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André Filipe Costa Pereira

The role of pre-mastectomy sentinel lymph node biopsy in the management of immediate breast reconstruction in breast cancer patients: a retrospective cohort study.

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Medicina clínica (Oncologia Mamária)

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

The role of pre-mastectomy sentinel lymph node biopsy in the management of immediate breast reconstruction in breast cancer patients: a retrospective cohort study.

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Eu, André Filipe Costa Pereira, abaixo assinado, nº mecanográfico 201704691, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 20/02/2024

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Dedicatória

Um obrigado às estações de rádio “Mega hits” e “Rádio Comercial” pela fonte de motivação e entretenimento fornecidas para a realização desta dissertação,
Um obrigado ao meu orientador de tese pela oportunidade que me proporcionou para realizar esta dissertação e pelo apoio prestado ao longo da mesma,
Um obrigado à minha co-orientadora pelo apoio prestado ao longo da realização desta dissertação,
Um obrigado aos meus amigos que de alguma forma me ajudaram neste percurso académico,
Um obrigado especial ao meu pai e à minha mãe pelo suporte prestado ao longo dos últimos anos… escusado será dizer “sem vocês nada disto seria possível”,
Um obrigado aos restantes membros da família,
Um obrigado especial ao meu irmão pelo apoio, aventuras e suporte incondicional neste percurso a que chamamos vida,

No primeiro ano da faculdade fui confrontado com a expressão “The difference between the impossible and the possible lies in a man's determination.” Foi até à escrita desta dedicatória que soube que foi Tommy Lasorda o autor desta enigmática expressão que marcou o meu percurso académico e pela qual estou eternamente grato.

Em memória do meu avô e da minha avó…obrigado pelo papel que tiveram no homem que hoje sou.

The role of pre-mastectomy sentinel lymph node biopsy in the management of immediate breast reconstruction in breast cancer patients: a retrospective cohort study.

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Author's contributions

RP: Data curation, formal analysis and interpretation, statistical analysis, manuscript original draft and editing.

BP: Data collection, formal analysis and interpretation, statistical analysis, manuscript review and editing.

JLF: Study design, data collection, statistical analysis and interpretation, manuscript review and editing, supervision, conceptualization

Declarations of interest: none

Summary: This study investigates the impact of a clinical approach involving sentinel lymph node biopsy before mastectomy to evaluate the need for post-mastectomy radiation therapy, after immediate reconstruction. Among patients with metastatic sentinel lymph node, 76% altered their initial plan of immediate breast reconstruction. The clinical relevance of primary sentinel lymph node biopsy in the management of IBR patients seems very low, since in our sample of patients this information was disregarded in 43% of cases.

Abstract

Background: Post-mastectomy radiation therapy (PMRT) typically poses a contraindication for immediate breast reconstruction (IBR). Sentinel lymph node biopsy (SLNB) becomes imperative to identify candidates more effectively for delayed breast reconstruction (DBR). This study aimed to assess the impact of an independent SLNB prior to mastectomy in determining the need for PMRT.

Methods: We conducted a retrospective analysis of patients who underwent primary SLNB followed by mastectomy at the Breast Centre of *Unidade Local de Saúde São João* from January 1st, 2011, to December 31st, 2020.

Results: In the analysis of 339 patients, 223 (69.9%) showed a negative SLNB result, and all of them proceeded with IBR. Within the pN+sn group, 23.9% (23/96) ultimately underwent IBR.

Despite being pN0sn, 3.6% (8/223) were proposed to receive PMRT; on the contrary, 42.7% (41/96) of the pN+sn patients were spared from it. In total, 15.4% of the cases were approached differently than planned.

Conclusions: A noteworthy 76% of the pN+sn patients had their IBR plan changed. Despite the clinical relevance of primary SLNB appearing very low, since in our sample of patients this information was disregarded in 43% of cases, it provides essential information for deciding on the timing of breast reconstruction.

Key words: Breast Neoplasms, Sentinel Lymph Node, Mastectomy, Mammaplasty, Radiotherapy.

1. Introduction

In the contemporary landscape of medicine, the impact of oncologic outcomes and psychosocial well-being on breast cancer (BC) patients' quality of life (QoL) is paramount. Achieving favorable aesthetic results plays a crucial role in mitigating these challenges.

Studies have highlighted that patients opting for immediate breast reconstruction (IBR) after mastectomy often experience high levels of satisfaction and encounter lower morbidity levels [1]. The existing body of literature indicates that IBR offers superior outcomes in terms of psychosocial well-being, body image, and sexual well-being when compared to delayed breast reconstruction (DBR) [1,2]. However, it is essential to acknowledge potential risks, such as surgical site infections and implant loss, associated with IBR [3]. Post-operative complications following breast reconstruction are prevalent and can significantly impact patient satisfaction. Therefore, a shared decision-making approach between patients and the surgical team is crucial, where individuals undergoing mastectomy are thoroughly advised and engage in discussions about their reconstruction options and expectations [4]. The assessment of individual risk factors is a pivotal step in evaluating and counseling BC patients before mastectomy and IBR. Factors such as smoking habits, high body mass index (BMI), diabetes, prior radiotherapy (RT), and the need for post-mastectomy radiation therapy (PMRT) should be carefully considered in the context of post-operative complications related to IBR [4,5].

PMRT is an integral component of the treatment regimen for many BC patients. While the adverse effects of radiotherapy on QoL and satisfaction levels are well-documented in some individuals [6,7], acceptable aesthetic outcomes have been reported following PMRT [8]. Autologous flap IBR has been associated with higher satisfaction levels and enhanced psychosocial well-being

compared to implant reconstruction [9]. However, PMRT following autologous flap reconstruction introduces the risk of volume loss, fat necrosis, and distortion of the reconstructed shape [4,10]. Prosthetic implant remains the most common choice for IBR, but PMRT in these cases can lead to complications such as capsule contracture, implant loss, compromised cosmetic outcomes, infections, and skin necrosis [4,11]. Nipple/skin-sparing mastectomy (NSSM) with IBR is a sophisticated and intricate procedure that demands time, expertise, and logistical considerations. Therefore, the decision-making process for IBR should be guided by a comprehensive health decision-making approach, aligning with the patient's expectations and considering the potential risks associated with PMRT.

Indications for PMRT in the treatment of BC patients are expanding. It is recommended for high-risk cases, characterized by tumor size exceeding 50 mm (T3) and the presence of four or more affected lymph nodes [4,12]. While some indications for PMRT remain controversial [12], certain guidelines strongly advocate for radiotherapy to the chest wall in cases with 1-3 positive axillary nodes [13,14]. This approach has demonstrated efficacy in reducing the risk of locoregional recurrence (LRR) and breast cancer-related mortality.

In our Breast Centre we select cT0-2 pN0 BC patients that need or request total mastectomy to receive IBR. Pre-mastectomy (primary) sentinel lymph node biopsy (SLNB) is an important step in the N staging, providing information about the presence of metastasis in the axillary nodes.

The purpose of this study was to evaluate the results of our clinical conduct, which is performing a previous and independent SLNB to select patients for IBR and to evaluate the indication for PMRT, that may result in DBR or no reconstruction (NR). We aimed to determine the rate of positive SLN and to identify potential risk factors, the proportion of postponed breast reconstructions and the long-term morbidity of PMRT after IBR.

2. Material and Methods

2.1. *Study design, setting and participants*

This is a retrospective cohort study. We collected and reviewed our prospectively gathered database of consecutive patients that underwent primary SLNB between January 1st 2011 and December 31st 2020, treated at the Breast Centre from *Unidade Local de Saúde São João* (ULSSJ). Data collection was limited to the year 2020, so a minimum of two years of follow-up could be achieved.

The study structure meets the requirements of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) regarding cohort studies [15].

2.2. *Inclusion and exclusion criteria*

Patients with invasive or *in situ* BC submitted or not to chemotherapy prior to the surgery, patients at high risk for BC (known germinative genetic mutation or other) and patients who request prophylactic mastectomy (because of cancer phobia), that underwent primary SLNB were included. Until 2016, high risk and prophylactic patients were proposed to primary SLNB, but since then this clinical practice was discarded, due to the low risk of SLN positivity and the putative morbidity.

2.3. *Diagnostic work-up*

All patients were assessed clinically, including breast and axilla inspection and palpation. All patients underwent mammography and breast and axilla ultrasound. Breast magnetic resonance imaging was performed in selected patients according to the Breast Centre clinical practice. cT was defined according to the imaging information. Suspicious axillary nodes were submitted to ultrasound guided needle biopsy. The diagnosis of malignancy was made by triple assessment in a multidisciplinary meeting.

2.4. ***Lymph node surgery and pathological assessment***

The SLNB was performed using a combined technique that merges the subareolar injection of 1cc of Patent Blue V dye and peritumoral injection of 1cc of Indocyanine Green. All macroscopically suspect, fluorescent and/or blue nodes were considered SLN. Axillary dissection included the removal of Berg levels 1 and 2 and spares the long thoracic nerve, the first two sensitive intercostobrachial nerves, the thoracodorsal bundle, and the axillary vein.

In invasive BC patients, the SLN were assessed by OSNA assay, provided the CK19 was positive; in the remaining patients, SLN were assessed by conventional H-E. All non-sentinel lymph nodes (NSLN) were analysed by conventional H-E.

