GROUPE EUROPÉEN DE CURIETHÉRAPIE - EUROPEAN SOCIETY FOR RADIOTHERAPY & ONCOLOGY (GEC-ESTRO)
BREAST CANCER WORKING GROUP

SINGLE-FRACTION VERY ACCELERATED PARTIAL BREAST IRRADIATION (sfVAPBI) IN LOW-RISK INVASIVE OR DUCTAL IN SITU BREAST CARCINOMA

PHASE II MULTICENTER TRIAL

National Clinical Trial Identifier Number: NTCxxxxxxxx

Study chairman:

Co-chairmen:

STUDY PROTOCOL Version 1.6

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I. SYNOPSIS

1. Rationale

Accelerated Partial Breast Irradiation (APBI) has demonstrated the non-inferiority compared to external beam radiotherapy (EBRT) in the conserving-treatment of early breast carcinoma by using high-dose-rate (HDR) multicatheter interstitial brachytherapy (MIBT). The standard treatment regimen is 7-8 sessions with two treatments per day, for a total treatment time of 4-5 days [1]. Based on 5-year results of the GEC-ESTRO very accelerated partial breast irradiation (VAPBI) phase I-II trial, in low-risk cases, 3-4 fractions delivered in 2 days reduced the overall treatment time with low rate of side effects and excellent oncological outcome [2].

Retrospective and prospective studies with a single fraction HDR MIBT-based VAPBI suggest that by further increasing the dose delivered in one fraction, the total treatment time can be reduced to a single session safely [3–5].

A phase II multicenter trial is proposed to confirm this hypothesis.

2. End points

Primary endpoints**:**

- Five-year incidence of late grade ≥ 2 side effects

Secondary endpoints:

- Incidence (5-year actuarial rate) of ipsilateral breast recurrence (IBR)
- Incidence (5-year actuarial rate) of regional relapse (RR)
- Incidence (5-year actuarial rate) of contralateral breast cancer (CBC)
- Incidence (5-year actuarial rate) of distant metastasis (DM)
- Incidence (5-year actuarial rate) of any relapse (local, regional or distant, whichever came first) for disease free survival (DFS)
- Incidence (5-year actuarial rate) of breast cancer death for cause specific survival (CSS)
- Incidence (5-year actuarial rate) of death by any cause for overall survival (OS)
- Incidence of acute side effects

- Cosmetic results at 5 years
- Quality of Life (QoL)

3. Selection criteria:

Inclusion criteria

- Stage 0 & I & II (< 3 cm) breast carcinoma
- Lesions of < 3 cm diameter
- Invasive carcinoma of any subtype and grade or DCIS
- Nodal status: pN0 or pN1mi (patients with pN1mi status can be treated, but due to the limited clinical evidence, individual decision is needed)
- M0: Absence of distant metastasis
- Clear resection margins by NSABP definition (no tumor on ink)
- Unifocal (multifocality limited within 2 cm) and unicentric breast cancer
- Age> 40 years
- Luminal A or B tumors
- Time interval from surgery preferably less than 12 weeks and no longer than 20 weeks, and from adjuvant chemotherapy less than 4 weeks
- HER2+ patients receiving postoperative anti-HER2 systemic therapy
- Specific signed consent form prior to treatment

Exclusion criteria:

- Stage II (≥ 3 cm), Stage III-IV breast cancer
- Surgical margins that cannot be microscopically assessed
- Extensive intraductal component (EIC+)
- Extensive lymphovascular invasion (LVI+) (focal is allowed)
- Triple negative breast cancer
- BRCA 1-2 mutation
- HER2+ patients not receiving postoperative anti-HER2 systemic therapy
- Neoadjuvant systemic therapy
- Paget's disease or pathological skin involvement
- Synchronous or previous breast cancer.
- Pregnant or lactating women

4. Outline

This is a prospective study, non-randomized, multicentric phase II trial. The primary outcome is late grade ≥ 2 side effects.

5. Projected accrual

250 patients in 2 years from 22 centers.

6. Treatment modality

All cases will be treated with interstitial multicatheter brachytherapy. The modality is postoperative implant, perioperative implant is not allowed.
A single fraction of 16 Gy in one day.

7. Definition of CTV and dosimetric requirements

The clinical target volume CTV will the tumor bed with a safety margin of 20mm in all directions (surgical margin + radiation margin), avoiding skin ≥5mm and pectoral muscle, as described by GEC-ESTRO recommendations [6, 7]. The volume enclosed by the reference isodose surface depends on the tumor size and on the size of the resection margins, mostly about 40-150cc.
CTV definition should be used according to the GEC-ESTRO recommendations [6, 7].
CTV dose constraints are D90≥100%, V100>95%, V150<35%, V200<15%, DNR<0.35.
Organs at risk (OARs) are skin, chest wall, lung and heart in left sided tumors. The dose values of OARs are registered according to the ESTRO-ACROP guidelines [8].
Dose volume adaptation is achieved by graphical optimization.
Dose homogeneity should be controlled keeping dose non-uniformity ratio (DNR) <0.35.
If constraints are not accomplished, the patient should be excluded from the study and can be treated with the standard approach.

8. Treatment Schedule

Time interval from final definitive breast surgical procedure to the brachytherapy implant is less than 12 weeks (84 days) and no longer than 20 weeks [8]. If patients receive chemotherapy, brachytherapy can be done before chemotherapy or not later than 4 weeks after finishing it.

9. Follow up

- Minimum follow-up frequency: 1, 3, 6 and 12 months after the implant, then annually for the first five years
- Documentation of acute side effects at 1 and 3 months
- Documentation of late side effects in the next visits
- Documentation of cosmetic results at baseline, at 6 months, 12 months and yearly thereafter until 5 years with digital photograph yearly
- Mammography annually for both breasts
- Documentation of QoL at baseline, at 3 months, 6 months, 1 year, 3 years and 5 years of follow-up

II. LISTING OF ABBREVIATIONS

APBI: accelerated partial breast irradiation

BCS: breast-conserving surgery

BCT: breast-conserving therapy

BT: brachytherapy

CI: coverage index

COIN: conformality index

CT: computer tomography

CTV: clinical target volume

CVS: cavity visualization score

DCIS: ductal carcinoma in situ

DHI: dose homogeneity index

DNR: dose non-uniformity ratio

EBI: external beam irradiation

EIC: extensive intraductal carcinoma

EORTC: European Organization for Research and Treatment of Cancer

ER: estrogen receptor

ETB: estimated tumour bed

FUP: follow-up period

GEC-ESTRO: Groupe Européen de Curiethérapie - European Society for Therapeutic Radiology and Oncology

Gy: Gray

HDR: high-dose-rate

HG: histological grade

HI: homogeneity index

IDC: infiltrating ductal carcinoma

ILC: infiltrating lobular carcinoma

ImTV: Imaging related Target Volume

Ir: Iridium

LDR: low-dose-rate

LF: local-field

LR: local recurrence

LTC: local tumour control

LVI: lympho-vascular invasion

MAST: mastectomy

MM: marginal miss

NR: not reported

NS: not significant

OARs: Organs at risk

PBI: partial breast irradiation

PR: progesterone receptor

PTV: planning target volume

QA: quality assurance

RR: relative risk

RT: radiotherapy

RTOG: Radiation Therapy Oncology Group

SMS: surgical margin status

TR: tumor bed recurrence

VAPBI: very accelerated partial breast irradiation

WBRT: whole breast radiotherapy

WS: whole surgical scar

3D: three-dimensional

III. BACKGROUND

1. APBI is a standard treatment

Some decades ago, breast-conserving surgery (BCS) overtook and replaced modified mastectomy by adding radiation therapy to the whole breast (WBI). As a result, removing the entire breast was no longer necessary because the radiation could eliminate residual tumor cells and prevent relapse. This change represented a new paradigm that was further consolidated as results on long-term effectiveness were reported [9, 10] . In the XXI century, we are witnessing another paradigm shift. For years accelerated partial breast irradiation (APBI) has been used in phase II studies, considering that, in early low-risk tumors, is not necessary to irradiate the entire breast, as the highest percentage of relapses occur in the area near the tumor or tumor bed. First a small phase III study with multicatheter technique showed that APBI is probably equivalent to WBI, but with a limited number of cases [11]. Several randomized trials were underway also with other methods of APBI, intraoperative radiotherapy (ELIOT [12] and TARGIT [13]), intracavitary [14] and external beam radiotherapy (EBRT) [15] techniques with variable results.

In October 2015, 5-year results of the European phase III study with APBI were published, using sole interstitial multicatheter brachytherapy versus WBI for low-risk invasive and in-situ carcinoma, in 1184 patients [16]. This study confirms definitively that partial breast irradiation is as effective as WBI for carefully selected patients with early breast cancer. This outcome was also confirmed by the 10-year results [1]. The cumulative incidence of local recurrence was 1.44% at five years and 3.51% at ten years with APBI in women over 40 years old, with unicentric small tumors under 3cm of diameter, with clear margins of at least 2mm, without involved lymph nodes, lymph or blood-vessel invasion, or extensive intraductal component. As consequence nowadays, adjuvant whole breast irradiation is no longer the only standard radiation treatment technique in early low-risk breast carcinomas. Worldwide the radiation oncologist can offer to patients with early breast cancer the option of APBI that allows finishing the adjuvant treatment in five days instead of 3-6 weeks and receiving at least fourfold lower doses of radiation to the heart and lung compared with WBI.

At this moment, we can confirm these good results particularly with the multicatheter brachytherapy technique, which allows to insert as many catheters as needed to cover a

wide clinical target volume (CTV) around the tumor bed. In summary, the partial breast irradiation is the reasonable excellent adjuvant treatment modality in selected patients with early-stage breast cancer.

2. Rationale for very accelerated partial breast irradiation

The primary rationale for APBI is the convenience for patients, the APBI makes possible to finish the whole radiation treatment in 4-5 days instead of 3-6 weeks. The lower dose to the organs at risk (OARs) is another important issue for use of APBI. In the U.S., the more frequent fractionation is 3.4 Gy x 10 sessions in five days. In Europe, a fractionation scheme of 7-8 fractions is usually employed.

Importantly, we know that the α / β ratio for breast cancer is low, about 4, therefore the fraction sensitivity of breast cancer can be exploited with higher fraction sizes, resulting in even more compressed treatment times [17]. This option would be advantageous for further reduction the total treatment time to finish the whole breast conserving procedure. But we must be careful for not to exceed the tolerance of normal tissues. The therapeutic window is narrow and the tumor control needs years to be confirmed. A too high dose per fraction can result in increase of complications, and a too low dose per fraction can yield high rates of recurrences.

In 2017, the GEC-ESTRO Breast Cancer Working Group started a Phase I-II trial to study if very accelerated partial breast irradiation (VAPBI) using 3–4 fractions could be equivalent to the standard 7-10 fractions. Eighty-one patients with low-risk invasive carcinomas underwent HDR MIBT. Thirty-three women received 4 fractions of 6.25 Gy in 2–3 days, and 48 subsequent patients 3 fractions of 7.45 Gy in 2 days. With a median follow-up of 62 months, the 5-year actuarial breast recurrence was 3.4% (two cases of local relapse). Gr.I. skin toxicity was 12.3%, gr.I. and gr.II. fibrosis was 22.2% and 9.9%, respectively. Cosmetic outcome was good or excellent in 95% [2].

In the TRIUMPH-T trial 185 low-risk breast cancer patients treated with brachytherapy applicators. Total dose was 22.5 Gy in 3 fractions of 7.5 Gy. With a median follow-up of 3.63 years there were 2 (1.1%) ipsilateral local recurrences, Grade 3 fibrosis at the treatment site was present in 1.7%, and the cosmesis were excellent or good in 94% of patients [18].

Workflow optimization of sfVAPBI:

Based on a description published in 2023, the sfVAPBI procedure optimization makes it possible to provide adjuvant breast irradiation for low-risk breast cancer patients during a single session (one round trip), including pre- and postirradiation consultations, as well as a 5-hour VAPBI procedure in 7 different steps [19].

Feasibility of sfVAPBI:

In Nice, 26 elderly patients with early breast cancer were enrolled in a prospective phase II trial. After lumpectomy a single fraction 16 Gy APBI was performed. After a median follow-up of 63 months, 5-year local recurrence-free survival, metastasis-free survival, cancer-specific survival, and overall survival rates were 100%, 95.5%, 100%, and 88.5%, respectively. There was no grade 3 side effect. Cosmetic evaluation was excellent or good in 100% [3].

Preliminary results for efficacy and toxicity of sfVAPBI:

In the study of Hannoun-Levi et al., two cohorts of 157 older patients with low-risk breast cancer treated with APBI were analyzed retrospectively. A total dose of 34 Gy in 10 fractions (109 pts.) or 16 Gy in 1 fraction (48 pts.) was delivered. After a median follow-up of 97 and 72 months, no significant difference was observed between the two groups for local recurrence, regional recurrence, distant metastases, disease-free survival, cause-specific survival and overall survival, further in terms of late toxicity and cosmetic results [5].

In a retrospective multicenter study 516 patients with low-risk breast cancer underwent lumpectomy + VAPBI, which was performed with 4 (4x6.2 Gy/2d, 144 pts.), 3 (3x7.45 Gy/2d, 167 pts.) or 1 fraction (1x16Gy or 1x18Gy/1d, 205 pts.). After a median follow-up of 44 months, the four-year cumulative incidence rate of local recurrence was 2%. Grade 2 and 3 late toxicities were observed in 7.2 and 0.6% respectively (no Gr.4) with no difference between 1 and ≥ 2 treatment days [4].

Quality of life after sfVAPBI:

Based on an auxiliary studies of the previously mentioned Nice investigation, APBI based on a single fraction of MIBT in older adults with low-risk breast cancer, appears to be feasible with a minimal loss of autonomy regarding Instrumental Activities of Daily

Living, no loss of autonomy in Activities of Daily Living, an acceptable decrease in other Comprehensive Geriatric Assessment Domains, and with no impact on global quality of life [20].

These investigations suggest that VAPBI in one-to-three days is feasible to decrease the total time of treatment.

3. Selecting the right dose per fraction

The way to choose the right dose and fraction is based on BED calculations. A comparison of APBI protocols is done by Rosenstein et al [21]. Depending on the α / β ratio the BED changes a lot. When we calculating with the generally accepted $\alpha / \beta = 4$ value of breast tumor, the standard 10 x 3.4 Gy, 8 x 4 Gy and 7 x 3.4 Gy have a BED_4 of 63-64 Gy. If we use only 4 fractions, the right dose per fraction should be 6.25 Gy, and with three fractions should be 7.45 Gy.

By the same reasoning, 16 Gy applied in one fraction shows higher BED and EQD2 values than previously mentioned more fractionated treatments (Table 1.).

However, these higher values are necessary. This is because the specific radiobiological effects of the possible reduction in re-oxygenation and re-arrangement must be taken into account when using a high dose delivered in a single fraction [22].

Furthermore, in the case of a single fraction, cells are unable to re-arrange through the cell cycle. Cells in more radio-resistant phases of the cell cycle, such as the S phase, tend to exhibit a greater level of survival compared with cells in more radiosensitive phases, such as G2 or mitosis [23].

From another point of view, the use of the linear quadratic model remains questionable for dose per fraction higher than 8 Gy.

On the whole, taking all this into account, the dose used for single-fraction treatment was determined on the basis of the local tumor control and acute/late side-effect results of the above-mentioned studies [3–5].

	Treatment days	Total dose (Gy)	BED Gy_4	BED Gy_{10}	BED Gy_2	EQD2 Gy_4
10 x 3.4 Gy	5 - 7	34	63	46	92	42
8 x 4 Gy	4 - 5	32	64	45	96	42.7
7 x 4.3 Gy	4	30.1	63	43	96	41.6
4 x 6.25 Gy	2 - 3	25	64	40.6	103	42.7
3 x 7.45 Gy	2	22.35	64	39	105.6	42.65
1 x 16 Gy	1	16	80	41.6	144	53.33

Table 1. Biological effective dose with different fractionation schemes

IV. OBJECTIVES-END POINTS

Primary endpoints:

- Five-year incidence of late grade ≥ 2 side effects

Secondary endpoints:

- Incidence (5-year actuarial rate) of ipsilateral breast recurrence (IBR)
- Incidence (5-year actuarial rate) of regional relapse (RR)
- Incidence (5-year actuarial rate) of contralateral breast cancer (CBC)
- Incidence (5-year actuarial rate) of distant metastasis (DM)
- Incidence (5-year actuarial rate) of any relapse (local, regional or distant, whichever came first) for disease free survival (DFS)
- Incidence (5-year actuarial rate) of breast cancer death for cause specific survival (CSS)
- Incidence (5-year actuarial rate) of death by any cause for overall survival (OS)
- Incidence of acute side effects
- Cosmetic results at 5 years
- Quality of Life (QoL)

V. STUDY SUMMARY

1. Design

This is a prospective study, non-randomized, multicentric phase I-II trial developed in different countries. The primary outcome is incidence and severity of grade ≥ 2 late side effects.

2. Study duration

Start of the study: March 2025
Duration of patient recruiting: 2 years
Duration of therapy: 1 days
Follow-up: max. 5 years
End of study: 2032

3. Participating centers

This is a multicenter study. Each investigator (study center) must be registered (See appendix).
Each investigator or group of investigators must obtain local ethic committee approval for this protocol before they can enroll patients.
Further it must be guaranteed, that the participating center can recruit at least 3 patients per year, can ensure appropriate quality assurance and also make possible for members of the study group to control it, if necessary.

VI. PATIENTS

1. Number

The sample size must be 250 patients in 2 years.

2. Inclusion criteria:

- Stage 0 & I & II (< 3 cm) breast carcinoma
- Lesions of < 3 cm diameter
- Invasive carcinoma of any subtype and grade or DCIS
- Nodal status: pN0 or pN1mi (pts. with pN1mi status can be treated, but due to the limited clinical evidence, individual decision is needed)
- M0: Absence of distant metastasis
- Clear resection margins by NSABP definition (no tumor on ink)
- Unifocal (multifocality limited within 2 cm) and unicentric breast cancer
- Age> 40 years
- Luminal A or B tumors
- Time interval from surgery preferably less than 12 weeks and no longer than 20 weeks, and from adjuvant chemotherapy less than 4 weeks
- HER2+ patients receiving postoperative anti-HER2 systemic therapy
- Specific signed consent form prior to randomization

3. Exclusion criteria:

- Stage III-IV breast cancer
- Surgical margins that cannot be microscopically assessed
- Extensive intraductal component (EIC+)
- Extensive lymphovascular invasion (LVI+) (focal is allowed)
- Triple negative breast cancer
- BRCA 1-2 mutation
- HER2+ pts. not receiving postoperative anti-HER2 systemic therapy
- Neoadjuvant systemic therapy
- Paget's disease or pathological skin involvement
- Synchronous or previous breast cancer.
- Pregnant or lactating women

VII. THERAPY

Below - taking into account the ESTRO recommendation of breast cancer clinical trials [24] - we establish in details the quality assurance, the guideline of target volumes and OARs delineation, dose/fractionation, templates, planning objectives for target volumes, constraints for OARs and techniques.

1. Timing of surgery and brachytherapy

Time interval from final definitive breast surgical procedure to the start of brachytherapy is preferably less than 12 weeks (84 days) and no longer than 20 weeks [8]. If patients receive chemotherapy, the brachytherapy can be started before systemic treatment (within 12 weeks). It is also possible to start radiation therapy after chemotherapy is completed according local protocols as soon as possible within 4 weeks after chemotherapy.

2. Target definition

The target volume consists of the tumor bed with an adequate safety margin in all directions. The "clinical target volume" (CTV) is in this case identical with the "planning target volume" (PTV). In some cases, restrictions have to be made in direction to the chest wall and skin, which is inevitable and unavoidable. For such cases, the boundaries of the CTV should be redefined as 5-7 mm below the skin surface, and 5 mm above the underlying ribs. The knowledge of the tumor-free margins is important, since the size of safety margins of implant volume depends on the size of these tumor-free resection margins. The distance of the border of the CTV (safety margin) to the tumor surface (tumor margin) must be at least 20 mm, because this area contains 80% of the microscopic tumor extensions around the primary macroscopic tumor. From these results we conclude: 20 mm minus the minimum tumor-free resection margin (A) is the safety margin (B) included in the CTV. The larger the tumor-free resection margin, the smaller the safety margin, so CTV: B = 20 - A (mm). (e.g. if the pathologist describes a minimum resection margin 12 mm lateral, 2 mm medial, 5 mm cranial, and 10 mm caudal, then the minimal

safety margin should around the tumor cavity (surgical scar, clips) should be lateral >8 mm, medial >18 mm, cranial >15 mm and caudal >10 mm).

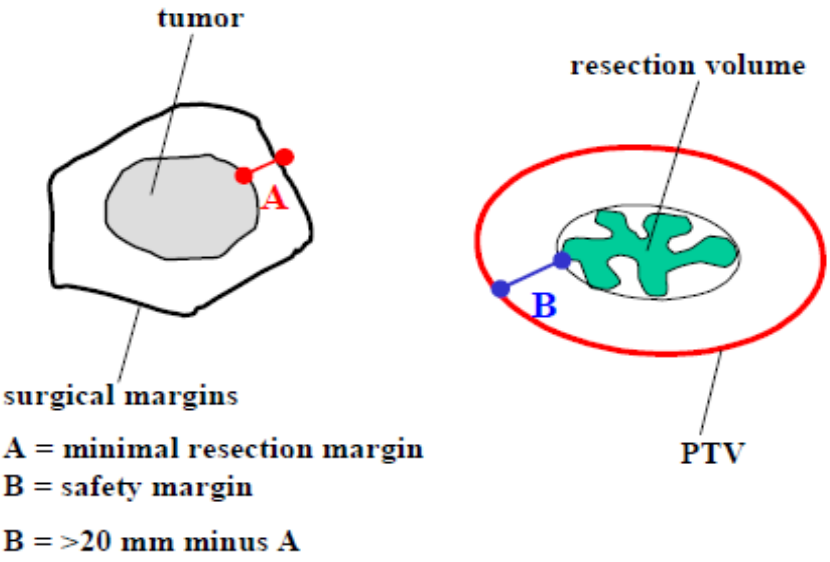


Figure 1. Definition of CTV and PTV

Of course, in most cases, these margins include a large amount of tissue in the lateral directions and especially in the direction to the nipple. Breast skin or thoracic wall are not the target volume for brachytherapy alone. The overlying skin is usually surgically removed with the superficially located tumors, and the residual skin does not need any treatment. For the localization of the target volume, any information source has to be taken into account, because the surgical scar alone is not enough for tumor bed localization.

The physician carries the responsibility for the planning of the implant and for the definition of the CTV. Before the insertion of catheters it is obligatory to know: mammograms and ultrasound images, surgical report and written histological findings. In the histological findings the description of the tumor-free resection margins in mm in all dimensions are important. Also, the CT or MR investigation can be helpful. It is optimal, if the tumor bed is marked with clips, ideally with 6 clips indicating the cranio-caudal, medio-lateral and antero-posterior borders of the resected volume.

The definition of CTV for adjuvant breast irradiation has evolved and the GEC-ESTRO Breast Working Group has published two recommendations for cases with closed cavity

and open cavity [6, 7]. Some surgeons close the cavity of tumorectomy and the postoperative CT planning is unable to distinguish a cavity to be delineated (closed cavity technique). It corresponds to the Cavity Visualization Score (CVS) 1, 2 and 3. In other cases, the surgeon leaves the cavity opened, which is fulfilled with blood or seroma. In this situation, surgical cavity can be delineated and a margin added to define the CTV (open cavity technique). It corresponds to the CVS 3, 4 and 5 [25, 26].

3. Delineation of the target

Delineation of the target – CTV (PTV) in closed cavity [6]

The following seven steps for target delineation after closed cavity surgery are recommended:

a. Perform a CT with radiopaque marks on the skin scar and nipple.
b. Delineation of clips, decide relevant and irrelevant clips (e.g. clips on the chest wall far from the tumor site, mark the surgical cavity, not the tumor bed, and are irrelevant).
c. Delineation of surgical bed – whole surgical scar (WS) inside the breast, if visible, from the skin scar to the bottom clips.
d. Delineation of ImTV (Imaging related Target Volume), defining the distance from the tumor to the skin and the chest wall in image studies.
e. Delineation of ETB (Estimated Tumour Bed): The addition of relevant surgical scar, clips and ImTV.
f. Delineation of CTV (Clinical Target Volume): Add a margin to the ETB according to the pathological distances to complete at least 20mm.
g. Delineation of PTV (Planning Target Volume). In case of uncertainties on position of clips – typically by large-breasted patients or in case of absence of clips or impaired visibility of surgical scar or cavity, an adapted PTV margin (5 to 10 mm) in the region of doubt can added.

   In the case of oncoplastic surgery no recommendations can be given, but CTV can be considered as the sum of the clipped area and the distance of 20 mm minus the smallest surgical free margin.

Delineation of the target – CTV (PTV) in open cavity [7]

At delineation of surgical cavity only the homogeneous part of the postoperative seroma has to be included in the contours and protrusions or sharp irregularities have to be excluded. When surgical clips are present, they have to be surrounded by the contour with close contact.

CTV is created from the outlined surgical cavity with a non-isotropic geometrical extension. In each direction the safety margin is calculated by taking into account the size of the free resection margin. The total size of safety margin is always 20 mm, which is the sum of the surgical and added safety margins. CTV is limited to chest wall/pectoral muscles and 5 mm below the skin surface.

4. Techniques

Breast implants can be carried out under general or local anaesthesia. For the implantation are needed: 20 cm long implantation needles (guide needles), templates in different sizes (with channels in square or triangular arrangement and with distances of the channels between 12 and 18 mm) (Fig. 2.).

The patient is placed in supine position with the ipsilateral arm in 90° abduction. Once the tumor centre is localized, and the three dimensions of the CTV and the PTV (length, width, and thickness) are defined and delineated on the patient's skin, implantation of the first needle follows, the so-called "guidance needle or reference needle" without or with template.

The position of this needle has to be selected in such a manner, that this needle is placed under the deepest place of the tumor bed and in the center of the lowest level of the implant. It is important to consider both the position of the clips and the tumor position in the preoperative mammograms (the tumor distance from the thorax wall is represented only in the preoperative ultrasound and mammography pictures!).

To ensure that the following needles will be implanted parallel and equally distant from each other afterwards a template of suitable size is placed over the guidance needle. Then the needles are implanted according to the rules of the Paris System parallel and equally distant from each other. In most cases, preferably they are inserted in a medio-lateral or cranio-caudal direction. In the outer quadrants it is possible to implant with needles orientated in a 45° angle. Usually, two or three planes of needles are implanted. A single plane implant is not allowed. Number and spacing between needles (template size) is

chosen to adequately cover the width and the thickness of the PTV. Nine to eighteen needles spaced 12-18 mm are usually required. Guide needles must be replaced by plastic tubes immobilized by buttons at both sides of the breast.

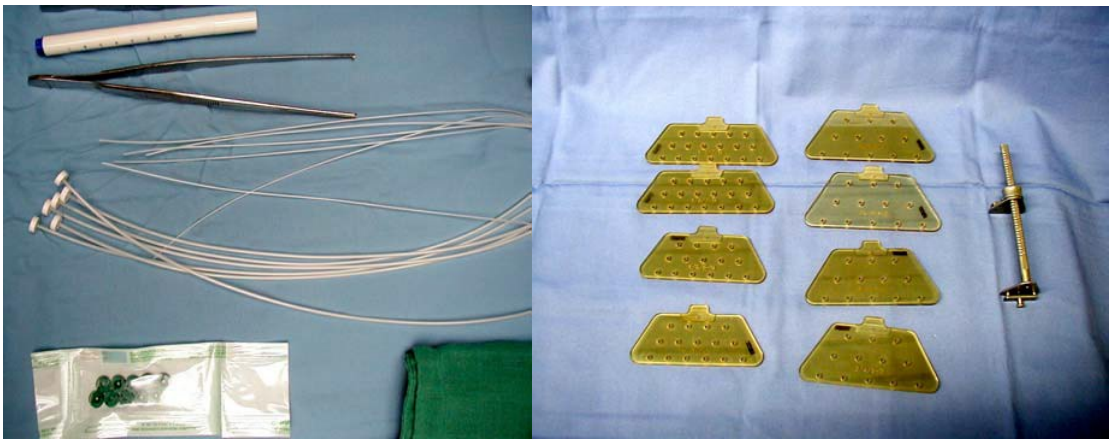


Figure 2. Plastic catheters and templates

An implantation of needles on a quadrant of the breast can be performed under a clinical assessment of the tumor bed, but the risk of geographical miss exists. Hence some image system to define the CTV to be implanted is mandatory. Depending on whether clips are present or not, and whether a residual open cavity is visible or not, several techniques are useful.

<u>CT guided implantation with open cavity:</u>

Pre-implant CT-scan for planning of the implant geometry and confirm that a CTV can be delineated, and post-implant CT-scan for treatment planning and documentation is mandatory.

CT-image based preplanning of implant geometry and PTV: A full CT-scan (with 3mm slice reconstruction thickness) of the breast should be done with template on the breast. Following contouring of the excision cavity in each slice, the

CTV can be generated manually or automatically by adding an appropriate safety margin around the excision cavity. Then, the boundaries of the PTV should be modified (if necessary) to 5-7mm below the skin surface, and 5 mm above the underlying ribs to avoid skin teleangiectasia and rib fracture. Following 3-D reconstruction of the PTV, position of implant needles can be defined using the needle-eye-view technique (Fig. 3.).

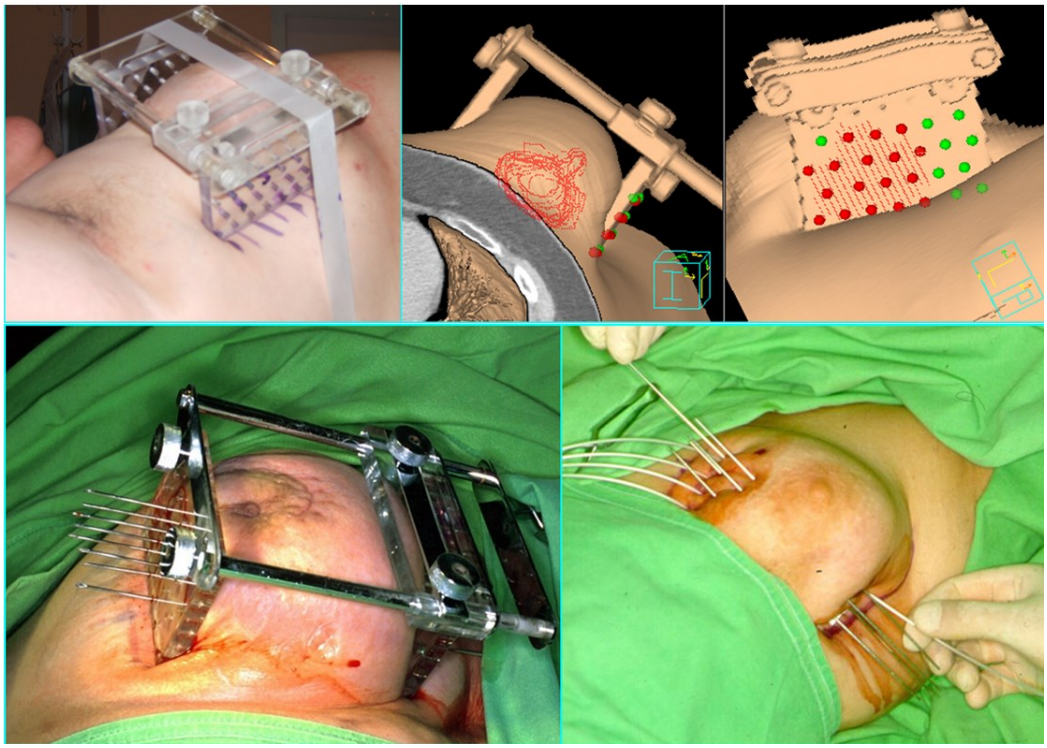


Figure 3. CT guided implantation with open cavity

Ultrasound guided implantation with open cavity:

Ultrasound can be used to delineate the open cavity. The needles are inserted and the position is verified to cover the whole cavity with margin. The number of planes is decided according to the cavity size (Fig. 4.).

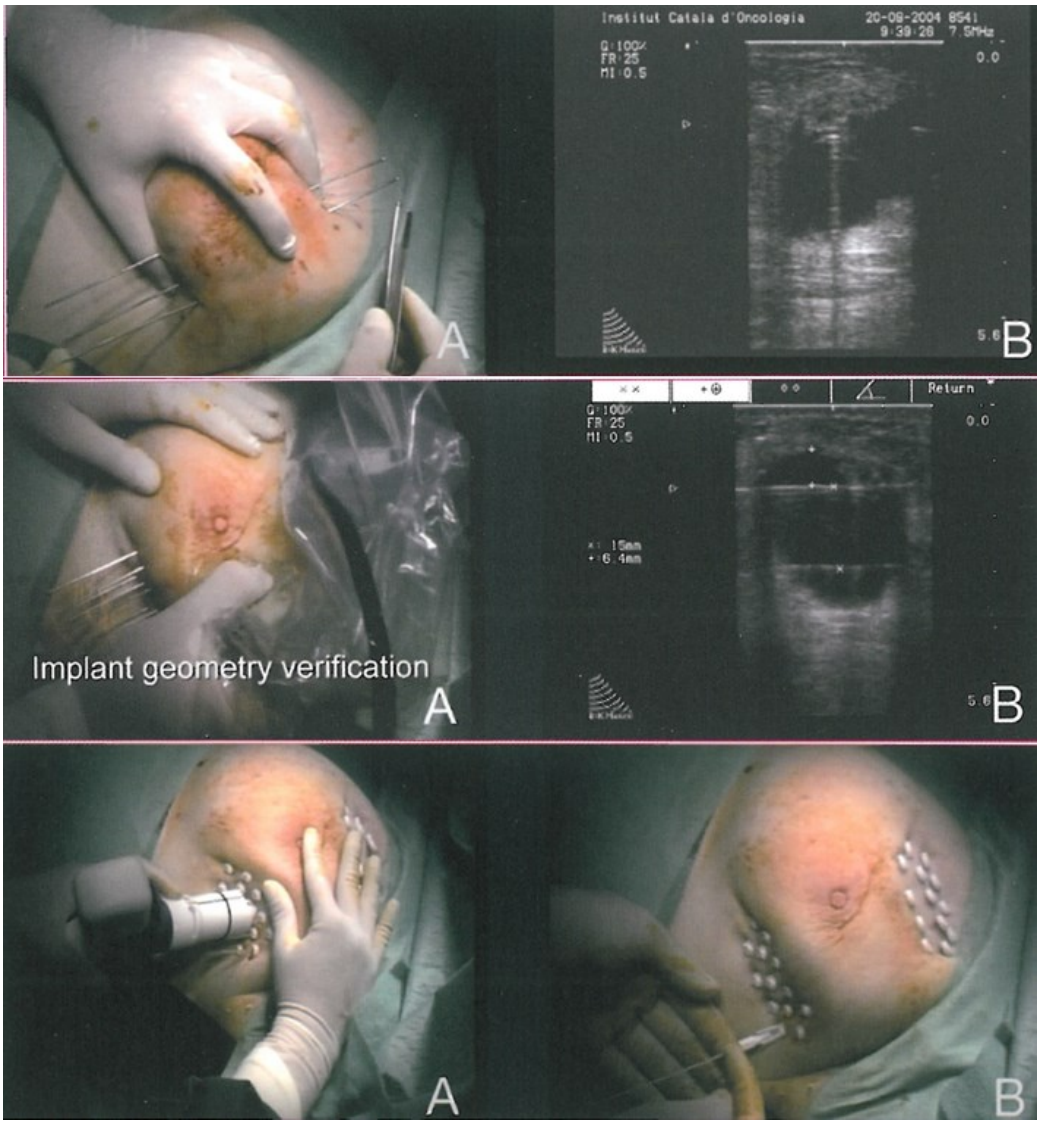


Figure 4. Ultrasound guided implantation with open cavity.

X-Ray guided implantation when clip marking of the tumor bed is present:

Under x-ray control, e.g. with the help of a conventional simulator or an Integrated Brachytherapy Unit (IBU) or a CT unit, the position of the clips and so the tumor bed are identified. Pre-implant CT scan and CT-based treatment planning is recommended. The optimal direction of the needles is determined and the appropriate point for insertion (entrance and exit points) of the needles at the skin is marked. As an alternative making a CT simulation on the basis of the same markings is acceptable. Post-implant CT scan is obligatory (Fig.5.).

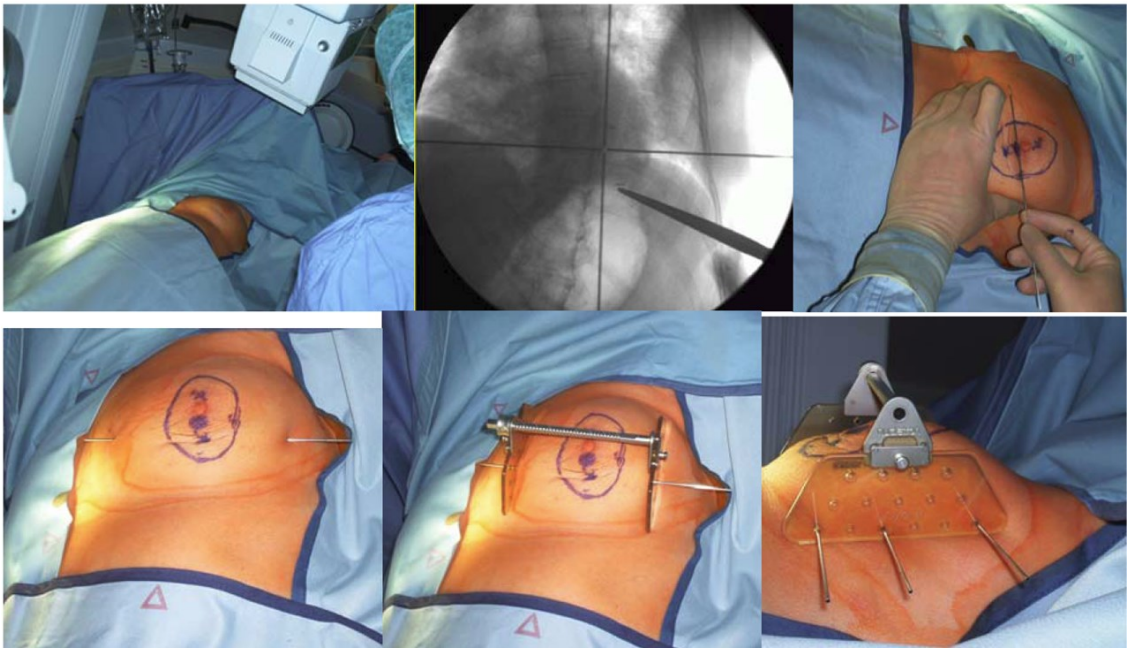


Figure 5. X-Ray guided implantation with closed cavity and clips markers.

Ultrasound guided implantation with closed cavity:

With closed clavity, a preplanning CT is mandatory in order to be sure that some marks allow us to know how to draw a CTV. Scar inside the tissue or clips, are necessary to do a clinical assessment of the volume to implant and be able to draw on the skin the volume to be implanted. Starting the procedure, with ultrasound, the scar is visible as a grey area under the skin compared with normal lobular areas. The distance from skin to the chest wall is measured and the deepest needle is visualized and corrected to keep it at the right position according to the depth where the tumor was placed in the mammograms. The rest of the needles are inserted and the number of planes is decided according to the distance to the skin (Fig. 6.).

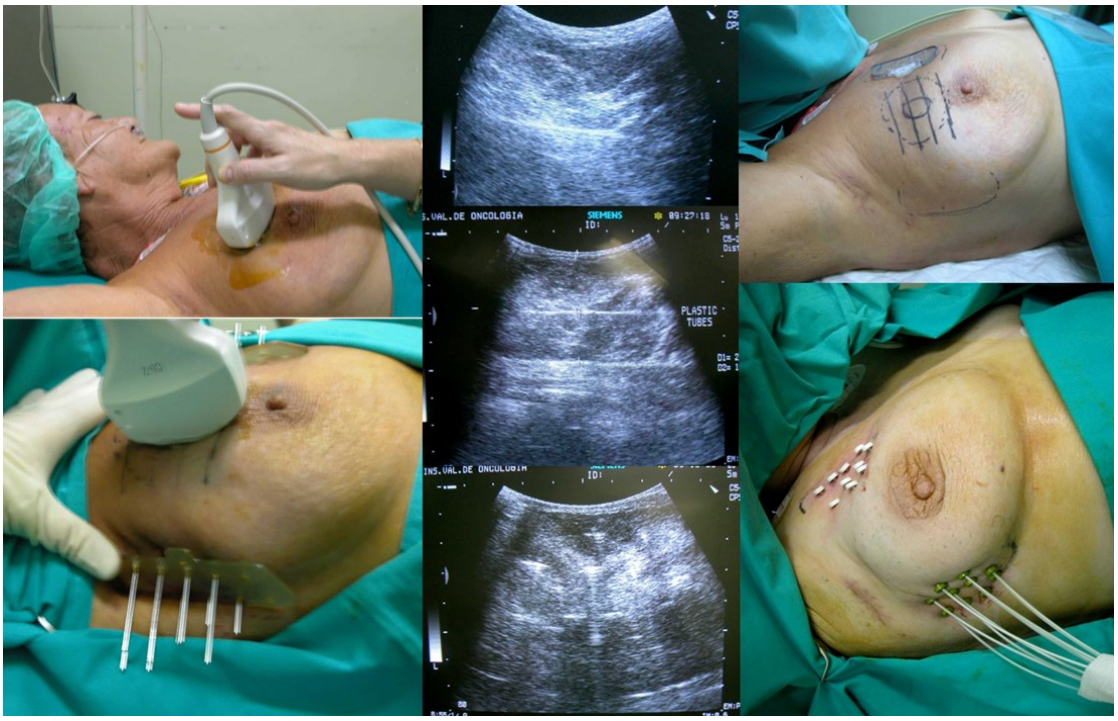


Figure 6. Ultrasound guided implantation with closed cavity.

5. CT-image based treatment planning:

After implantation a CT-scan (with ≤ 3 mm slice thickness) of the implanted breast should be performed for evaluation of the PTV coverage and planning. Following contouring of the excision cavity, the PTV can be generated as described previously (Fig. 7, 9.). When an open cavity is visible, diluted contrast can be inserted to better visualize the margins. The active source positions can be defined individually in each catheter.

Dose specification and prescription should be done according to the Paris system [27].

Geometrical dose optimization is allowed. The dose is usually prescribed to 85% of the MCD.

DVH analysis should be used to confirm that 100% of the prescribed dose covering >90% of the PTV (i.e. CI >0.9). If adequate coverage cannot be achieved, prescription of dose to a lower percentage isodose is allowed, keeping the DNR below 0.35. Otherwise, the implant should be improved with the addition of new implant catheters.

An alternative way of dose prescription for CT-image based treatment planning is to generate automatically dose points on the surface of the 3D reconstructed PTV (Fig. 8.).

Following the geometric optimization for volume implant, the dose can be prescribed to the “dose points on target”, keeping the DNR below 0.35. DVH analysis should be used to confirm that 100% of the prescribed dose covering >90% of the PTV (CI >0.9). If adequate coverage with acceptable dose homogeneity cannot be achieved, then the implant should be improved with the addition of new implant catheters. Reporting the value of MCD is mandatory.

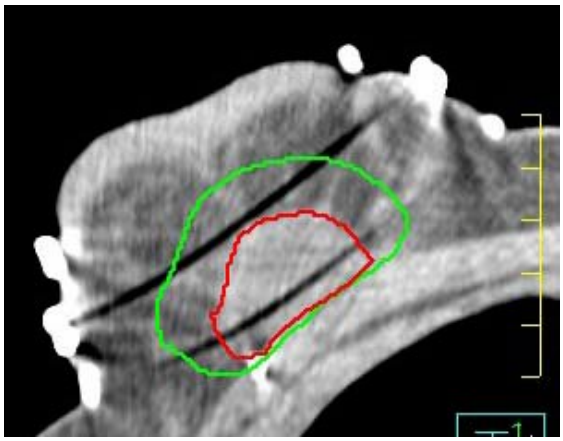


Figure 7. Post-implant CT-image based definition of the PTV. Excision cavity (red); PTV (green)

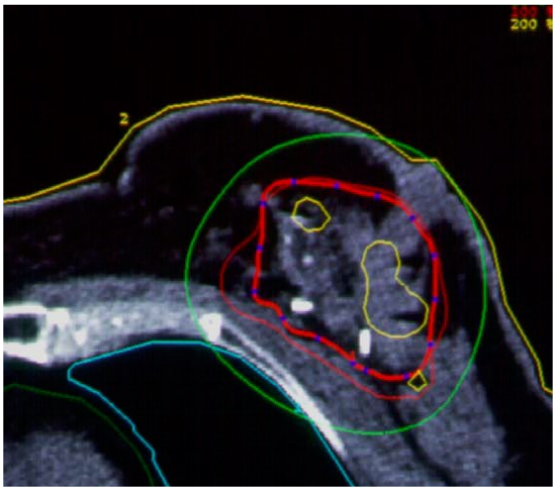


Figure 8. Dose prescription to “dose points on target”. PTV (thick red line); dose points defined on the surface of the PTV (blue points); 100% isodose line (thin red line); 50% isodose line (green line).

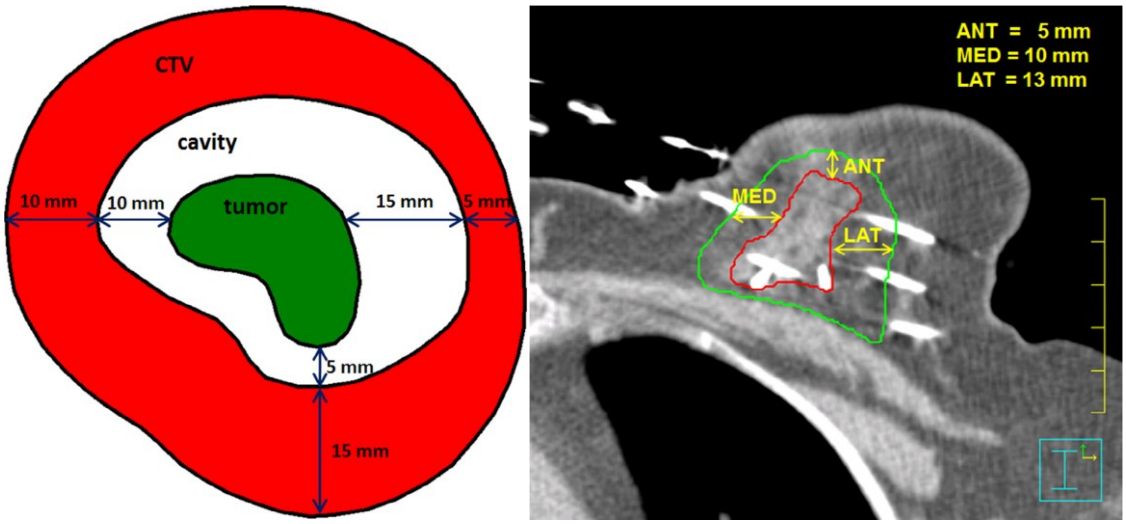


Figure 9. Schematic representation of relation of the resection cavity to the CTV. In all directions the total margin around the tumor is 20 mm. Different margins in anterior (ANT), medial (MED) and lateral (LAT) directions around the cavity (red) which have been calculated by taking into account the tumor-free surgical margins.

Treatment parameters for CT-image based planning:

- DVH analysis of target coverage will confirm 100% of the prescribed dose covering >90% of the PTV (CI >0.9).
- DNR (V150%/V100%) <0.35.
- Maximum skin dose <70%.
- For reporting values of volume of Dref, 1.5 x MCD, 1.5 x Dref, surface CI, DNR, MCD, DHI, COIN should be also given (see Appendix)

6. Dose specification

When treating with a single stepping source the length of the source steps has to be determined in that way, that the reference isodose encloses the tumor bed with an adequate safety margin (PTV). The reference isodose corresponds the MTD according ICRU 58 (in the ideal case congruently with the CTV). For this, several reference points according to ICRU 58 in the central implant plane must be defined. Calculating the

average value of doses at this individual reference points we receive the so-called "mean central dose" (MCD).

The reference dose enclosing the target volume is usually defined within the range of 80-90% of the MCD (usually 85%). A specification on isodoses smaller than 80% of the MCD has the consequence that the percentage of volume which is enclosed by larger isodoses (120 - 150%), increases. To avoid unwanted overdosing, we advise against this procedure. If the prescription isodose is lower than 80%, the DNR must be <0.35 (preferably <0.30). If these dose prescription and homogeneity constraints are not fulfilled, it must be the consequence to implant additional needles/catheters. It is necessary therefore that during the implantation the target volume must be covered by a sufficient number of needles/catheters.

The volume enclosed by the reference isodose surface depends on the tumor size and on the size of the resection margins (size of the PTV) - mostly about 40 - 200 cc. A volume over 200 cc should be exceeded only in justified cases. Smaller volumes mostly develop with a one-plane implant, which is not allowed in this study! As additional parameter for the quality of the implant the DNR must be calculated. The dose distribution is seen as sufficiently homogeneous, if the DNR is <0.35 (preferably <0.30). If these criteria are not fulfilled, physician and physicist should clarify the causes and look for improvements for the further procedure on an individual basis.

Recommended dose-limits for implant and PTV (adapted from [8]):

	Constraints
Implant	$V_{PD} \leq 200\ cm^3$ $DNR \leq 0.35$
PTV	$V_{100} \geq 90\%$ $V_{150} < 65\ cm^3$ $V_{200} < 15\ cm^3$ $COIN \geq 0.65$

Recommended dose-volume limits for OARs [8]:

Organ	Constraints
Ipsilateral non-target breast	$V_{90} < 10\%$ $V_{50} < 40\%$
Skin*	$D_{1cm3} < 90\%$ $D_{0.2cm3} < 100\%$
Rib	$D_{0.1cm3} < 90\%$ $D_{1cm3} < 80\%$
Heart**	MHD < 8% $D_{0.1cm3} < 50\%$
Ipsilateral lung	MLD < 8% $D_{0.1cm3} < 60\%$

* Skin volume is defined as a 5 mm shell below the body contour.
** Left sided lesion only, MHD: mean heart dose, MLD: mean lung dose

7. Prescription of Dose, Fractionation

We will treat the patient in one day, with the aim that the patient does not have to spend a single night with the implanted tubes and that the treatment can be provided on an outpatient basis.
The prescribed dose is 1x16 Gy.

8. Surgery

Within the present trial lumpectomy, wide excision or quadrantectomy should be utilized for suspected or known malignancy. Lumpectomy and wide excision are defined as resection with a significant margin of breast tissue. Lesions that are superficial should be ellipsed with a segment of skin that affords gross clearance of at least 1 cm for the lesion. The part of the pectoralis fascia which is next to the lesion should be included, if indicated. The specimen should be marked with different length sutures in order to tag at least three of the six axes of the mass for orientation purposes for the pathologist, for evaluation of the margins. Clips are used to mark the tumour site for the radiotherapist.

The standard treatment of the axilla within this trial is sentinel lymph node biopsy alone or axillary dissection is admissible with at least 6 removed nodes.

9. Drug therapy

Adjuvant sequential chemotherapy and/or hormonal therapy is allowed according to the local protocol of the treating center (keeping the time schedule defined in VII.1.).

VIII. DATA MANAGEMENT

1. Statistical considerations

Sample Size

Overview:

The primary goal of this trial is to estimate the rate of all late grade ≥ 2 toxicity (RTOG/EORTC skin, RTOG/EORTC subcutaneous tissue, hyperpigmentation, teleangiecteasia, fibrosis, fat necrosis, brachial lymphedema and breast pain) following treatment with a single-fraction brachytherapy.

Sample size derivation:

The sample size is calculated with type I error of 0.05, type II error of 0.2 (power of 80%) and a one-sided hypothesis (only excess of cases is of interest). Based on the 5-years results of the GEC-ESTRO vAPBI trial [2], we conservatively assuming a 'normal' rate of 9.9% grade 2 or higher late toxicity. Based on the 5-years results of the SiFEBI study [3], the expected rate of grade ≥ 2 side effects with a single-fraction treatment is 8%. Using the above data, calculated with the sample size calculator of the Statistica 12.5 software (StatSoft, USA), a minimum sample size is 196 patients. After adjusting the number of cases by 10% for ineligible or unanalyzable cases, this study requires a sample of at least 216 patients.

Analysis plan

Interim reports:

Interim reports will be prepared every six months until the last patient has been entered to the trial. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, the frequencies and severity of toxicity.

The analysis of late grade 3 toxicity:

This analysis will be carried out when each patient has had at least 18 months of follow-up. The time to the occurrence of late Grade 3 toxicity is defined as the time interval from the start of protocol treatment to the date of onset of late Grade 3. If no such toxicity is observed until the time of the analysis, the patient will be censored at the time of the analysis.

Estimation of secondary endpoints related to the efficacy:

Cumulative incidence approach will be used to estimate the failure rate for biochemical, disease-specific, local-regional and distant metastasis-free survival.

2. Data collection

Data collection will be done utilizing report forms in digital form, and also as hard copy. The digital report from the original is sent to the study centre, the hard copy remains on site with the local department.

Personal data of patients remain in the local participating centres. Only anonymized data will be passed on to the study centre via registered mail services. Access to the biometrical study centre is restricted to authorized users. In addition, within these precincts, access to electronic data, including the study databases mentioned, is restricted to a user group explicitly authorized. All these users sign a declaration that they will treat all data confidently.

3. Confidentiality

Study protocol and patient data forms are confidential and it is not allowed to communicate confidential data orally or in writing to unauthorized persons.

The information obtained as a result of this research is confidential and the investigator must ensure that the patient's anonymity will be maintained. All records, evaluation forms, and reports will be identified by an identification code to maintain confidentiality. The investigator should keep a separate log of patient's codes, names and addresses. All records should be kept in locked files. The chairmen may have access to this information in order to comply with any law or regulations, or in the interest of patient safety.

IX. PATIENT ASSESSMENTS

1. Clinical examinations

The study physician in each study center is responsible for the treatment, for the examinations before, during and after the treatment as well as for the appropriate documentation of each recruited patient.

The following examinations are obligatory:

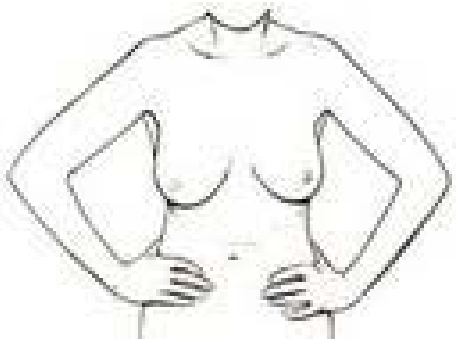
Examinations	Before irradiation	After irradiation	Follow-up examinations*
Informed consent	x		
Patient history	x	x	x
Clinical examination	x	x	x
Karnofsky, ECOG	x	x	x
Chest X-ray or CT	x		
Liver ultrasound	o		
Bone-scintigraphy	o		
Mammography and ultrasound of the breast			x*
Acute side effects		x	
Late side effects			x
Cosmetic results	x	x	x*
Digital photographs	x		x*
EORTC QLC-C30	x	x	x*
EORTC QLC-BR23	x	x	x*
Patient eligibility form	x		
Radiotherapy report form		x	
Follow-up form			x

*: for correct timing see table below, o: optional

Follow –up examinations	1	3	6	12	24	36	48	60	72	84	96	108	120
Patient history	x	x	x	x	x	x	x	x	x	x	x	x	x
Karnofsky, ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Inspection and palpation	x	x	x	x	x	x	x	x	x	x	x	x	x
Mammography of both breast				x	x	x	x	x	x	x	x	x	x
Documentation of acute side effects	x	x											
Documentation of late side effects			x	x	x	x	x	x	x	x	x	x	x
Documentation of cosmetic results			x	x	x	x	x	x	x	x	x	x	x
Digital photographs				x	x	x	x	x	x	x	x	x	x
Documentation of QoL		x	x	x		x		x	x	x	x	x	x

2. Cosmetic outcome

- Documentation of bra cup size of the untreated breast (category A, B, C and D or larger).
- Digital photographs from ventral (see example).



-Evaluation of the cosmetic result of the breast-conserving surgery based on the Harvard criteria system [28]:

- Patient's view (subjective): excellent, good, fair, poor.
- Doctor's view (using classification below): excellent, good, fair, poor.

Excellent (1): perfect symmetry, no visible distortion or skin changes, and no visible catheter entry/exit sequelae

Good (2): slight skin distortion, retraction or edema, any visible telangiectasia, any visible catheter entry/exit scar, or mild hyperpigmentation

Fair (3): moderate distortion of the nipple or breast symmetry, moderate hyperpigmentation, or prominent skin retraction, edema, or telangiectasia

Poor (4): marked distortion, edema, fibrosis, or severe hyperpigmentation

3. Side effects

Documentation of surgery-related pre-existing side effects with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [29] and with the RTOG/EORTC Late Radiation Morbidity Scoring Schema [30]. See tables below.

RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4
SKIN	None	Slight atrophy Pigmentation change. Some hair loss.	Patch atrophy; Moderate telangiectasia; Total hair loss.	Marked atrophy; Gross telangiectasia.	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement.	Necrosis

Common Terminology Criteria for Adverse Events v3.0 (CTCAE), Publish Date: June 10, 2003					
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
DERMATITIS associated with radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
HEMATOMA	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
INFECTION (wound)	Mild	Moderate	Severe	Life-threatening, disabling	Death
INTRA-OPERATIVE INJURY (Breast)	repair of injured organ/structure indicated	Partial resection of Injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	-
PAIN (Breast)	Mild pain not interfering with function	Moderate pain; pain or analgetics interfering with function, but not interfering with ADL	Severe pain; pain or analgetics severely interfering with ADL	Disabling	-

To assess fat necrosis, we use a classification system previously developed [31]:

Grade	Definition
0	No fat necrosis
1	Asymptomatic fat necrosis (only radiologic and/or cytologic findings)
2	Symptomatic fat necrosis not requiring medication (palpable mass with or without mild pain)
3	Symptomatic fat necrosis requiring medication (palpable mass with significant pain)
4	Symptomatic fat necrosis requiring surgical intervention

4. Quality of life (QoL)

Before starting radiotherapy, patients are intended to fill out an QoL-questionaire (EORTC QLQ-C30 including the Breast cancer module QLQ-BR23, see appendix) [32, 33]. Latest information about development of the QLQ-C30 and its modules (also different languages) may be found on the EORTC Quality of Life web pages, at: https://qol.eortc.org/questionnaires/

X. Determination of therapy safety

1. Collection, evaluation and reporting

All adverse clinical events (AE), whether observed by the investigator or reported by the patient, must be recorded in the Case Report Form together with details of the duration and severity of each episode, the action taken with respect to the treatment and the patient outcome. The investigator must evaluate each adverse event as to its relationship to the radiation treatment and as to whether or not it was serious.

Serious AE: An event that suggests a clinically significant hazard, contradiction, side effect or precaution. A serious AE includes any that is fatal or life threatening (at the time of occurrence), is permanently disabling or incapacitating, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer or overdose.

Toxicity should be observed and recorded using the criteria, which are attached in Appendix. Adverse events not included among the toxicity criteria should be evaluated using the scale 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening.

2. Documentation of unexpected events

ALL SERIOUS OR UNEXPECTED ADVERSE EVENTS, INCLUDING DEATH, WHICH OCCUR ON STUDY OR WITHIN 30 DAYS SUBSEQUENT TO WITHDRAWAL FROM STUDY, MUST BE REPORTED IMMEDIATELY TO Dr.

Viktor Smanykó BY TELEPHONE OR E-MAIL, REGARDLESS OF PRESUMED CAUSAL RELATIONSHIP:

		Tel Business	E-mail
Chairman			

3. Serious or unexpected events

Unexpected side effects are diseases, signs of disease or symptoms, that appear or aggravate after the patient was recruited to the trial.
The grading of an unexpected side effect will be performed with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).
If grading with these criteria is not possible, side effects will be classified with the following classification:

1. slight
2. moderate
3. severe
4. life threatening

For every event the causality with the treatment has to be evaluated and classified with the following classification:

1. no causality
2. causality possible
3. causality likely
4. causality proved.

Serious unexpected events are:

- Every death (independent of cause of death) that appears during and within 30 days after study-protocol-conformal treatment
- Life-threatening diseases
- Events that will lead to permanent disability
- Events that lead to or prolong hospitalization
- Secondary malignancies
- Symptomatic overdosing

- Congenital abnormalities

4. Patient insurance

All patients participating in this clinical trial will be insured for the standard insurance for radiation therapy in every Department of Radiation Oncology. All patients with such events should immediately inform the responsible local study physician.

XI. CONSENT AND WITHDRAWAL OF PATIENTS

1. Patient's consent and declaration of consent

Before a patient can be recruited for the protocol, the study concept and aim as well as possible alternatives must be explained to her and patient's consent must be declared by filling out and signing the Patient consent form (see appendix).

2. Patient's withdrawal

Patients may be withdrawn from the study for any of the following

1. Completed as per protocol (60 months follow-up)
2. Patient's own request
3. Unacceptable side-effects of treatment
4. Protocol violations, e.g. non-compliance, treatment schedule modification or dose modifications not specified by protocol
5. Investigator's considered opinion that it would be in the patient's best interest, e.g. deteriorating general condition of patient. The reason must be recorded by the investigator. The patient will be off-protocol and further treatment will be at the investigator's discretion
6. Loss to follow-up

XII. FINAL REPORT/ PUBLICATIONS

After completion of the study the clinical results will written by the study chairmen and published in a scientific journal. The sequence of the co-authors will be determined by the number of recruited patients.

Appendix I

Declaration of participation on the study for study physician

[*Date*]

The [*institution's name*] will participate as a study center in the

PHASE II MULTICENTER TRIAL:
SINGLE-FRACTION VERY ACCELERATED PARTIAL BREAST IRRADIATION (sfVAPBI) IN LOW-RISK INVASIVE OR DUCTAL IN SITU BREAST CARCINOMA

of the

GEC-ESTRO BREAST CANCER WORKING GROUP.

As the local investigator for this study, I have received the protocol of the above-mentioned Phase II multicenter trial dated ..... and agree to follow this protocol as written.

I confirm my commitment to contribute to this trial and to recruit and randomise at least 3 patients per year. Patient data will be documented properly, follow-up data assessed regularly as lined out in the protocol.

Name and signature of the local investigator: _____

Name and signature of the center's director: _____

(Stamp)

Appendix II

Patient Consent Form and Declaration of Consent

PHASE II MULTICENTER TRIAL:
SINGLE-FRACTION VERY ACCELERATED PARTIAL BREAST IRRADIATION (sfVAPBI) IN LOW-RISK INVASIVE OR DUCTAL IN SITU BREAST CARCINOMA

GEC-ESTRO BREAST CANCER WORKING GROUP.

Dear Patient!

You suffer from breast cancer. The conventional treatment consists of breast-conserving surgery (BCS) and an irradiation of the whole breast (WBI) following surgery. Recently, it has been shown that in the subgroup of women with breast cancer with a low risk of local recurrence the whole breast irradiation can be changed by an accelerated partial breast irradiation (APBI), restricted to the former tumor area. This kind of irradiation is performed by the implantation of small plastic tubes in general/local anaesthesia in the so called "tumor bed", the former cancer carrying area. Then a very small radiation source is able to reach the tissue at risk via those tubes. With this so-called "interstitial brachytherapy (iBT)", the radiation dose can be applied in only five-seven days, in contrast to a 3–6-week lasting whole breast irradiation, and in a smaller area than the external irradiation on the whole breast.

Together with other European radiotherapy clinics our hospital carries out an investigation to find out, on the basis of the available scientific knowledge, if you can receive this treatment only in one day. We expect in your favourable situation that partial breast irradiation leads to sufficient tumor control in the ipsilateral breast. A 100-percent-security is not reachable, but we can expect a very low percentage of local recurrences. The advantages of partial breast irradiation are a short treatment duration and a lower rate of side effects at the skin surface. The advantages of a "single-fraction very accelerated partial breast irradiation" (sfVAPBI) are a more comfortable tolerance of the plastic tubes and less probability of acute effects like infection or bleeding.
This Phase II treatment trial looks to know the secondary effects and cosmesis outcome of the same treatment in one day (a single fraction a day), removing the tubes the same day of the implantation and treatment.

<u>Side effects</u>
Possible side effects of sfAPBI are:
Acute effects: hematoma, radiodermatitis, oedema, implant infection, bleeding, pain.
Late effects: fibrosis of the skin and breast tissue, oedema, lipoid necrosis, teleangiectasia, pain.

<u>Confidentiality</u>
Your patient and treatment data will be only used anonymously for scientific evaluation. Your personal data will be kept confidential and never be published or given to third persons without removing your name.

Data management

You - as a participant in the study - explicitly consent to the hospital transferring the necessary data to the data processing centre.

Participant's Rights

Your participation is voluntary. You can choose not to take part or leave at any time without penalty or loss of benefits. Any new information that might affect your participation will be shared with you.

Contact Information

More information is available from the responsible physicians at your local hospital.
Local responsible physician:
[Name and Address of Hospital]
[Name of Physician]
[Telephone Number]

PHASE II MULTICENTER TRIAL:
SINGLE-FRACTION VERY ACCELERATED PARTIAL BREAST IRRADIATION (sfVAPBI) IN LOW-RISK INVASIVE OR DUCTAL IN SITU BREAST CARCINOMA

GEC-ESTRO BREAST CANCER WORKING GROUP.

Declaration of Consent

Of the patient after all questions regarding therapy and side effects are asked and answered.

Dr. ..... informed me that I can participate in a scientific trial to clarify the role of "single-fraction very accelerated partial breast irradiation (sfVAPBI)" in breast cancer treatment. I had the opportunity to ask all my questions to the items I was interested in.

I understand the concept of the study and declare my consent to participate. If I deny the planned treatment, I will not suffer from penalty or loss of benefit regarding the optimal medical treatment. I know that I can resign participation at any time and because of any cause.

I was assured that my personal data will be kept anonymous and unpublished, except I declared my clear consent.

I explicitly consent to the hospital transferring the necessary data to the data processing centre.

I received a copy of this patient consent form and declaration of consent.

Patient's name: .....

ID-Number: .....

.....
Place, date and signature of the patient

.....
Place, date and signature of the responsible physician

Appendix III

Eligibility Check

Inclusion Criteria

Criteria	Eligible	Exclusion
Breast cancer stage ≤ st.II.	• Yes	• No
Hystology	• Invasive carcinoma of any subtype and grade or DCIS	• No
Vessel Invasion	• Histopathololologically no or just focal lymph vessel invasion/ lymphangiosis (LVI+) • No blood vessel invasion/ hemangiosis (V0)	• Extensive lymph vessel invasion/ lymphangiosis (LVI+) • Blood vessel invasion/ hemangiosis (V1)
Tumor diameter ≤ 30 mm (histopathologically confirmed)	• Yes	• No
Nodal status (invasive cancer)	• Negative sentinel lymph node biopsy or micrometastasis (pN0 or pN1mi) • In case of ABD: pN0 or pN1mi (precondition: at least six lymph nodes histopathologically evaluated) (pts. with pN1mi status can be treated, but due to the limited clinical evidence, individual decision is needed)	• Positive macrometastasis at sentinel lymph node biopsy (pN1) • In case of ABD: pN1 or <6 lymph nodes histopathologically evaluated) • no axillary staging
Distant metastasis	• No (M0)	• Yes (M1)
Safety Margins	• Clear resection margins by NSABP definition (no tumor on ink)	• Positive resection margins or surgical margins that cannot be microscopically assessed
Luminal status	• Luminal A or B tumors • HER2+ pts. who receiving postoperative anti-HER2 systemic therapy	• Triple negative tumors • HER2+ pts. not receiving postoperative anti-HER2 systemic therapy

Growth pattern	• unifocal (multifocality limited within 2 cm) • unicentric	• multifocal over 2cm • multicentric
Patient's age > 40 years	• Yes	• No
Interval between definitive breast conserving surgery and radiotherapy	• ≤ 84 days • ≤ 28 days after completion of chemotherapy	• > 84 days • > 28 days after completion of chemotherapy
Signed informed consent	• Yes	• No

Appendix IV

Exclusion Criteria

Criteria	Exclusion	Eligible
Breast cancer stage > stage II	• Yes	• No
Safety margins histopathologically assessed	• No	• Yes
Extensive intraductal component (EIC+)	• Yes	• No
Extensive lymphovascular involvement (LVI+)	• Yes	• No
Pagets disease	• Yes	• No
Pathological skin involvement	• Yes	• No
Synchronous or previous ipsilateral breast cancer	• Yes	• No
Prior malignancy *(≤ 5 years prior to enrollment in study)* except non-melanoma skin cancer or cervical carcinoma FIGO I if patient is continuously disease-free	• Yes	• No
Pregnant or lactating woman	• Yes	• No
Collagen vascular disease	• Yes	• No
The presence of congenital diseases with increased radiation sensitivity, for example Ataxia telangiectatica or similar	• Yes	• No
Psychiatric disorders	• Yes	• No
Patient with breast anatomy deemed technically unsatisfactory for brachytherapy	• Yes	• No
Triple negative breast cancer	• Yes	• No
BRCA 1-2 mutation	• Yes	• No
HER2+ pts. not receiving postoperative anti-HER2 systemic therapy	• Yes	• No
Neoadjuvant systemic therapy	• Yes	• No

Appendix V

Patient Data Form

Patient Data	
• Initial name	• …
• Initial first name	• …
• Date of birth	• …
• Patient ID	• …
• Age at BCS	• …
• Karnofsky performance scale	• 100,90,80,70,60,50,40,30,20,10,0
• ECOG performance scale	• 0,1,2,3,4
• Informed consent	• Yes/No
• Study center	• …
Oncological history	
• Former neoplasia?	• Yes/No
• Specify	…
• Former radiotherapy?	• Yes/No
• Specify	…
Breast conserving surgery (BCS)	
• Date of BCS	• …
• BCS-type	• quadrantectomy, segmentectomy, lumpectomy, tumorectomy
• Axilla surgery	• Conventional axillary dissection with at least six nodes removed, sentinel lymph node biopsy, no lymph node dissection
• Brachial lymphedema (post BCS, pre-RT)	• Yes/No
Specify:	…
Pathology	
• Typing	• Invasive ductal carcinoma, Invasive papillary carcinoma, Invasive mucinous carcinoma, Invasive tubular carcinoma, Invasive medullary carcinoma, Invasive lobular carcinoma,
Specify, in case of 'other'	DCIS, other …
• Grading	• G1, G2, G3, G4
• Breast side	• Left, right
• Quadrant	• upper outer, upper inner, upper inner/outer, lower outer, lower inner, lower outer/inner, outer upper/lower, inner upper/lower, central
• Tumor-diameter in mm	• …
• Minimal safety margin in mm	• …
• pT-category	• pT1 mic, pT1a, pT1b, pT1c
• pN-category	• pN0, pN1mi, no axilla dissection
• Number of dissected nodes	• …
• Estrogene-receptor positive	• Yes/No
• Progesterone-receptor positive	• Yes/No
• C-erbB2 positive	• Yes/No
• Ki-67%	• …

Adjuvant systemic therapy	
• Antihormonal therapy Specify: Start of treatment: • Chemotherapy Specify: Start of treatment: • Anti-HER2 systemic therapy Specify: Start of treatment:	• Yes/No … … • Yes/No … … • Yes/No … .
Cosmetic result post BCS, pre radiotherapy	
• Bra cup size • Digital photography • Cosmesis – patient's view • Cosmesis – doctor's view	• A, B, C, D or bigger • Yes/No • excellent, good, fair, poor • excellent, good, fair, poor
Brachytherapy	
• Number of catheters • Number of implant planes • Reference isodose [%] • Total reference dose [Gy] • Mean Central Dose (MCD) [Gy] • Maximum dose Dmax (1,5 x MCD) [Gy] • Dose D150 (1.5 x Reference dose) [Gy] • Dose D90 (0.9 x Reference dose) [Gy] • Volume Vref [ml] • Volume V150 (D150) [ml] • Volume Vmax (Dmax) [ml] • Target definition • DNR • DHI • CI • COIN	• … • … • … • … • … • … • … • … • … • … • … • with clips, without CT / with clips, with CT / with clips, with IBU / with clips, with US / without clips, with CT / without clips, with US / not possible, patient withdrawn • … • … • … • …
Acute Toxicity (CTCAE v3.0)	
• Dermatitis associated with radiation • Hematoma • Infection (wound) • Intraoperative injury (breast) • Pain (breast)	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 • Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 • Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 • Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5 • Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5
Comments	
…	

Appendix VI

Follow-up Form

Patient Data	
• Initial name	• …
• Initial first name	• …
• Date of birth	• …
• Patient ID	• …
• Karnofsky performance scale	• 100,90,80,70,60,50,40,30,20,10,0
• ECOG performance scale	• 0,1,2,3,4
• Study center	• …
Follow-up status	
• Follow-up date	• …
• Follow-up period [months]	• …
• Free of disease	• Yes/No
• Status	• Alive/Dead
• Date of death	• …
• Cause of death	• breast cancer-related, not breast cancer-related
Specify:	…
Tumor status	
• Tumor status	• free from disease, local recurrence in field, local recurrence field margin, local recurrence out of field, regional lymph node recurrence, distant metastasis,
Specify in case of 'other':	other …
Specify in case of distant metastasis:	…
• Secondary malignancy:	• No / Yes, same organ / Yes, different organ
Specify:	…
• Meanwhile new therapy?	• No / Yes
Specify:	…
Begin/end of new therapy:	…
Late toxicity	
• Late Toxicity?	• No / Yes
Specify:	…
• EORTC/RTOG Skin	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
• EORTC/RTOG Subcutaneous tissue	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
• Pain	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
• Hyperpigmentation	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
• Fibrosis	• Grade 0, Grade 1, Grade 2, Grade 3
• Teleangiectasia	• Grade 0, Grade 1, Grade 2, Grade 3
• Tube marks	• Grade 0, Grade 1, Grade 2, Grade 3
• Fat necrosis	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
• Brachial lymphedema	• Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
Cosmetic result	
• Bra cup size	• A (small), B, C, D or bigger
• Digital photography	• Yes/No
• Cosmesis – patient's view	• excellent, good, fair, poor
• Cosmesis – doctor's view	• excellent, good, fair, poor
Comments	
…	

Appendix VII

Definitions of volumetric indices for brachytherapy

- PD: prescribed dose
- DNR (dose-nonuniformity ratio): ratio of the volumes encompassed by the isodose surfaces of the 150% and 100% of the PD
- CI (coverage index): fraction of the PTV receiving dose equal to or greater than the PD
- DHI (relative dose homogeneity index): fraction of the PTV receiving dose between 100% and 150% of the PD
- COIN (conformal index) = c1 x c2, where c1 = CI and c2 = PTVref/Vref, where PTVref is the volume of the PTV receiving dose equal to or greater than the PD, and Vref is the volume encompassed by the isodose surface.

Appendix VIII

Quality of Life Questionnaire EORTC QLQ- C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Quality of Life Questionnaire EORTC QLQ- BR23

EORTC QLQ-BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Did you have a dry mouth?	1	2	3	4
2. Did food and drink taste different than usual?	1	2	3	4
3. Were your eyes painful, irritated or watery?	1	2	3	4
4. Have you lost any hair?	1	2	3	4
5. Answer this question only if you had any hair loss: Were you upset by the loss of hair?	1	2	3	4
6. Did you feel ill or unwell?	1	2	3	4
7. Did you have hot flushes?	1	2	3	4
8. Did you have headaches?	1	2	3	4
9. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
10. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
11. Did you find it difficult to look at yourself naked?	1	2	3	4
12. Have you been dissatisfied with your body?	1	2	3	4
13. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at all	A little	Quite a bit	Very much
14. To what extent were you interested in sex?	1	2	3	4
15. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
16. Answer this question only if you have been sexually active. To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Did you have any pain in your arm or shoulder?	1	2	3	4
18. Did you have a swollen arm or hand?	1	2	3	4
19. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
20. Have you had any pain in the area of your affected breast?	1	2	3	4
21. Was the area of your affected breast swollen?	1	2	3	4
22. Was the area of your affected breast oversensitive?	1	2	3	4
23. Have you had skin problems on or in the area of your affected breast (e.g. itchy, dry, flaky)?	1	2	3	4

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