Original Article

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Evaluation of the Influence of Geodimensional and Histological Parameters on the Need for Margin Widening in Breast Lesions Marked With Magnetic Seeds

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ABSTRACT

Objective: Breast cancer is an important topic worldwide, posing morbidity and mortality to women. Considerable efforts have been put in the early recognition of malignancy through different screening methods, such as mammography and ultrasound. The precise localization of infraclinical malignant lesions is key in surgical management and magnetic seeds gather particular interest for this purpose. As with other systems, a need for reintervention may be needed to obtain adequate surgical margins. This work evaluated the relation between the need for surgical reintervention in order to obtain negative margins and geodimensional and histological parameters. The main objective was the identification of parameters significantly associated with reintervention for margin widening.

Materials and Methods: A retrospective analysis of 198 patients from a single centre was performed. The association between pre-defined geodimensional and histological parameters and the need for margin widening in infraclinical lesions marked with magnetic seed was evaluated.

Results: Results showed that reintervention to widen margins was significantly higher in patients with ductal carcinoma *in situ* (DCIS) in the pre-operative biopsy when compared with invasive carcinoma ($p = 0.03$) in the bivariate analysis. No statistically significant differences were observed between the need for reintervention and lesion size ($p = 0.197$), breast quadrant location ($p = 0.626$) and distance of skin to lesion ($p = 0.356$).

Conclusion: This work suggests that a more invasive margin clearance in lesions with a pre-operative DCIS diagnosis might obviate the need for reintervention to obtain negative margins. On the other hand, it is not necessary to be surgically more invasive in larger lesions, deeply located or that are present in a certain quadrant, since there are no significant differences regarding the need for reintervention.

Keywords: Breast cancer; recurrence; risk factors; surgery

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Key Points

- Mammography and ultrasound play a crucial role in detecting non palpable breast lesions.
- Magnetic seeds enable adequate location for the surgeon, but still, positive resection margins occur to some extent.
- This work investigated the relationship between the need for surgical reintervention in positive margins and specific geodimensional and histological parameters in breast cancer patients.
- Patients diagnosed with ductal carcinoma *in situ* (DCIS) during preoperative biopsy had a significantly higher likelihood of requiring reintervention compared to invasive carcinoma.
- No statistically significant differences were observed regarding lesion size, breast quadrant location, or lesion depth.

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Introduction

Breast cancer is an important health concern worldwide. It is the second most common cancer after skin cancer, and the second leading cause of cancer-related deaths among women globally, with an estimated mortality of nearly 700 000 and 2.3 million new cases diagnosed in 2020 alone. Nearly half (45.4%) of these are diagnosed in Asia - where nearly 50% of worldwide fatalities occur - with Europe being responsible for 23.5% (1, 2). It is a complex and heterogeneous disease, with several risk factors associated with its development including age, gender, family history of breast cancer, hormonal factors, lifestyle factors, and exposure to ionizing radiation (3). Age is the most significant risk factor for breast cancer, with the majority of cases occurring in women aged 50 years and above. The incidence of breast cancer varies across different countries and regions with highest numbers in North America, Europe, and Australia, and lowest in Africa and Asia. The incidence of breast cancer has been increasing, likely due to changes in lifestyle factors such as obesity, physical inactivity, and delayed childbearing, along with some forms of hormone replacement therapy and alcohol consumption (4). Despite significant progress made in its diagnosis and treatment, breast cancer remains a major public health issue.

Screening is crucial in the management and overall burden of the disease, since early detected lesions usually carry good prognosis and can be dealt with less invasive methods delivering good cosmetic outcomes (5). One aspect related with early lesions is that they are often non palpable and therefore not clinically detected, reinforcing the role for imaging screening. Methods available for detecting non-palpable lesions include mammography, ultrasound, and magnetic resonance imaging (MRI) (6-8). Mammography is the most widely used for detecting breast cancer and has been shown to reduce breast cancer mortality by up to 30% (9). However, mammography has limitations, particularly in young women with dense breast tissue, where cancers may be missed or masked. Ultrasound is a useful adjunct to mammography in these cases or in those with suspicious findings on mammography (10). MRI is a highly sensitive imaging modality and is particularly useful in high-risk women and those with a personal or family history of breast cancer.

Once a lesion is detected on image-based screening, providing its precise localization is crucial for further management, especially when considering a surgical approach. One of the first methods used for such a purpose were harpoon-wires. Its use dates back to the 1980s, when the development of mammography and breast imaging led to an increase in the detection of small, non-palpable breast lesions (11). These harpoon-wires can be inserted as an office procedure, under local anaesthesia, to conveniently locate the non-palpable lesion and the patient can return home the same day. However, there are also some disadvantages to consider, namely associated pain and discomfort, migration outside the vicinity of the lesion, bleeding and bruising and tissue damage from the wire barbs. In this way, alternatives to their use have been proposed, such as radio-guided occult lesion localization (ROLL) and radioactive seed localization (RSL) with advantages and disadvantages that are outside the scope of this article (12-15).

Magnetic seeds are a recent aid in the pre-operative localization of non-palpable breast lesions. The technique involves the insertion of a small magnetic seed into the breast tissue adjacent to the lesion under ultrasound or mammographic guidance. The seed possesses strong magnetic properties that can be easily detectable using specialized equipment, allowing the accurate location of the lesion during surgery. It can be placed in the breast up to one month before surgery, thereby obviating the need for a breast radiologist on the day of surgery. This technique provides increased accuracy, reduced surgical time, and improved patient comfort (16).

As with other techniques, a positive margin after breast-conserving surgery – defined by the presence of tumour cells at the edge of the surgical specimen our tumour on ink – can also occur with the use of magnetic seeds (overall estimates can reach 15%) (16-19). If the margins are positive, further surgery is required to achieve clear margins (20).

The main objective of this work was to analyse the relationship between the need for margin enlargement of excised breast lesions marked with magnetic seeds and geodimensional and histological parameters, in order to anticipate scenarios where reintervention for clear margins is more likely.

Materials and Methods

Study Design and Variables

A total of 198 patients were analysed retrospectively during a 2-year period (2018-2020) in Centro Hospitalar Universitário de Santo António (CHUdSA), Portugal. These have been submitted to excision of breast lesions previously marked with a magnetic seed (Magseed®, Sysmex Europe GmbH) by a radiologist under imaging aid (ultrasound in the majority of cases). In order to locate the marked lesions intraoperatively, the surgeon used a Sentimag® device (Sysmex Europe GmbH), which is a probe that contains a sensitive magnetometer that detects the magnetic seed. It emits an audible signal with variable pitches (alongside a coherent numeric value on screen) based on the proximity to the seed with higher pitched tones referring to closer proximity.

Eligibility criteria were as follows: Age 18 or higher, elective surgical procedure, existence of pre-operative histology, and absence of mastectomy as the proposed surgical procedure.

A set of variables were collected, namely: size of the lesion (wider axis in cm measured by ultrasound), distance of skin to lesion (determined by the smallest distance in cm between the skin and the magnetic seed measured on mammography scan), quadrant location of the lesion (defined as five regions quadrants, namely superolateral, superomedial, inferomedial, inferolateral and periareolar, and determined as described on the pre-operative ultrasound) and pre-operative histology [determined by dedicated biopsy and defined as ductal carcinoma *in situ* (DCIS), invasive carcinoma of no special type (NST), invasive lobular carcinoma, medullary carcinoma and benign]. Moreover, several other parameters were retrieved from this sample, including magnetic seed placement method, malignant/benign histology, need for reintervention, existence of complications - both related with the magnetic seed and the surgical intervention - and need for margin widening, the latter constituting the testing variable of our main hypothesis. A descriptive diagram is presented in Figure 1.

The patients were followed up for a minimum period of 2 years. Data were collected through the electronic database of the hospital.

The work was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Local Ethics Committee (CHUdSA 1_21/04/2022, date: 21.04.2023).

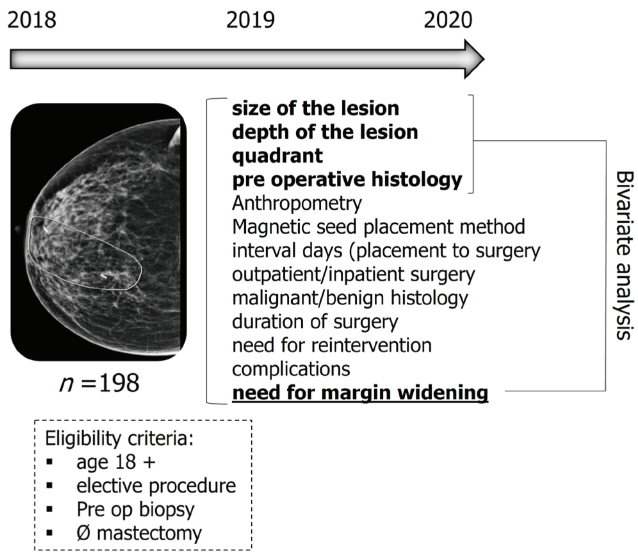

Figure 1. Study design and variables. A total of 198 patients were evaluated between 2018-2020. Among the several variables, those highlighted in bold were analysed in terms of their relevance in the need for margin widening

This paper was written with the aid of STROBE guidelines for observational original research studies (21).

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Kolmogorov-Smirnov test was used to evaluate parametric and nonparametric distributions. Comparison of categorical data was performed with Chi-square tests. Comparison of quantitative variables was performed using parametric and non-parametric tests, accordingly. All reported *p* values are two-tailed, with a *p* value of 0.05 indicating statistical significance. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27 (IBM Corp., Armonk, NY, USA) and are in accordance with international statistical reporting standards (22).

Results

A total of 198 cases were included in the study. Tables 1 and 2 summarise the variables analysed for this group of patients.

The patients had an average age of 60 years (59.34±12.969). The most common method for magnetic seed placement was ultrasound (68.2%) and a median time of 1 day was the interval between placement and the surgical procedure (1±3). Regarding location of the lesions, these were more prevalent in the superolateral quadrant (44.6%), followed respectively by superomedial quadrant (19.5%), inferomedial quadrant (13.8%), inferolateral (11.8%) and finally periareolar (10.3%). The average distance between the magnetic seed and the skin, measured on mammography scans was 24 mm (24.07±15.54). The majority of these patients were submitted to surgery in an inpatient setting (76.3%) with 23.7% being treated under outpatient surgery. The average time of surgery was 1h13m (73.71±40.32 min). The vast majority of excised lesions were malign (84.3%) with the remaining presenting a benign histology. The majority of these benign lesions were intraductal papilloma (45.8%) and fibrocystic lesions (33.3%). Representative mammography images of malignant lesions are presented in Figure 2.

Table 1. Categorical variables

		F	%
Magnetic seed placement method	Ultrasound	135	68.2
	Stereotaxis	46	23.2
	Ultrasound and stereotaxis	17	8.6
	(missing)	0	
Quadrant	Superolateral	87	44.6
	Superomedial	38	19.5
	Inferomedial	27	13.8
	Inferolateral	23	11.8
	Periareolar	20	10.3
	(missing)	3	
Inpatient/ outpatient	Inpatient	151	76.3
	Outpatient	47	23.7
	(missing)	0	
Malignant/ benign	Malignant	167	84.3
	Benign	31	15.7
	(missing)	0	
Reintervention	No	161	81.7
	Yes	36	18.3
	(missing)	1	
Magnetic seed related complications	Infection	1	0.5
	Ecchymosis	6	3.1
	None	189	96.4
	(missing)	2	
Margin widening	No	171	86.4
	Yes	27	13.6
	(missing)	0	
Biopsy	Ductal carcinoma *in situ*	42	21.4
	Invasive carcinoma NST	110	56.1
	Invasive lobular carcinoma	14	7.1
	Medullary carcinoma	1	0.5
	Benign	29	14.8
	(missing)	2	

NST: No special type

A need for reintervention by any cause, including need for margin widening, was generally low (18.3%). All the reinterventions occurred in non-cystic lesions. Among complications associated with the use of magnetic seed localization, the authors highlight ecchymosis (3.1%) and infection (0.5%). However, the vast majority of cases (96.4%) did not present any type of complication. A need for reintervention in order to attain negative margins was present in 13.6% of cases with the majority (86.4%) retrieving negative margins on the histological evaluation of the first specimen. Pre-operative histological analysis of malignant lesions showed that invasive carcinoma NST was the most prevalent (56.1%), followed by DCIS 21.4%, invasive lobular carcinoma (7.1%) and a residual number of cases of medullary

Table 2. Continuous variables

	Mean	Standard deviation	Median	Interquartile range	(missing)
Age (years)	59.34 (56.75–61.94)	12.97			3
Magnetic seed distance (mm)	24.07 (21.83–26.32)	15.54			0
Duration of surgery (min)	73.71 (67.00–80.42)	40.32			2
Lesion size (mm)			13	12	0
Interval days (placement to surgery)			1	3	0

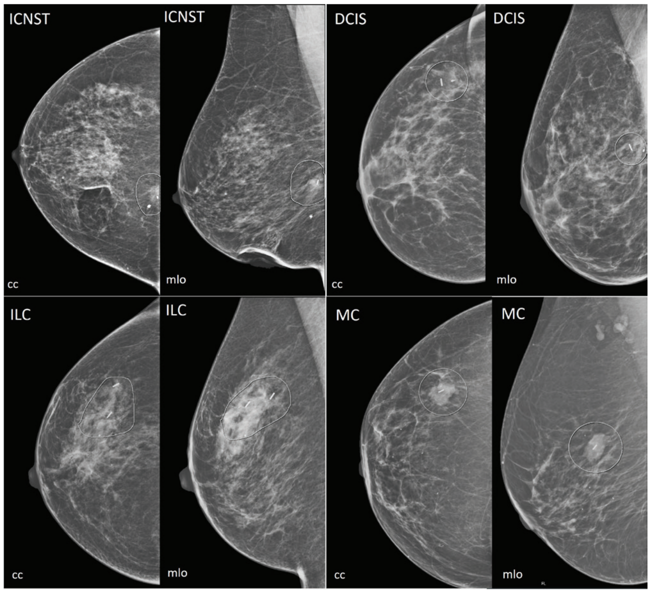

Figure 2. Representative mammograms of the different histological subtypes

ICNST: Invasive carcinoma of no special type; DCIS: Ductal carcinoma in situ; ILC: Invasive lobular carcinoma; MC: Medullary carcinoma; cc: Craniocaudal view; mlo: Mediolateral oblique view.

carcinoma (0.5%). Nine patients that were reoperated not due to margin widening: eight patients (89%) were resubmitted to surgery due to axillary node dissection and one (11%) was reoperated due to superficial wound infection.

A representative image of a magnetic seed after its placement in a breast lesion is shown in Figure 3.

The bivariate analysis of geodimensional and histological parameters is present on Table 3.

This encompassed the analysis of the patients which required reintervention due to a positive margin result in the index surgery with the following variables: size of the lesion measured by its longer axis on mammography scan; quadrant where the lesion was located as determined by the radiologist on ultrasound; distance of skin to lesion of the magnetic seed determined by the shortest linear distance between the seed and the skin measured on mammography scan; and finally pre-operative histology for the two most prevalent types, namely DCIS and invasive carcinoma NST.

On bivariate analysis, reintervention to widen margins was significantly more frequent when the patients had a pre-operative histological analysis of DCIS, as compared to those who had a histological diagnosis of invasive carcinoma NST (p = 0.03). Concerning the remaining three analysed groups, no statistically significant differences were observed between the need for reintervention and lesion size (p = 0.197), breast quadrant location (p = 0.626) and distance of skin to lesion defined by the distance between the magnetic seed and the skin (p = 0.356).

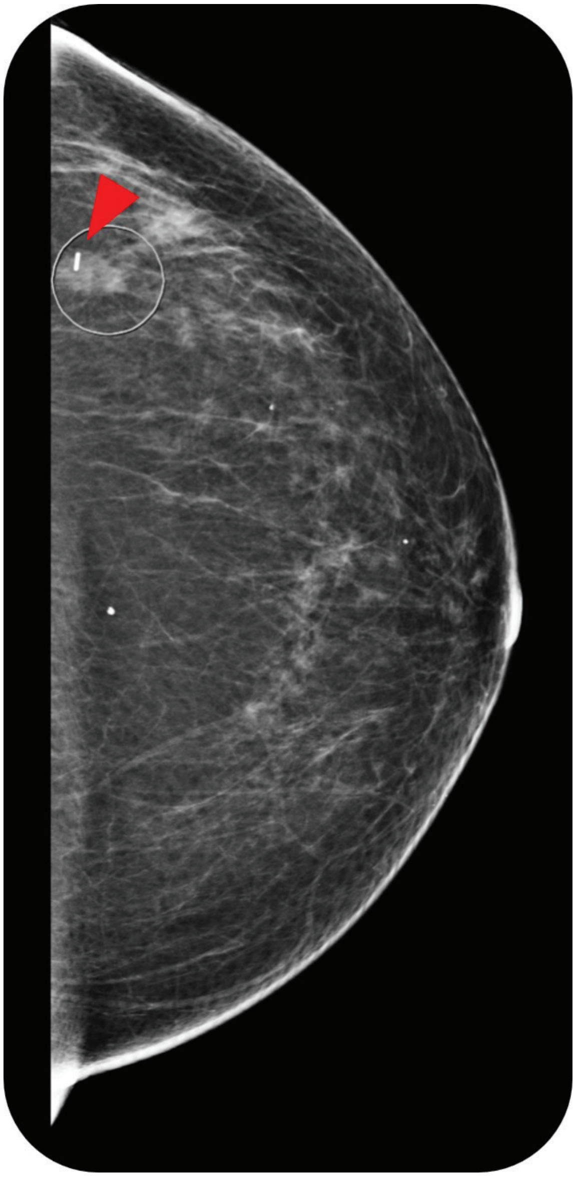

Figure 3. Mammography after placement of the magnetic seed (arrowhead)

Table 3. Bivariate analysis regarding the need for margin widening

Magnetic seed distance – Margin widening	$p = 0.356$	t
Quadrant – Margin widening	$p = 0.626$	$\varkappa^2$
Lesion size – Margin widening	$p = 0.197$	M-W
Biopsy – Margin widening	$p = 0.030$	$\varkappa^2$

t: t-test; $\varkappa^2$: Chi-square test; M-W: Mann-Whitney U test

Discussion nd Conclusion

Breast cancer is one of the most prevalent cancers in women worldwide, representing a relevant health problem with an estimated 2.3 million new cases diagnosed in 2020 (1). Early detection of breast lesions is important as it can lead to timely and adequate treatment, improving the chances of successful outcomes. Breast cancer screening methods have evolved over the years, and today, several techniques are available to detect early-stage lesions. Some of the most common screening methods include mammography, ultrasound, and MRI (6-8). In some cases, breast lesions may not be palpable, making their location crucial for surgical planning. Among the different techniques, recently developed magnetic seed localization may be used to aid in this matter. It has been shown to be effective in locating non-palpable breast lesions, with a high success rate and low complication rates (23). However, as in other methods of detection, magnetic seed localization has an associated percentage of positive margins, which can increase the risk of local recurrence, prompting the need for further surgery. Indeed, previous work by other authors have addressed this issue. The rates of positive margins reported among different techniques present some variability in terms of range but are overall comparable. The harpoon-wire has been shown to deliver 54–90% negative margins, RSL 74–96% and ROLL a rate of 67–87% negative margins (17-19). Concerning magnetic seed localization, work conducted by Powell et al. (16) reported an 85–86% negative margin rate after excision.

The main objective of this work was to evaluate the influence of geodimensional and histological parameters in the need for reintervention after tumorectomy under magnetic seed localization.

The authors analysed several parameters (detailed on Tables 1 and 2), namely pre-operative size of the lesion, quadrant where the lesion is located, the distance at which the lesion is located, and histology on pre-operative biopsy.

The results showed that there were a median 1-day time between magnetic seed placement and surgery. Indeed, in our institution, scheduling for magnetic seed placement is coordinated with the surgical procedure. After multidisciplinary group discussion, the patients are usually admitted in the morning for imaging evaluation and seed placement by the radiologist, being submitted to surgery during the same day. One of the main advantages associated with magnetic seed as compared to wire for example is the possibility to be implanted several days before the procedure without the associated discomfort and infection risk associated with the latter technique (23). Although our procedure is as abovementioned and the median of patients had the magnetic seed placed in the same day of surgery, some patients had its placement several days earlier benefiting from higher comfort at home in the days before surgery.

Regarding location, the lesions were mostly present in the superolateral quadrant (44.6%), followed respectively by superomedial quadrant (19.5%), inferomedial quadrant (13.8%), inferolateral quadrant (11.8%) and finally periareolar (10.3%). The superolateral is in fact the most common location for breast lesions (24), possibly due to the fact that lesions in this quadrant are more easily accessible and detectable during a physical examination or mammography. Lesions in other quadrants, such as superomedial or inferomedial, located close to the sternum and chest wall, may be more difficult to detect during physical examination or mammography being therefore less prevalent in the literature.

Most lesions were malignant (84.3%) with invasive carcinoma of no special type, being the most prevalent (56.1%), in accordance with the literature (16). DCIS was represented in 21.4% while invasive lobular carcinoma and medullary carcinoma represented minor percentages.

Our results are also in line with those reported in the literature regarding reintervention (overall result of 18.3% with a need for reintervention in order to attain negative margins in 13,6% in our cases). This indicates that although this technique is recent with a few hundred cases reported so far, it has a fast-learning curve providing success rates comparable to the other techniques more commonly used while alleviating some side effects such as discomfort, pain and elevated rate of site infection associated with others (25). An aggregated rate of complications of 3.5% is satisfactory, namely since the majority of those where local hematoma managed conservatively.

Focusing on the primary objective of this work, which was the evaluation of the influence of geodimensional and histological parameters on the need for margin re-excision, the authors found a statistically significant difference when comparing DCIS with invasive carcinoma on pre-surgery biopsy with a significantly higher need for reintervention in DCIS ($p = 0.03$). Indeed, similar findings have been described regarding in post-surgical specimens' margins of DCIS when compared to invasive breast carcinoma (16). DCIS is a non-obligate precursor non-contiguous lesion for invasive breast cancer that is confined to the milk ducts of the breast that has not invaded surrounding tissues (26). Such a histological difference from invasive breast carcinoma where cancer cells have broken the ductal barrier and progressed through the surrounding breast tissue, might confer altered mechanical properties to the tissue to be excised, despite the presence of the magnetic seed. Different mechanical properties of the tumour mass might facilitate an easier identification of its boundaries from the surrounding healthy tissues, allowing a more frequent attainment of negative margins. Indeed, since DCIS is confined to the ductal system it can be more difficult to visualize during surgery. Despite the usefulness of magnetic seed location in identifying a more precise location of the tumour, the probe will deliver an audible and visual signal over the tumour marker, not being able to clearly delimitate the tumour boundaries to the surgeon. This may explain to a certain extent the observed results. Also, a possible contributor is the fact that DCIS is tendentially more likely to be multifocal compared to invasive breast carcinoma. While invasive breast carcinoma can be multifocal as well, this is generally less common than in DCIS. The invasion of cancer cells into the surrounding tissue typically occurs from a primary tumour site and may spread to nearby lymph nodes or other areas, rather than developing multiple independent tumour sites within the breast [**27**]. In our institution, as in most, excised breast lesions identified with a magnetic seed are further screened under X-ray to confirm seed inclusion in the lesion area. *In loco* imaging evaluation by a dedicated breast radiologist might obviate the need for reoperation if margin assessment was considered adequate. Still, this process is not as accurate as histopathological analysis and would require nearly permanent availability from radiologists.

Regarding the geodimensional parameters, no statistically significant differences in terms of pre-operative size of the lesion (p = 0.197), quadrant where the lesion is located (p = 0.626), and the distance from the skin at which the lesion is located (p = 0.356), as shown on Table 3.

Overall, this work suggests that the surgeon should consider a wider margin excision if a patient has a pre-operative biopsy of DCIS when compared to invasive carcinoma, in order to decrease the likelihood of reintervention to obtain negative margins. No difference in terms of surgical gesture is apparently needed for lesions with larger size, more deeply located or that are present in a certain quadrant.

This work has inherent limitations. It describes the experience of a single centre in a western European tertiary hospital, which represents a certain reality. Nonetheless, the methods used are established in the current state of the art and the results are expected to translate similar healthcare scenarios. A reduced number of positive margins after tumorectomy in our series 13.6%, is in accordance with data described in the literature. These numbers, although positive regarding treatment, provide reduced numbers for statistical analysis during the chosen timeframe. Furthermore, the analysis of which margin is significantly most represented as positive is also hindered by this fact. Future studies shall benefit from including more centres and enrolling more patients with the expectancy that these will render higher absolute patients' number for statistical analysis.

Breast cancer is a relevant health issue and early detection of breast lesions is crucial for successful treatment outcomes. Magnetic seed localization is an effective technique for locating non-palpable breast lesions, but it has an associated percentage of positive margins as in other similar systems. This work suggests that a preoperative histology of DCIS on biopsy should prompt a wider margin excision, thereby decreasing the need for reintervention to attain clear margins. No such concern is needed regarding size of the lesion, its quadrant location and distance of skin to lesion at which it is located.

Ethics Committee Approval: The work was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Local Ethics Committee (CHUdSA 1_21/04/2022, date: 21.04.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.T.O., A.M., J.P.F., C.P., T.T., S.M., J.P.; Concept: J.T.O.; Design: A.M., S.M., J.T.O.; Data Collection or Processing: J.T.O., A.M., J.P.F., J.P.; Analysis or Interpretation: J.T.O.; Literature Search: J.T.O.; Writing: J.P.F., J.T.O., J.P.

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