2.5. ***Nipple/skin-sparing mastectomy and IBR***

After the primary SLNB, patients participated in a meeting with the breast surgical oncologist and the plastic surgeon. If the SLN was metastasized, the patient was proposed to receive a conventional, simple, curative mastectomy without IBR. If the SLN was free of metastasis, and the tumour was less than 50 mm, the patient was proposed to receive NSSM with IBR. The reconstruction technique was chosen from a wide range of options, varying from tissue expander to DIEP-flap, according to the patient's body structure and to the patient's will and expectations. NSSM was performed by the surgical oncologist and the reconstruction was performed by the plastic surgeon.

2.6 ***Comorbidities and IBR complications***

Information about patient`s comorbidities and IBR related morbidity after PMRT was extracted from the data documented in the patient's digital files.

2.7. ***Adjuvant PMRT***

Post-mastectomy radiotherapy means external radiation treatment to the thoracic wall or to the

reconstructed breast and not to the lymphatic drainage areas.

According to the protocol of our Breast Centre, to every invasive BC patient staged with a pT3 lesion, or with a pN1-3, should be offered adjuvant PMRT.

External radiation treatment to the lymphatic drainage areas was used in case of pN1sn without axillary dissection or in case of a pN2 after axillary dissection.

2.8. *Follow-up*

All patients were followed up by the plastic surgeon in the immediate post-operative period as well as in the long term. All patients were evaluated by the surgical oncologist at least twice in the first post-operative year and once yearly thereafter; clinical appointments with the medical and radiation oncologists were also provided, when needed. All patients performed mammography, breast and axillary ultrasound once a year.

2.9. *Statistics*

Database and statistical analysis were done on IBM SPSS Statistics 27.

Descriptive statistics were used to summarize the main characteristics of the sample. Continuous variables were summarized by measures of central tendency (mean or median, as applicable) and dispersion (standard deviation) and categorical variables were summarized by absolute (N) and relative (%) frequency. The Chi-square or Fisher's exact test, as appropriate, was used for comparison of proportions, while Student's t test or Mann–Whitney test was used for comparison of means or medians, respectively. A p value < 0.05 was considered statistically significant.

2.10. *Ethics, confidentiality and data safety*

Every case was designated by a serial number. Every study serial number was associated to a clinical file patient number. Only the main investigator had access to the association database. This study was approved by the Ethics Committee of ULSSJ (CE 94-23).

3. Results

The consecutively registered database yielded an initial sample of 339 patients with primary SLNB. Out of these, 20 were excluded, because they declined the IBR plan (due to fear of the surgery, religious convictions, etc.) or they showed significant co-morbidities (namely, high BMI, psychiatric impairment, etc.). All the excluded patients had a negative SLNB. The analysis was performed on the remaining 319 patients. (figure 1)

Patient demographics and pathological information are presented in Table 1. All patients were females. The median follow-up time was 67 months (range 7-145 months).

In the analysis of predictive factors for the SLN positivity (Table 2), the tumor size assessed by ultrasound had a significant effect both as a continuous variable (p=0.006) or as a discrete one: a higher proportion of positive SLN was observed among cT2-3 patients (p=0.031).

In what concerns the IBR plan, all the pN0sn patients underwent IBR; nevertheless, from the pN+sn group, 23.9% (23/96) of them ended up undergoing IBR. Considering the entire sample, in 7.2% of patients the treatment protocol was not complied with, seeking to act in favor of the patient will.

All 223 negative SLNB patients (pN0sn) underwent IBR (figure 1). Of these, eight individuals were proposed to PMRT for different reasons. One patient (cT2) exhibited an extensive ductal carcinoma in situ measuring 86 mm with seven foci of micro-invasion. Another patient (cT2) presented a 47 mm mixed invasive carcinoma, with lymphovascular invasion. Additionally, a patient (cT2) with mucopapillary invasive carcinoma measuring 50 mm and displaying lymphovascular invasion was proposed to PMRT. The remaining five patients voluntarily opted for IBR despite having a cT3 and pT3 invasive tumor, demonstrating a clear understanding of the associated risks with PMRT.

Of the patients with micrometastasis in the SLN (Figure 1; n=47), 32 (68.1%) were not submitted to

PMRT. Of these, 25 (NR n=6; DBR n=5; IBR n= 14) were not submitted to PMRT due to the low tumor burden indicated by the OSNA results and 7 patients (NR n=3; DBR n=1; IBR n=3) received external radiation treatment only to the axilla/periclavicular region. The remaining 15 (NR n=6; DBR n=6; IBR n=3) patients received PMRT as per protocol. Of these 3 IBR+PMRT patients, two had a cT2 that was upstaged to pT3, and one had two SLN affected with micrometastasis.

Of the patients with macrometastasis in the SLN (Figure 1, n=49), 9 (18.4%, NR n=4; DBR n=3; IBR n=2) were not submitted to PMRT; of these, 5 (NR n=3; DBR n=2) received exclusive external radiation treatment only to the axilla/periclavicular region; 2 (DBR n=1; IBR=1) did not undergo PMRT, because of a complete axillary dissection without invasion of NSLN, and 1 (IBR n=1) did not receive PMRT due to the previous diagnosis of a collagen disease with lung involvement. For the remaining patient who did not undergo PMRT (NR n=1), a clear explanation for not being treated with radiotherapy could not be obtained. The remaining 40 patients (NR n=19; DBR n=20; IBR n=1) received PMRT as per protocol. Among these, the patient with IBR+PMRT (IBR=1) performed IBR by their own risk.

Regarding the PMRT plan, 3.6% (8/223) were proposed to perform the treatment and 42.7% (41/96) were spared from it despite the protocol. In total, 15.4% (49/319) of the cases were approached differently than planned.

Considering exclusively the patients that underwent IBR (n=246), we examined the correlation between PMRT and the chronic complications (Table 3). PMRT did not exhibit a substantial effect on overall chronic complications or specific ones.

As showed in table 4, there was no discernible association between the various types of reconstruction performed (autologous or heterologous/ mixed) and the risk of chronic complications following PMRT.

As indicated in table 5, within the entire cohort of patients with IBR who experienced complications, whether they underwent PMRT or not, the presence of comorbidities was linked to chronic complications (p-values of 0.021). All the other specific comorbidities did not show a significant effect on the IBR chronic complications in both groups of patients.

4. Discussion

The present investigation assesses the impact of our clinical approach involving the performance of an independent SLNB before mastectomy to ascertain the need for PMRT, subsequently leading to postpone the breast reconstruction. We identified a 30.1% positivity rate for SLN, with 14.7% (47/319) attributed to micrometastasis and 15.4% (49/319) to macrometastasis. Among patients with pN+sn, a noteworthy 76% (73/96) changed their initial plan of IBR due to the elevated risk of PMRT-associated healing, aesthetic, or functional morbidity.

Few studies have elucidated the frequency of postponed breast reconstruction. In contrast to van Haaren et al study [4], which reported a 33% postponement rate for breast reconstruction in patients with macrometastasis, our investigation revealed significantly higher rates of deferral (94%, 46/49). This difference may be attributed to the fact that, in our study, SLNB was conducted prior to mastectomy, whereas van Haaren's study obtained the sentinel node intraoperatively using the OSNA technique [4]. Consequently, in our study, the initial indication for IBR could be modified in a much easier way, based on OSNA or histology data, facilitating patient consent through a more streamlined multidisciplinary decision-making process. Mannu et al further underscores that intraoperative evaluation of the sentinel node induces psychological stress in patients due to the inherent uncertainty surrounding the final result [16].

Another contributing factor to the variation in the rate of postponement lies in the inherent ambiguity surrounding indications for PMRT, as evident in the literature. The study by Jang et al underscores the critical importance of stratifying both tumor and patient characteristics to identify those who may benefit from PMRT [17]. Factors such as patient age and comorbidities, tumor characteristics (molecular subtype), and margin of resection emerge as key influencers in the PMRT decision-making process, showing that elderly people benefit from doing PMRT in pT1-2N1 tumors, with some other studies demonstrating that, in pT1-2 N1 with luminal A subtype, PMRT has impact in the overall survival [17-19]. Additionally, patients with pN1mic and pN1 status, particularly those with high-risk factors, should be considered for PMRT. Conversely, for patients with intermediate risk of recurrence and pT1-2N1 tumors, the indications for PMRT remain ambiguous [4, 17-18]. This multifaceted nature of PMRT indications, influenced by diverse patient and tumor factors, underscores the complexity of decision-making in this context. The need for individualized and nuanced considerations further emphasizes the importance of a tailored approach in determining the appropriateness of PMRT for each patient.

Despite the elevated rate of postponed breast reconstruction, the twenty-three patients with positive SLNB in our study that adhered to the initial IBR plan were guided by their own informed decision and awareness about PMRT implications. As indicated by several studies, the motivation behind patients opting for IBR despite a positive SLN lies in the desire to attain a sense of normality [20-21]. Notably, the research conducted by Flitcroft et al underscores that, despite the well-documented risks associated with PMRT, patients are steadfast in maintaining their decision due to a strong inclination towards both physical and psychosocial well-being [20-21].

Conversely, the primary rationale behind patients choosing DBR or opting for NR stems from the devaluation of the physical appearance in their decision-making process. Furthermore, factors such

as age and apprehension about complications associated with a secondary surgical procedure play a pivotal role in steering patients towards the decision to abstain from immediate reconstruction [20-22].

We were able to assess various predictive factors for SLN positivity and, as anticipated based on existing literature, tumor size determined by ultrasound proved to be a predictive factor for SLN positivity. Likewise, Minami et al demonstrated that tumor size in ultrasonography serves as a predictive indicator for the likelihood of a positive SLN [23]. The early age of the patients diagnosed with breast cancer and the presence of microcalcifications in the mammography were also associated with the risk of positivity of the sentinel node in other studies [24-26]. Fein et al found that a risk of 5 to 10% for axillary node positivity was associated with tumor sizes in mammography ranging from 6 to 10 mm [25]. It is important to note that our study aimed to evaluate predictive factors before anatomopathological assessment, and therefore, pathological tumor size was not included in the analysis. Nonetheless, numerous studies have indicated an association between pathological tumor size and an increased likelihood of SLN positivity [24, 26].

The complications of PMRT on IBR are well-documented. Across various studies, breast volume loss and fat necrosis emerge as the most frequent complications associated with PMRT after IBR, with a particular focus on the Deep Inferior Epigastric Perforator (DIEP) flap, recognized as the one of the most utilized and analyzed technique [10, 27-28].

In our study, all patients with an autologous flap who underwent PMRT exclusively utilized the transverse rectus abdominis myocutaneous (TRAM) pedicle flap, and no association was observed in terms of chronic complications (the same holds true for heterologous/mixed reconstructions). In heterologous reconstructions, capsular contracture stands out as a common complication in some studies, such as the one by Lam et al [29], revealing a higher risk of capsular contracture in patients

who underwent a two-stage reconstruction involving an expander followed by an implant after PMRT [29-30]. This risk of reconstruction failure was notably higher during the expansion phase (29.7% vs. 5%) [29-30]. El-Sabawi et al study reported a higher rate of capsular contracture types 3 and 4 in implants compared to expanders, although they underscored that favorable aesthetic outcomes can still be achieved with PMRT [8]. Despite these insights, the issue of complications related to PMRT remains a contentious topic because some studies demonstrate no increased prevalence of long-term complications, such as fat necrosis, after IBR with DIEP flap followed by PMRT [31-32].

We also explored the potential relationship between patient comorbidities and chronic complications in those undergoing PMRT. Having comorbidities was linked to chronic complications in the overall group of patients who did IBR. Roubaud et al research [33] underscore that specific patient conditions significantly influence the occurrence of complications following breast reconstruction. Additionally, smoking, overweight/obesity (BMI > 25) and having more than 65 years old were identified as high-risk factors that predispose to complications such as fat necrosis. [5, 33-35]. The combination of multiple risk factors further amplifies the risk of complications [5,33].

A constraint of our approach is the need for two surgical interventions. Although the isolated, primary, SLNB could be performed under local anesthesia and under an outpatient basis, it remains an operative procedure with inherent risks of complications, which requires the availability of operating theater time, and which has an impact on the patient's personal, family, and professional life. Furthermore, it prolongs the waiting time for curative breast tumor surgery. The primary SLNB avoids the anxiety associated with "not knowing the result" (as stated above), in the case of SLN biopsy with “frozen section” and peri-operative decision and allows a considered and personalized decision to be made, when choosing between IBR or DBR. Although there is scientific information

that relativizes the risk of complications or poor aesthetic results associated with IBR plus PMRT, for some women this risk may be intolerable. With the primary SLNB the patient will have all the relevant information to choose the timing of breast reconstruction.

The study's limitations include its retrospective nature, which introduces the possibility of missing data. The sample size, although spanning a long temporal series from 2011 to 2020, might still be a limiting factor in capturing certain significant values, such as those related to fat necrosis and volume asymmetry resulting from PMRT. Additionally, being an unicentric study may compromise the generalization of results beyond the specific context of the study site. Another relevant limitation is the fact that a formal evaluation of the aesthetic result was not carried out. Despite these constraints, it is noteworthy that this study, to the best of our knowledge, represents one of the pioneering efforts in Portugal to explore the association between primary SLNB and the choice between immediate or delayed breast reconstruction.

5. Conclusions

The clinical relevance of primary SLNB, in the management of IBR patients, seems very low, since in our sample of patients this information was disregarded in 43% of cases, suggesting a low impact on subsequent decisions regarding PMRT.

Furthermore, we also did not document a negative impact of PMRT after IBR.

Despite requiring two surgical procedures, in selected cases, the primary SLNB can provide the patient and the treatment team with remarkable information for deciding on the timing of breast reconstruction.

6. References

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7. Figure Legend

Figure 1. Flowchart 1:

SLNB, sentinel lymph node biopsy; **PMRT**, post mastectomy radiotherapy; **NR**, no reconstruction; **DBR**, delayed breast reconstruction; **IBR**, immediate breast reconstruction.

Attachment I – Figure 1. Flowchart 1

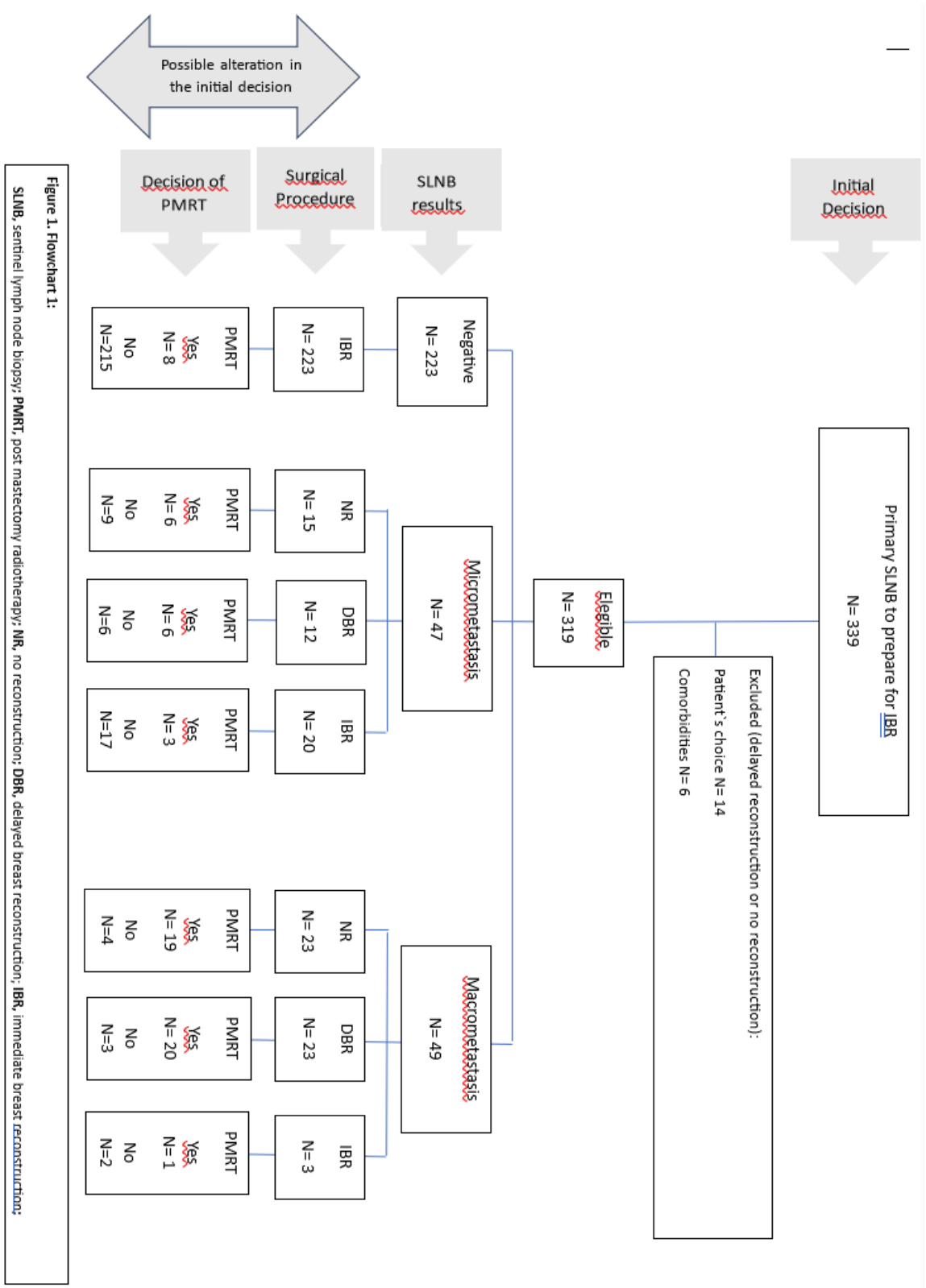

Figure 1. Flowchart 1:

SLNB, sentinel lymph node biopsy; **PMRT**, post mastectomy radiotherapy; **NR**, no reconstruction; **DBR**, delayed breast reconstruction; **IBR**, immediate breast reconstruction;

Attachment II- Tables

Table1. Patients characteristics

Variable	Value N=319
Age, mean (range)	47.82 (24-77)
Comorbidities, n (%)	
No	99 (30.9%)
Yes	221 (69.1%)
Type of comorbidities, n (%)	
Psychiatric disease (yes)	76 (23.8%)
Smoke habits (yes)	53 (16.6%)
HBP (yes)	49 (15.4%)
BMI >= 30 (yes)	39 (12.2%)
Dyslipidemia (yes)	30 (9.4%)
Osteoarticular disease (yes)	29 (9.1%)
Cardiovascular disease (yes)	24 (7.5%)
Lung disease (yes)	16 (5.0%)
DM (yes)	14 (4.4%)
Previous radiotherapy (yes)	2 (0.6%)
Others* (yes)	59 (18.5%)
Reason for mastectomy, n (%)	
Invasive Carcinoma	253 (79.3%)
Carcinoma in situ	57 (17.9%)
Proliferative lesions with atypia	4 (1.3%)
Patient exclusive will	3 (0.9%)
Genetic mutation	2 (0.6%)
Mammography tumor size in mm, median	35.74
Ultrasound tumor size in mm, median	20.79
MRI tumor size in mm, median	33.86
cT (TNM) classification, n (%)	

cTx	3 (0.9%)
cT1	149 (46.7%)
cT2	120 (37.6%)
cT3	47 (14.7%)
pT (TNM) classification, n (%)	
pTis	57 (17.9%)
pT1a	22 (6.9%)
pT1b	40 (12.5%)
pT1c	80 (25.1%)
pT2	88 (27.6%)
pT3	21 (6.6%)
Unknown	9 (3.4%)
pN (TNM) classification, n (%)	
pN0	223 (69.9%)
pN1	86 (27.0%)
pN2	10 (3.1%)
SLNB results, n (%)	
Negative (0 to 250 copies)	223 (69.9%)
Micrometastization (215 to 5000 copies)	47 (14.7%)
Macrometastization (> 5000 copies)	49 (15.4%)
Type of reconstruction, n (%)	
Autologous	95 (38.6%)
Heterologous	131 (53.3%)
Mixed (latissimus dorsi with prosthesis)	20 (8.1%)
Type of autologous, n (%)	
Pedicled TRAM flap	73 (76.8%)
DIEP flap	19 (20.0%)
Free TRAM flap	3 (3.2%)
Type of heterologous, n (%)	
Retroperitoneal tissue expander	81 (61.4%)

Retroperitoneal direct prothesis	30 (22.7%)
Prepectoral tissue expander	14 (10.6%)
Direct prepectoral prosthesis without dermal matrix	4 (3.0%)
Direct prepectoral prosthesis with dermal matrix	2 (1.5%)
Dual plane direct prothesis	1 (0.8%)

Abbreviations: **HBP**, high blood pressure; **BMI**, body mass index; **DM**, diabetes mellitus; **MRI**, magnetic resonance imaging; **SLNB**, sentinel lymph node biopsy; **TRAM**, transverse rectus abdominis muscle; **DIEP**, deep inferior epigastric perforators; ***** rheumatic disease, thyroid disease, psoriasis, inflammatory bowel disease, hematologic disease.

Table 2. Predictive factors for SLNB positivity

	SLNB negative N=223	**SLNB positive** N=96	**P value**
Age (median, years)	47.00	46.00	0.317*
Tumor Size by Mammography (median, mm)	22.00	24.00	0.492*
Tumor Size by Ultrasound (median, mm)	17.00	20.00	0.006*
Tumor Size by Ultrasound (mm) T1 T2-3	 113 (60.4%) 74 (39.6%) **[1]	 42 (46.7%) 48 (53.3%) **[2]	0.031***
Tumor Size by MRI (median, mm)	29.00	33.00	0.421*
cT (TNM) cT0 cT1 cT2 cT3	 3 (1.3%) 107 (48.0%) 78 (35.0%) 35 (15.7%)	 0 (0%) 42 (43.8%) 42 (43.8%) 12 (12.5%)	0.336***
BMI (median, kg/m^2)	23.00	24.00	0.055*
BMI (kg/m^2) =<30 >30	 197 (88.3%) 26 (11.7%)	 67 (83.7%) 13 (16.3%) **[3]	0.293***

Abbreviations: **SLNB**, sentinel lymph node biopsy; **MRI**, magnetic resonance imaging; **BMI**, body mass index; *Mann Whitnney test; **[1]Missing data for 36 patients; **[2]Missing data for 6 patients; **[3]Missing data for 16 patients; ***Pearson's chi-square test.

Table 3. Association of chronic complications with PMRT in the IBR patients

	PMRT N=246		
	No N=234	**Yes** N=12	**P value**
Total chronic complications			0.363
No	89 (38.0%)	3 (25.0%)	
Yes	145 (62.0%)	9 (75.0%)	
Pain in the operated area without consultation required			0.628
No	222 (94.9%)	11 (91.7%)	
Yes	12 (5.1%)	1 (8.3%)	
Pain in the operated area with consultation required			0.648
No	230 (98.3%)	12 (100.0%)	
Yes	4 (1.7%)	0 (0.0%)	
Capsular contracture grade 1-2			0.309
No	227 (97.0%)	11 (91.7%)	
Yes	7 (3.0%)	1 (8.3%)	
Capsular contracture grade 3-4			0.979
No	215 (91.9%)	11 (91.7%)	
Yes	19 (8.1%)	1 (8.3%)	
Chronic dermatitis			
No	234 (100.0%)	12 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)	
Long term cutaneous necrosis			
No	234 (100.0%)	12 (100.0%)	
Yes	0 (0.0%)	0(0.0%)	
Long term prosthesis exposure			
No	234 (100.0%)	12 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)	
Breast volume asymmetry			0.156
No	127 (54.3%)	4 (33.3%)	
Yes	107 (45.7%)	8 (66.7%)	
Nipple position assimmetry			0.740

No Yes	220 (94.0%) 14 (6.0%)	11 (91.7%) 1 (8.3%)	
Animation deformity No Yes	 225 (96.2%) 9 (3.8%)	 11 (91.7%) 1 (8.3%)	0.443
Rippling No Yes	 213 (91.0%) 21 (9.0%)	 12 (100.0%) 0 (0.0%)	0.278

Abbreviation: **PMRT**, post mastectomy radiotherapy.

Table 4. Association between the type of reconstruction and chronic complications after PMRT

	Type of Reconstruction in IBR patients that performed PMRT N=12		
	Autologous* N=5	**Heterologous**** N=7	**P value**
Total chronic complications			
No	1 (20.0%)	2 (28.6%)	0.735
Yes	4 (80.0%)	5 (71.4%)	
Pain in the operated area without consultation required			
No	4 (80.0%)	7 (100%)	0.217
Yes	1 (20.0%)	0 (0.0%)	
Pain in the operated area with consultation required			
No	5 (100%)	7 (100%)	
Yes	0 (0.0%)	0 (0.0%)	
Capsular contracture grade 1-2			
No	5 (100%)	6 (85.7%)	0.377
Yes	0 (0.0%)	1 (14.3%)	
Capsular contracture grade 3-4			
No	5 (100%)	6 (85.7%)	0.377
Yes	0 (0.0%)	1 (14.3%)	
Chronic dermatitis			
No	5 (100%)	7 (100%)	
Yes	0 (0.0%)	0 (0.0%)	
Long term cutaneous necrosis			
No	5 (100%)	7 (100%)	
Yes	0 (0.0%)	0 (0.0%)	
Long term prosthesis exposure			

No Yes	5 (100%) 0 (0.0%)	7 (100%) 0 (0.0%)	
Breast volume asymmetry No Yes	 1 (20.0%) 4 (80.0%)	 3 (42.9) 4 (57.1%)	 0.408
Nipple position assimmetry No Yes	 5 (100%) 0 (0.0%)	 6 (85.7%) 1 (14.3%)	 0.377
Animation deformity No Yes	 5 (100%) 0 (0.0%)	 6 (85.7%) 1 (14.3%)	 0.377
Rippling No Yes	 5 (100%) 0 (0.0%)	 7 (100%) 0 (0.0%)	

Abbreviations: **PMRT**, post mastectomy radiotherapy**; IBR**, immediate breast reconstruction; ***** Transverse rectus abdominus myocutaneous (TRAM) pedicle flap (N=5)**; **** Retroperitoneal tissue expander (N=5), retroperitoneal direct prothesis (N=1), direct prepectoral prosthesis without dermal matrix (N=1).

