TITLE	**INTRA-OBS: Observational study of intra-operative partial irradiation of invasive ductal breast carcinomas with a good prognosis** Protocol ID: 2009/OBS-01 N° NCT : NCT04414202
SPONSOR	**CRLC [Regional Anti-Cancer Center] Val d'Aurelle** 208, rue des Apothicaires 34298 Montpellier cedex 5, France
COORDINATOR	**Dr C. LEMANSKI** CRLC [Regional Anti-Cancer Center] Val d'Aurelle 34298 Montpellier Cedex 5, France Tel: +33 (0)467613134
INDICATION	Invasive breast cancer with a good prognosis that is accessible to breast-conserving surgery.
METHODOLOGY	***Monocentric*** observational study
RATIONALE	Due to screening, T1N0 early-stage breast cancer now accounts for more than 50% of the tumors diagnosed in France. The prognosis of these tumors is good, even excellent in women ≥ 65 years of age, with specific survival of 98% at 5 years. The treatment of these tumors ~~most often~~ combines breast-conserving surgery and external whole breast irradiation for 6.5 weeks. A true de-escalation of treatment *is taking place with these tumors, both surgically and medically*. Surgery therefore now prefers breast-conserving methods in combination with exeresis of the sentinel lymph node only. In the same way, in many international studies, radiotherapy has been evaluating the possibility of reducing both: - the irradiation volume at the excision site (partial irradiation) - the duration of this irradiation (accelerated radiotherapy) Between 2004 and 2007, the CRLC [Regional Anti-Cancer Center] thus evaluated the feasibility and the oncological results of intra-operative partial irradiation via a phase II study in women 65 years of age and older with T1N0M0 hormone-sensitive tumors with a good prognosis. From 2010 to 2013, the ICM carried out an observational study of these tumors with an excellent prognosis. In July 2009, the American Society for Radiation Oncology (ASTRO) published a consensus statement with specific recommendations and indications for accelerated partial breast irradiation (APBI). This APBI technique has been developing in France over the past 5 years within the framework of clinical studies and in compliance with the 2012 recommendations of the French National Cancer Institute. This APBI can be given by 3D external radiotherapy or, as in this study, by intra-operative radiotherapy (IORT) in order to obtain optimal precision and spare as much of the surrounding healthy tissue as possible.

	We therefore propose a cohort study to prospectively analyze the results of this technique applied to the indications strictly defined by the ASTRO.
↳ **OBJECTIVES**	**Primary:** Local intra-mammary relapse rate **Secondary:** - Cosmetic results - Survival without metastatic relapse - Satisfaction of the patient with regard to her treatment - Impact of the accelerated treatment on the maintenance of autonomy in elderly patients
↳ **PATIENT SELECTION**	**INCLUSION CRITERIA**: -. Women 60 years of age or older, - Histologically proven invasive ductal breast cancer or of a histologically favorable sub-type (mucinous, tubular or colloid), -. Unifocal tumor, - T1 (diameter ≤ 20 mm), - N0 (pN0 or pNi+), - M0, - Gland exeresis margins ≥ 2 mm, - Estrogen receptor positive, - Information and non-opposition of the patient. **EXCLUSION CRITERIA:** -. Inflammatory breast cancer, - Associated peri-tumoral lymphatic - Associated extensive intra-ductal component - Invasive lobular carcinoma - Pure ductal carcinoma *in situ*, - Sarcoma or lymphoma-type non-epithelial tumor - Synchronous bilateral breast cancer, - Any prior neo-adjuvant treatment: radiotherapy, chemotherapy, hormone therapy
↳ **TREATMENT**	The treatment combines extended tumorectomy with axillary dissection (sentinel lymph node) in addition to 20 Gy of per-operative partial irradiation at the tumor site.
↳ **NUMBER OF PATIENTS**	The number of patients is based on a recruitment potential of 50 patients per year for 3 years, i.e. 150 patients.
↳ **STATISTICAL ANALYSIS**	We seek to demonstrate that the intra-mammary relapse rate is not increased, i.e. a local relapse rate for patients over 60 years of age of between 4 and 7.3% at 10 years.
↳ **STUDY PERIOD**	3 years of inclusion. 10 years of follow-up.

2- STUDY RATIONALE

Breast carcinoma remains the most common cancer in women in France, where it is currently a major public health issue, accounting for 37% of new cases of cancer (1).
Its incidence increases considerably and regularly between 30 and 60 years of age, reaching a maximum plateau (at 320 cases in 100 000) in women 60 to 80 years of age (2).

At the same time, breast cancer mortality has been decreasing since 1980 thanks to the improvement in treatments along with earlier diagnosis (1).
Therefore, the early pT1N0 stages (diameter ≤ 2 cm without lymph node involvement), which currently account for 50 to 60% of diagnosed tumors (1), have a specific survival of 88% at 5 years. This percentage rises to 96% in patients 65 years of age and older (4).

From a therapeutic standpoint, over the past 30 years, many international studies (5-7) have demonstrated that the combination of breast-conserving surgery and external radiotherapy administered over the entire breast was equivalent to mastectomy in terms of survival. It has now also been shown that the addition of this adjuvant radiotherapy to breast-conserving surgery increases overall survival (8-9). Today, this surgery consists of a tumorectomy and axillary sentinel lymph node dissection.
This radio-surgical combination is therefore the most common strategy.

More recently, studies have shown that the addition of supplementary irradiation at the excision site further reduced the risk of local relapse (10), bringing it down to 6% with no differentiation based on age after 10 years of follow-up.
Based on this, considering the most often very localized nature of this relapse, over the past years, many radiotherapy teams have developed the concept of Partial Breast Irradiation (PBI), proposing a reduction in irradiation volume (reduction in the irradiated volume of the breast, but also of the adjacent healthy organs such as the underlying heart and lungs).

This partial irradiation therefore allows for an interesting de-escalation of treatment.
Today, it is therefore being evaluated in many international studies using various irradiation techniques (interstitial curietherapy, MammoSite, intra-operative irradiation or 3D conformal radiation therapy).

At the Montpellier CRLC [Regional Anti-Cancer Center], which has a great deal of experience in intra-operative irradiation using electron therapy in breast cancer (11-12), we thus conducted a phase II study

(13) between 2004 and 2007 evaluating the feasibility and reliability of this technique within the framework of single-dose intra-operative partial irradiation for tumors with an excellent prognosis (hormone sensitive T1N0M0 invasive ductal carcinoma in patients 65 years of age and older).

With regard to the primary objective, the dosimetric results proved the reliability and reproducibility of the technique. With regard to the secondary objectives, the oncological results turned out to be good (2 intra-mammary relapses out of 42 patients and 100% of patients alive and disease-free at 30 months). The cosmetic results were also considered to be good to excellent in 90% of patients.
The immense clinical advantage of this intra-operative technique over the other partial irradiation techniques is its accelerated mono-fractionated character.
Radiotherapy is thus administered during surgery and relieves the patient of 6 and a half weeks of demanding, costly, out-patient radiotherapy that elderly patients often have a hard time accepting.
This APBI technique must however only be used in well-defined indications for tumors with an excellent prognosis for which the risk of occult microscopic disease in the rest of the non-irradiated breast is the lowest.
It was with this objective that in July 2009 the American Society for Radiation Oncology (ASTRO) reviewed all of the 4 randomized studies and the 38 published studies conducted between 1993 and 2008 regarding ABPI. This learned society then published a consensus statement (Smith, etc.) that very precisely defined the characteristics of a group of patients that could routinely benefit from this partial irradiation outside of a clinical study context.

These criteria correspond to all the points that we have retained for our phase II study conducted at the Montpellier CRLC, thus validating the routine practice today of partial irradiation for:

- patients ≥ 60 years of age
- without known BRCA1/2 genetic mutation
- with an invasive cancer (exclusion of pure ductal carcinoma *in situ*) histologically proven by biopsy
- invasive ductal type or histologically favorable type (mucinous, tubular, colloid)
- T1: tumor diameter ≤ 20 mm (radiologically on the pre-operative MRI or ultrasound and extemporaneous measurement)
- Clinical N0 (and extemporaneously)
- Of any SBR grade
- Without vascular or lymphatic emboli (on the pre-operative biopsy)
- With estrogen receptors (ER+)
- Having received no neo-adjuvant treatment

In conclusion, we are thus proposing a monocentric cohort study (this intra-operative technique is only used in France in this Center) to prospectively analyze the course of all the patients treated with intra-operative partial irradiation at the Montpellier CRLC.

3-OBJECTIVES OF THE STUDY

3.1 Primary objective

To evaluate the local relapse rate after local treatment combining extended tumorectomy with axillary (sentinel lymph node) dissection and per-operative partial irradiation of the tumor bed.

3.2 Secondary objectives

To study:

- Cosmetic results
- Survival without metastatic relapse
- Satisfaction of the patient with regard to her treatment.
- Impact of accelerated treatment on the maintenance of autonomy in elderly patients

4-METHODOLOGY

4.1 Study type

This is a monocentric observational study.

4.2 Patient registration

The patients will be seen before surgery at a pre-operative consultation. Information will be given orally and in writing (annex 2).
After checking the inclusion and exclusion criteria, eligible patients will be registered.

Registration will be carried out by fax **(+33 (0)4 67 61 37 18**) at the biostatistics coordination center of the CRLC Val d'Aurelle **during the stay in the surgical unit once the results of the extemporaneous analysis have been obtained**.

4.3 Inclusion evaluation

Patients who are eligible for the study must have an initial evaluation **during the 10 weeks prior to registration.**

This evaluation will include:
Physical examination

- WHO index, weight, height
- Bra size (band and cup size)
- 2D tumor size
- ADL and IADL indexes (annexes 4 and 5) evaluated by the investigator or CRA
- Listing of co-morbidities and concomitant treatments

Para-clinical examinations
- Bilateral mammography
- Bilateral breast ultrasound with 2D measurement of tumor size
- Breast MRI may be recommended, but remains optional
- Chest X-ray
- Liver ultrasound or abdominal CT scan
- Bone scintigraphy
- Photograph of both breasts straight on and the profile of the breast to be treated

4.4 Follow-up evaluation during the study

The follow-up of patients treated in the study is conventional monitoring in compliance with the current recommendations.
It will be based on a physical examination every semester for the first 5 years. This clinical follow-up will then be carried out annually from the 6th to the 10th year.
The para-clinical examinations will be limited to annual mammography and breast ultrasound. Breast MRI remains optional. In case of suspected local relapse (clinical and/or radiological), histological confirmation will be obtained.

The evaluation of autonomy (ADL and IADL) (annex 3) as well as the patient satisfaction index (annex 4) will be evaluated at 3 weeks, 6 months and 12 months of treatment to assess its impact.

4.5 End of study evaluation and long-term follow-up

At the end of the 10 years of observation of the study, in compliance with current recommendations, the patients will have annual clinical and radiological monitoring, as usual.

If the patient withdraws or stops the study, the examination will be carried out at the planned date on the follow-up calendar (except for withdrawal from the study for an exceptional reason with conduct of the end of study examination within the 3 days following the withdrawal).

5-PATIENT SELECTION

5.1 Inclusion criteria

1. Women 60 years of age or older,
2. Histologically proven invasive ductal breast cancer or of a histologically favorable sub-type (mucinous, tubular or colloid),

3. Unifocal tumor,

4. T1 (diameter ≤ 20 mm), as per the pre-operative MRI and/or ultrasound dimensions and after per-operative confirmation (extemporaneous examination),

5. N0 (pN0 or pNi+),

6. M0,

7. Gland exeresis margins ≥ 2 mm,

8. Estrogen receptor positive,

9. Information and non-opposition of the patient

5.2 Exclusion criteria

1. Inflammatory breast cancer,
2. Associated peri-tumoral lymphatic
3. Associated extensive intra-ductal component
4. Invasive lobular carcinoma
5. Pure ductal carcinoma in situ,
3. Sarcoma or lymphoma-type non-epithelial tumor
7. Synchronous bilateral breast cancer,
8. Any prior neo-adjuvant treatment: radiotherapy, chemotherapy, hormone therapy

6-TREATMENT ADMINISTERED IN THE STUDY

6.1 Surgery

6.1.1 Breast-conserving surgery

- Skin incision

The skin incision must be suited to the size and the location of the tumor to allow for exeresis in one piece. It must also allow for the insertion of the localizer necessary for irradiation.

- Tumorectomy:

The gland exeresis aims to obtain complete resection of the tumor, centered by pre-operative localization, with safety margins.

- Orientation of the specimen and any other resections

The surgeon must give the pathologist the oriented operative specimen and with stained margins as per the current recommendations. An extemporaneous measurement of the gland exeresis margins will always be carried out per-operatively. The tumor must be resected with a minimum gland margin of 2 mm.

- Axillary node dissection must preferably be of the sentinel lymph node type.

6.2 INTRA-OPERATIVE RADIOTHERAPY

6.2.1 Technique

Per-operative irradiation must be localized precisely on the tumor bed. The gland resection areas of the tumorectomy site are mobilized for this, brought closer together and sutured by the surgeon. A circular localizer is then placed opposite the excision site and fixed to the table using a jointed metal device in order to avoid any mobilization. Its diameter (between 4 and 6 cm) is chosen based on the tumor diameter.

The patient is then transferred under the dedicated linear accelerator located inside the surgical block. This localizer is then positioned in perfect alignment with the targeting device of the accelerator. Anesthesia monitoring of the patient is ensured during the transfer and during irradiation using several fixed and mobile monitors. The interval between surgery and per-operative radiotherapy is 30 to 35 minutes.

6.2.2 Per-operative irradiation

The choice of electron beam energy is decided by the radiotherapist based on the tumor diameter and the thickness of the area to be treated, assessed jointly with the surgeon. An energy of 6 to 13 MeV is usually used.
The dose delivered to the tumor bed is 21 Gy, which is calculated based on the isodose of 90%.

6.2.3 Remodeling and clips

After the intra-operative radiotherapy, clips will always be left in place in the tumor bed in order to facilitate later follow-up of the surgical area.
The surgeon will carry out breast remodeling in order to optimize the later final cosmetic result.

6.3 Anatomical pathology analysis

The operative and sentinel lymph node specimens are analyzed as per the conventional recommended procedures.
The limits are considered negative if there is a safety margin of at least 2mm between the tumour and the resection margin marked with ink (Fisher 1994).6.3 Additional local treatments

6.4 Conduct of the study

During the consultation with the surgeon, intra-operative partial irradiation is offered to patients who meet the recommended criteria. The patient is invited to participate in the observational study.

6.5 Systemic treatments

Chemotherapy, if necessary, will be started at least 3 weeks after surgery with per-operative irradiation.
Hormone therapy will be initiated after surgery and per-operative irradiation.

7-EVALUATION OF EFFICACY

The summary table of investigations is given in annex 1.

7.1 Primary endpoint

The primary endpoint of this study is the local relapse rate, defined as the number of intra-mammary relapses in the treated breast (regardless of the quadrant and including the skin) and homolateral lymph node, assessed at 10 years.

7.2 Secondary endpoints

- Study of survival without metastatic relapse, overall survival and specific survival.
- Evaluation of the cosmetic result (annex 4)
- Assessment of the impact of this accelerated treatment on the maintenance of subject's autonomy using the geriatric scale (ADL, IADL) (annex 3).
-Satisfaction of the patient (annex 4)

8-STATISTIC ANALYSIS

The number of patients is not limited.

However, based on a potential recruitment of 50 patients per year, this study can be analyzed after a recruitment period of 3 years, or about 150 patients.

The primary assessment will be the rate of intra-mammary relapse, which should remain the same as after traditional irradiation of the entire breast. This rate of recurrence is estimated in the age series reported by EORTC (10) between 4 and 7.3% at 10 years for patients over 60 years of age (2 to 3.7% at 5 years for exponential distribution , with a unilateral confidence interval of 10%). The finding of a number of relapses 10 / 150 cases at 5 years – during the intermediate analysis - would lead to questioning this technique.

9- REGULATORY AND ETHICAL ASPECTS

9.1 General considerations

This study does not involve changes in the management of patients related to the performance of any additional examination, does not result in the performance of any additional examination and does not change the doctor-patient relationship. It does not fall within the scope of the amended law on biomedical research, known as the Huriet-Sérusclat law of 9 August 2004.

A statement of the study will be made to the National Commission for Information Technology and Freedoms (CNIL).

The Committee on the Protection of Persons of XXXXXXX issued an opinion on XXXXXX.

9.2 Patient information

Prior to the completion of this study, the patient will be informed about the purpose of the research, the course and duration of the study, the benefits, potential risks and constraints of the study as well as the nature of the product under investigation and the advice given by the CPC (art. L.1122-1).

All information will be summarized in a patient information leaflet that will be given to each patient.

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