# A randomized controlled trial testing hyaluronic acid spacer injection for skin toxicity reduction of Permanent Breast Seed Implant (PBSI)

Published: 28-11-2016
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The primary objective is to evaluate and report the effect of an injected hyaluronic acid spacer on the rate of telangiectasia following PBSI.

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Breast neoplasms malignant and unspecified (incl nipple) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47314

**Source**
ToetsingOnline

**Brief title**
skin toxicity reduction of permanent breast seed implants

### Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Skin vascular abnormalities
- Breast therapeutic procedures

**Synonym**
early stage breast cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Sint Franciscus Gasthuis
**Source(s) of monetary or material Support:** Stichting Coolsingel ;Stichting Theia;Franciscus Vriendenfonds (subsidies;geen sponsor)

## Intervention

**Keyword:** brachytherapy, breast cancer, skin toxicity, spacer

## Outcome measures

### Primary outcome

Occurrence of teleangiectasia, following Bentzen's four point scale (LENTSOMA),

after 2 years.

### Secondary outcome

Local recurrence, disease free and overall survival

Side effects/ adverse events( including

o Pain (acute and late) (LENTSOMA)

o Redness

o Skin induration (acute or late CTCAE 4.03):

o Radiation dermatitis (acute) RTOG/EORTC ánd CTCAE 4.03:

o Subcutaneaous induration (late ) RTOG/EORTC

o Pigmentation (acute and late) LENTSOMA/Bentzen :

o Surgical Site Infection (Acute) CDC

Cosmetic and functional results

Health related Quality of Life

Cost effectiveness

Validation of a Dutch translation of the BCTOS questionnaire

# Study description

**Background summary**

1 out of 8 women develop breast cancer. Breast conserving therapy has been shown to be as effective as ablative therapy in the treatment of a selected group of early stage breast cancer patients. Postoperative irradiation of the breast is part of the breast conserving therapy. Along with the fact that local recurrences usually occur close to the primary tumor, this stimulated worldwide research on various forms of partial breast irradiation and cosmesis and quality of life.With Permanent Breast Seed Implant (PBSI), a form of brachytherapy, radioactive seeds are implanted percutaneously into the surgical cavity. Palladium-103 seeds, with a half-life of 16.8 days, and a therapeutic dosage after 84 days, appear to be the most appropriate for this purpose.
5-year results of several multicentre trials on Permanent Breast Seed Implant (PBSI) were reported in 2015. In total, 134 patients with early stage invasive breast cancer were treated with a permanent breast seed implant as the sole adjuvant radiation treatment after breast conserving surgery. The trials accrued patients based on the guideline for accelerated partial breast irradiation (APBI) of the American Society for Radiation Oncology (ASTRO). The outcomes included overall and disease-free survival and local recurrence at 5 years. The true local recurrence rate was compared using 2-tailed paired t tests for control estimates calculated using the Tufts University ipsilateral breast tumor recurrence and Memorial Sloan Kettering ductal carcinoma in situ nomograms. The observed local recurrence rate at a median follow-up period of 63 months was 1.2%, similar to the estimate for whole breast irradiation (1.4% p=0.23), The 5-year overall survival rate was 97.4% SD ± 1.9%, and the disease free survival rate was 96.4% SD ± 2.1%.
The most common side effects of PBSI are skin-related. Acute skin toxicity comprises a moist desquamation in 16% with PBSI, which is lower than with WBI. Late skin toxicity leads to fibrosis and induration or telangiectasia. The latter occurs in 25% of the patients after PBSI, slightly more than after WBI5. Telangiectasia corresponds to the dilation of an abnormal neo-vasculature in the skin following the destruction of normal capillaries by the radiation treatment. Due to their prominent appearance, telangiectasia have a negative effect on cosmesis, the patient*s body image and quality of life6-7. Therefore, interventions to reduce the clinical appearance of telangiectasia may impact a patient*s overall well-being or quality of life7. The use of a subcutaneously injected spacer, to increase the distance between the radiation sources and the skin, could reduce skin toxicity after PBSI. Studies in patients with prostate cancer who underwent brachytherapy, show that the use of a hyaluronic acid spacer reduced rectal dose. This spacer is reabsorbed in 6 to 12 months and is

not associated with an increased risk of infection8. Hyaluronic Acid is widely used as a dermal filler in cosmetic industry. The use of a spacer in breast cancer patients has never been done before. In this study the effect of a hyaluronic acid spacer on skin toxicity after PBSI will be investigated in a randomized controlled trial. All patients in the study will receive PBSI as sole adjuvant radiation therapy with or without spacer injection, depending on their treatment allocation. The primary outcome measure is the occurrence of telangiectasia at two years.
In addition, the effect of PBSI on cosmesis, quality of life (both patient-reported), wound infection, local recurrence and (disease free) survival and cost effectiveness will be assessed and compared to a comparable group of patients getting standard radiation treatment. This will be the first study on PBSI in Europe. If the results of this study are favourable, PBSI can be a very patient-friendly and cost-effective alternative for external whole breast irradiation in breast conserving therapy.

## Study objective

The primary objective is to evaluate and report the effect of an injected hyaluronic acid spacer on the rate of telangiectasia following PBSI.

## Study design

A multicenter double blinded, parallel group randomized controlled trial comparing the use of an injected spacer during PBSI to PBSI without spacer injection. It is set up to investigate the superiority of the intervention. Allocation ratio will be 1:1

for more details see study protocol

## Intervention

Intervention group receives PBSI treatment with spacer injection, control group receives PBSI without spacer injection.

for more details see study protocol

## Study burden and risks

Application of Barrigel or Restylane SubQ, off-label, in breast cancer patients to reduce skin toxicity during Permanent Breast Seed Implant is expected to be a safe and effective treatment. Previous studies with hyaluronic acid based injections for other indications in the breast showed no significant risks for patients.
We conclude that the benefits of the treatment when used as intended

considerably outweigh the risks.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

* Female
* Age * 50 years
* A confirmed histological diagnosis of
* invasive ductal carcinoma (IDC), Papillary/tubular/cribriform/medullar carcinoma,DCIS or combination of these tumortypes
* Treated by breast conserving surgery with axillary node dissection (with a minimum of 6 nodes sampled) or sentinel lymph node biopsy
* A maximum tumor size of 3 cm
* Clear surgical margins at ink for IDC and * 2 mm for DCIS, or re-excision negative

* PBSI technically feasible
* Node negative (axillary lymph node dissection or sentinel node biopsy), nodes with isolated tumor cells are eligible
* Informed consent signed

### Exclusion criteria

* Lymphovascular invasion
* Known allergy for hyaluronic acid
* Neo-adjuvant chemotherapy
* Active auto immune disorder with severe vasculitis component
* Uncontrolled and complicated diabetes insulin-dependent
* Pregnancy
* Cosmetic breast implants
* Pacemaker/ICD
* Psychiatric or addictive disorder that would preclude attending follow-up
* Post-operative wound infection or abscess following CDC criteria
* Lobular features on histology (pure or mixed) or sarcoma histology
* Triple negative tumors
* Extensive in situ carcinoma
* Multicentric disease (in more than one quadrant or separated by 2 cm or more)Bilateral breast cancer
* Recurrent breast cancer
* Paget*s disease of the nipple
* Metastases or active other cancer (defined by malignancy in<5 year, excluding curatively treated CIS cervix, Stage 1/grade 1 endometrium carcinoma or successfully treated non-melanoma skin cancer.
* Patients presenting with a post-surgical fluid cavity * 2.5 cm in diameter in the direction of implanted needled as determined on the planning US, resistant to 4 weeks of hot compresses application
* Clear delineation of the target volume on CT is not possible (WBR recommended)
* Having a volume to be implanted over 150cc
* Having a target volume too close to skin such that the 90% isodose overlaps the skin surface over more than 1 cm2
* Inability to read Dutch

## Study design

### Design

Study type: Interventional

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|---|---|
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 08-09-2017 |
| Enrollment: | 231 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Generic name: | subcutaneous injection of hyaluronic acid (Barrigel of Restylane SubQ) as a spacer during PBSI |
| Registration: | Yes - CE outside intended use |

## Ethics review

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| Approved WMO Date: | 28-11-2016 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 17-10-2017 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 08-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL56210.078.16 |