PROTOCOL

ONCOLOGICAL OUTCOME AND COSMESIS AFTER INTRAOPERATIVE PARTIAL BREAST IRRADIATION IN EARLY STAGE BREAST CANCER PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

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Iridium Cancer Network, Antwerp, Belgium
GZA, Hospitals St Augustinus, University of Antwerp

1.2. TITLE OF THE TRIAL
ONCOLOGICAL OUTCOME AND COSMESIS AFTER INTRAOPERATIVE PARTIAL BREAST IRRADIATION IN EARLY STAGE BREAST CANCER PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY.

1.3. STUDY COORDINATORS
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1.4. PARTICIPATING CENTRES
Iridium Cancer Network, Antwerp, Belgium

1.5. ETHICS COMMITTEES THAT HAVE APPROVED THE TRIAL
The Ethics Committee of GZA, Hospitals St Augustinus, University of Antwerp

1.6. MONITORING
Data centre of the department of Radiation Oncology and Translational Cancer Research Unit (CORE).

1.7. INTERVENTION
None; descriptive observational study.

1.8. OBJECTIVE
To assess the local recurrence rate, overall survival and cosmetic effect of intraoperative partial breast irradiation in female patients with early stage breast cancer.

1.9. STUDY DESIGN
A prospective study designed to assess the local recurrence rate, overall survival and cosmetic effect of patients with early stage breast cancer, treated with accelerated partial breast irradiation.

1.10. STUDY POPULATION
Patients diagnosed with early stage breast carcinoma referred for radiotherapy in the GZA, Hospitals St Augustinus.

Inclusion criteria:
- Histologically proven invasive ductal adenocarcinoma

- Patient age > 70 years and cT1
- Patient age > 80 years and cT1 or cT2
- Unicentric lesion on mammogram and MRI
- Hormone receptor positive (ER/PR)
- HER-2 status negative
- Ability to undergo mammography and US
- Planned surgery at the GZA, Hospitals St Augustinus
- Written informed consent

Exclusion criteria:

- Clear lymfovascular invasion (LVI)
- Distant metastases
- Prior irradiation of the chest wall

1.11. NUMBER OF PATIENTS

This study is descriptive by nature; therefore no formal power calculation has been performed.

1.12. MAIN OUTCOME MEASUREMENTS

The main outcome measurement is the rate of local recurrence.

1.13 SECONDARY OUTCOME MEASUREMENTS

Overall survival, cosmesis, imaging difficulties and postoperative complications

2. INTRODUCTION AND RATIONALE

Over the last three decades, breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) consisting of 5 weeks of daily external beam radiotherapy (RT) with or without additional irradiation to the tumour bed became the standard of care for early breast cancer. Multiple randomized clinical trials and meta-analyses have demonstrated the effectiveness and safety of WBI (Fisher, Clarke).

Until a few years ago, all patients received an additional boost to the former tumor bed. The EORTC boost – no boost study showed that adding a boost of 8 fractions of 2 Gy improved local control for all patients, but the largest absolute benefit was seen in young patients. Considering the increase in risk of moderate to severe fibrosis, combined with the small absolute benefit in older patients, most agree that the extra radiation dose can be avoided in most patients older than age 70 years with small, low-grade tumors. (Bartelink 2007, Bartelink 2015)

Most of the local recurrences (LR) found after breast-conserving therapy are within or close to the tumor bed. (Elkhuizen) This pattern of recurrence was confirmed by the update of the NSABP B-06 trial. (Fisher 2002) In the EORTC boost trial, however, 29% of all LR were found outside the area of the original tumor. (Bartelink 2007) Still, a recent review of BCT trials showed that the site of local recurrences after BCT was mostly in the tumor bed, with less

than 10% of LR elsewhere in the breast. (Sanders) This led to the concept of partial breast irradiation.
With accelerated partial breast irradiation (APBI), a limited volume of breast tissue is irradiated, allowing for a higher dose per fraction compared to whole breast irradiation (WBI), which is favorable considering the low α/β ratio, and thus higher sensitivity to high dose per fraction.

There are different ABPI methods available: interstitial brachytherapy (ITB), intracavitary brachytherapy, intra-operative radiotherapy (IORT) and three-dimensional external-beam radiotherapy (3D CRT). The invasive methods are frequently used for APBI, because of the advantage of delivering radiation directly to the target volume, i.e. the tumor bed. Furthermore, it is more convenient for the patient because of the considerably lower number of visits to the radiotherapy department. However, an important limitation of these methods is the absence of complete pathology information during the procedures, including information about the tumor free margins, thereby limiting the ability to define the exact area of breast tissue surrounding the lumpectomy cavity which is at risk.

Over the past several years, there has been growing interest in the use of APBI as an alternative to WBI. Several multicenter, randomized clinical trials have been initiated to compare the effectiveness and safety of APBI and WBI and the results are awaited. Meanwhile, to treat patients outside the context of prospective clinical trials, both American (ASTRO)(Smith) and European (GEC-ESTRO)(Polgar) experts published recommendations on patient selection criteria.

Results concerning cosmetic outcome after IORT APBI differ widely, ranging from good/excellent cosmetic results in 89% of the patients (Formenti 2012) to 21% unacceptable cosmesis at a median follow up of 2.5 years, leading to early closing of the trial (Jagsi 2010). Most published results involve single-centre studies with small numbers of patients and short follow-up. Emphasizing the need to investigate this in a large cohort.

3. OBJECTIVE

To assess the local recurrence rate, overall survival and cosmesis of intraoperative partial breast irradiation in older female patients with early stage breast cancer.

4. STUDY DESIGN

A prospective study designed to assess the local recurrence rate, overall survival and cosmesis of patients with early stage breast cancer, treated with accelerated partial breast irradiation.
All eligible consecutive patients will be asked to sign an informed consent form and standardized questionnaires will be filled in by the physician at fixed time points during follow-up.
For statistical analysis we will compare retrospective with a similar group of patients treated with external beam radiotherapy. This control group consists in female patients older than 70 years with a low risk histologically proven invasive ductal adenocarcinoma treated with external beam irradiation in Iridium Cancer network of the breast without a boost.

5. STUDY POPULATION

5.1. POPULATION

The study group consists of consecutive patients diagnosed with early-stage breast cancer fulfilling following criteria for partial breast irradiation:

5.2. INCLUSION CRITERIA

- Histologically proven invasive ductal adenocarcinoma
- Patient age > 70 years and cT1
- Patient age > 80 years and cT1 or cT2
- Unicentric lesion on mammogram and MRI
- Hormone receptor positive (ER/PR)
- HER-2 status negative
- Ability to undergo mammography and US
- Planned surgery at the GZA, Hospitals St Augustinus
- Written informed consent

5.3. EXCLUSION CRITERIA

- Clear lymfovascular invasion (LVI)
- Distant metastases
- Prior irradiation of the chest wall

The control group for local recurrence consists of patients older than 70 years, diagnosed with early-stage breast cancer with following characteristics: T1, grade I or II and hormone receptor positive.

6. TREATMENT / INTERVENTION

6.1 SURGERY OF THE BREAST

All patients will be treated by experienced surgeons, all located at the GZA Hospitals, St Augustinus, using state-of-the-art methods.
A wide local excision and sentinel lymph node (SLN) sampling is performed. Surgical margin status and SLN is evaluated by intraoperative cytology. If the cytology is negative, IORT is administered to the tumorbed.

6.2. RADIOTHERAPY OF THE BREAST

6.2.1. IORT

IORT will be administered directly after lumpectomy using an IORT dedicated mobile accelerator (Liac mobile linear accelerator). An applicator tube with a 4 cm to 8 cm diameter collimates the electron beam according to cover the lumpectomy coavity with a margin of 10-20 mm. High-energy electron (6–12 MeV) beam radiotherapy will be administered,

delivering a total dose of 21 Gy (prescribed at the 90% isodose) to the lumpectomy cavity. The electron energy must be sufficient to apply 21 Gy at the 90% isodose for the full thickness of the glandular tissue at risk.

7. PRIMARY AND SECONDARY OUTCOME ASSESMENT

7.1. LOCAL RECURRENCE

Ipsilateral breast tumor recurrence (IBTR) is defined as any (invasive or DCIS) recurrence within the ipsilateral breast, with or without distant recurrence. IBRT-free survival is calculated as the time from the date of diagnosis to the date of the first documented evidence of IBRT confirmed by biopsy.

7.2. OVERALL SURVIVAL

The secondary endpoint is overall survival, defined from the date of diagnosis to the date of death from any cause, or the date of last follow-up.

7.3. COSMESIS

Cosmetic outcome will be measured by different factors possibly influencing the cosmesis: postoperative complications, fibrosis, telangiectasias, pain, oedema, ulceration or atrophy. These criteria are scored before the treatment and at every follow-up visit by the physician. The cosmesis is scored by the physician on a 4-point scale. Cosmesis is graded as follows: (i) excellent —the treated breast almost identical to the untreated breast; (ii) good—there was minimal difference between the treated and untreated breast; (iii) fair— there was obvious difference between the treated and untreated breast; and (iv) poor—there was major aesthetic sequelae in the treated breast.
Finally, an overall patient reported score on a 4-point scale concerning cosmesis and function is asked as subjective self-evaluation.

8. FOLLOW-UP

Patients are monitored at 4 month intervals following completion of the treatment during the first 2 years. Subsequent follow-ups are every 6 months till 5 years after the treatment, then once yearly. The standardized questionnaires will be filled in by the physician during the first 3 years after completion of the treatment.

9. ETHICAL CONSIDERATIONS AND INFORMED CONSENT

9.1 Informed Consent

Prior to study procedures each potential patient will receive complete information about the nature and purpose of this study. A Patient Information document will be given as well as the Informed Consent form. Patients who decide to participate in this study will properly

sign the informed consent. The form will be kept in the medical file and the patient will receive a copy.

9.2. WITHDRAWAL OF INDIVIDUAL SUBJECTS

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

10. ADMINISTRATIVE ASPECTS

10.1 Handling and storage of data and documents

Before starting the treatment all patients included in this pilot study will be registered at the data centre of the Department of Radiotherapy at GZA.
The eligibility criteria must be previously evaluated. The handling of personal data will comply with the Dutch personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP) and the privacy regulations of the hospital GZA. Only persons/authorities allowed to access this data are the members of the Independent Ethics Committee of the hospital GZA, members of the research team and the Health Inspection. This might be necessary to inspect the accuracy and quality of the study.

11. REFERENCES

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