

STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN (SUMMARY)

Official Title: Technique of Per-Operative Radiotherapy (RPO) by Papillon +TM in Localized Breast Cancer

NCT Number: NCT03121469

Date: Version N°2.0 December 3rd 2024

1. Study Objective : Breast cancer, like the majority of cancers, has an incidence which increased with age. Breast cancer in elderly women from an age of more than 70 years is defined but even from the age of 60, a simplified conservative treatment appears to be of interest. It is reserved for well selected tumors, small sizes, with low risk of local relapse. In practice, the ratio of tumor to breast volume optimizes the selection of patients who can benefit from conservative treatment. Standard conservative treatment is represented by tumorectomy (with axillary or sentinel lymph node) associated with irradiation of the entire breast. A dose of 60 Grays in 6 weeks is considered as standard. To reduce radiation therapy, accelerated partial irradiation of the breast (IPAS) is a widely explored research pathway with several technical options. Among these IPAS techniques, per-operative radiotherapy (RPO) is an alternative that can be performed by various techniques: electrontherapy or by X-rays of 50 Kv, or even by MammositeTM or interstitial brachytherapy but in this case with an irradiation carried out at a distance from the intervention which has been used to set up the vectors to carry out this irradiation secondarily. Currently, 7 randomized trials tested the results of IPAS, including 2 in perioperative ELIOT (Electron Intraoperative therapy) and TARGIT A (Targeted intraoperative radiotherapy. The TARGIT trial started in 2003 recruited 1730 patients in the total breast irradiation arm (ITS) and 1721 patients in the partial irradiation arm (IPAS). It is a worldwide recruitment on 5 continents. It compares for the T1N0 stages after 50 years a standard treatment (tumorectomy associated with axillary node exploration and spreading irradiation: 60 Gy / 6 weeks) to per-operative radiotherapy delivering with the IntrabeamTM 50 Kv a dose of 20 Gy in 30 minutes at the surface of the tumor excision cavity. The results show, with a median follow-up of 60 months, that there are significantly more local relapses in the IPAS arm (1.3% vs 3.3%, $p = 0.042$) but that if RPO is performed during surgical time (Not deferred) the rate of local relapse is only 2.1%. There was no difference in overall survival and mortality from intercurrent disease was lower in the RPO group. The results of F Wenz and the German teams published recently at the DEGRO German Congress show that for the 185 patients included in Mannheim in the TARGIT A trial there is no local relapse at 5 years in the arm RPO and that the G3 toxicity rate is <5%. For patients included in the TARGIT E trial (patients > 70 years) out of 273 patients treated in 20 German centers, there was 1 local relapse and no severe toxicity. (Strahl 2016). The rate of patients in Germany requiring external radiotherapy is less than 3%; Indicating a good selection of patients and appropriate treatment. In Germany and Spain the RPO 50 Kv of the breast is

admitted to the financial assumption by the insurance companies. In France, a recent report (May 2016) of the HAS considers that the rendered medical service of the RPO is still not validated and that this technique must always be carried out within a framework of clinical research which justifies the present study. Alternative to Intrabeam TM. The Philips RT50TM x 50 KV radiotherapy radiotherapy device, introduced in 1948, has been used to treat skin, eyelid and rectal cancers. It could be used for breast cancer RPO to irradiate the areola-nipple plaque (MAP) after total subcutaneous mastectomy retaining PAM. Since this device is no longer manufactured, a new 50 KV device, Papillon 50TM has been used since 2009 in 10 centers in Europe (France, UK, Sweden, Denmark and Switzerland) with good results and a good tolerance in cancers of the Rectum, skin and eyelids. In 2010, the Center Antoine Lacassagne was awarded a research contract by the French National Research Agency (ANR) to develop and evaluate applicators to irradiate various tumors (skin, rectum, vagina). With the PAPILLON 50 BTM device, during the year 2011, the surgeons in the surgery of an applicator irradiating the tumoral area of excision on a volume of two thirds of sphere, made it possible for surgeons Center Antoine Lacassagne to note a good coverage of the tissues at risk of residual disease. In the TARGIT test, the Intrabeam™ irradiates a practically spherical volume. The good results of the TARGIT test and the argument of a large volume irradiated cells have justified an evolution of the Papillon 50™ device. A specific applicator was designed and tested between 2010 and 2012 to realize an RPO in breast cancer: Applicator NBA (Nice Breast Applicator) who obtained a European patent held by the Center Antoine Lacassagne. In October 2016 ARIANE put on the market a device (Papillon + TM) which, thanks to an original X-ray tube and using the NBA applicator, irradiates satisfactorily (310 °) Resection after lumpectomy. This irradiation is comparable to that achieved by the Intrabeam apparatus. The advantage of the Papillon + TM device is its high dose rate, which can deliver the dose of 20 Gy (to the surface of the NBA applicator) in 2 to 4 minutes instead of 30 minutes using the Intrabeam technique . Moreover, in view of the results of the TARGIT A trial, it is necessary to add to our RPO protocol, post-operative radiotherapy of the whole breast depending on whether the final histological result is in favor of an intermediate risk of relapse. In the absence of adjuvant chemotherapy, postoperative radiotherapy will be started within 5 to 8 weeks after surgery. The aim of this clinical research is to validate the use of the PAPILLON + TM device for the RPO of small breast cancers in patients over 60 years.

2. Study Design & Population :

Design :

Phase 1/2 study, open, monocenter, non-randomized

Population :

Female patients defined as low risk of recurrence according to the GEC-ESTRO recommendations.

3. Eligibility Criteria

Inclusion Criteria:

- Patient with grade 1 or 2 invasive ductal adenocarcinoma or ductal carcinoma in situ, regardless of grade (found on mammography by an outbreak of Single microcalcification with a diameter not exceeding 2 cm or a tumor opacity <2 cm),
- Patient aged 60 years or older (patients 60 years of age in the year may be included);
- Unilateral adenocarcinoma, unifocal, positive HR, non-overexpressed HER-2 - T1 N0 radio-clinical , Operable patient with breast volume compatible with conservative surgery,
- Patients who have been made aware of the information sheet and have given their written signed informed consent.
- Patients benefitting from social health insurance coverage.

Exclusion Criteria:

- Age less than 60 years
- Patient with grade 3 invasive breast carcinoma
- Patient with lymphatic invasion / peri-nerve involvement / vascular emboli
- Metastatic patient
- Multifocal and / or bilateral tumor
- N1 proved by ultrasound guided
- Patient with psychological and / or psychiatric disorders
- Vulnerable patient: a person deprived of liberty by an administrative or judicial decision, a major person who is the object of a legal protection measure or is unable to express his / her consent

4. Statistical Analysis Plan (SAP)

- **Primary Outcomes:** In vivo measurement of the delivered radiation dose during intraoperative radiotherapy (IORT).

- **Analysis:** Descriptive statistics were used to calculate percentages and 95% Confidence Intervals (CI).
- **Safety:** All-cause mortality was tracked descriptively. No formal sample size calculation or complex sequential modeling was required for this interventional study.