be managed anonymously.

11. LIMITATIONS OF THE STUDY

Several limitations to this study need to be acknowledged:

- Due to the fact that IOUS is an operator-dependent technique, it requires surgeons to be trained in the use of US and close collaboration with radiologists and pathologists. Indeed, a surgeons' learning curve will be observed as it happens with all technician dependent methods, it is required that surgeons become more familiar with the use of intraoperative ultrasound. Hence, with appropriate instruction and experience, breast surgeons may attain a level of competency that will enable to perform US-guided BCS for both palpable and non-palpable breast cancers.

- Inability to report the impact of intraoperative ultrasound on subsequent breast cancer events such as local recurrences or rate of re-excisions. In order to achieve this goal, a longitudinal follow-up through a discontinued regression design is required. The reported rates of re-excisions and local recurrences previous to IOUS margin assessment will be compared with the re-excision and local recurrence rates after the implementation of the intraoperative ultrasound technique.

- Taking into consideration that the present study will be carried out in a single-institution centre, additional research will be required to confirm our findings.

12. WORK PLAN

Investigators: Joan Oliveras (JO), Ester Vila (EV), Miguel Alonso (MA), Francesc Tuca (FT), Eugeni Bonet (EB)

Collaborators: statistician, radiologists

The sequence of activities carried out by the research team is gathered in 5 phases:

1. **Coordination phase** (3 months)

   It will involve all the investigators and collaborators.

   The research operative protocol will be elaborated with a detailed definition of the study variables. At the beginning of the study, an organizational meeting for the research team will be performed, where the study chronogram will be scheduled and the data collection circuits will be set up. Furthermore, before the definitive data collection and the study setting up, a short pilot study will be undertaken in order to correct or improve possible shortages or deficiencies from the study design. Problem identification, suggestions, and final elaboration and evaluation of the research protocol will be carried out. Additionally, surgeons training period will take place within this phase. They will be taught and instructed by radiologists familiar to breast sonography.

   Every six months, a coordination meeting will be held and data quality controls will be performed with the aim of evaluating the consistency of the collected data. Before getting started, the research protocol will be submitted to the hospital's ethical committee in order to receive its approval for allowing the study to be carried out.

2. **Field work** (18 months)

   It will involve all the investigators.

   During a recruitment period of 18 months, a detailed field sampling will be executed according to the inclusion and exclusion criteria specified above. With each recruited patient: (A) patients will be asked to willingly join the study, once they agree to participate, they will have to read carefully the information sheet and sign the consent form; (B) during the surgical intervention, an intraoperative ultrasound margin assessment of the excised specimen will be performed by the surgeon. Then, the specimen will be send to pathology service in order to be analyzed. The margin's measured distances by both approaches, IOUS and pathologic assessment, will be

recorded in the study database; (C) data from her medical history regarding preoperative localization images and biopsy findings will be also introduced in the same database. All the study variables and covariables will be taken into account within the recorded data; (D) every participant will receive a postcard communicating research team's gratitude for their cooperation in the study.

3. **Data extraction and processing database** (9 months)

   It will involve the statistical support.

   Data will be entered in the created database by the statistician every 6 months alongside with the periodic data quality control in order to subsequently analyse all the collected data. Regularly, an analysis of data will be performed in order to control its evolution.

4. **Data analysis** (3 months)

   It will involve all the investigators and statistical consultant.

   After processing the database, all data collected will be analysed using the appropriate statistical test. Firstly, a descriptive and bivariate analysis will be conducted and, secondary, a multivariate analysis using a multiple lineal regression and an aligned mixed model will be performed.

5. **Interpretation, publication and dissemination of the results** (3 months)

   It will involve all the investigators and collaborators.

   A final report evaluation interpreting the outcomes will be written and the results will be discussed among all investigators and collaborators. If the results of the study conclude that intraoperative ultrasound is a reliable technique for assessing margin status, we will try to spread the evidence-based knowledge by publishing scientific articles in prestigious scientific journals.

   It is important that the findings of this research are widely disseminated. The dissemination strategy includes conference presentations, meetings, and training sessions, among others.

13. TIME SCHEDULE

The proposed work plan has been divided into 5 phases spanning 24 months. The schedule of project tasks is shown below:

		TIME							
		2015				2016			
PHASE	**PERSONAL**	**Jan-Mar**	**Apr-June**	**July-Sept**	**Oct-Dec**	**Jan-Mar**	**Apr-June**	**July-Sept**	**Oct-Dec**
Coordination phase	All the team								
Field work	JO, EV, MA, FT, EB								
Data extraction and processing database	Statistical support								
Data analysis	Investigators and statistical support								
Interpretation, publication and dissemination of the results	All the team								

14. AVAILABLE MEANS TO CARRY OUT THE PROJECT

The project will take place at Hospital Universitari Dr. Josep Trueta in Girona, where the centre will provide all means for developing the study. The breast pathology unit has in coordination the radiology service where the image techniques are undertaken, the gynaecology service that performs the surgery and the pathologic service that analysis the tumour. Additionally, the hospital will provide the informatics equipment suitable for processing database for the study development without additional cost. Nonetheless, the sonographic probe and the statistician will be paid by the project.

15. BUDGET

		BUDGET PROPOSAL		
		Quantity	**Cost per unit**	**Cost**
Personnel costs	Statistician	1	35€/h	1680 €
Goods and services	**Consumables**			
	- Saline serum - Plastic sleeves for IOUS probe (*Microtex*) - Plastic sleeve for ultrasound	160 160 160	0.50€ 0.98€ 1.20€	80€ 156.8€ 192€
	Consumer durables			
	Ultrasound probe	1	7000€	7000€
Travel and subsistence arrangements	**Dissemination of the results**			
	Inscription to Congreso de la Sociedad Española de Senología y Patología Mamaria (SESPM)	1	600€	600€
	Costs of the trip: - Flights - Accommodation	 2 2	 130€ 170€	 260€ 340€
Publication	Publishing fees	1	1500€	1500€
TOTAL				**11,808.8€**

16. ANNEXES

16.1. ANNEX I. Histology and staging

❖ BREAST CANCER HISTOLOGY

The main histopathological breast cancer types are the following:

IN SITU CARCINOMAS	INVASIVE CARCINOMAS
- NOS (not otherwise specified) - Intraductal (DCIS, LCIS) - Paget's disease and intraductal	- NOS - Ductal - Inflammatory - Medullary, NOS - Medullary with lymphoid stroma - Mucinous - Papillary (predominantly micropapillary pattern) - Tubular - Lobular - Paget's disease and infiltrating - Undifferentiated - Squamous cell - Adenoid cystic - Secretory - Cribriform

Adapted from:

- *Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ. WHO Classification of Tumours of the Breast. 4th ed. Lyon: IARC; 2012.*

❖ BREAST CANCER STAGING

The AJCC (American Joint Committee on Cancer) breast cancer classification is based on TNM: (1) Primary Tumour; (2) Regional Lymph Node; (3) Distant Metastasis.

▪ Primary Tumour (T)

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumour ≤20 mm in greatest dimension
T1 mi	Tumour ≤1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

- **Regional Lymph Node (N)**

Nx	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

- **Distant Metastasis (M)**

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

❖ ANATOMIC STAGE

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Reference:

- *Breast. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010, pp 347-76*

16.2. ANNEX II. Histological Grade

The histological grade is determined by the Nottingham Histologic Score System (the Elston-Ellis modification of Scarff-Bloom-Richardson grading system)

The grade of a tumour is determined by assessing morphologic features: **(1)** tubule formation**, (2)** nuclear pleomorphism and **(3)** mitotic count.

1. Glandular (Acinar) / Tubular Differentiation

Score 1	>75% of tumour area forming glandular/tubular structures
Score 2	10% to 75% of tumour area forming glandular/tubular structures
Score 3	<10% of tumour area forming glandular/tubular structures

2. 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, often with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms

3. Mitotic Count (using a high power field diameter of 0.50 mm)

Score 1	Less than or equal to 7 mitoses per 10 high power fields
Score 2	8-14 mitoses per 10 high power fields
Score 3	Equal to or greater than 15 mitoses per 10 high power fields

Each of these features is assessed with a value of 1 (favourable) to 3 (unfavourable), and the scores for all three categories are added together. A combine score of 3-5 points is designated as grade 1; a combined score of 6-7 points is grade 2; a combined score of 8-9 points is grade 3.

Gx	Grade cannot be assessed
G1	Low combined histological grade (favourable)
G2	Intermediate combined histological grade (moderately favourable)
G3	High combined histological grade (unfavourable)

Reference:

- *Breast Cancer and Breast Pathology [Internet]. Baltimore: Johns Hopkins University, Faculty of Medicine; 2012 [cited 2014 Oct 25]. Available from: http://pathology.jhu.edu/breast/grade.php*

16.3. ANNEX III. Information sheet

FULL D'INFORMACIÓ AL PACIENT

Nom de l'estudi:

FIABILITAT DE L'ECOGRAFIA INTRAOPERATÒRIA EN L'AVALUACIÓ DELS MARGES QUIRÚRGICS EN DONES CANDIDATES A CIRURGIA CONSERVADORA DE MAMA

Agraïm el seu interès pel que fa a la seva col·laboració en l'estudi que estem duent a terme des de la Unitat de Patologia Mamària (UPM) de l'Hospital Universitari Dr. Josep Trueta de Girona. A continuació, li expliquem en que consisteix l'estudi. L'equip que en forma part li respondrà qualsevol dubte o qüestió que li pugui sorgir.

Quin és l'objectiu de l'estudi?

Aquest estudi té com a principal objectiu avaluar si l'ecografia intraoperatòria és una bona eina per obtenir uns adequats marges de resecció quirúrgica en dones que pateixen un càncer de mama, i són candidates a una cirurgia conservadora de mama.

Actualment, el tractament d'elecció per les pacients diagnosticades de càncer de mama en estadis inicials és la cirurgia conservadora de mama, és a dir, la preservació del pit mitjançant l'extirpació únicament del tumor juntament amb una quantitat de teixit sa circumdant. Aquest teixit sa, confereix el que anomenem marge de resecció quirúrgica i és de capital importància pel que fa al risc de recurrència, és a dir, la reaparició del càncer. Així, doncs, cal que els marges ressecats estiguin lliures de cèl·lules tumorals.

Què passarà si hi participo?

Vostè seguirà el procediment diagnòstic i terapèutic habitual segons el protocol establert per la Unitat de Patologia Mamària de l'Hosipital Universitari Dr. Josep Trueta. Així, doncs, aquest estudi no suposarà cap procediment diagnòstic ni terapèutic addicional. El que pretenem avaluar és el tumor extirpat durant la intervenció quirúrgica un cop aquest ja s'hagi extret.

D'acord amb l'objectiu del nostre estudi, realitzarem una ecografia intraoperatòria de la peça extirpada en el mateix acte quirúrgic per tal de valorar els marges de resecció. Si durant aquest procés detectem que hi ha un marge amb presència de tumor, procedirem a ampliar-lo en el mateix acte quirúrgic, evitant, doncs, la necessitat d'haver-ho de fer en una segona cirurgia.

És obligatori participar-hi?

La participació a l'estudi és totalment voluntària. Si decideix participar-hi, se li demanarà que signi el consentiment informat segons el qual vostè ha entès tot el que concerneix participar en aquest estudi. Contràriament, si decideix no participar-hi, això no afectarà ni modificarà el pla assistencial que ha de rebre.

Què he de fer per participar-hi?

Per dur a terme aquest estudi i atenent a les disposicions legals vigents li sol·licitem que ompli la següent autorització. Abans i després de firmar el document de consentiment informat, pot preguntar tot el que cregui convenient als metges i personal sanitari responsable de l'estudi.

Les meves dades es manejaran de forma confidencial?

Sí. La informació recollida per aquest estudi serà tractada i regulada segons la Llei Orgànica de Protecció de Dades de Caràcter Personal (15/1999) segons la qual, les seves dades seran manejades de forma confidencial i només seran utilitzades amb finalitat d'investigació. La seva identificació personal estarà codificada a través d'una sèrie numèrica aleatoritzada.

Què passarà si canvio d'opinió en el decurs de l'estudi?

Si renuncia a seguir participant en l'estudi una vegada iniciat, no suposarà cap càstig ni pèrdua de beneficis per vostè. Se li demanarà que segueixi els controls i seguiment habituals.

Què se'n farà de la informació obtinguda a partir de l'estudi?

Els resultats seran publicats en revistes d'interès científic relacionades amb l'àrea de coneixement corresponent a la patologia mamària per tal que altres centres i pacients puguin aprofitar les troballes del nostre estudi. Recordi que totes les seves dades de caràcter personal són confidencials i, per tant, seran manejades de forma anònima.

Moltes gràcies per la seva atenció,

Unitat de Patologia Mamària de l'Hospital Universitari Dr. Josep Trueta de Girona

16.4. ANNEX IV. Informed consent

CONSENTIMENT INFORMAT

Declaració del pacient,

Declaro que he estat correctament informat pel membre responsable de l'equip investigador a sota esmentat; sobre els objectius de l'estudi així com sobre el procés de selecció de les dades personals; també declaro que he estat informat sobre l'ús de caire científic que es farà de les meves dades personals, així com sobre el fet que la participació en l'estudi és totalment voluntària, que puc formular les preguntes que jo consideri oportunes i que puc sol·licitar la retirada i eliminació de les meves dades personals en qualsevol moment de l'estudi. A més, he rebut una còpia d'aquest mateix document.

NOM, COGNOMS i DNI del pacient:

FIRMA: DATA:

NOM, COGNOMS i DNI del professional de salut que ha informat al pacient:

FIRMA: DATA:

Apartat per a la revocació del consentiment informat

Jo, _____

amb DNI _____ revoco el consentiment de participar en l'estudi anteriorment esmentat.

FIRMA: DATA: