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Assessment of IORT application in early stage breast cancer surgery

A cross-sectional study

FINAL DEGREE PROJECT

BREAST PATHOLOGY UNIT

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1. ABREVIATIONS

ALND	Axillary lymph node dissection
APBI	Accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
BCS	Breast conserving surgery
BCT	Breast conserving therapy
CT	Computed tomography
DCIS	Ductal carcinoma in situ
EBRT	External beam radiotherapy
ER	Estrogen receptor
ESMO	European Society of Medical Oncology
HUJT	Hospital Univesitari Josep Trueta
IBTR	Ipsilateral breast tumour recurrence
IDC	Invasive ductal carcinoma
IORT	Intraoperative radiotherapy
LVI	Lymphovascular invasion
MRI	Magnetic Resonance Imaging
PgR	Progesterone receptor
RT	Radiotherapy
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
TNBC	Triple negative breast cancer
US	Ultrasounds
WBRT	Whole breast radiotherapy
WHO	World Health Organization

2. ABSTRACT

Background:	Breast conserving therapy has been proved to be equivalent to mastectomy-based treatment and nowadays is the standard of care approach for patients with early-stage breast cancer. Adjuvant radiotherapy has demonstrated to improve local control after breast conserving surgery is performed. Since most local recurrences appear at or near the localization of the primary tumour, accelerated partial-breast irradiation (APBI) techniques have been developed. This form of radiation allows to target smaller breast tissue. Intraoperative radiotherapy (IORT) is a form of APBI that enables to deliver a single dose of irradiation to the tumour bed during the surgical frame time, which shortens the treatment time and improves the quality of life of the patients. This procedure was supported by two randomized trials and today IORT is an established alternative to traditional whole breast radiotherapy (WBRT) for selected patients. Based on the evidence regarding IORT, in 2019 a clinical protocol for the application of this modality of radiotherapy was introduced in *Hospital Universitari Josep Trueta* (HUJT) in Girona. The patients who meet its eligibility criteria undergo breast conserving surgery plus IORT. However, some patients still require additional external beam radiotherapy (EBRT) due to adverse outcomes in the final pathological assessment.
Objective:	The aim of this study is to perform an assessment of the current Protocol for IORT application of HUJT. Our objective is to identify possible eligibility criteria that may be adjusted with the intend to reduce the number of patients who require additional EBRT after the initial IORT treatment.
Participants:	Women diagnosed with early-stage breast cancer who underwent breast conserving surgery plus IORT in HUJT.
Methods:	A cross-sectional design carried out in the Breast Pathology Unit of HUJT, a tertiary referral hospital in Girona. The study will be carried out from 2020 to 2022. Data on tumour features, pathological outcomes and patient characteristics will be collected and ascertained.
Keywords:	*early-stage breast cancer, breast cancer, breast conserving treatment, intraoperative radiation, radiation therapy*

3. INTRODUCTION

3.1. BREAST CANCER OVERVIEW

3.1.1. EPIDEMIOLOGY

Breast cancer is the most frequently diagnosed cancer in women. However, in males it is a rare condition and only represents 1% of cases. Overall, it is the most common malignancy in the age range of 15-49 years (13%) and the third one in the age range of 50-59 years (9%) considering both genders [1,2].

According to the WHO Global Cancer Observatory (GLOBOCAN) 2018 registry, nearly 2.09 million cases were diagnosed in 2018 in women **worldwide**, a 24.2% of the total of new cases of cancer in females (Figure 1) [3].

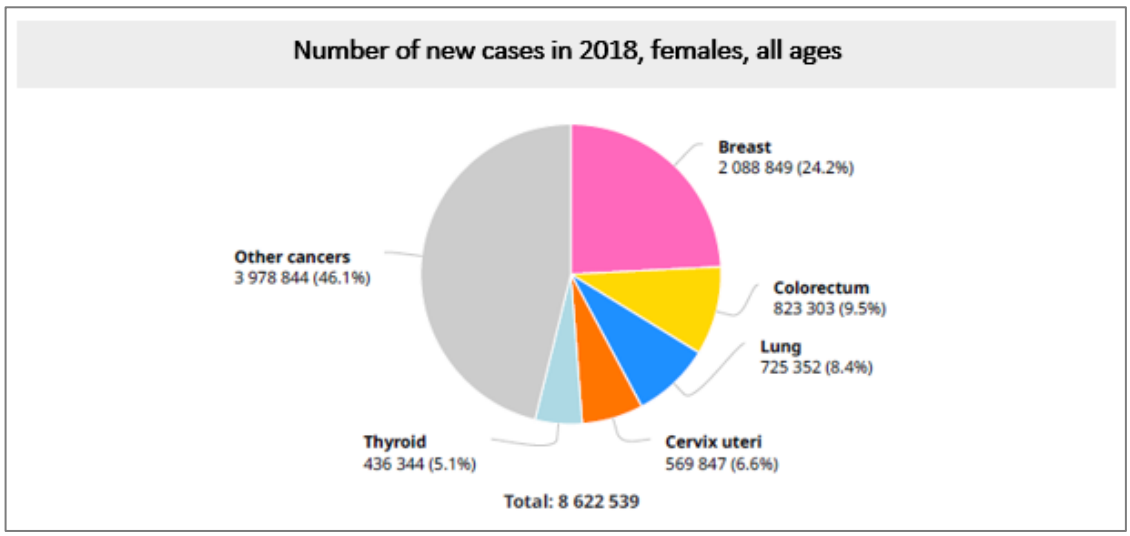

Figure 1. Distribution of the number of new cancer cases in females in 2018 worldwide [3].

The age-standardized world incidence rate (ASR) in females was 46.3 per 100.000, the highest one, followed by lung cancer ASR world incidence (Figure 2) [3]. Nevertheless, incidence rates are higher in higher-income regions than in lower-income regions [4].

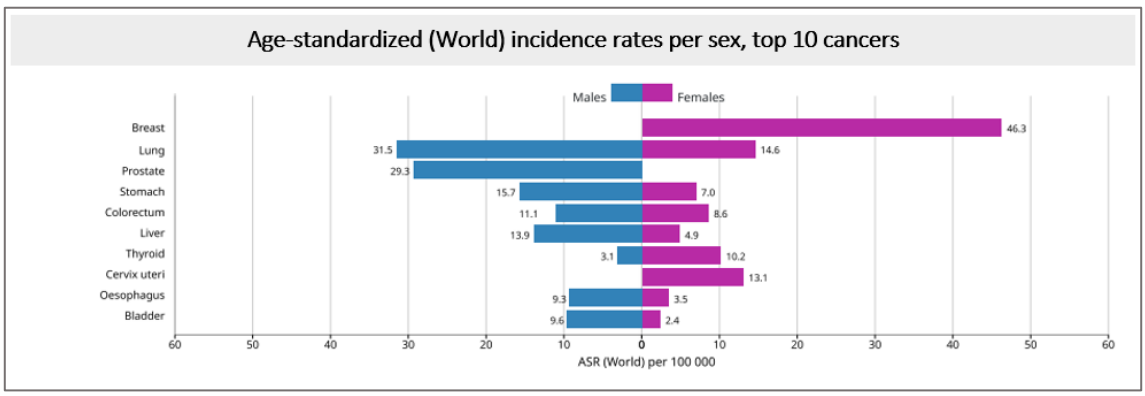

Figure 2. Age standardized worldwide incidence rates per women and men [3].

Breast cancer incidence has arisen because of the ageing population and the introduction of screening programmes [1]. Moreover, an increase on the incidence rate is expected, following the tendency of the last years and by 2040 the estimated number of incident cases in females is 3.06 million.

In 2018, a total of 626 679 deaths from breast cancer were registered, being the leading cause of cancer death among women. The risk of developing breast cancer between the age of 0-74 years for females is 5.03% while the risk of dying from it in this age range is 1.41% [2,3]. However, mortality rates also vary depending on the region and breast cancer survival is significantly lower in low- and middle-income countries than in high-income countries [4].

In **Spain**, 27 747 new cases of breast cancer were diagnosed in women in 2015 and the estimated number of new cases for 2020 is 32 953, followed by colon cancer (12 635 cases). In 2018, 6 534 deaths cases were reported, also being the primary cause of cancer death and ahead of lung cancer (4 959 cases) and colon cancer (4 575 cases). According to *Red Española de Registros de Cáncer* (REDECAN), the overall 5-year net survival rate in female patients diagnosed with breast cancer during the period of 2008-2013 was 85.5%, being the third malignancy with better survival outcomes after thyroid (93.1%) and skin melanoma cancer (88.9%). However, the stage at the moment of the diagnosis has to be taken into account [5,6].

In the **Province of Girona**, from 2010 to 2012, breast cancer was also the most diagnosed malignancy among women: 1 214 new cases were reported (with a mean of 405 cases per year), which represented the 27.8% of the total. The mean age was 60.8 years and it was also the primary cause of cancer death among females [7]. According to the *Instituto Nacional de Estadística*, in 2018, 120 women died in the region because of breast cancer, representing the 11.4% of all Catalonia [8].

Most women (61%) are diagnosed at an early stage whilst in the 31% of the cases there is regional involvement. Distant disease is present in only 5% of the patients [9].

The implementation of **mammography screening programmes** in many health systems have had an impact on the incidence rates, increased the proportion of in situ tumours and caused higher survival rates and lower mortality rates. However, opportunistic early diagnosis and therapeutic improvements also have an effect on these indicators [6,10].

Current ESMO Clinical Practice Guidelines recommend an annual or every 2 years mammography in women aged 50-69 years (where most benefit has been shown) and annual mammography

and annual MRI when there is relevant family history of breast cancer (with or without BRCA mutations) [1].

3.1.2. RISK FACTORS

Several **risk factors** for breast cancer have been identified [4,11,12]:

a) **Nongenetic, nonmodifiable risk factors**:
   - Age. Incidence increases with age and peaks at age 60.
   - Racial and ethnicity differences. Black women are more susceptible to have more aggressive subtypes with negative ER and, in premenopausal women, triple negative tumours are more frequent among black women.
   - Younger age at menarche (before 11 years old) and older age at menopause (older than 55 years) through effects on reproductive hormone levels and long-lasting changes in the mammary gland.
   - Previous history of breast cancer.
   - Increased breast density (less fatty tissue and more glandular and fibrous tissue).
   - Exposure to ionizing radiations at younger age.

b) **Nongenetic, modifiable risk factors**:
   - Changing reproductive patterns such as nulliparity and older age at first full-term pregnancy. Breastfeeding and multiparity seem to be protective factors.
   - Hormone replacement therapy after menopause, especially when it includes both estrogen and progesterone unlike when only estrogen formulas are used.
   - Dietary factors, tobacco and alcohol consumption, sedentarism and obesity after menopause.

c) **Genetic risk factors**:
   - Positive family history of breast cancer in first degree relatives.
   - BRCA1 and BRCA2 mutations (causing about 3% of breast cancers). These genetical alterations should be suspected and so considered high-risk patients in those with: strong family history of breast, ovarian, pancreatic and/or high grade or metastatic prostate cancer; diagnosis of breast cancer before the age of 50; diagnosis of TNBC before the age of 60; personal history of ovarian cancer or second breast cancer or male sex [1].