Table 5. Association between patient comorbidities and IBR complications

	IBR patient complications (with and without PMRT)			IBR patient complications after PMRT		
	Chronic Complications N=246			Chronic Complications N=12		
	No	Yes	*p*	No	Yes	*p*
Had comorbidities			0.021			0.735
No	21 (22.8%)	57 (37.0%)		1 (33.3%)	4 (44.4%)	
Yes	71 (77.2%)	97 (63.0%)		2 (66.7%)	5 (55.6%)	
BMI>30 kg/m^2			0.128			0.371
No	77 (83.7%)	139 (90.3%)		2 (66.7%)	8 (88.9%)	
Yes	15 (16.3%)	15 (9.7%)		1 (33.3%)	1 (11.1%)	
Smoking Habits			0.081			0.371
No	73 (79.3%)	135 (87.7%)		2 (66.7%)	8 (88.9%)	
Yes	19 (20.7%)	19 (12.3%)		1 (33.3%)	1 (11.1%)	
Previous radiotherapy			0.195			
No	91 (98.9%)	154 (100%)		3 (100%)	9 (100%)	
Yes	1 (1.1%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Diabetes Mellitus			0.797			
No	89 (96.7%)	148 (96.1%)		3 (100%)	9 (100%)	

Yes	3 (3.3%)	6 (3.9%)		0 (0.0%)	0 (0.0%)	
Cardiovascular disease			0.521			
No	84 (91.3%)	144 (93.5%)		3 (100%)	9 (100%)	
Yes	8 (8.7%)	10 (6.5%)		0 (0.0%)	0 (0.0%)	
Psychiatric disease			0.858			0.546
No	72 (78.3%)	122 (79.2%)		3 (100%)	8 (88.9%)	
Yes	20 (21.7%)	32 (20.8%)		0 (0.0%)	1 (11.1%)	
Pulmonary Disease			0.754			
No	87 (94.6%)	147 (95.5%)		3 (100%)	9 (100%)	
Yes	5 (5.4%)	7 (4.5%)		0 (0.0%)	0 (0.0%)	
Osteoarticular disease			0.125			0.546
No	88 (95.7%)	139 (90.3%)		3 (100%)	8 (88.9%)	
Yes	4 (4.3%)	15 (9.7%)		0 (0.0%)	1 (11.1%)	
Dyslipidemia			0.179			
No	80 (87.0%)	142 (92.2%)		3 (100%)	9 (100%)	
Yes	12 (32.5%)	12 (7.8%)		0 (0.0%)	0 (0.0%)	

High Blood Pressure			0.072			0.371
No	72 (78.3%)	134 (87.0%)		2 (66.7%)	8 (88.9%)	
Yes	20 (21.7%)	20 (13.0%)		1 (33.3%)	1 (11.1%)	

Abbreviations: **PMRT**, post mastectomy radiotherapy; **IBR**, immediate breast reconstruction; **BMI**, body mass index.

Attachment III- Strobe Statement

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract "The role of pre-mastectomy sentinel lymph node biopsy in the management of immediate breast reconstruction in breast cancer patients: a retrospective cohort study"	Página 7 Parágrafo 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found "We conducted a retrospective analysis of patients who underwent primary SLNB followed by mastectomy at the Breast Centre of *Unidade Local de Saúde São João* from January 1st, 2011, to December 31st, 2020." "In the analysis of 339 patients, 223 (69.9%) showed a negative SLNB result, and all of them proceeded with IBR. Within the pN+sn group, 23.9% (23/96) ultimately underwent IBR. Despite being pN0sn, 3.6% (8/223) were proposed to receive PMRT; on the contrary, 42.7% (41/96) of the pN+sn patients were spared from it. In total, 15.4% of the cases were approached differently than planned." **"**A noteworthy 76% of the pN+sn patients had their IBR plan changed. Despite the clinical relevance of primary SLNB appearing very low, since in our sample of patients this information was disregarded in 43% of cases, it provides essential information for deciding on the timing of breast reconstruction."	Página 8 Parágrafo 3-6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported "In the contemporary landscape of medicine, the impact of oncologic outcomes and psychosocial well-being on breast cancer (BC) patients' quality of life (QoL) is paramount. Achieving favorable aesthetic results plays a crucial role in mitigating these challenges. Studies have highlighted that patients opting for immediate breast reconstruction (IBR) after mastectomy often experience high levels of satisfaction and encounter lower morbidity levels [1]. The existing body of literature indicates that IBR offers superior outcomes in terms of psychosocial well-being, body image, and sexual well-being when compared to delayed breast reconstruction (DBR) [1,2]. However, it is	Página 9-10 Parágrafo 2-6

		essential to acknowledge potential risks, such as surgical site infections and implant loss, associated with IBR [3]. Post-operative complications following breast reconstruction are prevalent and can significantly impact patient satisfaction. Therefore, a shared decision-making approach between patients and the surgical team is crucial, where individuals undergoing mastectomy are thoroughly advised and engage in discussions about their reconstruction options and expectations [4]. The assessment of individual risk factors is a pivotal step in evaluating and counseling BC patients before mastectomy and IBR. Factors such as smoking habits, high body mass index (BMI), diabetes, prior radiotherapy (RT), and the need for PMRT should be carefully considered in the context of post-operative complications related to IBR [4,5]. PMRT is an integral component of the treatment regimen for many BC patients. While the adverse effects of radiotherapy on QoL and satisfaction levels are well-documented in some individuals [6,7], acceptable aesthetic outcomes have been reported following PMRT [8]. Autologous flap IBR has been associated with higher satisfaction levels and enhanced psychosocial well-being compared to implant reconstruction [9]. However, PMRT following autologous flap reconstruction introduces the risk of volume loss, fat necrosis, and distortion of the reconstructed shape [4,10]. Prosthetic implant remains the most common choice for IBR, but PMRT in these cases can lead to complications such as capsule contracture, implant loss, compromised cosmetic outcomes, infections, and skin necrosis [4,11]. Nipple/skin-sparing mastectomy (NSSM) with IBR is a sophisticated and intricate procedure that demands time, expertise, and logistical considerations. Therefore, the decision-making process for IBR should be guided by a comprehensive health decision-making approach, aligning with the patient's expectations and considering the potential risks associated with PMRT. Indications for PMRT in the treatment of BC patients are expanding. It is recommended for high-risk cases, characterized by tumor size exceeding 50 mm (T3) and the presence of four or more affected lymph nodes [4,12]. While some indications for PMRT remain controversial [12], certain guidelines strongly advocate for radiotherapy to the chest wall in cases with 1-3 positive axillary nodes [13,14]. This approach has demonstrated efficacy in reducing the risk of locoregional recurrence (LRR) and breast cancer-related mortality. In our Breast Centre we select cT0-2 pN0 BC patients that need or request total mastectomy to receive IBR. Pre-mastectomy (primary) SLNB is an important step in the N staging, providing information about the presence of metastasis in the axillary nodes”	
Objectives	3	State specific objectives, including any prespecified hypotheses	Página 10 Parágrafo 7

		"The purpose of this study was to evaluate the results of our clinical conduct, which is performing a previous and independent SLNB to select patients for IBR and to evaluate the indication for PMRT, that may result in DBR. We aimed to determine the rate of positive SLN and to identify potential risk factors, the proportion of postponed breast reconstructions and the short and long-term morbidity of PMRT after IBR."	
Methods			
Study design	4	Present key elements of study design early in the paper "This is a retrospective cohort study. We collected and reviewed our prospectively gathered database of consecutive patients that underwent primary SLNB between January 1st 2011 and December 31st 2020, treated at the Breast Centre from ULSSJ. Data collection was limited to the year 2020, so a minimum of two years of follow-up could be achieved"	Página 11 Parágrafo 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection "This is a retrospective cohort study. We collected and reviewed our prospectively gathered database of consecutive patients that underwent primary SLNB between January 1st 2011 and December 31st 2020, treated at the Breast Centre from ULSSJ. Data collection was limited to the year 2020, so a minimum of two years of follow-up could be achieved."	Página 11 Parágrafo 3
		"Patients with invasive or *in situ* BC submitted or not to chemotherapy prior to the surgery, patients at high risk for BC (known germinative genetic mutation or other) and patients who request prophylactic mastectomy (because of cancer phobia), that underwent primary SLNB were included. Until 2016, high risk and prophylactic patients were proposed to primary SLNB, but since then this clinical practice was discarded, due to the low risk of SLN positivity and the putative morbidity"	Página 11 Parágrafo 6
		"All patients were assessed clinically, including breast and axilla inspection and palpation. All patients underwent mammography and breast and axilla ultrasound. Breast magnetic resonance imaging was performed in selected patients according to the Breast Centre clinical practice. cT was defined according to the imaging information. Suspicious axillary nodes were submitted to ultrasound guided needle biopsy. The diagnosis of malignancy was made by triple assessment in a multidisciplinary meeting."	Página 11 Parágrafo 8
		"All patients were followed up by the plastic surgeon in the immediate post-operative period as well as in the long term. All patients were evaluated by the surgical oncologist at least twice in the first post-operative year and once yearly thereafter; clinical appointments with the medical and radiation oncologists were also provided, when needed. All patients performed mammography, breast and axillary ultrasound once a year."	Página 13 Parágrafo 21

Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up "This is a retrospective cohort study. We collected and reviewed our prospectively gathered database of consecutive patients that underwent primary SLNB between January 1st 2011 and December 31st 2020, treated at the Breast Centre from ULSSJ. Data collection was limited to the year 2020, so a minimum of two years of follow-up could be achieved."	Página 11 Parágrafo 3
		"Patients with invasive or in situ BC submitted or not to chemotherapy prior to the surgery, patients at high risk for BC (known germinative genetic mutation or other) and patients who request prophylactic mastectomy (because of cancer phobia), that underwent primary SLNB were included. Until 2016, high risk and prophylactic patients were proposed to primary SLNB, but since then this clinical practice was discarded, due to the low risk of SLN positivity and the putative morbidity."	Página 11 Parágrafo 6
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		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Not applicable as our study does not use matching to control for confounding.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable "Patients with invasive or in situ BC submitted or not to chemotherapy prior to the surgery, patients at high risk for BC (known germinative genetic mutation or other) and patients who request prophylactic mastectomy (because of cancer phobia), that underwent primary SLNB were included. Until 2016, high risk and prophylactic patients were proposed to primary SLNB, but since then this clinical practice was discarded, due to the low risk of SLN positivity and the putative morbidity."	Página 11 Parágrafo 6
		"All patients were assessed clinically, including breast and axilla inspection and palpation. All patients underwent mammography and breast and axilla	Página 11 Parágrafo 8

ultrasound. Breast magnetic resonance imaging was performed in selected patients according to the Breast Centre clinical practice. cT was defined according to the imaging information. Suspicious axillary nodes were submitted to ultrasound guided needle biopsy. The diagnosis of malignancy was made by triple assessment in a multidisciplinary meeting."	
"The SLNB was performed using a combined technique that merges the subareolar injection of 1cc of Patent Blue V dye and peritumoral injection of 1cc of Indocyanine Green. All macroscopically suspect, fluorescent and/or blue nodes were considered SLN. Axillary dissection included the removal of Berg levels 1 and 2 and spares the long thoracic nerve, the first two sensitive intercostobrachial nerves, the thoracodorsal bundle, and the axillary vein. In invasive BC patients, the SLN were assessed by OSNA assay, provided the CK19 was positive; in the remaining patients, SLN were assessed by conventional H-E. All non-sentinel lymph nodes (NSLN) were analysed by conventional H-E."	Página 12 Parágrafo 10,11
"After the primary SLNB, patients participated in a meeting with the breast surgical oncologist and the plastic surgeon. If the SLN was metastasized, the patient was proposed to receive a conventional, simple, curative mastectomy without IBR. If the SLN was free of metastasis, and the tumour was less than 50 mm, the patient was proposed to receive NSSM with IBR. The reconstruction technique was chosen from a wide range of options, varying from tissue expander to DIEP-flap, according to the patient's body structure and to the patient's will and expectations. NSSM was performed by the surgical oncologist and the reconstruction was performed by the plastic surgeon."	Página 12 Parágrafo 13
"Information about patient`s comorbidities and IBR related morbidity after PMRT was extracted from the data documented in the patient's digital files."	Página 12 Parágrafo 15
"Post-mastectomy radiotherapy means external radiation treatment to the thoracic wall or to the reconstructed breast and not to the lymphatic drainage areas. According to the protocol of our Breast Centre, to every invasive BC patient staged with a pT3 lesion, or with a pN1-3, should be offered adjuvant PMRT. External radiation treatment to the lymphatic drainage areas was used in case of pN1sn without axillary dissection or in case of a pN2 after axillary dissection."	Página 12, 13 Parágrafo 17-19
	Página 13

		"All patients were followed up by the plastic surgeon in the immediate post-operative period as well as in the long term. All patients were evaluated by the surgical oncologist at least twice in the first post-operative year and once yearly thereafter; clinical appointments with the medical and radiation oncologists were also provided, when needed. All patients performed mammography, breast and axillary ultrasound once a year."	Parágrafo 21
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group "All patients were assessed clinically, including breast and axilla inspection and palpation. All patients underwent mammography and breast and axilla ultrasound. Breast magnetic resonance imaging was performed in selected patients according to the Breast Centre clinical practice. cT was defined according to the imaging information. Suspicious axillary nodes were submitted to ultrasound guided needle biopsy. The diagnosis of malignancy was made by triple assessment in a multidisciplinary meeting."	Página 11 Parágrafo 8
		"The SLNB was performed using a combined technique that merges the subareolar injection of 1cc of Patent Blue V dye and peritumoral injection of 1cc of Indocyanine Green. All macroscopically suspect, fluorescent and/or blue nodes were considered SLN. Axillary dissection included the removal of Berg levels 1 and 2 and spares the long thoracic nerve, the first two sensitive intercostobrachial nerves, the thoracodorsal bundle, and the axillary vein. In invasive BC patients, the SLN were assessed by OSNA assay, provided the CK19 was positive; in the remaining patients, SLN were assessed by conventional H-E. All non-sentinel lymph nodes (NSLN) were analysed by conventional H-E."	Página 12 Parágrafo 10,11
		"After the primary SLNB, patients participated in a meeting with the breast surgical oncologist and the plastic surgeon. If the SLN was metastasized, the patient was proposed to receive a conventional, simple, curative mastectomy without IBR. If the SLN was free of metastasis, and the tumour was less than 50 mm, the patient was proposed to receive NSSM with IBR. The reconstruction technique was chosen from a wide range of options, varying from tissue expander to DIEP-flap, according to the patient's body structure and to the patient's will and expectations. NSSM was performed by the surgical oncologist and the reconstruction was performed by the plastic surgeon."	Página 12 Parágrafo 13
			Página 13

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		"All patients were followed up by the plastic surgeon in the immediate post-operative period as well as in the long term. All patients were evaluated by the surgical oncologist at least twice in the first post-operative year and once yearly thereafter; clinical appointments with the medical and radiation oncologists were also provided, when needed. All patients performed mammography, breast and axillary ultrasound once a year."	Página 13 Parágrafo 21
Bias	9	Describe any efforts to address potential sources of bias "Data collection was limited to the year 2020, so a minimum of two years of follow-up could be achieved." "Patients with invasive or in situ BC submitted or not to chemotherapy prior to the surgery, patients at high risk for BC (known germinative genetic mutation or other) and patients who request prophylactic mastectomy (because of cancer phobia), that underwent primary SLNB were included. Until 2016, high risk and prophylactic patients were proposed to primary SLNB, but since then this clinical practice was discarded, due to the low risk of SLN positivity and the putative morbidity."	Página 11 Parágrafo 3 Página 11 Parágrafo 6
Study size	10	Explain how the study size was arrived at Not applicable - given the analysis that was performed, all patients fulfilling the inclusion criteria were evaluated	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why "Database and statistical analysis were done on IBM SPSS Statistics 27. Descriptive statistics were used to summarize the main characteristics of the sample. Continuous variables were summarized by measures of central tendency (mean or median, as applicable) and dispersion (standard deviation) and categorical variables were summarized by absolute (N) and relative (%) frequency. The Chi-square or Fisher's exact test, as appropriate, was used for comparison of proportions, while Student's t test	Página 13 Parágrafos 23-24

		or Mann–Whitney test was used for comparison of means or medians, respectively. A p value < 0.05 was considered statistically significant." "Every case was designated by a serial number. Every study serial number was associated to a clinical file patient number. Only the main investigator had access to the association database. This study was approved by the Ethics Committee of ULSSJ (CE 94-23)."	Página 13 Parágrafo 26
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding "Database and statistical analysis were done on IBM SPSS Statistics 27. Descriptive statistics were used to summarize the main characteristics of the sample. Continuous variables were summarized by measures of central tendency (mean or median, as applicable) and dispersion (standard deviation) and categorical variables were summarized by absolute (N) and relative (%) frequency. The Chi-square or Fisher's exact test, as appropriate, was used for comparison of proportions, while Student's t test or Mann–Whitney test was used for comparison of means or medians, respectively. A p value < 0.05 was considered statistically significant."	Página 13 Parágrafos 23-24
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		(*b*) Describe any methods used to examine subgroups and interactions "Database and statistical analysis were done on IBM SPSS Statistics 27. Descriptive statistics were used to summarize the main characteristics of the sample. Continuous variables were summarized by measures of central tendency (mean or median, as applicable) and dispersion (standard deviation) and categorical variables were summarized by absolute (N) and relative (%) frequency. The Chi-square or Fisher's exact test, as appropriate, was used for comparison of proportions, while Student's t test or Mann–Whitney test was used for comparison of means or medians, respectively. A p value < 0.05 was considered statistically significant."	Página 13 Parágrafos 23-24
		"Every case was designated by a serial number. Every study serial number was associated to a clinical file patient number. Only the main investigator had access to the association database. This study was approved by the Ethics Committee of ULSSJ (CE 94-23)."	Página 13 Parágrafo 26
		(*c*) Explain how missing data were addressed Not applicable because all the study population was compared (*d*) If applicable, explain how loss to follow-up was addressed Not applicable because no loss to follow-up was reported.	

		(*e*) Describe any sensitivity analyses Not applicable because there was no need for any sensitivity analyses.	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed "The consecutively registered database yielded an initial sample of 339 patients with primary SLNB. Out of these, 20 were excluded, because they declined the IBR plan (due to fear of the surgery, religious convictions, etc.) or they showed significant co-morbidities (namely, high BMI, psychiatric impairment, etc.). All the excluded patients had a negative SLNB. The analysis was performed on the remaining 319 patients. (figure 1). Patient demographics and pathological information are presented in Table 1. All patients were females. The median follow-up time was 67 months (range 7-145 months)." (b) Give reasons for non-participation at each stage Not applicable given the retrospective nature of the study (c) Consider use of a flow diagram Figure 1.	Página 14 Parágrafo 2,3 Página 28 Figure1. Flowchart1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders "Patient demographics and pathological information are presented in Table 1. All patients were females." (b) Indicate number of participants with missing data for each variable of interest Not applicable because there was no missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount) "The median follow-up time was 67 months (range 7-145 months)."	Página 14 Parágrafo 3 Página 14 Parágrafo 3
Outcome data	15*	Report numbers of outcome events or summary measures over time Figure 1. Table 1,2,3,4 and 5.	Página 28-40 Figure 1. Flowchart1 Table1,2,3,4 and 5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included "In the analysis of predictive factors for the SLN positivity (Table 2), the tumor size assessed by ultrasound had a significant effect both as a continuous variable (p=0.006) or as a discrete one: a higher proportion of positive SLN was observed among cT2-3 patients (p=0.031). In what concerns the IBR plan, all the pN0sn patients underwent IBR; nevertheless, from the pN+sn group, 23.9% (23/96) of them ended up undergoing IBR. Considering the entire sample, in 7.2% of patients the treatment protocol was not complied with, seeking to act in favor of the patient. All 223 negative SLNB patients (pN0sn) underwent IBR (figure 1). Of these, eight individuals were proposed to PMRT for different reasons. One patient (cT2) exhibited an extensive ductal carcinoma in situ measuring 86 mm with seven foci of micro-invasion. Another patient (cT2) presented a 47 mm mixed invasive carcinoma, with lymphovascular invasion. Additionally, a patient (cT2) with mucopapillary invasive carcinoma measuring 50 mm and displaying lymphovascular invasion was proposed to PMRT. The remaining five patients voluntarily opted for IBR despite having a cT3 and pT3 invasive tumor, demonstrating a clear understanding of the associated risks with PMRT. Of the patients with micrometastasis in the SLN (Figure 1; n=47), 32 (68.1%) were not submitted to PMRT. Of these, 25 (NR n=6; DBR n=5; IBR n= 14) were not submitted to PMRT due to the low tumor burden indicated by the OSNA results and 7 patients (NR n=3; DBR n=1; IBR n=3) received external radiation treatment only to the axilla/periclavicular region. The remaining 15 (NR n=6; DBR n=6; IBR n=3) patients received PMRT as per protocol. Of these 3 IBR+PMRT patients, two had a cT2 that was upstaged to pT3, and one had two SLN affected with micrometastasis. Of the patients with macrometastasis in the SLN (Figure 1, n=49), 9 (18.4%, NR n=4; DBR n=3; IBR n=2) were not submitted to PMRT; of these, 5 (NR n=3; DBR n=2) received exclusive external radiation treatment only to the axilla/periclavicular region; 2 (DBR n=1; IBR=1) did not undergo PMRT, because of a complete axillary dissection without invasion of NSLN, and 1 (IBR n=1) did not receive PMRT due to the previous diagnosis of a collagen disease with lung involvement. For the remaining patient who did not undergo PMRT (NR n=1), a clear explanation for not being treated with radiotherapy could not be obtained. The remaining 40 patients (NR n=19; DBR n=20; IBR n=1) received PMRT as per protocol. Regarding the PMRT plan, 3.6% (8/223) were proposed to perform the treatment and 42.7% (41/96) were spared from it despite the protocol. In total, 15.4% of the cases were approached differently than planned. Considering exclusively the patients that underwent IBR (n=246), we examined both acute and chronic complications and the correlation between PMRT and the chronic complications (Table 3). PMRT did not exhibit a substantial effect on overall chronic complications or specific ones.	Página 14-16 Páragrafo 4-12

		As showed in table 4, there was no discernible association between the various types of reconstruction performed (autologous or heterologous/ mixed) and the risk of chronic complications following PMRT. As indicated in table 5, within the entire cohort of patients with IBR who experienced complications, whether they underwent PMRT or not, the presence of comorbidities was linked to chronic complications (p-values of 0.021). All the other specific comorbidities did not show a significant effect on the IBR chronic complications in both groups of patients." (*b*) Report category boundaries when continuous variables were categorized "In the analysis of predictive factors for the SLN positivity (Table 2), the tumor size assessed by ultrasound had a significant effect both as a continuous variable (p=0.006) or as a discrete one: a higher proportion of positive SLN was observed among cT2-3 patients (p=0.031)." Table 2 (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not applicable as no risk measures were computed	Página 14 Parágrafo 4 Página 32 Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Not applicable as no risk measures were computed	
Discussion			
Key results	18	Summarise key results with reference to study objectives "We identified a 30.1% positivity rate for SLN, with 14.7% (47/319) attributed to micrometastasis and 15.4% (49/319) to macrometastasis. Among patients with pN+sn, a noteworthy 76% (73/96) changed their initial plan of IBR due to the elevated risk of PMRT-associated healing, aesthetic, or functional morbidity. Few studies have elucidated the frequency of postponed breast reconstruction. In contrast to van Haaren et al study [4], which reported a 33% postponement rate for breast reconstruction in patients with macrometastasis, our investigation revealed significantly higher rates of deferral (94%, 46/49). This difference may be attributed to the fact that, in our study, SLNB was conducted prior to mastectomy, whereas van Haaren's study obtained the sentinel node intraoperatively using the OSNA technique [4]. "Another contributing factor to the variation in the rate of postponement lies in the inherent ambiguity surrounding indications for PMRT, as evident in the literature." "We were able to assess various predictive factors for SLN positivity and, as anticipated based on existing literature, tumor size determined by ultrasound proved to be a predictive factor for SLN positivity".	Página 16 Parágrafo 2,3 Página 16 Parágrafo 4 Página 18 Paragrafo 8

		"The complications of PMRT on IBR are well-documented. Across various studies, breast volume loss and fat necrosis emerge as the most frequent complications associated with PMRT after IBR, with a particular focus on the Deep Inferior Epigastric Perforator (DIEP) flap, recognized as the one of the most utilized and analyzed technique [10, 28-29]. In our study, all patients with an autologous flap who underwent PMRT exclusively utilized the transverse rectus abdominis myocutaneous (TRAM) pedicle flap, and no association was observed in terms of chronic complications (the same holds true for heterologous/mixed reconstructions). "We also explored the potential relationship between patient comorbidities and chronic complications in those undergoing PMRT. Having comorbidities was linked to chronic complications in the overall group of patients who did IBR. "	Página 18 Parágrafo 9 ´ Página 19 Parágrafo 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias "A constraint of our approach is the need for two surgical interventions. Although the isolated, primary, SLNB could be performed under local anesthesia and under an outpatient basis, it remains an operative procedure with inherent risks of complications, which requires the availability of operating theater time, and which has an impact on the patient's personal, family, and professional life. Furthermore, it prolongs the waiting time for curative breast tumor surgery. The study's limitations include its retrospective nature, which introduces the possibility of missing data. The sample size, although spanning a long temporal series from 2011 to 2022, might still be a limiting factor in capturing certain significant values, such as those related to fat necrosis and volume asymmetry resulting from PMRT. Additionally, being an unicentric study may compromise the generalization of results beyond the specific context of the study site. Another relevant limitation is the fact that a formal evaluation of the aesthetic result was not carried out"	Página 19-20 Parágrafos 11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence "The primary SLNB avoids the anxiety associated with "not knowing the result" (as stated above), in the case of SLN biopsy with "frozen section" and peri-operative decision and allows a considered and personalized decision to be made, when choosing between IBR or DBR. Although there is scientific information that relativizes the risk of complications or poor aesthetic results associated with IBR plus PMRT, for some women this risk may be intolerable. With the primary SLNB the patient will have all the relevant information to choose the timing of breast reconstruction." "The clinical relevance of primary SLNB seems very low, since in our sample of patients its information was disregarded or exceeded in 43% of cases; furthermore, we also did not document a negative impact of PMRT after IBR.	Página 19-20 Parágrafo 11 Página 20 Parágrafo 2,3

		Despite requiring two surgical procedures, in selected cases, the primary SLNB can provide the patient and the treatment team with remarkable information for deciding on the timing of breast reconstruction"	
Generalisability	21	Discuss the generalisability (external validity) of the study results "Additionally, being an unicentric study may compromise the generalization of results beyond the specific context of the study site"	Página 20 Parágrafo 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Funding not applicable Author's contributions RP: Data curation, formal analysis and interpretation, statistical analysis, manuscript original draft and editing. BP: Data collection, formal analysis and interpretation, statistical analysis, manuscript review and editing. JLF: Study design, data collection, statistical analysis and interpretation, manuscript review and editing, supervision, conceptualization	Página 7 Parágrafo 18-20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is

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Attachment IV- Author Guidelines

AUTHOR GUIDELINES

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financial support for the study. (Other acknowledgments must be supplied at the end of the manuscript, as the last element of the text, before the references.)

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the author. List all authors for up to four authors. For five or more authors, list the first three authors followed by "et al." Note the following examples:

Journal Articles

1. Nozuc M, Lee I, Manning JM, et al.: Oxygenation in tumors by modified hemoglobins. *J Surg Oncol* 1996;62:109-114.

Books

2. Bollack CG, Jacqmin D (eds). *Basic Research and Treatment of Renal Cell Carcinoma Metastasis*. New York: Wiley-Liss, 1990.

Chapters in Books

3. Katzner M, Schvingt E: Operative treatment of bone metastases secondary to renal carcinoma. In Bollack CG, Jacqmin D (eds). *Basic Research and Treatment of Renal Cell Carcinoma Metastasis*. New York: Wiley-Liss, 1990:151-168.

Abstracts

4. Abstract in a meeting program: Mendez MF, Manoc-Espalliar R, Lanska DJ, Burstine TH: Epilepsy and suicide attempts [abstract]. In American Academy of Neurology 41st annual meeting program: 1989 Apr 13–19: Chicago. Cleveland (OH): Edgefl Communications. 1989:295. Abstract PP369. 5. Abstract in a journal Issue: Fohrman SA, Joinor KA: Binding of the third component of complement C3 by Taxoplasma gondii [abstract]. Clin Res 1987;35:475A.

Figure Legends. This section contains descriptive legends typed in double spacing for each illustration. Legends must define all abbreviations and acronyms used in the figure. Any permissions should also be stated here.

Journal Style Notes:

-All material, including references, must be double spaced and have generous margins.
-Number all pages in sequence: title page, synopsis, abstract plus key words, text, references, figure legends, tables, and figures.
-Manuscripts must be thoroughly checked for accuracy of all mathematical calculations, typing of numerals, spelling and typographical errors, and conformance to journal style.
-State whether *P* values are derived from either one-tailed or two-tailed tests. Exact *P* values must be supplied.
-When it is necessary to mention the trade names of equipment, instruments, or supplies, the name of the supplier, city, state, or country, must be given, and the trade name must be noted with either trademark (®) or the register mark (®). Use generic names whenever possible.
-In the text, all results quoted as percentages must show both the numerators and the denominators.
-Measurements of length, height, weight, and volume are reported in metric units (meter, kilogram, liter, etc.) or their decimal equivalents. Temperatures are given in degrees Celsius. Blood pressure is given in millimeters of mercury (mm Hg). Hematologic and clinical chemistry measurements are reported in the metric system using the International System of Units (IS).

-Acronyms should be used only if they are broadly recognized and absolutely essential. They must be defined at the first mention (in the title, synopsis, abstract, text, etc.). If acronyms are used, provide a list of the acronym and description before the reference section.

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Figure Files. Each file must contain a single figure and be named by figure number (ie, Figure 1, Figure 2, etc.). Individually uploaded panels (A, B) will not be accepted. Figures can be in TIF, EPS, JPEG, PDF, or PNG format, but must meet the resolution requirements outlined below:

Resolution

• 1200 dpi for line art (simple bar graphs, charts, or nonphotographic artwork)
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Supplemental Files.

SUBMISSION TYPES

Commentary. Invited commentary of an accepted manuscript. Text must be less than 1 double-spaced page and contain no references.

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Letters to the Editor. Brief reports or letters regarding articles published in the Journal, concisely written in an objective, constructive fashion, will be considered for publication. The Editor reserves the right to shorten text, delete objectionable comments, and make any other changes that may be necessary to comply with the style of the journal. The Editor may forward Letters to the Editor to the corresponding author of the article under discussion to afford an opportunity for rebuttal. The paper under discussion must be listed first in the reference list. If necessary, one figure and one table prepared in accordance with journal guidelines may be included. Up to 10 references may be included, typed double spaced on a separate page. Authors should indicate their permission for publication of their letters in a postscript to the body of the letter. Brief reports with more than one author should carry a postscript stating that all authors are familiar with the contents of the report and agree to its publication. No abstract is required.

How I Do It. Brief communications of authors' innovations in clinical or research techniques that simplify procedures or improve results are invited. Authors should briefly state the problem, describe the solution, and give a short summary of the results, where appropriate. These manuscripts should be clearly marked as "How I Do It," typed double spaced throughout, and submitted in complete triplicate. Acronyms should be used only if absolutely essential and should be defined. When it is necessary to mention trade names of equipment, instruments, or supplies, the name of the supplier, city, state, and countries must be mentioned, and trade names must be noted with TM or ®. If techniques are described, appropriate high-quality illustrations should accompany the manuscript.

Research Article. Text must be within 20 double-spaced pages, excluding the title page and Abstract, but including references. Abstract must be within 200 words and formatted with the following headings: Background and Methods, Results, Conclusions, and Discussion.

Review Article. A review of a specific topic of current interest, most commonly found in *Seminars to Surgical Oncology*. Text must be within 20 double-spaced pages, including references. An unformatted abstract must be included with no more than 75 words.

Inappropriate Submissions and Publications

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of duplicate publications using similar data (ie, attesting that work submitted is original when, in fact, it was submitted to or accepted by another journal); 2) Falsification of data, copyright, or information regarding conflict of interest; 3) Submission of work from other sources that was not done by the author (plagiarism); 4) Authorship (allowing one's name to appear as an author or adding an author to a manuscript) without substantial input or without having agreed to submission of the manuscript.

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characters.

2. Provide up to five topic-specific key words or phrases in the key word field.
3. Be sure your key words and phrases appear in your abstract several times, but don't go overboard or the search engine may kick you out.
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2. National Library of Medicine: List of journals indexed in Index Medicus. Washington, DC: US Government Printing Office (published annually). Available at: http://www.nlm.nih.gov/pubs/libprog.html.
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Attachment V- Ethic Commission Deliberation

SÃO JOÃO

DELIBERAÇÃO DO CONSELHO DE ADMINISTRAÇÃO

Após apreciação e pareceres favoráveis da Comissão de Ética e do Centro de Epidemiologia Hospitalar, considerando que se encontram reunidos os requisitos e demais trâmites previstos no circuito para submissão de projetos de investigação no Centro Hospitalar Universitário de S. João e em conformidade com as disposições legais em vigor, o Conselho de Administração – ao abrigo das competências previstas no Artigo 71.º dos Estatutos dos hospitais, centros hospitalares, institutos portugueses de oncologia e unidades locais de saúde, aprovados pelo Decreto-Lei n.º 52/2022, de 4 de agosto – delibera:

1. Aprovar a realização do projeto de investigação:
   - "The role of pre-mastectomy sentinel node biopsy in the management of immediate reconstruction in breast cancer patients: a cohort study".
   - Serviço(s) onde decorrerá o projeto de investigação: Centro da Mama.
   - Investigador(a) principal: André Filipe Costa Pereira.
2. Remeta-se à Comissão de Ética para os procedimentos adequados e demais trâmites convenientes.

CONSELHO DE ADMINISTRAÇÃO DO CENTRO HOSPITALAR UNIVERSITÁRIO DE S. JOÃO, EPE • REUNIÃO DE 4 DE MAIO DE 2023

Presidente do Conselho de Administração

Prof.ª Doutora Maria João Baptista

Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
Prof.º Doutor Roberto Roncon	Enfermeiro Paulo Emílio Mota	Dr.ª Sofia Leal	Dra. Fernanda Oliveira

› Comissão de Ética
› Centro de Epidemiologia Hospitalar
› Direção Clínica

CE 94/2023

MEC-IHO11-1

Centro de Epidemiologia Hospitalar

Tomei conhecimento. Nada a opor. À DC.

28 de Abril de 2023

A Diretora do Centro de Epidemiologia Hospitalar

(Prof.ª Doutora Ana Azevedo)

DIRECÇÃO CLÍNICA
03 MAIO 2023

n.º 94 / 2023

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

Nome do Investigador Principal:

André Filipe Costa Pereira

Título da Investigação:

The role of pre-mastectomy sentinel node biopsy in the management of immediate reconstruction in breast cancer patients: a cohort study.

Pretendendo realizar no(s) Serviço(s) de:

Centro de Mama

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 01 *de* Março *de* 2023 .

André Pereira
assinatura

SÃO JOÃO | Encarregado de Proteção de Dados / Data Protection Officer
Entrada 11/04/2023

•Centro Hospitalar São João•
Centro de Epidemiologia Hospitalar
27,4,2023

CES-IM005-0

Parecer da Comissão de Ética do
Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: The role of pre-mastectomy sentinel node biopsy in the management of immediate reconstruction in breast cancer patients: a cohort study

Nome do Investigador Principal: André Filipe Costa Pereira

Onde decorre o Estudo: No Centro de Mama do CHUSJ. Apresentou declaração do Prof. Doutor José Luís Fougo, que será o profissional de ligação.

Objetivos do Estudo:
Avaliar os resultados da realização da biópsia do gânglio sentinela na seleção das pacientes para o procedimento de reconstrução imediata da mama.
Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação do Prof. Doutor José Luís Fougo e da Doutora Bárbara Peleteiro, que também são co-investigadores.

Conceção e Pertinência do estudo:
Será utilizada a base de dados de pacientes do Centro de Mama do Centro Hospitalar Universitário São João que realizaram biópsia do gânglio sentinela entre 01/01/2011 até 01/01/2020, para identificar os pacientes que tem indicação para reconstrução imediata da mama, após realização e análise do gânglio sentinela.
Estão definidos os critérios de inclusão e as variáveis a recolher.

Benefício/risco: Não aplicável

Confidencialidade dos dados:
A cada caso/ paciente é atribuído um número de série. Cada número de série corresponde ao número do processo de cada caso /paciente.
Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável
***Curriculum* do investigador**: Adequado à investigação.
Data previsível da conclusão do estudo: julho de 2024

Conclusão: Proponho um parecer favorável à realização do estudo.

Porto, 24 de março de 2023

O Relator da CE,