3.2. CLASSIFICATION AND SUBTYPES

Breast cancer can be categorized according to **histology** and **molecular markers**:

- **Histological determination** should be made according to the World Health Organization (WHO) classification (ANNEX I). Breast tumours can be mainly classified into in situ carcinoma and invasive carcinoma. Both categories can be further subclassified [13].

  The most common histological subtypes are invasive carcinoma of the breast: not otherwise specified (NOS, previously named ductal carcinoma) (70%-75%) and lobular carcinoma (12%-15%) [1].
- The **immunohistochemical** (IHC) **classification** is based on the measurement of the expression of estrogen receptors (ER), progesterone receptors (PgR) and the overexpression of HER2 (human epidermal growth factor receptor 2, also known as c-erbB-2 or neu). Four molecular subtypes can be differentiated (Table 1). These tissue-based molecular markers provide a prognostic value and therefore they should be determined for all invasive carcinomas for decision-making. Luminal A, Luminal B and HER2-enriched tumours are likely to have a response to targeted therapies while triple negative subtypes do not and have quicker growth [14,15].

Ki67 index marker gives additional information to assess proliferation and predict chemosensitivity. However, it is relevant for ER-positive and HER2-negative tumours given that for HER2-positive and triple negative tumours chemotherapy is needed [16].

Table 1. Breast cancer subtypes based on biomolecular markers and Ki67.
[Adapted from : Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [1]]

TUMOR SUBTYPE	LUMINAL A-LIKE	LUMINAL B-LIKE		HER2-enriched	Basal-like o triple negative (TNBCs)
		HER2 negative	HER2 positive		
DEFINITION	·ER positive ·HER2 negative ·PgR high ·Ki67 low*	·ER positive ·HER2 negative and: ·Ki67 high* or ·PgR low	·ER positive ·HER2 positive ·any Ki67* ·any PgR	·ER absent ·PgR absent ·HER2 positive	·ER absent ·PR absent ·HER2 negative

** The most used cut- off value is 20%: values of ≥30% can be considered clearly high proliferation; those of ≤10% clearly low.*
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor

3.3. DIAGNOSIS

Proper assessment is required when a women has breast symptoms or changes like a lump, local pain, nipple or skin changes and for positive screening outcomes [16].

The combination of clinical examination and imaging is used for the diagnosis of breast cancer. Afterwards, pathological evaluation is required for confirmation [17].

Clinical examination consists of bimanual palpation of the breasts and regional lymph nodes. If symptoms are present, assessment for distant metastases is required.

Bilateral mammography and ultrasounds (US) of the breast and regional lymph nodes are used for the **imaging**. An MRI of the breast should be considered in certain situations: for family breast cancers associated with BRCA mutations, lobar tumours, dense breasts, suspicion of multifocality (≥2 tumour foci in the same quadrant of the breast) or multicentricity (≥2 tumour foci in different quadrants of the same breast), clinical-imaging discrepancy, before neoadjuvant systemic therapy, for inconclusive imaging findings and breast implants [1].

BI-RADS (Breast Imaging Reporting and Data System) is the standardized reporting and classification system for the findings in mammography, ultrasounds and MRI of the breast and its suspicion for malignancy, relating final assessment categories to management recommendations (ANNEX II) [18].

Pathological evaluation should be done through a core needle biopsy of the tumour (obtained by US or stereotactic guidance if possible) and US-guided fine-needle aspiration or core biopsy if lymph nodes involvement is suspected for cytology/histology assessment. In case of multifocality or multicentricity, all lesions should be biopsied.

Final diagnosis should be based on the WHO classification (ANNEX I) and TNM staging system (ANNEX III) and should include prognostic information such as tumour grade (ANNEX IV), hormone receptor and HER2 status and gene expression information (HER2 gene amplification using in situ hybridisation technique) if available [1,19].

Tumour type and grade are revaluated in the definitive surgical specimen and predictive markers should be retested in case of hormone receptor and HER2 negativity or when there is discrepancy with the histopathological characteristics.

In case of patients in high-risk groups, genetic testing and counselling for BRCA1/BRCA2 mutations should be proposed.

Extension study in early-stage breast cancer is addressed to locoregional disease since asymptomatic distant metastases are uncommon. For axillary staging, lymph node specimens are examined mostly from a lymph node biopsy (SLNB) procedure. SLNB is the standard technique in clinically node-negative (not palpable and not visible on imaging) breast cancer.

A chest CT scan, abdominal imaging (US, CT or MRI) and a bone scan may be performed in patients with: positive axillary nodes in the clinical exploration, large tumours (≥5cm), aggressive biology or when clinical signs, symptoms or laboratory values suggest the presence of metastases. PET-TC may be considered when then the findings are inconclusive and in high-risk patients [1,16].

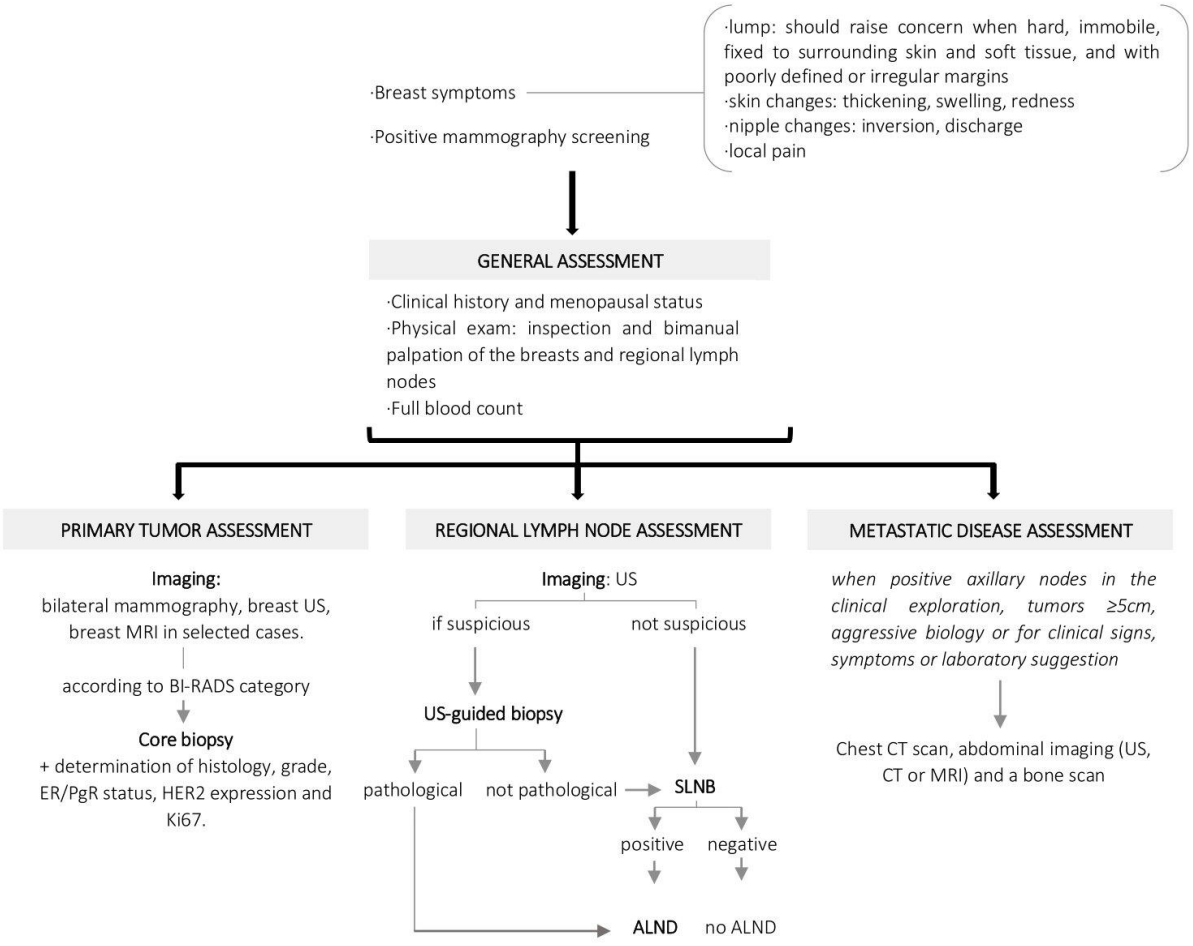

Figure 3. Summary of the general diagnostic work-up for breast cancer. *US, ultrasounds; MRI, Magnetic Resonance Imaging; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CT, Computed Tomography scan*

3.4. EARLY-STAGE BREAST CANCER MANAGEMENT

3.4.1. CONCEPT AND PROGNOSTIC FACTORS

According to the National Institute of Cancer, early-stage breast cancer refers to when it has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB and stage IIIA breast cancers.

For early-stage breast cancer, the most relevant **prognostic factors** are [16,20]:

- **Regional lymph node status (N)**. It is the most important item. There is a linear relationship and the greater the number of nodes, the lower the survival rate. With no lymph affectation, at 10 years after surgery the probability of survival is at 90%, while cases of ≥4 positive nodes showed survival rates of less than 20%.
- **Tumour size (T)**. In tumours of < 1 cm the survival rate is at 90%, while for tumours of 2-5cm the rate is at 70%.
- **Tumour histology**. Pleomorphic, metaplastic and high-grade neuroendocrine varieties have worse prognosis.
- **Tumour grade**. It is an independent parameter of the size and regional lymph node involvement.
- **ER/PgR status**. However, they have more significance as predictive factors (for treatment decision-making).
- **HER2 expression**. Tumours with an over-expression of this protein have a more aggressive course.
- **Presence of peritumoral vascular invasion** is related to lymph node metastases and local recurrences.
- **Proliferation markers** (such as Ki-67).

The most significant factors are lymph node status, tumour size and histological grade. These items, combined to hormone receptor status and HER2 expression, are used to decide the adjunctive therapy in each case.

In patients who receive conserving therapy (BCT) the status of the surgical margins (if there are cancer cells extending past the edge) and presence of ductal carcinoma in situ are related to ipsilateral breast recurrence [1].

3.4.2. TREATMENT OPTIONS

Treatment of early-stage breast cancer combines local modalities (surgery and radiotherapy) and systemic treatment (chemotherapy, endocrine therapy and molecular target therapies). Decision-making should be done according to the tumour burden and biology and the patient's characteristics [1,21].

Local treatment includes surgical resection, sampling or removal of axillary lymph nodes with the option of postoperative radiotherapy. **Systemic therapy** may be neoadjuvant, adjuvant or both[22].

Surgery consists of breast-conservation surgery (BCS) or a mastectomy. Excision of the primary tumour may be the first step of treatment or it can be done after systemic therapy. In any case, it is the basis of the curative breast treatment.

BCS is the primary option for early-stage breast cancer if possible. Non-free surgical margins have significant impact on local recurrence after BCS. The optimal margin width is no tumour at the inked margin (no cancer cells extending past the edge) in invasive breast cancer and >2 mm for ductal carcinoma in situ. Positive margins require further surgery [16].

Apart from a simple mastectomy, techniques that preserve as much of the breast skin as possible, such as a skin-sparing mastectomy (SSM) or a nipple-sparing mastectomy (NSM), may be performed [1]. Breast reconstruction should be proposed to all women undergoing a mastectomy, as an immediate or delayed procedure based on the oncological situation and preference of the patient [22].

Mastectomy and BCS plus radiation have showed to be equivalent in terms of relapse-free and overall survival.

Regarding to the **axillary management**, lymph node removal has both diagnostic and therapeutic intentions (to determine the extent and to remove cancerous cells). Axillary lymph node dissection (ALND) is not needed in all patients with positive SLN. ACOSOG Z0011 trial reported that for patients with clinical T1–T2 cN0 invasive breast cancer and 1 or 2 positive SLNs (before systemic therapy) undergoing BCS, SLNB is enough with the possibility to add posterior axillary radiation. Moreover, SLNB can be performed instead of straight ALND when cN1 is converted to cN0 (after neoadjuvant treatment) and thus patients can benefit from locoregional tumour downstaging [16,22].

Radiotherapy (RT) may be directed to the whole breast or a part of the breast (if a lumpectomy is performed), to the chest wall and to the regional lymph nodes [22]. The different modalities of RT and its indications and evidence have been summarized into Table 2 [1,22–25].

RT application after surgery improves disease-free and overall survival in patients diagnosed with early-stage breast cancer with lymph node affectation and/or after BCS is performed. This would be done through the elimination of possible residual malignant cells and/or the induction of an abscopal effect (which refers to a phenomenon of tumour regression at a site distant from the primary site of radiotherapy) [16,26].

BCS followed by external beam radiation therapy (EBRT) is the standard care for early-stage breast cancer when feasible. Hypofractionation schedules of 15-16 fractions of ≤3 Gy per fraction are preferred for routine postoperative RT [1].

Partial breast irradiation techniques are being used in selected patients instead of WBRT based on the fact that most breast cancer recurrences occur in the same quadrant of the breast in which the primary tumour appeared [27].

The indications for **systemic therapy** are based on the molecular type, tumour burden and risk of recurrence. It is preferable to administer the chemotherapy as neoadjuvant for better surgical outcomes if the reduction of the tumour is feasible. Adjuvant endocrine therapy for a minimum of 5 years is the standard for luminal tumours: in premenopausal women, tamoxifen (binds to and inhibits ER) +/- ovarian-suppressing medication (inhibits oestradiol production) is used; and, in postmenopausal women, tamoxifen and aromatase inhibitors can be used alone or in sequence. In HER2-positive tumours, neoadjuvant chemotherapy plus anti-HER2 therapy is the standard. In TNBC, chemotherapy, preferably neoadjuvant, is administered [16].

Table 2. Radiotherapy modalities for the treatment of breast cancer [1,22–25].

MODALITY OF RT	DEFINITION		ESMO RECOMMENDATIONS AND EVIDENCE
WBRT after BCS	Radiation is delivered to the affected breast.		·Recommended after BCS. ·Reduces the 10-year risk of recurrence by 15%. ·A meta-analysis concluded that the delivery of RT after lumpectomy is related to lower locoregional or distant recurrence (from 35.0% to 19.3%).
APBI after BCS	Localized modality delivered only to the part of the breast where the tumour was removed.	**Brachytherapy** Placement of radioactive sources into the breast tissue to deliver high doses of radiation to a limited area. Multiple interstitial catheters or an intracavitary balloon catheter can be used.	·May be considered in patients with low risk for local recurrence: ≥50 years old, with unicentric, unifocal, node-negative, non-lobular breast cancer, up to 3 cm with no presence of extensive intraductal components or vas-cular invasion and with negative margins. ·Recurrence rates equivalent to WBRT were reported for external beam techniques and brachy-therapy. ·Higher ipsilateral recurrence rates were reported for IORT compared to WBRT.
		External beam APBI APBI is performed through an external approach.	
		Intraoperative radiotherapy (IORT) A single dose delivery of radiation limited to the tumour bed at the time of BCS.	
Post-mastectomy RT	Radiation delivered to the chest wall and the mastectomy scar.		·Recommended for high-risk patient: with affected resection margins, affected axillary lymph nodes and T3-T4 tumours. ·Reduces the 10-year risk of recurrence by 10% in node-positive patients.
Regional RT	Radiation delivered to regional lymph nodes.		·Recommended for patients with affected lymph nodes: the irradiated level is defined based on risk factors and tumour characteristics. ·Should not be done to the operated area of the axilla after ALND.

RT, radiotherapy; WBRT, whole breast radiotherapy; BCS, breast cancer surgery; APBI, accelerated partial breast irradiation; IORT, intraoperative radiotherapy; ALND, axillary lymph node dissection
Note: External beam radiotherapy (EBRT) includes WBRT, post-mastectomy RT, regional RT and some modalities of APBI.

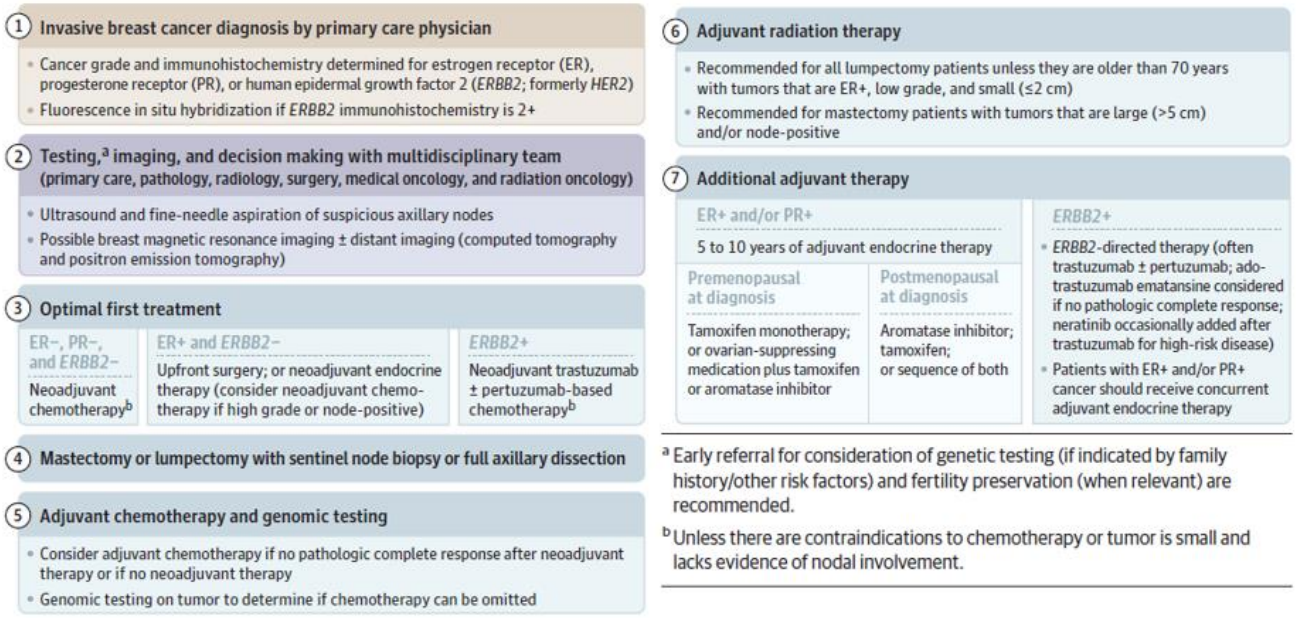

Figure 4. Typical Stage I to III Invasive Breast Cancer Management Algorithm [21].

3.5. IORT USE IN EARLY-STAGE BREAST CANCER

Intraoperative radiotherapy (IORT) for early-stage breast cancer is an APBI technique that applies one single dose of radiation to the tumour bed during the surgical intervention after the tumour resection [28,29]. Thereby, targets the tissue at highest risk of recurrence and minimizes excessive radiation exposure to healthy breast tissue [30]. However, some protocols have used IORT as a second procedure.

The difference between IORT and other APBI procedures is that IORT is mostly applied in the intraoperative time frame, while other APBI techniques are performed post-operatively. All forms of APBI are addressed to a smaller volume of tissue than WBRT and thus reduce potential lung and cardiac toxicities due to the RT treatment [28]. The pros and cons of IORT application have been summarized into Table 3 [28,30–33].

Table 3. Pros and cons of intraoperative radiotherapy [28,30–33].

PROS AND CONS OF INTRAOPERATIVE RADIOTHERAPY (IORT)	
ADVANTAGES	·Offers direct view and targeting of the high-risk tissue area. ·Avoids selection of mastectomy in women who do not have access to a RT centre or with co-morbidities that prevent them from attending. ·Has favourable toxicity profiles: it has been related to lower skin side effects, fewer lung fibrosis and deaths from cardiovascular causes when compared to WBRT. ·Has better patient convenience and cost-saving and thus decreases non-compliance to post-operative RT. ·Avoids some possible unfavourable outcomes related to EBRT: ·Difficulty of accurate delivery of RT with oncoplastic surgery techniques (breast tissue is rearranged for better cosmetic outcomes). ·Surgery complications may delay the adjuvant RT delivery. ·Clips that are placed during surgery to better localize the tumour bed for RT planning may move. ·No delay for patients who also must receive chemotherapy as part of the treatment.
DISADVANTAGES	· Lack of definitive pathological information on the tumour size, histology, margins and nodal status. ·Higher recurrence rates when compared to conventional EBRT (according to two clinical trials). ·Risk of requiring additional EBRT. ·Increased operating times. ·Has been related to increased fat necrosis (when compared to WBRT). ·Requires specialized devices, staff training and operating room equipment efforts.
RT, radiotherapy; WBRT, whole breast radiotherapy; EBRT, external beam radiotherapy	

Most local recurrences occur in the same quadrant as the primary tumour. It has been suggested that the wound healing process and inflammation induced after the tumour resection might stimulate the growth of possible remaining malignant cells [27]. The application of direct radiation during surgery changes the microenvironment of breast cancer cells, which is thought to have a crucial paper in the risk recurrence. Studies have suggested that irradiation may modify protein expression, downregulate the expression of epidermal growth factor (EGF) and EGF receptor activation and thus prevent breast cancer cell growth.

Specialized equipment is necessary for IORT application. Technologies that either deliver electrons (with energies ranging from 3 to 12 MeV) or 50 kV X-rays (with doses of 20-21 Gy) are available [28].

Two prospective randomized controlled trials to date have compared standard WBRT to IORT following BCS. Both reported low recurrence rates for the IORT modality, though increased risk of ipsilateral breast tumour recurrence (IBTR; at the site of surgery and in the same quadrant as the primary tumour) after IORT, and pointed out the relevance of patient selection.

In the ELIOT trial of the European Institute of Oncology of Milan, an electron IORT technique was used. With a median follow-up of 5.8 years, it concluded that there was no significant difference in the overall survival (OS) between both groups. However, the IBTR was higher in the IORT group (4.4% versus 0.4% in the WBRT group) even though it was within the prespecified margin of 7.5% for local recurrence. Moreover, the 5-year recurrence rates were higher for those treated with IORT. Higher IBRT rates were associated with: tumour size >2 cm, ≥4 positive nodes, poorly differentiated tumours, negative ER tumours and TNBC. Adverse events to the skin were significantly fewer in the IORT group [(34)].

In the TARGIT-A trial, a low-energy x-ray source for IORT was used. It was a multicenter non-inferiority trial with a median follow-up of 2.4 years. Researchers anticipated a 15% probability of unfavourable findings on the definitive pathology leading to additional WBRT after the initial IORT. The features were: positive margins, extensive intraductal component and the presence of invasive lobular carcinoma. The study showed similar recurrence rates between both groups and the overall survival was higher for the IORT group [(35)]. Recently, updated results of the TARGIT-A trial on long term survival and local control outcomes were published. The data presented showed that TARGIT-IORT is non-inferior to WBRT in terms of local control and overall survival at five-year complete follow-up based on the trial selection criteria [(36)].

A meta-analysis of the evidence comparing the efficacy and safety of IORT to WBRT concluded significantly higher risk of IBTR with IORT. However, it was due to moderate heterogeneity on patient selection and appropriate identification of low-risk local recurrence patients was recommended [(37)].

These trials provided a framework for clinical guidelines and, nowadays, IORT has been established as an option to WBRT and it is a suitable treatment for appropriately selected patients with early-stage breast cancer.

The updated American Society for Radiation Oncology (ASTRO) consensus includes into the suitable group to receive IORT the following criteria: age of ≥50 years, negative margins by at least 2 mm, Tis-T1 and screen-detected ≤2.5cm low to intermediate nuclear grade DCIS resected with margins negative at ≥3 mm (ANNEX V) [(23)].

If the final pathological assessment of the surgical specimen shows positive margins or positive sentinel nodal involvement, additional EBRT may be indicated and the previous applied IORT acts as a boost to the tumour bed (as an extra dose of radiation to cover the initial tumour site) [(28,38)].

Several institutions have published their experience regarding to IORT application in breast cancer surgery. Their eligibility criteria for IORT treatment and results on the number of patients requiring additional EBRT have been summarized into Table 4.

Table 4. Summary of several institutions experience on IORT treatment.

STUDY	SAMPLE	PROTOCOL CRITERIA	PATIENTS REQUIRING ADDITIONAL EBRT
Barrou et al.[39]	·280 patients ·Treated from 2012 to 2015	·Menopausal patients; ·No personal history of ipsilateral breast cancer; ·≥55 years old; ·Tumour features: IDC, grade 1-2 and size ≤20 mm; ·Positive hormone receptors; ·HER2-negative; ·No metastatic or nodal invasion; ·No LVI.	**45.7% (128 patients)** Due to: ·Nodal invasion (58 patients) ·LVI (31 patients) ·III grade (18 patients) ·Size (12 patients) ·Positive margins (24 patients) ·Association with large DCIS (32 patients)
Rana et al.[40]	·127 patients ·Treated from 2009 to 2016	·Age ≥60 years; ·Tumour features: IDC, no pure DCIS, size ≤2 cm ·Surgical margins ≥2 mm; ·No LVI ·Positive estrogen receptor; ·Unicentric lesion; ·No BRCA 1/2 mutation; ·No prior neoadjuvant therapy.	**9.4% (12 patients)**
Silverstein et al.[41]	·984 patients (a total of 1000 breast cancers; 16 bilateral) ·Treated from June 2010 to August 2017	·Tumour size ≤30 mm; ·Tumour margins ≥2 mm for both invasive and non-invasive disease; ·No extensive LVI; ·Negative axillary lymph nodes.	Treatment after protocol deviations (in 305 patient): ·Re-excision + WBRT **in 9/305 (3%)** ·WBRT alone in **109/305 (36%)**
Obi et al.[42]	·201 patients ·Treated from 2011 to 2019	Not specified	**1.0% (2 patients)**
Melnik et al.[43]	·158 patients ·Treated from 2014 to 2018	·≥60 years; ·Unifocal disease; ·Tumour size ≤3 cm; ·Negative margins; ·Positive hormone receptor; ·No lymph node involvement.	**14% (23 patients)** Due to: ·Lymph node involvement ·Positive HER2-receptor ·Close posterior margins ·High Oncotype Recurrence Score

LVI, lymphovascular invasion; IDC, invasive ductal carcinoma, DCIS, Ductal carcinoma in situ; WBRT, whole breast radiotherapy

3.6. APPLICATION OF IORT IN HOSPITAL UNIVERSITARI JOSEP TRUETA

In 2019 a clinical protocol to treat patients diagnosed with early-stage breast cancer with IORT after BCS was implemented in *Hospital Universitari Josep Trueta* (HUJT).

In order to receive this modality of radiotherapy, these patients must meet specific inclusion criteria for IORT application as sole partial radiation and none of the exclusion criteria.

The established **eligibility criteria** are the following:

- Women over 60 years of age;
- Tumour histology of invasive ductal carcinoma, mucinous carcinoma, tubular carcinoma or medullar carcinoma;
- Tumour size of less than 2.5cm (cT1-T2);
- No lymph node involvement (pN0);
- Unifocal and unicentric tumours;
- Patients eligible for BCT;
- Tumour grade of I-II;
- Free surgical margins;
- Positive hormone receptors;
- No lymphovascular invasion;
- No BRCA1/2 mutations;
- No extensive carcinoma in situ (DCIS) component (>25%).

All these items must be accomplished. In order to be eligible for IORT treatment all patients must meet the following preoperative criteria of the protocol: to be over 60 years old, tributary to BCT and present an unifocal and unicentric tumour and to not present clinical lymph node involvement (cN0), presence of extensive carcinoma in situ (DCIS) component (>25%) or BRCA1/BRCA2 mutations. The other criteria are obtained after the final pathological assessment of the surgical specimen or they might change after the evaluation (due to histological discordance between the initial biopsy and the lumpectomy sample). Therefore, when all the criteria are not met, patients must receive additional EBRT after the initial IORT treatment.

With regards to the modality of IORT which is applied, low-energy X-rays are used to deliver the RT. The equipment consists of a portable device with a mobile arm which contains a miniature source of photons of 50 kV X-rays and 300 µA.

Once the tumour resection is completed, a spherical applicator is introduced within the breast cavity, where the tumour bed was located. Applicators of different sizes can be used according

to the volume of the breast cavity. A purse-string suture is used to approximate the extremes of the incision and so the applicator to the breast tissue (Figure 5).

The duration of the treatment is approximately 10-20 minutes, which depends on the applicator size. During the time that IORT is being delivered, all the staff must leave the operating room. If there is an adverse outcome concerning the patient, the radiation delivery can be stopped manually (ANNEX VI).

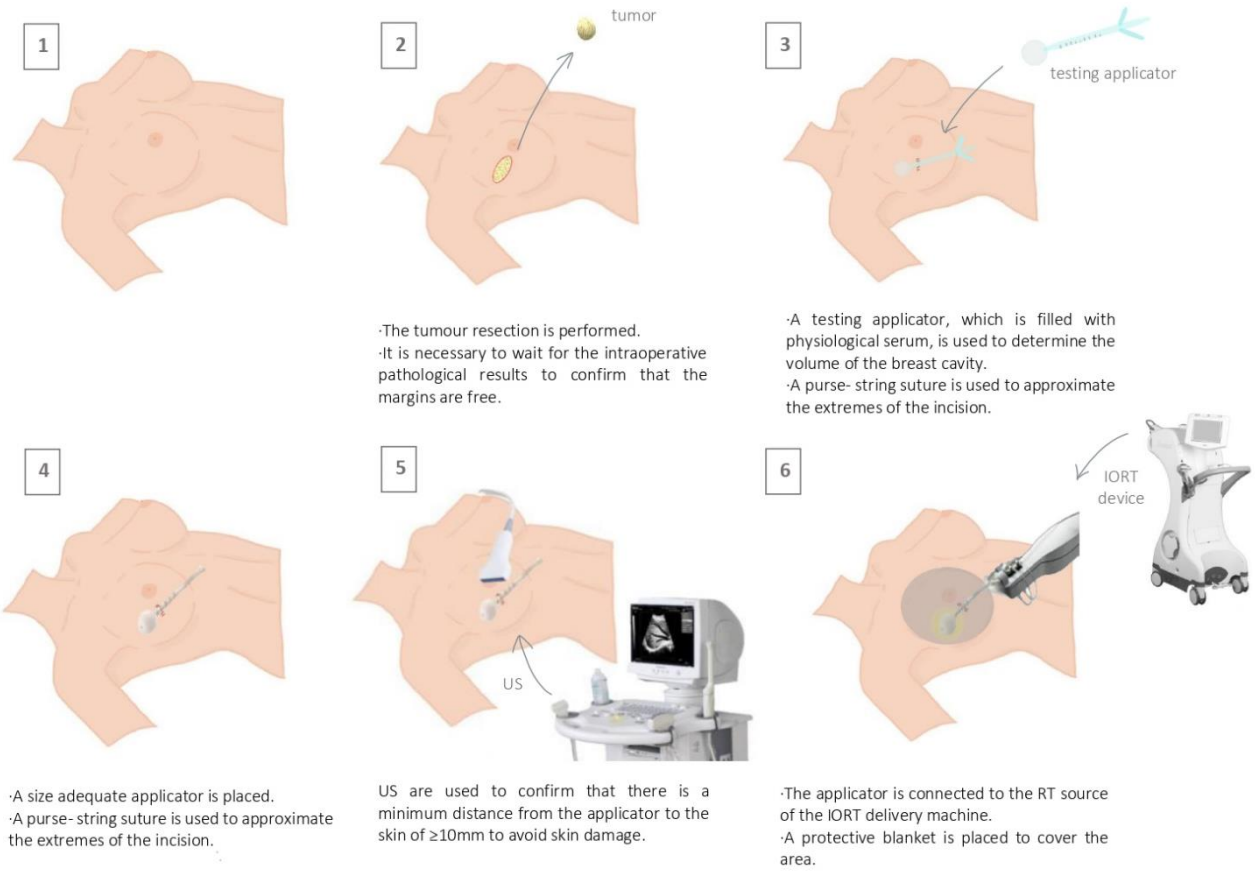

Figure 5. Summary of intraoperative radiotherapy procedure.

4. JUSTIFICATION

Breast cancer is the most diagnosed cancer among women and the primary leading cause of cancer death in this group [2,3,5–8]. Likewise, an increase on its incidence is expected. Hence, the relevance of its management. It is mostly diagnosed at an early stage and, for this reason, the majority of the newly detected tumours are eligible for BCT [1,9].

Nowadays, IORT is a well-established option in selected patients when BCS is performed as an alternative to traditional WBRT. Clinical trials have evaluated this modality of RT and several studies are gathering information on the follow-up. All of them emphasize the importance of careful patient selection when IORT is indicated.

In order to receive IORT as sole partial radiation, patients must meet specific eligibility criteria. However, some of these criteria are confirmed once the final pathological assessment is carried out and thus are not available when the IORT treatment is performed. That is why, when the pathology report shows unfavourable outcomes, additional ERBT must be delivered to minimize the risk of recurrence.

In response to the evidence related to IORT treatment, HUJT implemented a protocol for its application in patients diagnosed with early-stage breast cancer. Nevertheless, a given number of patients who receive IORT still require additional EBRT.

So far, it has been more than year since the introduction of this clinical protocol and we consider that it is time that its application is assessed. We inquire the following:

1. What is the proportion of patients treated with IORT who require posterior EBRT?
2. Why these patients treated with IORT require posterior ERBT? Which eligibility criteria for IORT treatment is not accomplished?

We believe that an evaluation of the current Protocol for the treatment with IORT will identify inclusion criteria that may be adjusted and thus reduce the number of patients who require posterior EBRT treatment.

We have special interest in the surgical margin status and nodal affectation for their prognostic implications. However, these features are obtained and confirmed after the surgical specimen is examined and cannot be addressed clinically. Once their repercussion on the indication of additional ERBT is determined, we think that it could open a debate on putting the focus on clinicopathologic factors predictive of negative nodes and negative margins.

For instance, a more careful preoperative assessment may be beneficial, such as a meticulous evaluation of mammographic and other imaging studies for traits to better estimate the extent of the tumour. Or, in the other hand, intraoperative procedures such as the assessment of sentinel nodes during the surgery frame time and excision techniques such as taking additional tissue to enhance free surgical margins could be considered [28].

5. HYPOTHESIS

The number of patients who require additional EBRT after IORT application may be reduced by modifying the eligibility criteria of the current Protocol for the treatment with IORT in early-stage breast cancer.

6. OBJECTIVES

The aim of the present study is to assess the clinical protocol for IORT used in early-stage breast cancer surgery since its application in *Hospital Universitari Josep Trueta*.

In order to achieve this, the following objectives have been set:

1. To describe the clinical and tumour characteristics of the patients diagnosed with early-stage breast cancer who received IORT treatment: age, histology, tumour size, tumour grade and hormone receptor status.
2. To determine the percentage of patients who required posterior EBRT.
3. To gather and provide data regarding why these patients treated with IORT required posterior ERBT after the final anatomopathological evaluation. This is our main objective. It will be based on:
    - Those features that may change after the definitive anatomopathological evaluation: histology, tumour size, tumour grade and hormone receptor status.
    - Those criteria that are confirmed once the surgical specimen is assessed: margin status, presence of peritumoral vascular invasion (blood and/or lymph vessel invasion) and nodal metastases.
4. To identify possible risk factors associated to unfavourable outcomes in the final pathological assessment.
5. To give recommendations to adjust the indications for IORT of the current protocol if feasible with the intent to reduce the number of patients that may require posterior EBRT.

7. SUBJECTS AND METHODS

7.1. STUDY DESIGN

This study will have a cross-sectional design since a group of patients will be described at a specific point in time.

It will be carried out at the Breast Pathology Unit of *Hospital Universitari Josep Trueta* (HUJT), a tertiary referral center in Girona. The Breast Pathology Unit is a multidisciplinary team constituted by gynaecologists, general surgeons, oncologists, radiotherapists, plastic surgeons, radiologists and pathologists.

7.2. STUDY POPULATION

The study will be focused on patients diagnosed with early-stage breast cancer in HUJT who underwent breast conserving surgery plus IORT.

A core needle biopsy is used in the preoperative diagnosis of the breast tumour. The preoperative assessment also includes a bilateral mammography, US, an MRI of the breast and fine needle aspiration (FNA) of suspicious lymph nodes as indicated in the established internal guidelines. The final diagnosis is based on the evaluation of the surgical specimen.

7.3. SUBJECTS SELECTION

7.3.1. INCLUSION CRITERIA

Patients who **underwent IORT** treatment and met the **preoperative** inclusion criteria of the clinical protocol to receive IORT:

- Women of ≥60 years of age;
- With:
    - Tumour histology of invasive ductal carcinoma, mucinous carcinoma, tubular carcinoma or medullar carcinoma;
    - Tumour size of less than 25mm (cT1-T2);
    - Tumour grade of I-II;
    - Positive hormone receptors tumours;
    - Unifocal and unicentric tumours;
- Eligible for BCT;
- With cN0 (no clinical lymph node involvement).

7.3.2. EXCLUSION CRITERIA

- Patients with BRCA1/BRCA2 mutations;
- Presence of extensive carcinoma in situ (DCIS) component (>25%).

7.4. SAMPLING

7.4.1. SAMPLE SELECTION

Our sample will be obtained through a consecutive non-probabilistic sampling since patients who endured IORT in HUJT according to the previously specified criteria will be included into the study. The sample recruitment will take place in the Breast Pathology Unit of HUJT throughout 18 months.

7.4.2. SAMPLE SIZE

Sample size calculation was performed using the GRANMO application. Since our main objective consists of the determination of a proportion, the sample size has been calculated for a proportion estimation on a population.

Accepting an alfa risk of 0.05 and a precision of +/- 5 %, 196 subjects are necessary. It is assumed a proportion of 0.15 (patients with unfavourable outcomes) based on other studies as reference[35]. Since it is a cross-sectional study and data will be collected retrospectively, no drop-out rate is expected.

It is estimated that in HUJT approximately 60 patients might undergo breast conserving surgery plus IORT per year. Since the implementation of this modality of treatment in the center, 60 women have already received IORT. That is why it is predicted that in a period of two years from now the sample size will be reached.

7.5. VARIABLES

7.5.1. INDEPENDENT VARIABLES

The independent variables will be those criteria of the protocol that may lead to additional EBRT delivery when they are not accomplished, which are the items that are either confirmed or obtained after the definitive pathological evaluation is performed. The following variables will be collected postoperatively for all the patients included in the study. Moreover, they will be also gathered from the preoperative evaluation for the group of patients who required additional EBRT in order to assess the changes.

1. Those tumour features that may change after the definitive anatomopathological evaluation is performed:
   - Histological type. It is defined according to WHO classification.
   - Tumour grade. It is based on the appearance (morphologic features) of tumour cells under the microscope and it indicates how quickly the tumour is likely to grow and spread. It is determined by the Nottingham Histologic Score System.
     It will be collected as Grade I, Grade II or Grade III.
   - Hormone receptor status. It is determined by immunohistochemical techniques.
     The following combinations will be considered: positive hormone receptor status (when ER-positive and PgR-positive; ER-positive and PgR-negative; or ER-negative and PgR-positive) and negative hormone receptor status (when ER-negative and PgR-negative).

   These three features are obtained in the initial diagnosis from a core biopsy of the tumour and in the final evaluation from the surgical specimen.

   - Tumour size. Clinically, it is estimated from imaging techniques (mammography, US, and MRI). Postoperatively it is measured in millimetres from the surgical specimen by the pathologist.
     The size will be categorized according to the TNM staging system into: T1 (≤20 mm); T2 of ≤25 mm; and T2 of >25 mm. T2 includes tumour sizes from >20 mm to ≤50 mm, but we divided it into the previous specified categories based on the eligibility criteria of IORT procedure.

2. Those features that are obtained once the surgical specimen is assessed by the pathologist:
   - Margin status. It is defined by the distance from the edge cut to the tumour in the resected specimen. The six sides of a breast are considered: the anterior, posterior, superior, inferior, external and internal margin. It will refer to whether cancerous cells extending past the edge are present or not (presence of tumour within the inked surgical margin).
     It will be collected as a nominal dichotomic qualitative variable: negative (no cancerous cells) or positive (presence of cancerous cells).
   - Presence of peritumoral vascular invasion (LVI). It refers to blood and/or lymph vessel invasion by tumoral cells.
     It will be defined as a nominal dichotomic qualitative variable: yes or no.

- Nodal metastases. It is determined from a SLN biopsy.
  It will be categorized as: no regional lymph node metastasis (pN0), micrometastases (pN1mi) or macrometastases (≥pN1a).

The variables that will be collected have been summarized into the following tables:

Table 5. Variables related to tumour features of all patients treated with IORT.

TUMOR CHARACTERISTICS OF PATIENTS WHO RECEIVED IORT		
CHARACTERISTIC		VALUE
		N (TOTAL)
TUMOUR HISTOLOGY	Invasive ductal carcinoma	
	Mucinous carcinoma	
	Tubular carcinoma	
	Medullar carcinoma	
	Other histology	
TUMOUR SIZE	cT1	
	cT2 of ≤ 25mm	
	T2 of >25mm	
TUMOUR GRADE	I	
	II	
	III	
HORMONE RECEPTOR STATUS	ER+ and PgR+	
	ER+ and PgR-	
	ER- and PgR+	
	ER- and PgR-	

Table 6. Variables to assess changes that lead to additional EBRT.

CHANGES IN TUMOR FEATURES THAT LEAD TO ADDITIONAL EBRT				
FEATURE	PREOPERATIVE STATUS	POSTOPERATIVE STATUS	VALUE	
			n	N (TOTAL)
CHANGE IN TUMOR HISTOLOGY				
	IDC	Other histology		
	Mucinous carcinoma			
	Tubular carcinoma			
	Medullar carcinoma			
CHANGE IN TUMOR SIZE				
	cT1	T2 of >25mm		
	cT2 of ≤ 25mm			
CHANGE IN TUMOR GRADE				
	I	III		
	II			
CHANGE IN HORMONE RECEPTOR STATUS				
	POSITIVE	NEGATIVE	-	

Table 7. Variables that suppose an adverse outcome in the final pathological assessment.

ADVERSE PATHOLOGICAL OUTCOMES THAT LEAD TO ADDITIONAL EBRT		
OUTCOME		VALUE
POSITIVE MARGIN STATUS		
PRESENCE OF VASCULAR INVASION		
NODAL METASTASES (pN)	Micrometastases (pN1mi)	
	Macrometastases (≥pN1a)	

7.5.2. DEPENDENT VARIABLE

The outcome variable is requiring additional EBRT (after the initial IORT treatment). It will include WBRT +/- regional lymph node RT depending on whether the pathology report shows nodal involvement or not.

This variable will be measured as a nominal dichotomic qualitative variable: yes or no.

7.5.3. COVARIABLES

Other variables will be also registered and included in order to describe the patients' characteristics and identify possible risk factors associated to unfavourable outcomes in the final pathological assessment.

1. Patient features:
   - Age. It will be measured in years (at the moment of the diagnosis).
     It is a continuous quantitative variable.
   - Obesity. It will be defined as dichotomic qualitative variable: yes (body mass index >30 kg/m2) or not a (body mass index ≤30 kg/m2).
   - History of breast cancer. It will be gathered as a categorial qualitative variable as: no history, personal history, family history or personal plus family history.
2. Tumour characteristics:
   - Localization. It is determined with the imaging techniques (mammography, MRI). It will be categorized based on the quadrant of the breast involved: upper inner quadrant, upper outer quadrant, lower inner quadrant, lower outer quadrant, upper junction, inner junction, outer junction, lower junction or central.
3. Surgical technique:
   - Intraoperative margin status. It will be defined based on the margin distance in millimetres of the 6 sides of the tumour. It is obtained from the evaluation of the surgical fresh piece during the surgery frame time.
4. Imaging characteristics:
   - Microcalcifications detected on mammography. It will be collected according to the size of the microcalcifications measured in millimetres.

7.6. METHODS OF DATA COLLECTION

For data collection, a computer-based database using Microsoft Excel will be created. The patients' identity will be codified to build the database with the aim to purse a pseudonymisation procedure. The information will be collected from the electronic medical records of the SAP system.

The information will be obtained from:

- Pathology report. The initial and definitive reports based on a core biopsy and the surgical specimen assessment respectively will provide information on the tumour characteristics, surgical margin status, LVI and lymph node involvement.

- **Radiology report**. Imaging techniques (mammography, MRI, US) reports will be used to obtain the preoperative estimation of the tumour size and its localization.
- **Electronic Clinical History**. It will provide information on the patient characteristics.

The following table summarizes the data collection process:

Table 8. Data collection sources.

SOURCE	DATA RESOURCE	DATA COLLECTED
Pathology report	PREOPERATIVE Core needle biopsy of the tumour	·Histological type ·Tumour biology ·Tumour grade
	INTRAOPERATIVE Fresh surgical assessment	·Surgical margin status
	POSTOPERATIVE Surgical specimen assessment (of the tumour and sentinel lymph nodes)	·Histological type ·Surgical margin status ·Tumour grade ·LVI ·Tumour biology ·Lymph node involvement
Radiology report	PREOPERATIVE Mammography, MRI, US	·Tumour size ·Microcalcifications ·Tumour localization
Clinical History	-	·Age ·History of breast cancer ·BMI

8. STATISTICAL ANALYSIS

Statistical calculations will be performed using the IBM Statistical Package for Social Science (SPSS) software and Microsoft Excel will be used to collect and manage the data.

Univariate analysis:

A description of the clinical and tumour characteristics of all patients who underwent IORT will be carried out. Moreover, the proportion of patients who required additional EBRT will be determined. For this subgroup of patients, the description of such features will be performed according to their preoperative and postoperative status in order to determine which changes in the final pathological assessment led to additional EBRT delivery.

In the descriptive analysis, variables will be defined as qualitative or quantitative.

- Qualitative or categoric variables will be expressed as percentages and proportions.
- Quantitative variables will be described as mean ± standard deviation or with median and interquartile range (25-75) depending on normal distribution of the variables.

Bivariate analysis:

A comparison of clinical and tumour characteristics between the subgroup of patients who required additional EBRT (because of unfavourable outcomes in the final pathological evaluation) and the subgroup of patients who received only IORT will be performed.

Chi-Square test will be used for the comparison of categorical variables and T-Student test will be used to analyse the quantitative variables.

Multivariate analysis:

A multivariate regression logistic model will be used to estimate odds ratio and 95% confidence intervals for the identification of possible risk factors associated to unfavourable outcomes in the final pathological assessment.

A p value <0,05 will be considered statistically significant.

9. ETHICAL AND LEGAL ASPECTS

This project will be carried out according to ethical aspects established by international and national standards.

All members of the Breast Pathology Unit will be notified about the development of this project.

The protocol will be presented to the Clinical Research Ethical Committee (CEIC) of *Hospital Universitari Josep Trueta*, which will evaluate whether this study complies with the criteria for being approved. The objections and recommendations given by the Committee will be considered and introduced.

It will be executed according to the requirements established by the World Health Association in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* (last updated in October 2013). The four ethical principles of autonomy, beneficence, non-maleficence and justice will be followed. Moreover, the *Spanish Organic Law 14/2007 on Biomedical Research*, which regulates biomedical investigation involving human subjects in Spain, will be considered.

Personal information will be addressed and collected following the *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27th April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation)* and the *Spanish Organic Law 3/2018, of 5th of December on Protection of Personal Data and Guarantee of Digital Rights.*

The patients will be given the participant information sheet (ANNEX VII) and they will be asked to sign a written informed consent to be included in the study (ANNEX VIII). The patients who have already underwent BCS plus IORT will be contacted to obtain its consent.

In any case, a computer-based databased will be created and patient's identity will be codified with the aim of processing the data anonymously to preserve patient confidentiality. Furthermore, there will be a technical separation since the creation of the database and the analytical part of the study will be carried out by different researchers. All data will exclusively be used for the development of the study.

The investigators will have to declare conflict of interest if they exist.

10. LIMITATIONS OF THE STUDY

Several limitations of this study need to be acknowledged:

- Since this study has a cross-sectional design, there will be no follow-up and therefore the impact of IORT application on clinical outcomes such as local recurrence or survival rates cannot be ascertained. Given the recency of the introduction of this modality of RT to the clinical practice, most studies on IORT that have been carried out highlight the need of longer follow-up periods. However, these indicators should be assessed based on at least a median follow-up of 5 years which is not available yet at HUJT.
- The results will be obtained from a single institution internal protocol and consequently it might not be extrapolated to other centers. However, the present work may serve as basis for other institutions and a future multicentric study may be considered. This would allow to perform more precise estimations because a larger sample size would be reached.
- Some covariables might not be collected because of lack of information in the medical history.

11. WORK PLAN AND CHRONOGRAM

The research team will be comprised of:

- Study coordinator, who will be responsible for the supervision of the project and coordination of the research team and will also be a coinvestigator in the study.
- Main investigator, who will be responsible for the elaboration of the protocol, participants recruitment, data collection and database creation, results interpretation, writing of the conclusions and results publication.
- Coinvestigators (surgeons of the Breast Pathology Unit), who will be responsible for the participants recruitment and will participate in the results interpretation, writing of the conclusions and results publication.
- Statistician, who will perform the statistical analysis and provide statistical advice when needed.

The study will be carried out from September 2020 to December 2022, both included. The sequence of activities will be organized into 5 phases:

PHASE 0. Study design (6 months).

- First meeting (July 2020).
  The development of this project was accorded and decided in July 2020 by Dr. Ester Vila (study coordinator) and Amina Aissati (main investigator).
- Protocol elaboration (September 2020- December 2020).
  This protocol has been elaborated from September 2020 to November 2020. After the definition of the objectives, a literature review was performed and afterwards this protocol was redacted. The protocol will be discussed with all the research team members to ensure that everyone agrees with the approach and to collect suggestions and identify possible problems that may come up.

PHASE 1. Protocol approval and coordination (3 months).

- Presentation and approval by the Ethics Committee (January 2021-March 2021).
  This project will be presented to the Ethics Committee of HUJT. The recommendations given by the Committee will be considered and introduced.
- Team coordination (March 2021).
  An organizational meeting will be held between the study coordinator, the main investigator and the rest of the research team. The study chronogram will be scheduled and the tasks of each member of the team will be specified.

PHASE 2. Field work (18 months).

- Participants recruitment (April 2021- September 2022).

  It will involve the four surgeons of the Breast Pathology Unit (the study coordinator and coinvestigators) and the main investigator.

  Since the surgeons are the ones that visit the patients and participate in the decision-making regarding the treatment, every time BCS plus IORT is indicated and pursued, they will have to assess if the patient meets the inclusion criteria to be included into the study. Afterwards, the patient will be proposed to join the study and will be given the participant information sheet and the consent form, which will have to be signed.

  The patients who have already underwent BCS plus IORT will be identified through an updated database of the Breast Pathology Unit of patients submitted to IORT treatment. They will be contacted by the main investigator, who will inform them and ask for their consent.
- Data collection (April 2021- September 2022).

  The main investigator will collect all the data (variables and covariables) from the electronic medical history (SAP system), which will be introduced into the study database.

PHASE 3. Statistical analysis. (1 month).

- Database processing and data analysis (October 2022).

  It will involve the statistician, who will process the database and will analyse the collected data using the appropriate statistical tests.

PHASE 4. Interpretation, publication and dissemination of the results. (2 months).

- Interpretation of the results (November 2022).

  It will involve all the research team, who will meet to interpret and discuss the analysed data. A final report evaluation will be elaborated and if the results of the study conclude that the current protocol of HUJT can be adjusted, recommendations for its modification will be performed.
- Publication and dissemination of the results (December 2022).

  In order to share HUJT experience with this modality of treatment, we will try to present our findings in the *Congreso de la Sociedad Española de Senología y Patología Mamaria (SESPM)* and publish the study as a journal article.

PHASE	TASK	PERSONNEL	PERIOD									
			2020		2021				2022			
			Jul	*Sept-Dec*	*Jan-Mar*	*Apr-Jun*	*Jul-Sept*	*Oct-Dec*	*Jan-Mar*	*Apr-Jun*	*Jul-Sept*	*Oct-Dec*
PHASE 0 Study design	First meeting	Main investigator and study coordinator										
	Study protocol elaboration	Main investigator										
PHASE 1 Protocol approval and coordination	Approval by the Ethics Committee	Main investigator, study coordinator and CEIC										
	Team coordination	All team										
PHASE 2 Field work	Participant recruitment	Investigators										
	Data collection	Main Investigator										
PHASE 3 Statistical analysis	Database processing and data analysis	Statistician										
PHASE 4 Interpretation, publication and dissemination of the results	Interpretation and of the results	All team										
	Publication and dissemination of the results											

12. BUDGET

This project will evaluate a procedure (IORT treatment) which is already implemented and performed in the clinical practice in HUJT, thereby no additional material or goods will be required.

The investigators will perform the tasks related to this study (patient recruitment, data collection and interpretation of results) as part of their work activity.

EXPENSES	BUDGET PROPOSAL		
	QUANTITY	COST PER UNIT	COSTS (€)
PERSONNEL COSTS			
Investigator team	5 investigators	0	0€
SERVICES			
Statistician	40h	40€/hour	1600€
DISSEMINATION AND PUBLICATION			
Inscription to *Congreso de la Sociedad Española de Senología y Patología Mamaria (SESPM)*	1	600€	600€
Costs of the trip:			
- Flights	2	130€	260€
- Accommodation	2	180€	360€
Publication	1	1500€	1500€
TOTAL			**4320€**

13. FEASIBILITY

This project will be carried out at *Hospital Universitari Josep Trueta*. The center will provide the means for the execution and development of this study.

This work consists of an assessment of a clinical protocol of a treatment modality which is already performed in the center. The patients will follow the usual diagnostic and therapeutic process according to the guidelines established by the Breast Pathology Unit. No additional procedures will be required.

All the material needed to execute this project is available at HUJT. The hospital will provide the informatics equipment for the study development. However, a statistician will be hired to perform the statistical analysis.

14. IMPACT

IORT has become a well stablished alternative to traditional WBRT for selected patients with early-stage breast cancer. Nevertheless, some patients still require additional EBRT delivery after the initial IORT treatment due to unfavourable outcomes in the final pathological assessment.

This has many consequences. It implies an emotional impact for the patients since they must endure further treatment. Moreover, EBRT has been associated to increased toxicity such as pulmonary fibrosis, lymphedema and cardiac deaths. It also has economic implications in the health care system.

All the studies carried out highlight the relevance of proper patient selection.

This projects intents to identify eligibility criteria of the current Protocol for IORT application of HUJT that can be adjusted and thus reduce the cases of additional EBRT delivery.

If the obtained results are relevant, recommendations for the modification of the current Protocol will be performed.

Thereby, this project aims to serve as a tool and resource for the Breast Pathology Unit of HUIT to improve the management and the decision-making of patients diagnosed with early-stage breast cancer.

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ANNEXES

ANNEX I. HISTOLOGICAL CLASSIFICATION OF BREAST TUMORS (WHO)

UPDATED 2019 WHO CLASSIFICATION OF TUMORS OF THE BREAST	
EPITHELIAL TUMORS	-
INVASIVE BREAST CARCINOMA	·Infiltrating duct carcinoma (NOS) ·Oncocytic carcinoma ·Lipid rich carcinoma ·Glycogen rich carcinoma Sebaceous carcinoma ·Lobular carcinoma NOS ·Tubular carcinoma ·Cribriform carcinoma NOS ·Mucinous adenocarcinoma ·Mucinous cystadenocarcinoma NOS ·Invasive micropapillary carcinoma of breast ·Metaplastic carcinoma NOS, 8575/3
RARE AND SALIVARY GLAND TYPE TUMORS	·Secretory carcinoma ·Acinar cell carcinoma ·Mucoepidermoid carcinoma ·Polymorphous adenocarcinoma ·Adenoid cystic carcinoma ·Classic adenoid cystic carcinoma ·Solid basaloid adenoid cystic carcinoma ·Adenoid cystic carcinoma with high grade transformation ·Tall cell carcinoma with reversed polarity
NEUROENDOCRINE NEOPLASMS	·Neuroendocrine tumor ·Neuroendocrine tumor, grade 1 ·Neuroendocrine tumor, grade 2 ·Neuroendocrine carcinoma NOS ·Neuroendocrine carcinoma, small cell ·Neuroendocrine carcinoma, large cell
EPITHELIAL - MYOEPITHELIAL TUMORS	·Pleomorphic adenoma ·Adenomyoepithelioma NOS ·Adenomyoepithelioma with carcinoma ·Epithelial-myoepithelial carcinoma
NON-INVASIVE LOBULAR NEOPLASIA	·Atypical lobular hyperplasia ·Lobular carcinoma in situ NOS ·Classic lobular carcinoma in situ ·Florid lobular carcinoma in situ ·Lobular carcinoma in situ, pleomorphic,
DUCTAL CARCINOMA IN SITU (DCIS)	Ductal carcinoma, non infiltrating, NOS ·DCIS of low nuclear grade ·DCIS of intermediate nuclear grade ·DCIS of high nuclear grade
BENIGN EPITHELIAL PROLIFERATIONS AND PRECURSORS	·Usual ductal hyperplasia ·Columnar cell lesions including flat epithelial atypia ·Atypical ductal hyperplasia
ADENOSIS AND BENIGN SCLEROSING LESIONS	·Sclerosing adenosis ·Apocrine adenoma ·Microglandular adenosis ·Radial scar / complex sclerosing lesion
PAPILLARY NEOPLASMS	·Intraductal papilloma ·Ductal carcinoma in situ, papillary ·Encapsulated papillary carcinoma ·Encapsulated papillary carcinoma with invasion ·Solid papillary carcinoma in situ ·Solid papillary carcinoma with invasion ·Intraductal papillary adenocarcinoma with invasion
ADENOMAS	·Tubular adenoma NOS ·Lactating adenoma ·Duct adenoma NOS

MESENCHYMAL TUMORS	-
VASCULAR TUMORS	·Hemangioma NOS ·Perilobular hemangioma ·Venous hemangioma ·Cavernous hemangioma ·Capillary hemangioma ·Angiomatosis ·Atypical vascular lesión ·Lymphatic atypical vascular lesion resembling lymphangioma ·Vascular atypical vascular lesion resembling hemangioma ·Postradiation angiosarcoma ·Epithelioid angiosarcoma ·Angiosarcoma ·Epithelioid angiosarcoma
FIBROBLASTIC AND MYOFIBROBLASTIC TUMORS	·Nodular fasciitis ·Myofibroblastoma ·Desmoid type fibromatosis ·Inflammatory myofibroblastic tumor
PERIPHERAL NERVE SHEATH TUMORS	·Schwannoma NOS ·Neurofibroma NOS ·Granular cell tumor NOS ·Granular cell tumor, malignant
SMOOTH MUSCLE TUMORS	·Leiomyoma NOS ·Cutaneous leiomyoma ·Leiomyoma of the nipple and areola ·Leiomyosarcoma NOS
ADIPOCYTIC TUMORS	·Lipoma NOS ·Angiolipoma NOS ·Liposarcoma NOS
OTHER MESENCHYMAL TUMORS AND TUMOR-LIKE CONDITIONS	·Pseudoangiomatous stromal hyperplasia
FIBROEPITHELIAL TUMORS	·Fibroadenoma NOS ·Phyllodes tumor NOS ·Periductal stromal tumor ·Phyllodes tumor, benign ·Phyllodes tumor, borderline ·Phyllodes tumor, malignant ·Hamartoma
TUMORS OF THE NIPPLE	·Nipple adenoma ·Syringoma NOS ·Paget disease of the nipple
MALIGNANT LYMPHOMA	·Diffuse large B cell lymphoma NOS ·Burkitt lymphoma NOS/Acute leukemia ·Endemic Burkitt lymphoma ·Sporadic Burkitt lymphoma ·Immunodeficiency associated Burkitt lymphoma ·Breast implant associated anaplastic large cell lymphoma ·Mucosa associated lymphoid tissue lymphoma ·Follicular lymphoma NOS
METASTATIC TUMORS	-
TUMORS OF THE MALE BREAST	·Gynaecomastia ·Carcinoma ·Invasive carcinoma ·In situ carcinoma

Adapted from:
Agarwal I, Blanco L. WHO classification. PathologyOutlines.com website.
Available from: https://www.pathologyoutlines.com/topic/breastmalignantwhoclassification.html.
Accessed October 11th, 2020.

ANNEX II. BI-RADS CLASSIFICATION OF BREAST TUMORS

ULTRASOUND

Tissue composition *(screening only)*	a. Homogeneous background echotexture – fat b. Homogeneous background echotexture – fibroglandular c. Heterogeneous background echotexture	
Masses	Shape	Oval
		Round
		Irregular
	Orientation	Parallel
		Not parallel
	Margin	Circumscribed
		Not circumscribed - Indistinct - Angular - Microlobulated - Spiculated
	Echo pattern	Anechoic
		Hyperechoic
		Complex cystic and solid
		Hypoechoic
		Isoechoic
		Heterogeneous
	Posterior features	No posterior features
		Enhancement
		Shadowing
		Combined pattern
Calcifications	Calcifications in a mass	
	Calcifications outside of a mass	
	Intraductal calcifications	
Associated features	Architectural distortion	
	Duct changes	
	Skin changes	Skin thickening
		Skin retraction
	Edema	
	Vascularity	Absent
		Internal vascularity
		Vessels in rim
	Elasticity assessment	Soft
		Intermediate
		Hard
Special cases	Simple cyst	
	Clustered microcysts	
	Complicated cyst	
	Mass in or on skin	
	Foreign body including implants	
	Lymph nodes – intramammary	
	Lymph nodes – axillary	
	Vascular abnormalities	AVMs (arteriovenous malformations/ pseudoaneurysms)
		Mondor disease
	Postsurgical fluid collection	
	Fat necrosis	

MAMMOGRAPHY

Breast composition	a. The breasts are almost entirely fatty b. There are scattered areas of fibroglandular density c. The breasts are heterogeneously dense, which may obscure small masses d. The breasts are extremely dense, which lowers the sensitivity of mammography	
Masses	Shape	Oval
		Round
		Irregular
	Margin	Circumscribed
		Obscured
		Microlobulated
		Indistinct
		Spiculated
	Density	High density
		Equal density
		Low density
		Fat-containing
Calcifications	Typically benign	Skin
		Vascular
		Coarse or "popcorn-like"
		Large rod-like
		Round
		Rim
		Dystrophic
		Milk of calcium
		Suture
	Suspicious morphology	Amorphous
		Coarse heterogeneous
		Fine pleomorphic
		Fine linear or fine-linear branching
	Distribution	Diffuse
		Regional
		Grouped
		Linear
		Segmental
Architectural distortion		
Asymmetries	Asymmetry	
	Global asymmetry	
	Focal asymmetry	
	Developing asymmetry	
Intramammary lymph node		
Skin lesion		
Solitary dilated duct		
Associated features	Skin retraction	
	Nipple retraction	
	Skin thickening	
	Trabecular thickening	
	Axillary adenopathy	
	Architectural distortion	
	Calcifications	
Location of lesion	Laterality	
	Quadrant and clock face	
	Depth	
	Distance from the nipple	

MAGNETIC RESONANCE IMAGING

Amount of fibroglandular tissue (FGT)	a. Almost entirely fat b. Scattered fibroglandular tissue c. Heterogeneous fibroglandular tissue d. Extreme fibroglandular tissue		Associated features	Nipple retraction	
				Nipple invasion	
				Skin retraction	
				Skin thickening	
Background parenchymal enhancement (BPE)	Level	Minimal		Skin invasion	Direct invasion
		Mild			Inflammatory cancer
		Moderate		Axillary adenopathy	
		Marked		Pectoralis muscle invasion	
	Symmetric or asymmetric	Symmetric		Chest wall invasion	
		Asymmetric		Architectural distortion	
Focus			Fat containing lesions	Lymph nodes	Normal
Masses	Shape	Oval			Abnormal
		Round		Fat necrosis	
		Irregular		Hamartoma	
	Margin	Circumscribed		Postoperative seroma/hematoma with fat	
		Not circumscribed - Irregular - Spiculated	Location of lesion	Location	
				Depth	
	Internal enhancement characteristics	Homogeneous	Kinetic curve assessment Signal intensity (SI)/time curve description	Initial phase	Slow
		Heterogeneous			Medium
		Rim enhancement			Fast
		Dark internal septations		Delayed phase	Persistent
					Plateau
					Washout
Non-mass enhancement (NME)	Distribution	Focal	Implants	Implant material and lumen type	Saline
		Linear			Silicone - Intact - Ruptured
		Segmental			Other implant material
		Regional			Lumen type - Single - Double - Other
		Multiple regions			
		Diffuse			
	Internal enhancement patterns	Homogeneous		Implant location	Retroglandular
		Heterogeneous			Retropectoral
		Clumped		Abnormal implant contour	Focal bulge
		Clustered ring			
Intramammary lymph node				Intracapsular silicone findings	Radial folds
Skin lesion					Subcapsular line
Non-enhancing findings	Ductal precontrast high signal on T1W				Keyhole sign (teardrop, noose)
	Cyst				Linguine sign
	Postoperative collections (hematoma/seroma)			Extracapsular silicone	Breast
	Post-therapy skin thickening and trabecular thickening				Lymph nodes
	Non-enhancing mass			Water droplets	
	Architectural distortion			Peri-implant fluid	
	Signal void from foreign bodies, clips, etc.				

BI-RADS® ASSESSMENT CATEGORIES

Category 0:	**Mammography:** Incomplete – Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison **Ultrasound & MRI:** Incomplete – Need Additional Imaging Evaluation	
Category 1:	Negative	
Category 2:	Benign	
Category 3:	Probably Benign	
Category 4:	Suspicious	Mammography & Ultrasound: Category 4A: Low suspicion for malignancy Category 4B: Moderate suspicion for malignancy Category 4C: High suspicion for malignancy
Category 5:	Highly Suggestive of Malignancy	
Category 6:	Known Biopsy-Proven Malignancy	

Source:

D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013

ANNEX III. STAGING SYSTEM FOR CARCINOMA OF THE BREAST (AJCC)

- DEFINITION OF THE AJCC TNM CATEGORIES:

DEFINITION OF PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	**Tis (DCIS)***: Ductal carcinoma in situ **Tis(Paget)**: Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension **T1mi**: Tumor ≤1mm in greatest dimension **T1a**: Tumor >1 mm but ≤5 mm in greatest dimension **T1b**: Tumor >5 mm but ≤10 mm in greatest dimension **T1c**: Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules; invasion of the dermis alone does not qualify as T4 **T4a**: Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4 **T4b:** Ulceration and/or ipsilateral satellite nodules and/or oedema (including *peau d'orange*) of the skin, which does not meet the criteria for inflammatory carcinoma **T4**c: Both T4a and T4b are present **T4d**: Inflammatory carcinoma
**Lobular carcinoma in situ (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition*	

DEFINITION OF REGIONAL LYMPH NODES- CLINICAL (cN)	
cNX*	Regional lymph nodes cannot be assessed (e.g. previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s) **cN1mi**:** micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases **cN2a**: Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures **cN2b**: Metastases only in ipsilateral internal mammary nodes and in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement **cN3a:** Metastases in ipsilateral infraclavicular lymph node(s) **cN3b:** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) **cN3c:** Metastases in ipsilateral supraclavicular lymph node(s)
Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastases by SLNB of FNA/core needle biopsy respectively, with no further resection of nodes. **The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.* ***cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.*	

DEFINITION OF REGIONAL LYMPH NODES- PATHOLOGICAL (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g. not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only **pN0(i+)**: ITCs only (malignant cell cluster no larger than 0.2mm) in regional lymph node(s) **pN0(mol+)**: Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by SLNB **pN1mi**: Micrometastases (approximately 200 cells, larger than 0.2mm, but none larger than 2.0mm) **pN1a:** Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm **pN1b**: Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs **pN1c:** pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumour deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in ≥10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by SLNB in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes **pN3a**: Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0mm); or metastases to the infraclavicular (level III axillary lymph) nodes **pN3b**: pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b **pN3c**: metastases in ipsilateral supraclavicular lymph nodes
Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastases by SLNB of FNA/core needle biopsy respectively, with no further resection of nodes.	

DEFINITION OF DISTANT METASTASIS (M)	
M0	No clinical or radiographic evidence of distant metastases **cM0(i+)**: No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if non-regional nodes, metastases greater than 0.2 mm

- AJCC ANATOMIC AND PRGONOSTIC STAGE GROPUS:

ANATOMIC STAGE/PROGNOSTIC GROUPS			
STAGE	**T**	**N**	**M**
STAGE 0	Tis	N0	M0
STAGE IA	T1 (+T1mi)	N0	M0
STAGE IB	T0	N1mi	M0
	T1 (+T1mi)	N1mi	M0
STAGE IIA	T0	N1	M0
	T1 (+T1mi)	N1	M0
	T2	N0	M0
STAGE IIB	T2	N1	M0
	T3	N0	M0
STAGE IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
STAGE IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
STAGE IIIC	Any T	N3	M0
STAGE IV	Any T	Any N	M1
·T0 and T1 tumours with nodal micrometastases (N1mi) are staged as IB. *·T2, T3 and T4 tumours with nodal micrometastses (N1mi) are staged using the N1 category.* *·M0 includes M0(i+)*			

Adapted from:
Gabriel NH, James LC, Carl JD, Stephen BE, Elizabeth AM, Hope SR, et al. Breast. In: Mahul BA, ed. American Joint Committee on Cancer (AJCC). AJCC cancer staging manual, 8th ed. New York, NY: Springer, 2017:589-628

ANNEX IV. HISTOLOGICAL GRADE

The grade of a breast cancer is a prognostic factor and is representative of the "aggressive potential" of the tumour. The histological grade is determined by the Nottingham Histologic Score System (the Elston-Ellis modification of Scarff-Bloom-Richardson grading system).

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

Each of these features is scored from 1-3 and then the scores are added to give a final total score ranging from 3-9. The final total score is used to determine the grade in the following way:

- **Grade I.** Tumours have a total score of 3-5.
- **Grade II**. Tumours have a total score of 6-7.
- **Grade III.** Tumours have a total score of 8-9.

SCORE	GLANDULAR/TUBULAR DIFFERENTIATION	NUCLEAR PLEOMORPHISM	MITOTIC COUNT*
Score 1	>75% of tumour forms glands	Uniform cells with small nuclei similar in size to normal breast epithelial cells.	< 7 mitoses per 10 high power fields
Score 2	10% to 75% of tumour forms glands	Cells larger than normal with open vesicular nuclei, visible nucleoli, and moderate variability in size and shape.	8-15 mitoses per 10 high power field
Score 3	<10% of tumour forms glands	Cells with vesicular nuclei, prominent nucleoli, marked variation in size and shape.	> 16 mitoses per 10 high power fields
**The mitotic count score criteria varies depending on the field diameter of the microscope used by the pathologist. The pathologist will count how many mitotic figures are seen in 10 high power fields. The criteria above use a high-power field diameter of 0.52 mm.*			

Source:
Breast Cancer and Breast Pathology [Internet]. Baltimore: Johns Hopkins University, Faculty of Medicine; 2020. Available from: https://pathology.jhu.edu/breast/staging-grade/

ANNEX V. ASTRO EVIDENCE-BASED CONSENSUS STATEMENT FOR ACCELERATED PARTIAL BREAST IRRADIATION: RECOMMENDATIONS FOR THE TREATMENT WITH IORT

Table 1 Comparison of patient groups in original and updated consensus statements

Patient group	Risk factor	Original	Update
Suitability	Age	≥60 y	≥50 y
	Margins	Negative by at least 2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50-59 y	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the pathologic factors below and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm [a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(-) • Clinically unifocal with total size 2.1-3.0 cm [b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

[a] The size of the invasive tumor component.
[b] Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

Source:
Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol [Internet]. 2017 Mar 1; 7(2):73–9.

ANNEX VI. INTRAOPERATIVE RADIOTHERAPY PROCEDURE

1. A quality control of the IORT device is carried out by the Medical Physics Service.
2. Once the tumour resection and the sentinel node biopsy (if applicable) are performed, it is necessary to wait for the intraoperative margin assessment. A free margin of ≥2mm should be ensured.
3. The breast cavity volume is estimated with a testing applicator (a Foley urinary catheter). The balloon is filled with an adequate volume of physiological serum according to the radiation oncologist and introduced into the cavity. The balloon must be in full contact to the tumour bed.
4. The surgeons close the incision with a suture and together with the radiation oncologist verify with the sonogram that there is a distance of ≥10 mm from the balloon surface to the skin.
5. A definitive applicator of an adequate size is chosen and filled with physiological serum. It is used to replace the testing applicator.
6. Step 4 is repeated.
7. The radiation oncologist measures the distance that the source of the device has to travel to reach the applicator.
8. The applicator is connected to the IORT device and a protective blanked is placed to cover the area.
9. The medical staff leaves the operating room and IORT is applied.
10. Once the treatment is applied, the radiation oncologist disconnects the applicator and drains the balloon, checking that the emptied volume matches the introduced volume. The applicator is removed from the breast cavity.
11. Finally, the surgeons close the cavity.

ANNEX VII. PARTICIPANT INFORMATION SHEET

FULL D'INFORMACIÓ PEL PACIENT

NOM DE L'ESTUDI: AVALUACIÓ DE L'APLICACIÓ DE LA RIO EN LA CIRURGIA ONCOLÒGICA DE MAMA: UN ESTUDI TRANSVERSAL.

Ens dirigim a vostè per informar-la sobre un estudi que s'està realitzant a la Unitat de Patologia Mamària (UPM) de l'Hospital Universitari Josep Trueta de Girona i voldríem sol·licitar la seva col·laboració. El present estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Univesitari Josep Trueta.

Per què es realitza aquest estudi i quin és el seu objectiu?

Aquest estudi té com a principal objectiu avaluar l'actual Protocol d'aplicació de radioteràpia intraoperatòria en la cirurgia oncològica de mama de l'Hospital Universitari Josep Trueta.

Actualment, les pacients diagnosticades de càncer mama en estadi precoç i que compleixen els criteris del protocol són tributàries al tractament amb tumorectomia seguida d'una sola dosi de radioteràpia intraoperatòria en comptes de radioteràpia externa posterior a la cirurgia. No obstant això, algunes pacients requereixen radioteràpia externa addicional a causa de troballes desfavorables en l'avaluació anatomopatològica final.

Amb l'avaluació que es durà a terme, es pretén identificar criteris del protocol que poden ser modificats per tal d'ajustar les indicacions d'aquesta modalitat de tractament i així reduir el nombre de pacients que requereixen radioteràpia externa addicional.

Què implicarà la meva participació?

Aquest estudi és observacional per la qual cosa vostè seguirà el procediment diagnòstic i terapèutic habitual segons el protocol establert per la Unitat de Patologia Mamària de l'Hosipital Universitari Josep Trueta. No suposarà cap procediment diagnòstic ni terapèutic addicional.

El que pretenem avaluar són els resultats de la biòpsia diagnòstica (BAG) que ja se li va realitzar i de l'anatomia patològica del tumor extirpat durant la intervenció quirúrgica. D'altra banda, també volem recollir algunes dades de la seva història clínica relacionades amb la seva malaltia.

És obligatòria la participació?

La participació a l'estudi és totalment voluntària. Si decideix no participar-hi, això no afectarà ni modificarà el pla assistencial que ha de rebre ni la relació amb l'investigador.

Vostè té el dret de revocar el consentiment en qualsevol moment, sense cap mena de perjudici en el seu tractament mèdic.

Com es protegirà la meva confidencialitat?

La informació recollida en aquest estudi serà tractada segons la Llei Orgànica de Protecció de Dades de Caràcter Personal i Garantia dels Drets Digitals (3/2018) i el Reglament 2016/679 del Parlament i del Consell Europeu. Les seves dades seran tractades de forma totalment confidencial, sense accés a aquestes per part de tercers, i només seran utilitzades amb finalitat d'investigació.

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

Els resultats seran utilitzats per a la modificació de l'actual Protocol clínic per al tractament amb radioteràpia intraoperatòria de l'Hospital Universitari Josep Trueta. En cas de publicació dels resultats a través de publicacions i/o congressos per tal que altres centres i pacients puguin aprofitar les troballes del nostre estudi, les seves dades de caràcter personal són confidencials i, per tant, seran tractades de forma anònima. En cap moment serà possible la identificació dels participants.

Moltes gràcies per la seva atenció i interès.

Si té alguna pregunta no dubti en realitzar-la. L'equip que forma part de l'estudi li respondrà qualsevol dubte o qüestió que li pugui sorgir.

Si està d'acord en participar en aquest estudi, se li entregarà una còpia d'aquest document i el formulari de Consentiment Informat, que haurà de signar d'acord amb les normatives legals vigents.

ANNEX VIII. INFORMED CONSENT

CONSENTIMENT INFORMAT

Declaració de la pacient:

Jo, _____,
amb DNI _____, declaro que he llegit el document informatiu sobre l'estudi que se m'ha entregat i he estat correctament informada pel membre responsable de l'equip investigador a sota esmentat.

He rebut suficient informació sobre l'estudi i entenc que la meva participació en l'estudi és totalment voluntària.

Dono el meu permís perquè les dades de la meva història clínica siguin utilitzades per l'equip investigador per fins relacionats amb aquest estudi. He estat informada sobre l'ús de caire científic que es farà de les meves dades personals. Entenc que es respectarà la confidencialitat de les meves dades.

He pogut formular les preguntes que he considerat oportunes i entenc que puc sol·licitar la retirada i eliminació de les meves dades personals en qualsevol moment de l'estudi sense haver de donar justificacions i sense afectar la meva assistència sanitària.

Declaro que se m'ha entregat una còpia del Full d'Informació pel Pacient i una còpia d'aquest Consentiment Informat.

SIGNATURA DE L'INVESTIGADOR/A: SIGNATURA DE LA PACIENT:

DATA: DATA:

- -

REVOCACIÓ DEL CONSENTIMENT

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

SIGNATURA: DATA: