

EORTC COOPERATIVE GROUP FOR RADIOTHERAPY
Chairman: H. Bartelink
EORTC BREAST CANCER COOPERATIVE GROUP
Chairman: R.D. Rubens

PROTOCOL 22881 AND 10882

Phase III study in the conservative management of breast carcinoma by
tumorectomy and radiotherapy: assessment of the role of a booster dose of
radiotherapy.

**SECOND REVISED EDITION
JANUARY 1994**

Study Coordinators:

H. Bartelink, J.C. Horiot, E. van der Schueren

Writing Committee:

H. Bartelink (1), J.H. Borger (1), P.H. Helle (2), J.C. Horiot (3), J.W.H. Leer (6),
J.L. Peterse (1), B. Pierquin (4), E. van der Schueren (5), E. Van Limbergen (5),
J. Vilcoq (7), F. Zoetmulder (1).

EORTC Data Center: M. van Glabbeke, Statistician.

M. Pierart, Data Manager for the Radiotherapy Group.

- (1) Netherlands Cancer Institute, Amsterdam.
- (2) Daniel Den Hoed Cancer Centre, Rotterdam.
- (3) Centre G.F. Leclerc, Dijon.
- (4) C.H.U. Henri Mondor, Creteil.
- (5) U.Z. St. Rafael, Leuven.
- (6) A.Z. Leiden.
- (7) Institut Curie, Paris.

INDEX

1. Introduction.	p 5
2. Objectives of the study.	8
3. Design of the trial.	9
4. Selection of patients.	11
5. Surgery	12
6. Radiotherapy.	14
7. Investigation before therapy and follow-up.	23
8. Definition of the criteria for analysis of the trial	25
9. Assessment of cosmetic result.	25
10. Registration and stratification.	27
11. Statistical considerations.	28
12. Ethical considerations.	29
13. Administration of the trial.	29
14. Publication	30
15. Bibliography.	31
16. Addenda.	36

1. INTRODUCTION.

Breast conservative treatment (BCT) for small breast cancers has been studied in many retrospective and prospectively randomized clinical studies (1,2,3,4,5,6,7,8). European and American trials on small breast cancers (<3-4 cm) comparing combined conservative surgery and irradiation with (modified) radical mastectomy show no difference in patient survival and local control rates (4,5,6). The EORTC Breast Cancer Cooperative Group has just finished a large study including more than 900 patients, most of them with stage II breast cancer. In this randomized trial radical mastectomy was compared with breast conservation treatment for patients with tumors up to 5 cm. A rather aggressive approach was used by combining tumor excision with one or more centimetres free margin, external beam radiation of the whole breast to a dose of 50 Gy and a boost dose of 25 Gy in the tumor area. The preliminary results show equal, very high local control rates in both arms. However, the cosmetic results in the BCT group require improvement (8). The present trial wants to investigate the importance of the radiation dose level on local control and cosmetic outcome.

Local Control

At present the long term follow-up data from the prospective randomised trials are limited to about 5 years, while retrospective studies provide follow-up data up to 20 years (9,10). Local breast cancer recurrence rates vary from 2-9% at 5 years and from 8 to 13% at 10 years (1-10). Follow-up data up to 15 and 20 years are available from the studies of Kurtz and Harris (9,10), showing breast recurrence rates of about 15% at 15 years and 20% at 20 years. From these data a constant fall of local control rate at 1% per year is suggested up to a local failure rate of 15% at 15 years, which may be partly explained by the development of new primary tumors, as in the opposite breast.

With regard to local breast recurrence many host and tumor factors have been mentioned as playing a role such as: age, tumor size, histologic type, and histologic grade (2,3,7,11,12,13, 14,15,16). Treatment factors such as extent of local excision (clear margin), radiation dose to the tumor bed and adjuvant chemotherapy have also been suggested as having an impact on local control (4,5,7,12,13,14). The influence of most of these factors and their relation to each other still has to be clarified.

Local recurrence after radical mastectomy varies from 10-20% depending on lymph node status and tumor size and bears a bad prognosis with 5-year survival rates of 12-36%, 80-100% of the patients showing distant metastases at the time of presentation or shortly after local failure (17). Ninety percent of the local recurrences after mastectomy occur before 5 years of follow-up.

The prognosis of local recurrence after BCT seems to be different. Salvage mastectomy can be performed in the majority of cases; NED survival rates after salvage mastectomy vary from 55-84% at 5 years and 50-70% at 10 years (9,10,16).

Booster Dose

Although the principal questions concerning BCT, such as safety, local control and patient acceptance seem to have been answered, many still remain. One important item is the role of the radiation dose level, part of it usually administered over small volumes (boost irradiation).

Recurrent breast cancer after BCT probably arises from residual tumor. Most recurrences are found at the site of the original tumor (12,16) and show the same histological appearance, indicating that recurrence in most cases represents failure of initial therapy to eradicate locally residual tumor.

In a radiological and pathological study of 282 mastectomy specimens, Holland et al. calculated that in the case of invasive carcinomas, less than 5 cm in size, wide excision with a tumor free margin of 2 cm would result in residual foci of invasive carcinoma in 14% and in situ carcinoma in 28% of their cases (28). With a 4 cm margin, considered equivalent to quadrantectomy, residual tumor was still found in 10% of the cases.

In the NSABP study, in which patients were randomised after microscopic complete excision, a local breast recurrence rate of 28% at 5 years is found after tumorectomy without irradiation of the breast (4). After 50 Gy whole breast irradiation a local recurrence rate of 7% is found after 5-year follow-up. Veronesi, after quadrantectomy, 50 Gy whole breast irradiation and a boost of 10 Gy, finds 3% local breast recurrence, not considering another 3% recurrences outside the quadrantectomy area as local failure (5). Bartelink recently published his institute's results of tumorectomy (1 cm margin), 50 Gy whole breast irradiation and 25 Gy Iridium volume implant at the excision area, showing a breast recurrence rate of 2% at 6 years, irrespective of involvement of the excision margins by tumor (7).

The radioresponsiveness of human breast cancer has been estimated in the past by Fletcher (29) and Timothy et al. (30); they observed a tumor control rate for microscopic tumor by 50 Gy (2 Gy F/5 wks) of 95% and 90% respectively. ~~More recently~~, Denham made an educated guess of 75-80% tumor control rate in remaining breast tissue after BCT (tumor dose 50 Gy) (31). These data are derived from clinical studies on breast cancer irradiation. In the same review it is stated that for control of more extensive tumors a dose larger than 70 Gy is needed. A dose response relationship for local control of T1-T2 tumors treated by tumor excision and radiotherapy was shown by Van Limbergen et al. (12). An 8-year local control rate of 66% was found for doses less than 50 Gy in 5 weeks (2 Gy/fr) of 84% for doses of 60-70 Gy, of 91% for 70-80 Gy and of 100% for patients treated with doses higher than 80 Gy in 13 weeks. Arriagada et al. (32) had similar conclusions concerning the dose response relationship of

human breast cancer. In their study, a dose effect curve, derived from patients irradiated for both microscopic or macroscopic tumors, predicts a 50% reduction of local recurrence if the tumor dose is raised by 15 Gy (32). From these data one might conclude that whole breast irradiation to a dose of 50 Gy after very wide tumorectomy (quadrantectomy) will inevitably result in some recurrences in the remaining breast tissue. However the recurrence rate should be very small: 10% of 20-25% = 2-2.5% at the most (supposing equal radioresponsiveness in invasive carcinoma and ductal carcinoma in situ).

More limited surgery results in a higher risk of persistence of tumor which should be treated to a higher dose level over a sufficient volume. The boost volume to be treated by radiotherapy depends on the surgical tumor-free margins and should be extended to a total of 4 cm to compete with the results of quadrantectomy. With respect to the dose level of the boost irradiation two possibilities can be considered. First: if persistence of only microscopic tumor foci is suspected, for example after a complete tumorectomy with a 1 cm tumor-free margin in a patient with an otherwise normal mammography, a margin of 3 cm has to be treated to a higher dose level, which in this case could be 60 Gy to obtain a control rate of 90% or more. Secondly: if persistence of more extensive tumor is suspected, for example after incomplete tumorectomy, the dose level should be higher for a control rate above 90% (> 60 Gy) (30,31). Local recurrence rates after complete tumorectomy and 50 Gy whole breast irradiation, greatly depend on whether tumor-free margins are obtained by surgery and can be estimated to vary from 2-10%. It should be stressed that these considerations do not hold for special pathologic tumor types such as invasive cancer with an extensive DCIS component, which have a higher local recurrence rate (4,7).

Cosmesis and fibrosis

Cosmetic results of BCT have been acceptable to excellent in the majority of the cases and the treatment result is very much appreciated by the patients (18,19,20,21). Surgical and radiotherapeutic factors have their influence on cosmesis and have been studied extensively. Breast retraction, fibrosis and skin changes (teleangiectasia) have a major impact on cosmetic outcome. Evaluation of cosmetic results is difficult due to inter- and intra-observer bias and should include quantitative methods if possible (18,22,23,24,25). Cosmetic results show changes during the course of time (18,22), a fact that should be born in mind in comparative evaluation.

Breast fibrosis and telangiectasiae show a dose effect relationship which should be further defined for example in an α/β formalism (22,23,25). Treatment volume in boost irradiation has an impact on late soft tissue complications but its influence on fibrosis has not been defined yet (26). Apart from these questions follow-up of BCT may pose problems in patients with localised radiation fibrosis (27).

Conclusion

The aggressive approach, as used in the EORTC Study 10801, demonstrates that a high local control can be obtained, equal to radical mastectomy, for patients with breast cancer up to 5 cm diameter. The disadvantage of such an aggressive approach is, however, that the cosmetic results will be poor in part of the treated patient group (8).

A prospective study is therefore required to investigate the price to be paid for using a less aggressive treatment schedule by reducing the radiation booster dose, in order to improve the cosmetic results. Also the prospective follow-up of a large number of patients receiving the same therapy with standardised techniques might be extremely helpful in further identifying subsets of patients in whom local treatment can be reduced.

2. OBJECTIVES OF THE STUDY

- 2.1. To investigate the role of the booster dose in BCT with respect to:
 - a. the effect on the local recurrence rate.
 - b. the effect on the cosmetic results.

3. DESIGN OF THE TRIAL

3.1. Outline of the study

All patients with breast carcinomas that can be locally excised with an acceptable cosmetic outcome are eligible for this trial (T1-2 N0-1 M0).

A tumorectomy with a margin of 1 to 2 cm will be performed. This will be followed by external irradiation of 50 Gy in 5 weeks to the whole breast.

Patients with a microscopically complete excision will be randomised between **no boost and 15 Gy (interstitial)/16 Gy (external)**, while patients with microscopically incomplete excision will be randomised between a booster dose of **10 Gy and 25 Gy (interstitial)/26 Gy (external)**.

Incomplete excision is defined as microscopical invasion of section margins by invasive cancer.

Selection of patients :

T1-2 N0-1 M0 breast cancer patients who have undergone macroscopically radical local excision of the primary tumor.

Pretreatment :

- excision of the primary tumor with a margin of 1 to 2 cm.

- radiotherapy of the whole breast: 50 Gy/5 weeks (in 25 fractions, 2 Gy/fraction).

This dose has to be prescribed at the intersection of the two beam axes in the middle of the breast tissue (33), point A (see figure 2 page 15), provided that this is a relevant point in the target volume.

Randomisation :

1. complete resection (microscopically)

50 Gy whole breast (defined at point A)	R/ ↗ ↘	no boost 15 Gy boost (interstitial modalities) 16 Gy boost (external modalities) in 8 fractions of 2 Gy (defined at <u>point B</u> , see figure 3 page 15)
--	-----------	--

2. incomplete resection (microscopically)

50 Gy whole breast (defined at point A)	R/ ↗ ↘	10 Gy boost 25 Gy boost (interstitial modalities) 26 Gy boost (external modalities) in 13 fractions of 2 Gy (defined at point B)
--	-----------	--

3.2. Treatment of adjacent lymph nodes

a. axillary nodes

In premenopausal patients, axillary dissection has to be performed. In postmenopausal patients axillary dissection is also recommended. For this patient group, however, irradiation of the clinically negative axilla would be acceptable.

b. parasternal nodes (Internal mammary chain)

Irradiation of the parasternal nodes is recommended in patients with medial tumours, with lateral tumors and positive axillary nodes and to patients not receiving an axillary dissection. It is acceptable not to give the parasternal irradiation.

Each centre should provide protocol guidelines according to different clinical situations for the treatment of peripheral lymphatics, ensuring balance between the two treatment groups. Addendum 1 contains general guidelines for the treatment of the adjacent lymph nodes.

3.3. Adjuvant systemic therapy

In premenopausal patients, with positive lymph nodes, it is advised to give 6 cycles of adjuvant CMF-chemotherapy.

Perioperative chemotherapy is allowed.

Radiotherapy should not be delayed for more than 9 weeks after the excision of the primary tumor in cases where no adjuvant chemotherapy is administered, and should not be delayed for more than 6 months in cases where chemotherapy is given.*

Each center should fix its policy regarding adjuvant systemic therapy prior to starting and this should be stated as the policy of the center for the duration of the trial.

In all postmenopausal patients, Tamoxifen 20 mg per day will be given during 2 years.

* Chemotherapy given before the start of radiotherapy cannot be reported separately on the clinical report forms, and is best also reported as "perioperative chemotherapy".

4. SELECTION OF PATIENTS

4.1. Eligibility criteria

- 4.1.1. Histological diagnosis of invasive mammary cancer including all subtypes of invasive adenocarcinoma.
- 4.1.2. Tumorectomy carried out based on the technical criteria defined in paragraph 5: macroscopic margin of security of 1 to 2 cm around the lesion.
- 4.1.3. T1-2 (0-5 cm) clinically assessed
(on clinical examination and/or radiology,
non palpable lesions can be entered)
N0-1 pathologically assessed
M0 breast cancer.

4.2. Criteria for exclusion

- 4.2.1. Age over 70 years.
- 4.2.2. Residual microcalcifications on mammogram, or gross residual disease in the breast after removal of the tumor, unless reexcision has been performed.
- 4.2.3. All histological types of malignancies other than invasive adenocarcinoma.
- 4.2.4. In situ carcinoma of the breast, without invasive tumor.
- 4.2.5. Multiple tumor foci in more than one quadrant.
- 4.2.6. Tumorectomy performed more than 9 weeks before the start of radiotherapy in cases where no adjuvant chemotherapy is given, and more than 6 months before the start of radiotherapy if chemotherapy is given.
- 4.2.7. Previous history or synchronous malignant tumor in the other breast.
- 4.2.8. Previous history of malignant disease, except adequately treated carcinoma in situ of the cervix or basal cell carcinoma of the skin.
- 4.2.9. Concurrent pregnancy or lactation.
- 4.2.10. ECOG performance scale more than two.

5. SURGICAL CONSIDERATIONS

(for pathological examination of excisional biopsy - see addendum 3).

5.1. Tumor excision.

5.1.1. Aim:

The aim of the excision is to remove all macroscopic infiltrating carcinoma and all microscopic ductal carcinoma in situ while maintaining an optimal cosmetic appearance of the breast.

5.1.2. Skin incisions:

In principle semi-circular incisions over the involved segment are advised because of their better cosmetic appearance after healing. This is especially the case in the upper part of the breast. In cases of ill-defined tumors and extensive microcalcifications a radial incision might be of advantage because of better exposure. Centrally placed tumors are best approached via a semi-circular incision along the margin of the areola. No skin is removed except in cases of well defined attachment of tumor to the skin. In these cases a limited area of skin overlying the tumor can be resected in continuity with the tumor. Separate incisions for tumor excision and axillary clearance are preferred. Only in cases of tumors in the axillary tail of the breast, an en-bloc procedure via one incision is advised.

5.1.3. Extent of excision:

5.1.3.1. Palpable tumors:

The complete palpable abnormality is excised with a macroscopical margin of 1 to 2 cm of normal surrounding breast tissue, also suspicious calcification on mammography should be excised completely. It is advisable to mark the excision specimen carefully to allow the pathologist to indicate the localisation of possible tumor positive margins.

5.1.3.2. Non palpable tumors, diagnosed on mammography:

These are either densities on mammography with irregular margins or areas of microcalcification. It is of help if these lesions are localized more precisely before surgery, either by putting in a localisation wire or a dye-injection under mammographic control. In view of the difficulty to localise the lesion during surgery, it is often wise to maintain margins of at least 2 cm around the suspected area. It is advisable to confirm the presence of the mammographic lesion in the resected tissue by specimen mammography. Also in these cases the specimen should be marked to allow the pathologist to indicate the localisation of possible tumor positive margins.

5.1.3.3. It is recommended to place one marker (clip) centrally at the deepest site of the excision area. This will help the radiotherapist to choose an adequate booster area.

5.1.4. Indications for re-excision:

1. Presence of gross macroscopic tumor in the margin of the excision, indicating that macroscopic tumor has been left behind. This does not apply to cases where the bulk of tumor has been macroscopically completely excised but only to cases where microscopic extensions of infiltrating carcinoma have been transected and left behind.
2. Presence of residual microcalcifications on control mammography is believed to represent gross residual tumor and are an exclusion criteria for the trial. In these cases, re- excision is advised. If the tumor is then reexcised with a normal control mammography, patients can be allowed for randomization provided that the delay between radiotherapy and reexcision is within the time limit (see 4.2.6).

5.2. Definition of "second operation" on the on-study form

All patients with removal of extra breast tissue after an initial excision of the primary tumor (including a margin with macroscopic normal breast tissue) should be scored as "second operation", even when this re-excision occurs during the first surgery. Axillary dissections are therefore not considered to be "second operations" and should not be reported as such, even when they are separately performed in a second session.

6. RADIOTHERAPY.

6.1. Patient contours

6.1.1. Position of patient.

Patient treatment position should be supine. The position should be maintained both at planning and treatment procedures. The technique of lateral decubitus, as used at the Institut Curie in Paris (8) is also accepted. For the boost treatment with external beams lateral or dorsal decubitus, normal position of the breast or compression technique are accepted. The criteria of prescribed dose and dose homogeneity, however, should be fulfilled.

6.1.2. Transverse sections and reference points (see figures 1 - 4 page 15).

Three transverse sections should be determined either with a computer tomograph or with other body contour devices. The following sections, perpendicular to the treatment table, should be determined:

1. The central plane : through the centre of the target volume equidistant from the cranial and caudal borders of the fields covering the whole breast. This plane contains the axes of the two tangential beams which intersect at point A;
2. The tumor plane: through the centre of the primary tumor site. This plane will be chosen in the middle of the scar of the tumorectomy, or through the centre of the tumor excision area marked by a clip. The tumor plane contains point B, located in the centre of the primary tumor excision area;
3. The border plane (I inferior, or S superior): through a level 2 cm from the cranio-caudal border of the target volume (**i.e. from the border of the breast tissue, and not from the field border**), in the opposite direction of the tumor plane.

If the tumor plane is closer than 2 cm from the central plane, then such a separate section can be excluded and will be assumed to coincide with the central plane. In this case both inferior and superior sections should be determined. The **maximum and minimum** absorbed dose in each cross section should also be specified.

If the position or topography of the patient is changed before external boost therapy, transverse sections through the tumor excision area should be taken in that position.

SPECIFICATIONS OF THE DOSE IN DIFFERENT PLANES

Fig 1

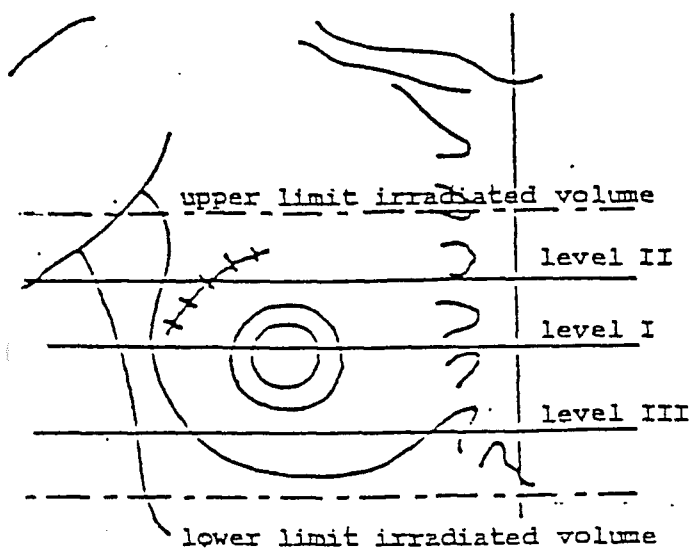
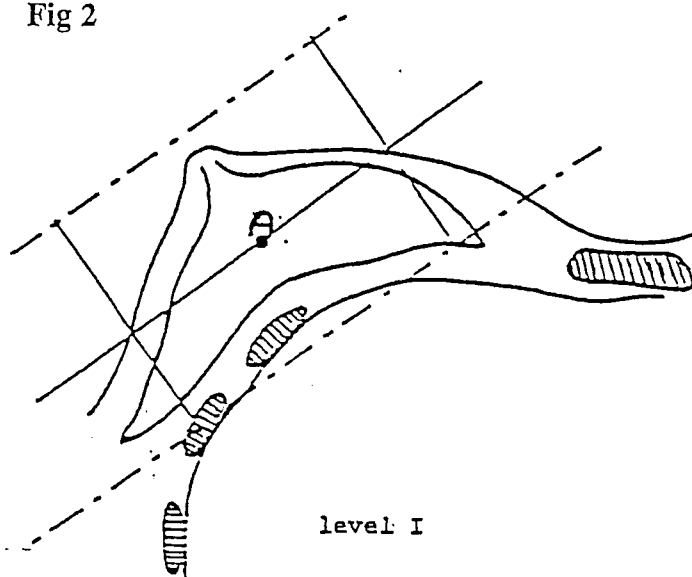


Fig 2



A = target absorbed dose
(reference point ICRU)

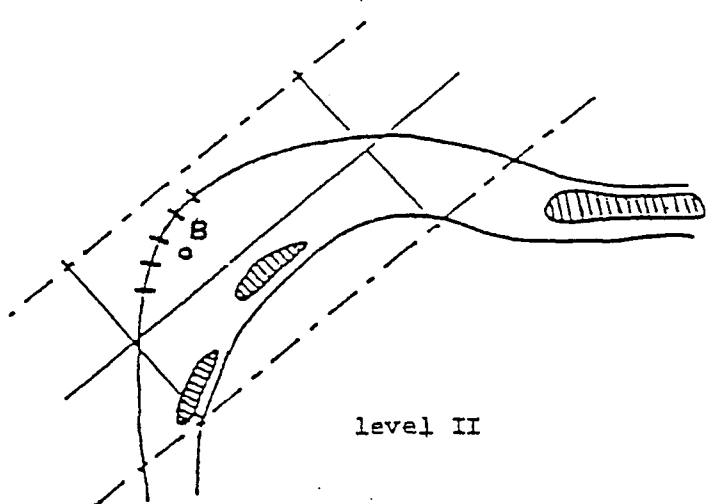


Fig 3

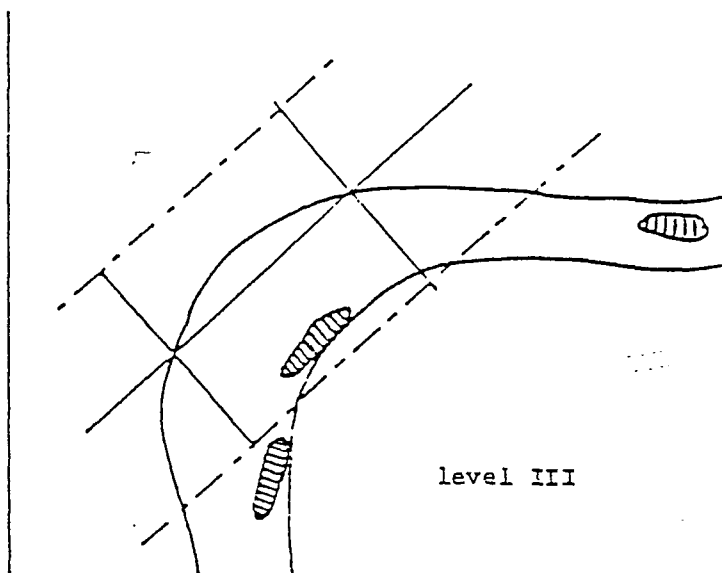


Fig 4

A = target absorbed dose in the central cross section
B = tumor bed dose in cross section at tumor level

6.2. Target and tumor volumes

The target and tumor volumes must always be described, independently of the dose distribution, in terms of the patient's anatomy and topography, and the physical dimensions given. It must be clearly recognised that volumes are treated, even if representations of volumes and dose distributions are usually represented only in two dimensions. **The target areas in each transverse section, as well as Point A and B, should be clearly indicated, and the primary tumor site area should also be drawn in the tumor plane. Point B should be indicated even in patients receiving no boost.**

6.2.1. Target volume of the whole breast irradiation.

It should include the whole of the mammary gland, and a margin of at least 1 cm in dorsal and in craniocaudal direction, correcting for intra- and inter-treatment variations in patient positioning. The skin is excluded from the target volume.

6.2.2. Primary tumor site volume.

It represents the site of the primary tumor, with a safety margin of 1.5 cm around the primary tumor after microscopic radical excision and of 3 cm after incomplete excision or in case of invasive cancer with extensive DCIS component. This volume shall be treated by the boost.

6.3. Treatment technique

For the target volume (the whole breast): the ballistics of the treatment will be constituted by two tangential opposing fields, ventro-medial and dorso-lateral, preferably with dorsal beam edge alignment (with an angle of up to 10 degrees, at maximum, between the axes, to minimise the dose to the lung). The dorsal border of both fields should be sufficiently, at least 1 cm, outside the contour of the breast. Wedge filters or compensators are advisable in order to obtain a dose distribution within the variation stated in paragraph 6.6.1..

In cranial-caudal direction the fields should have at least 1 cm margin between the edge of the field and the breast tissue. Beam trimmers and/or a half-beam device may be used. The two tangential fields should be treated with equal weights. All fields should be treated daily.

For the primary tumor site volume (boost), the following techniques are accepted:

- Two (tangential or wedged pair) external photon beams.
- One electron beam. The criteria of prescribed dose and dose homogeneity should be fulfilled.
- Interstitial therapy. It will be given with one or several planes, depending on the primary tumor site volume and according to the rules of the Paris system. It is advisable, in order to avoid late radiation teleangiectasia, to take care, if possible, not to deliver high doses to the dermal vascular plexuses in the overlying skin. The most superficially located needles should thus stay at least 5 mm (depending on the geometrical configuration of the implant) below the overlying skin surface. For the same reason guide needles or tubes should not be loaded with radioactive material in the first 5 mm below the skin.

6.4. Radiation Quality

- External beams:
 - Co-60 gamma-ray beams with a minimum SSD of 80 cm, or X-ray beams in the range of 4 to 8 MV are accepted.
 - Electron beams are also accepted as a boost modality. The energy of the electron beams should be chosen in such a way that the 85% isodose surface encompasses the boost target volume.
- Interstitial therapy:
 - Iridium-192 wires and 137-Cesium needles are accepted.
 - Radium needles should be avoided.

6.5. Dose specification

6.5.1. In the target volume: (see figures page 18)

The dose to the whole breast should be 50 Gy and should be specified at point A, in agreement with ICRU report 50 (33). Point A is defined as the intersection of the beam axes, provided that this is a relevant point in the target volume (Fig.5).

When the intersection of the beam axes is not a relevant point (as in half beam techniques, Fig.6), point A should be chosen in the central plane, on the line perpendicular to the dorsal beam edge 2/3 from the line between the dorsal beam edge and the skin (Fig.7).

Fig 5

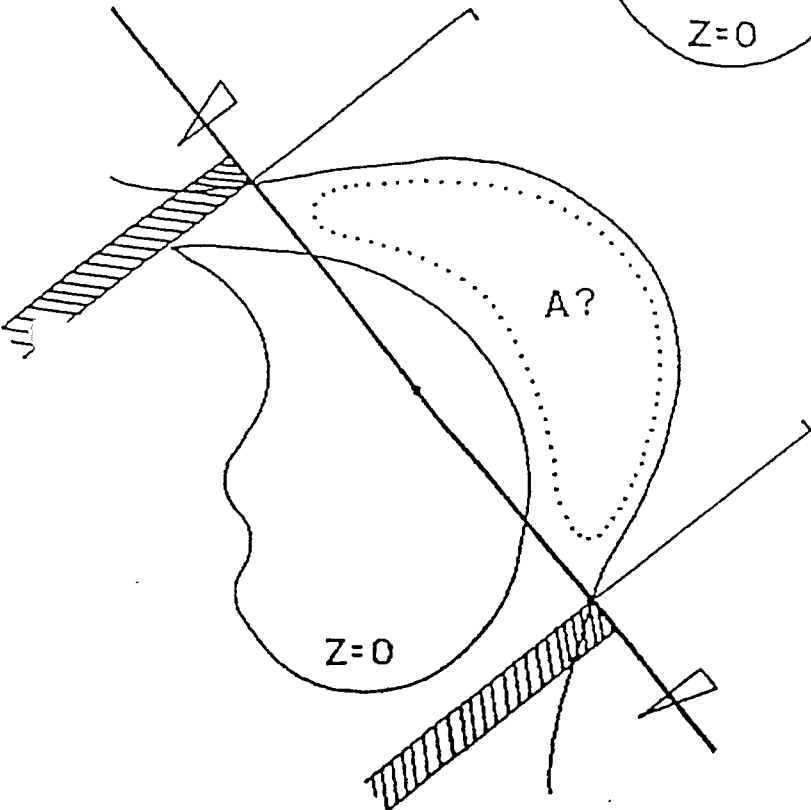
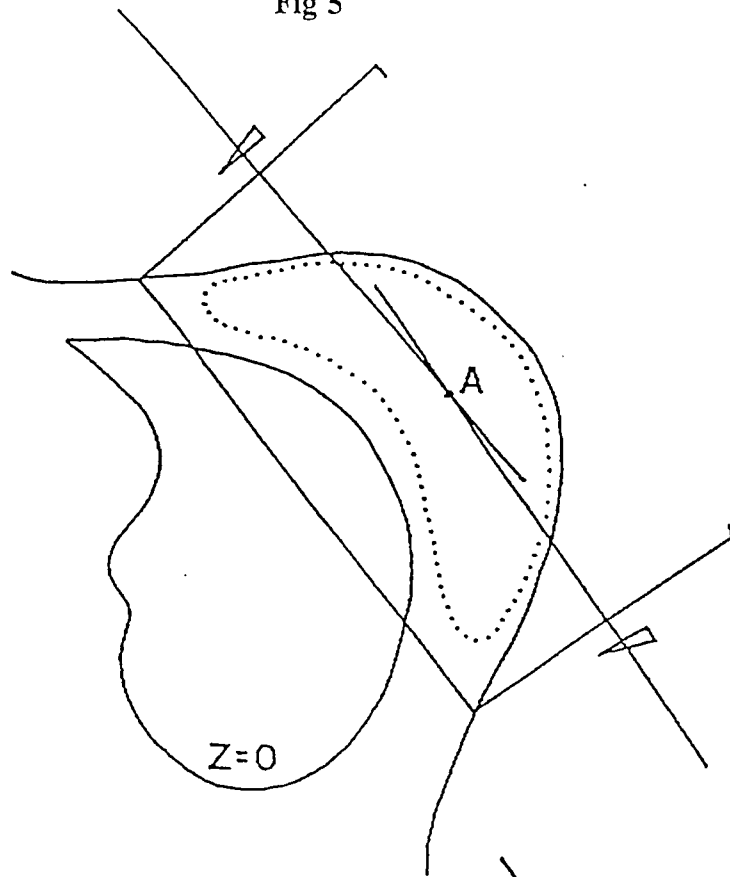


Fig 6

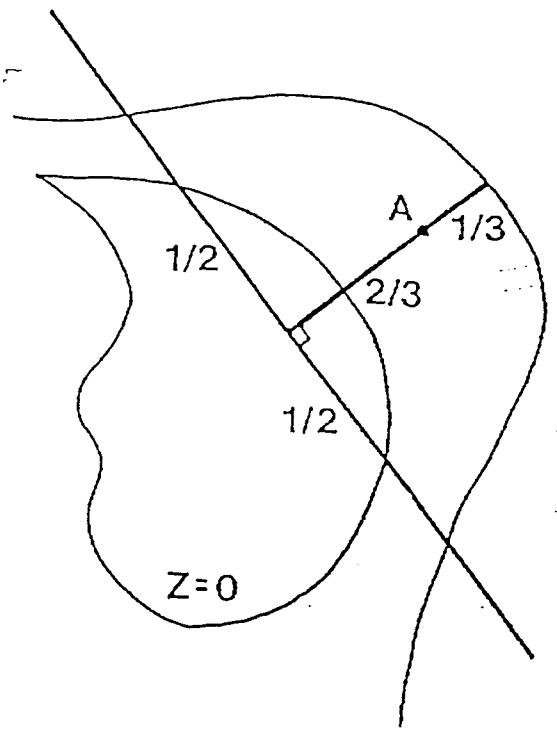


Fig 7

6.5.2. In the primary tumor site volume:

The boost dose should be specified at point B (center of the tumor excision area). This dose is fixed and independent from the dose delivered to point B during the external irradiation of the whole breast*. E.g. when a patient is randomized to receive a booster dose of 10 Gy, and has received a lower dose of 46 Gy at point B (and 50 Gy in point A) during whole breast irradiation, this patient should receive a booster dose of 10 Gy and not of 14 Gy at point B.

- External photon irradiation: the booster dose should be specified in point B.
- External electron irradiation: the dose is specified as maximum dose, the tumor excision area should be within the 85% isodose line.
- Interstitial irradiation: the dose should be prescribed according to the Paris system. The specification is 85% of the average basal dose.

6.6. Dose homogeneity

The dose distribution (isodose pattern) should be calculated for the central plane, whereas it is recommended to provide information also on dose distributions in the tumor plane and in the border plane.

6.6.1. In the whole breast for the initial 50 Gy:

The minimal dose in any point in the three sections should not be more than 5% lower than the nominal dose at point A. The maximum dose in these sections, minimum area 2 cm², will be registered. This should be 10%, at maximum, higher than the nominal dose at point A.

6.6.2. Lung density correction:

Most commercial treatment planning systems have heterogeneity correction algorithms that are sufficiently accurate to predict the magnitude of dose increase due to presence of lung in the tangential fields (34). It is recommended to apply lung density corrections in the dose calculation procedure for all three planes.

* The dose in point B from the whole breast irradiation should be reported separately on the radiotherapy form and should NOT include the booster dose.

6.7. Time - dose pattern

The dose to point A will be 50 Gy in 5 weeks given in 25 fractions of 2 Gy, 5 days a week. Both tangential fields should be treated in the same treatment session.

For patients who will receive:

- **Interstitial therapy:** a treatment free interval of about 15 days after the end of the external radiotherapy is advisable. The dose to the 85% isodose line shall be 10, 15 or 25 Gy with a recommended dose rate of about 10 Gy a day (0.42 Gy/h). Correction for the total dose should not be performed even if the dose rate differs from the recommended dose rate.

- **External beam boost:** it is preferred to continue the radiotherapy without any split. The dose to point B will be 10, 16 or 26 Gy, 5 days a week and 2 Gy per fraction to point B (5 fr of 2 Gy = 10 Gy, 8 fr of 2 Gy = 16 Gy, 13 fr of 2 Gy = 26 Gy).

6.8. Boost irradiation volume: Equations for calculation of the booster volumes

The boost irradiation volumes will be reported according to the following equations:

- Electron boosts:
Volume = (field length) x (field width) x (depth of 85% depth dose).
- Interstitial boosts: (Paris System; volume within the reference dose [85%])
L = length of Iridium wire, E = écartement, spacing between wires, n = number of spacings.

Double plane implant:

- Square distribution in axial plane:

Length L x 0.7
Width nE + (0.54 x E)
Thickness E x 1.55

Volume = length x width x thickness

- Triangular distribution in axial plane:

Length L x 0.7
Width nE + (0.4 x E)
Thickness E x 1.3

Volume = length x width x thickness

Single plane implant:

Length $L \times 0.7$

Width $nE + (0.66 \times E)$

Thickness $E \times 0.6$

Volume = length x width x thickness

- Photon beam boosts:

Tangential beams

Volume = (field length) x (maximum distance dorsal beam edge to the skin, Y) x (thickness of traversed tissue; this is diameter entrance-exit of dorsal beam edge, Z), divided by 2 (fig 8).

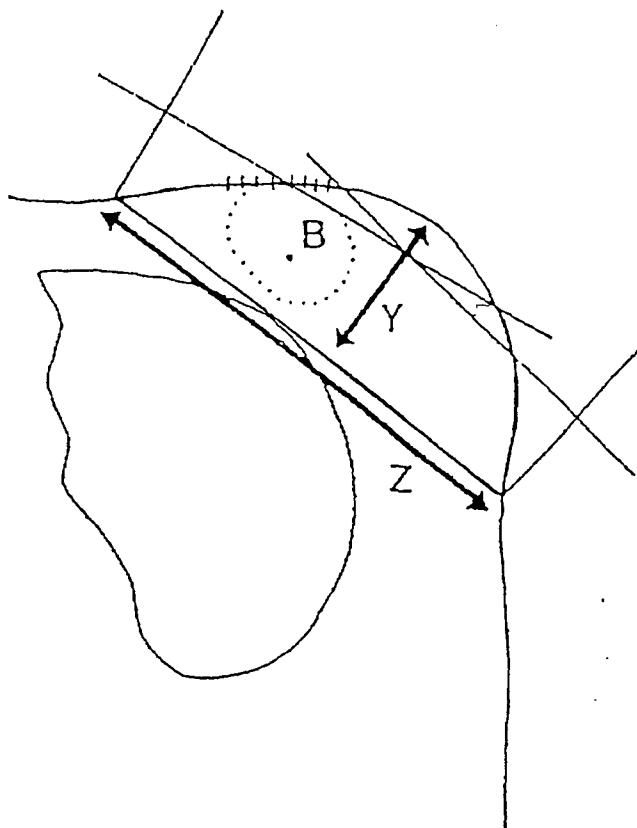


Fig 8

6.9. Quality assurance

6.9.1. Quality control at the institute.

- simulation films should be made for each field; for interstitial therapy orthogonal films should be made;
- verification films for external fields should be made
- calculation of the dose and the monitor units/treatment time should be made independently by two persons.

6.9.2. Dummy Run (35).

6.9.3. In vivo Dosimetry (36,37,38).

6.9.4. Initial check radiotherapy data at the Data Center (39).

6.9.5. Individual Case Review (40).

7. INVESTIGATION BEFORE THERAPY AND FOLLOW-UP

7.1. A routine screening for distant metastases.

7.2. Histopathologic report, to be provided by the local pathologist.

- macroscopic tumor size
- microscopic evaluation of the completeness of excision
- tumor type (according WHO 1981)
- in case of axillary dissection : number of lymph nodes
- number of positive nodes
- upon randomisation pathological material has to be sent for central review to the secretariat of the Radiotherapy Department, Ms. Frances Godson, Netherlands Cancer Institute, Antoni Van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.

7.3. After surgery: postoperative mammography before the start of radiotherapy.

7.4. Before the start of radiotherapy: photographs of the both breasts (slides or colour prints) as indicated on page 26.

7.5. Follow-up

7.5.1.: Follow-up check ups will be carried out every 4 months during 2 years and every 6 months until the 5th year and then yearly.

7.5.2.: Photographs of the two breasts will be taken in identical circumstances as described on page 26, every 3 years.

7.5.3.: Control mammography every year.

7.5.4.: Locoregional situation will be assessed at every clinical examination. Cosmetic results will be scored every 3 years.

EDRTC
22881/19882

OUTLINE OF INVESTIGATIONS BEFORE THERAPY AND DURING FOLLOW-UP.

BEFORE RANDOMIZATION	BEFORE START RT	DURING FOLLOW-UP
<p>Complete information on:</p> <ul style="list-style-type: none">- menopausal status- age- clin. tumor size- pN- complete PA- DCIS- date of surgery <p>Routine screening for distant metastases</p>	<p>Mammography</p> <p>Photographs both breasts</p>	<p>Follow-up intervals:</p> <ul style="list-style-type: none">- 4 monthly: 2 years- 6 monthly: up to 5 years- thereafter: yearly <p>Investigations:</p> <ul style="list-style-type: none">- clinical examination- locoregional evaluation <p>Yearly: mammography</p> <p>3yearly: cosmetic evaluation photographs both breasts</p>

8. DEFINITION OF THE CRITERIA OF THE ANALYSIS OF THE TRIAL.

- 8.1. All the patients will be followed until death.
- 8.2. The time of follow-up will be counted starting from the date of tumorectomy.
- 8.3. Time of local disease-free survival is defined as starting from the date of tumorectomy until the first sign of local recurrence.
- 8.4. Local recurrence will have to be confirmed by histology or cytology.
- 8.5. The occurrence of the proven local recurrence needs a topographical description:
 - 8.5.1. Recurrence in the site of the primary tumor.
 - 8.5.2. Recurrence within the scar.
 - 8.5.3. Recurrence in the skin outside the scar.
 - 8.5.4. Recurrence in the breast tissue but outside booster area.
 - 8.5.5. Recurrence in the breast, outside irradiated volume.
 - 8.5.6. Diffuse recurrence.
- 8.6. A regional recurrence is defined as:
 - 8.6.1. A nodal failure in the ipsilateral axilla, internal mammary, infraclavicular or supraclavicular region.
 - 8.6.2. Regional recurrences should preferably be confirmed by cytology or histology.

9. ASSESSMENT OF THE COSMETIC RESULT.

The cosmetic outcome and assessment of therapy sequellae will be scored regularly. Therefore colour print photographs or slides have to be taken immediately after surgery (before radiotherapy), and thereafter every 3 years.

Photographs must be taken with the patient in standing position. Two frontal views, one with the arms lifted upwards, one with the arms along the body and one profile view (taken from the treated side) with the arms lifted upwards are mandatory.

Marks should be made on the skin at the incisura jugularis, and on the midline 25 cm lower, to allow quantitative measurement of breast retraction (see below). An external review panel will score qualitatively the cosmetic result, based on the pictures, using a 4 point categoric scale.

Summary of the guidelines for the local investigator:

- Three photographs should be taken from every patient
 - after surgery and before radiotherapy
 - thereafter every 3 years.
- Colour photographs or slides are preferred (Polaroid's are less desirable).
- Photographs have to be taken with the patient in standing position:
 - two frontal views:
 - one with the arms along the body
 - one with the arms lifted upwards
 - one profile (slightly oblique) view, taken from the treated side, with the arms lifted upwards.
- Marks on the skin have to be drawn (a cross, +)
 - at the incisura jugularis and
 - on the midline 25 cm lower, to allow quantitative measurements, with NO radiotherapy fields drawn yet on the patient, so before the simulation.
- Patient identification on photographic material:
 - 1. institution number.
 - 2. family name (in full), first name can be added but is not essential.
OR initials of the patient (3), from first name and family name
but consistent with:
 - other patient initials from the same institution
 - reported initials (on the on-study forms) to the Data Center.
 - 3. sequential identification number of the patient.
 - 4. date when photographs were taken !
- Photographs should be sent to:
Frances Godson,
Department of Radiotherapy,
Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital,
Plesmanlaan 121, 1066 CX Amsterdam,
The Netherlands.

10. REGISTRATION AND STRATIFICATION

Patients should be registered at the Data Center within a maximum of 5 weeks after surgery, and after verification of the eligibility criteria, by telephone (32.2.7741600), or Eurocode (direct line: 32.2.7741633, PTT network: 2062.210142). The following information will be requested:

- Protocol number (22881/10882).
- Institution number.
- **Randomizing for Radiotherapy Cooperative Group, Breast Cancer Cooperative Group, or both.**
- Name of the person who is calling.
- Name of the responsible radiotherapist.
- Patient name (optional) or identification code.
- Local patient's chart number (optional if the name is given).
- Date of birth and patient's age (less/equal to or more than 40 years).
- **Menopausal status.**
- **Clinical tumor volume less or equal to 3 cm or larger than 3 cm.**
- Nodes pathologically positive or negative.
- Resection microscopically complete or incomplete.
- Presence of DCIS.

Stratification will be done based on:

- Menopausal status.
- Tumor size (clinical).
- Nodal status.
- Presence of DCIS.
- Age (< 40 or more).
- Institute.

11. STATISTICAL CONSIDERATIONS

11.1. Initial guidelines.

The sample size for this trial is calculated separately for patients undergoing complete resection or incomplete resection to ensure enough power to make conclusions within each group.

The endpoint of interest is the cosmetic effect within a range of a 5% difference in local control rate.

It is estimated that 90% of the patients treated by standard treatment are free of local recurrence at 10 years. 330 patients should be treated in each treatment arm (a total of 660 for complete resection patients and 660 for incomplete resection) and followed for 10 years. This number will ensure with 80% probability that the upper 90% confidence limit for the true difference of local recurrence-free rates at 10 years will not exceed 5%, if there is actually no difference in efficacy (ref. 1).

In order to evaluate the cosmetic results, the scale developed by Aaronson et al. (ref. 2) will be used. The scale proved to be useful in evaluating the cosmetic results of BCT in T1/T2 breast cancer (EORTC-ECOG trial 10801). Preliminary analysis (based on 158 patients) indicated overall good to excellent results in 2/3 of the patients (ref. 3). The number of patients to be accrued in the trial will provide high power (80%) to detect a possible shift of 10% in the rate of overall good cosmetic results.

- ref. 1: Makuch R. and Simon R.: Sample Size Requirements for evaluating a Conservative Therapy, Cancer Treat Rep 62: 1037-1040 (1987).
- ref. 2: Aaronson N. et al.: Evaluation of Breast Conserving Therapy: Clinical Methodological and Psychosocial Perspectives. Eur J Surg Oncol 14: 133-140 (1988).
- ref. 3: Aaronson N. et al.: The Cosmetic Results of Breast Conserving Therapy. Proceedings 4th EORTC Breast Cancer Conference, June 30 - July 3, 1987.

11.2. Appendix.

After 3 years of recruitment, the group has demonstrated that it could achieve a recruitment rate of 1000 patients a year in the 'complete resection' group. Therefore, it was decided to extend the aims of the trial for this category of patients, and to evaluate if the addition of the booster dose of radiotherapy had any impact on survival.

The 10 years survival rate in this patient population is estimated at 80%. The new aim of the study will be to investigate if the addition of boost radiotherapy could improve this 10 years survival rate by 5%, to be at least 85%.

Because it is very unlikely that such study could be repeated, we have chosen small values for α and β : $\alpha=0.01$ and $\beta=0.1$.

Under those assumptions, in order to detect a 5% difference in the 10 years survival rate, a total of 3442 patients evaluable for survival would be required. Because of the good prognosis of the patients and the length of the follow-up period, we estimate that a maximum of 30% of the patients might be lost to follow-up. Therefore, a total of approximately 5000 patients with a complete resection will be registered in the trial.

12. ETHICAL CONSIDERATIONS

Informed consent for entry will be sought according to the practice of each participating centre.

13. ADMINISTRATION OF THE TRIAL

The trial will be administered by the EORTC Data Center in Brussels for the forms and by Ms. Frances Godson (Radiotherapy Department, Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands) for pictures and pathology.

Slides of the primary tumor and photographs should be sent within 1 month after randomization to Ms. Frances Godson.

The following forms have to be sent to the Data Center within the indicated time period:

Within two weeks after randomisation :

- on study form.

At the end of radiotherapy :

- radiotherapy form.

Every year :

- follow-up form.

Every three years :

- cosmetic evaluation.

All forms and all questions concerning data management or statistics should be addressed to :

Ms. Marianne Pierart, Data manager,
or to **Ms. M. Van Glabbeke, Statistician,**
EORTC Data Center, Ave. E. Mounier 83, Bte 11, 1200 BRUSSELS, Belgium.
Telephone: 32.2.7741600, Randomization only: 32.2.7741600
(Eurocode; direct line 32.2.7741633, PTT network 2062.210142).

All other questions should be addressed to the study coordinators:

H. Bartelink tel. 31.20.5122122

J.C. Horiot tel. 33.80.737517

E. van der Schueren tel. 32.16.336430

14. PUBLICATION

The authors of publications (written or oral communications, intermediate reports or final analyses) on the results on this trial will be:

- the coordinators of the trial and a representative of each center participating with at least 10 % of evaluable patients.
- the data manager and the statistician will also be co-authors for written communications.

All the information gathered through this trial will be the property of the Radiotherapy and the Breast Cancer Cooperative Groups of the EORTC and can only be used with the formal agreement of the coordinator and the president of each group.

15. REFERENCES

1. Amalric R., Santamaria F., Robert F., Seyle J., Altshuller C., Pietra J.C., Amalric F., Kurtz J.M., Spitalier J.M., Brandone H., Ayme Y., Pollet J.F., Bressac C., Fondarai J.: Conservation therapy of operable breast cancer - results at five, ten and fifteen years in 2216 consecutive cases. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New surgical and radiotherapeutic techniques. Philadelphia, J.B. Lippincott Company 1983: 15-23.)
2. Calle R., Vilcoq J.R., Pilleron J.P., Schlienger P., Durand J.C.: Conservative treatment of operable breast carcinoma by irradiation with or without limited surgery - ten years results. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New surgical and radiotherapeutic techniques. Philadelphia, J.B.Lippincott Company 1983: 3-9.)
3. Pierquin B.: Conservation treatment for carcinoma of the breast: experience of Creteil - ten years results. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New surgical and radiotherapeutic techniques. Philadelphia, J.B.Lippincot Company 1983: 11-15.)
4. Fisher B., Bauer M., Margolese R., Poissin R., Pilch Y., Redmund C., Fisher E., Wolmark N., Geutsch M., Montague E., Suffer E., Weckerham L., Luner H., Glass A., Shibata M., Deckers P., Ketcham A., Oischi R., Russel I.: Five year results of a randomized trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *New Engl J Med* 312, 665, 1985.
5. Veronesi U., Delvecchio H., Greco M., Lumi A., Muscolini G., Rosponi A., Saccozzi R., Zucali R.: Results of quadrantectomy, axillary dissection and radiotherapy (QUART) in T1N0 patients. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New Surgical and radiotherapeutic techniques. Philadelphia, J.B. Lippincott Company 1983: 91-101.)
6. Sarrazin D., Le M., Fontaine M.F., Arriagada R.: Conservative treatment versus mastectomy in T1 or small T2 breast cancer - a randomized clinical trial. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New surgical and radiotherapeutic techniques. Philadelphia, J.B. Lippincott Company 1983: 101-111.)
7. Bartelink H., Borger J.H., Van Dongen J.A., Peterse J.L.: The impact of tumor size and histology on local control after breast conserving therapy. *Rad Oncol* 11: 297-305, 1988.

8. Van Dongen J.A., Bartelink H., Aaronson N., Fentiman I., Hayward J.L., Lerut T., Millis R., Olthuis G., Peterse J.L., Rotmensz N., van der Schueren E., Sylvester R., The S.K., Winter J., Van Zyl K. (for the EORTC Breast Cancer Group): Randomized clinical trial to assess the value of breast conserving therapy (BCT) in stage I and stage II breast cancer; EORTC Trial 10801. In: Proceedings 4th European Conference on Clinical Oncology and Cancer Nursing, Madrid, November 1-4, p.105 (Abstract p.105, no 394), London 1987.
9. Harris J.R., Recht A., Amalric R., Calle R., Clark R.M., Reid J.G., Spitalier J.M., Vilcoq J.R., Hellman S.: Time course and prognosis of local recurrence following primary radiation therapy for early breast cancer. *J Clin Oncol* 2: 37, 1984.
10. Kurtz J.M., Amalric R., Delouche G., Pierquin B., Roth J., Spitalier J.M.: The second ten years: long time risks of breast conservation in early breast cancer. *Int J Rad Oncol Biol Phys* 13: 1327-1332, 1987.
11. Koper P., van Putten W., The S.K., Treurniet-Donker A.P., Reichgelt B.A., Helle P.A., Meerwaldt J.H., Seldenrath J.J., Subandono A.J., Wijnmaalen A.J., Van Geel A.N., Wiggers T., Meischke-de Jong M.L.: Treatment results of lumpectomy and radiotherapy for early breast cancer, a survey of 966 patients. In: Proceedings 4th EORTC Breast Cancer Working Conference, London 1987.
12. Van Limbergen E., Van den Bogaert W., van der Schueren E., Rijnders A.: Tumor excision and radiotherapy as primary treatment of breast cancer, analysis of patients and treatment parameters and local control. *Rad Oncol* 8: 1-9, 1987.
13. Connolly J.L., Schnitt S.J., Harris J.R., Hellman S., Cohen R.B.: Pathologic correlates of local tumor control following primary radiation therapy in patients with early breast cancer. (In: Harris J.R., Hellman S., Silen W.: Conservative management of breast cancer. New surgical and radiotherapeutic techniques. Philadelphia, J.B. Lippincott Company 1983: 123-135.)
14. Recht A., Connolly J.L., Schnitt S.J., Cody B., Love S., Osteen R.T., Patterson W.B., Shirley R., Silen W., Come S., Henderson I.G., Silver B., Harris J.R.: Conservative surgery and radiation therapy for early breast cancer: results, controversies and unresolved problems. *Semin Oncol* 13: 435-449, 1986.
15. Delouche G., Bachelot F., Premont M., Kurtz J.M.: Conservative treatment of early breast cancer: long term results and complications. *Int J Rad Onc Biol Phys* 13: 29-34, 1986.

16. Clarke C.M., Le M.G., Sarrazin C., Lacombe M.J., Fontaine F., Travagli J.P., May-Levin F., Contesso G., Arriagada R.: Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institute Gustave-Roussy. *Int J Rad Onc Biol Phys* 11 137-145, 1985.
17. Smith I.: Recurrent disease. (In: Harris J.R., Hellman S., Henderson I.C., Kinne D.W.: *Breast diseases*. Philadelphia 1987, J.B. Lippincott Company: 373- 374.)
18. Beadle G.F., Silver B., Botnick, Hellman S., Harris J.R.: Cosmetic results following primary radiation therapy for early breast cancer. *Cancer* 54, 2911-2918, 1984.
19. Danoff B.F., Pajak T.F., Solin L.J., Goodman R.L.: Excisional biopsy, axillary node dissection and definitive radiotherapy for stages I and II breast cancer. *Int J Rad Onc Biol Phys* 11: 479-483, 1985.
20. Bartelink H., Van Dam F., Van Dongen J.: Psychological effects of breast conserving therapy in comparison with radical mastectomy. *Int J Rad Onc Biol Phys* 11: 381-385, 1985.
21. Ray G.R., Fish V.J., Lee R.M., Marzoni F.A. Jr., Trollope M.L., Kuos M., Gribble M.: Biopsy and definitive radiation therapy in stages I and II carcinoma of the female breast. *Int J Rad Onc Biol Phys* 5: 23-28, 1983.
22. Dewar J.A., Benhamou S., Benhamou E., Arriagada R., Petit J.Y., Fontaine F., Sarrazin D.: Cosmetic results following lumpectomy, axillary dissection and radiotherapy for small breast cancers. *Rad Oncol* 12: 273-280, 1988.
23. Harris J.R., Leven M.S., Svensson G., Hellman S.: Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Rad Onc Biol Phys* 5: 257, 1979.
24. Pezner R.D., Lipsett J.A., Vora N.L., Desai K.R.: Limited usefulness of observer-based cosmesis scales employed to evaluate patients treated conservatively for breast cancer. *Int J Rad Onc Biol Phys* 11: 1117-1119, 1985.
25. Van Limbergen E., van der Schueren E., Vantongelen K.: Cosmetic evaluation of breast conserving treatment for mammary cancer. 1. Proposal of a quantitative scoring system. *Rad Oncol* 16:159-167, 1989.
26. McRae D., Rodgers J., Dritschillo. Dose-volume and complications in interstitial implants for breast carcinoma. *Int J Rad Onc Biol Phys* 13: 525-529, 1987.

27. Von Dengel H., Leibergsperger H., Glatt E., Reisner K., Haase W.: Mammography following tissue preserving treatment for carcinoma of the breast. *Fortschr. Röntgenstr.* 146 (5): 532-538, 1987.
28. Holland R., Veling S.H.J., Mravunac M., Hendriks J.H.: Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast conserving therapy. *Cancer* 56: 979-990, 1985.
29. Fletcher G.: Textbook of radiotherapy. Philadelphia 1980. Lea and Febiger p. 550.
30. Timothy A.R., Overgaard J., Overgaard M., Wang C.C.: Treatment of early carcinoma of the breast. *Lancet* 11: 25-28, 1979.
31. Denham J.W.: The radiation dose response relationship for control of primary breast cancer. *Rad Oncol.* 7: 107, 1986.
32. Arriagada R., Mouriessse H., Sarrazin D.: Radiotherapy alone in breast cancer. Analysis of tumor parameters, tumor dose and local control in the experience of the Gustave-Roussy Institute and the Princess Margaret Hospital. *Int J Rad Onc Biol Phys* 11: 1751, 1985.
33. International Commission on Radiation Units and Measurements. Dose specification for reporting external beam therapy with photons and electrons. Report 50. ICRU Publication, Bethesda, Maryland, USA, in press.
34. Chin L.M., Siddon R.L., Cheng C.W., Rice R.K., Mijnheer B.J.: Influence of lung on 3-D dose distributions of tangential breast treatments. Proceedings 9th International Conference on the Use of Computers in Radiation Therapy, Scheveningen, The Netherlands, 169-172, 1987.
- △ 35. van Tienhoven G., van Bree N.A.M., Mijnheer B.J. and Bartelink H.: Quality assurance of the EORTC trial 22881/10882: "assessment of the role of the booster dose in breast conserving therapy": the dummy run. *Rad Oncol* 22, 290-298, 1991.
- △ 36. Hamers H.P., Johansson K.A., Venselaar J.L.M., de Brouwer P., Hansson U., and Moudi C.: Entrance and exit TL-dosimetry in the conservative treatment of breast cancer: a pilot study for the EORTC Radiotherapy Cooperative Group. *Rad Oncol* 22, 280-284, 1991.
- × 37. Hansson U. and Johansson K.A. Quality audit of radiotherapy with EORTC mailed in water TL-dosimetry. *Rad Oncol* 20, 191-196, 1991.

38. Heukelom S., Lanson J.H., van Tienhoven G. and Mijnheer B.J.: In vivo dosimetry during tangential breast treatment. *Rad Oncol* 22, 169-279, 1991.
39. Vantongelen K., Leunens G. and Borger J.H.: Initial check of radiotherapy data in early breast cancer protocol (EORTC 22881/10882). Proceedings ESTRO 9th annual meeting, Monte Catini, Sept 1990.
40. van Tienhoven G., Leunens G., Vantongelen K., Garavaglia G., Gonzalez Gonzalez D., Horiot J.C., Johansson K.A., Pierart M., Van den Bogaert W., van der Schueren E. and Bartelink H.: Quality assurance of EORTC trial 22881/10882: 'Assessment of the role of the booster dose in breast conserving therapy': The individual case review. Proceedings ESTRO 11th annual meeting, Malmö, Sept 1992.

16. ADDENDA

- addendum 1: Treatment of adjacent lymph nodes.
- addendum 2: UICC staging for breast cancer.
- addendum 3: Pathology.
- addendum 4: Quantitative assessment of radiofibrosis of breast contour and nipple position asymmetry.

Addendum 1 : TREATMENT OF ADJACENT LYMPH NODE STATIONS.

Internal mammary lymph nodes

Special care should be taken to avoid over- or under-doses at the junction of the tangential fields and the irradiation of this lymph node chain. It is advised to give first priority to the irradiation of the whole breast, adaptations should be sought in the irradiation of the internal mammary lymph node chain when necessary, for example in patients with medially located tumors. In the latter, no junction is accepted over the tumor bed area.

The target volume includes at least the first three intercostal spaces. The dose should be specified at 2 cm depth (according to the ICRU 50 guidelines).

Axillary lymph nodes

N0: In premenopausal patients, axillary staging is advised by means of a complete axillary dissection. Indications for postoperative radiotherapy should be given according to the guidelines per centre. In postmenopausal patients radiotherapy or axillary dissection can be chosen.

N1: Complete axillary dissection is advised in all N1 patients. Postoperative radiotherapy should be given according to the guidelines of the participating centre.

Addendum 2 : UICC STAGING FOR BREAST CANCER.

TNM Clinical Classification

T - Primary tumor

- TX Primary tumor cannot be assessed.
T0 No evidence of primary tumor.
Tis Carcinoma in situ: intraductal carcinoma, or lobular carcinoma in situ, or Paget's disease of the nipple with no tumor.

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

- T1 Tumor 2 cm or less in greatest dimension.
T1a: 0.5 cm or less in greatest dimension.
T1b: More than 0.5 cm but not more than 1 cm in greatest dimension.
T1c: More than 1 cm but not more than 2 cm in greatest dimension.
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension.
T3 Tumor more than 5 cm in greatest dimension.
T4 Tumor of any size with direct extension to chest wall or skin.
T4a: Extension to chest wall
T4b: Oedema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast.
T4c: Both 4a and 4b, above.
T4d: Inflammatory carcinoma.

Note : Chest wall includes ribs, intercostal muscles and serratus anterior muscle but not pectoral muscle.

Note : Inflammatory carcinoma of the breast is characterised by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying palpable mass. If the skin biopsy is negative and there is no localized, measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d).

When classifying pT, the tumor size is a measurement of the invasive component. If there is a large in situ component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm) the tumor is coded pT1a. Dimpling of the skin, nipple retraction or other skin changes, except those in T4, may occur in T1, T2 or T3 without affecting the classification.

N - Regional Lymph Nodes

- NX Regional lymph nodes cannot be assessed (e.g. previously removed).
- N0 No regional lymph node metastasis.
- N1 Metastasis to movable ipsilateral axillary node(s).
- N2 Metastasis to ipsilateral axillary node(s) fixed to one another or to other structures.
- N3 Metastasis to ipsilateral internal mammary lymph node(s).

M - Distant Metastasis

- MX Presence of distant metastasis cannot be assessed.
- M0 No distant metastasis.
- M1 Distant metastasis (includes metastasis to supraclavicular lymph nodes).

The category M1 may be further specified according to the following notation:

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	HEP	Peritoneum	PER
Brain	BRA	Skin	SKI
Lymph nodes	LYM	Other	OTH

pTNM Pathological Classification

pT - Primary Tumor

The pathological classification requires the examination of the primary carcinoma with no gross tumor at the margins of resection. A case can be classified pT if there is only microscopic tumor in a margin. The pT categories correspond to the T categories.

pN - Regional Lymph Nodes.

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (level 1). Such a resection will ordinarily include 6 or more lymph nodes.

- pNX Regional lymph nodes cannot be assessed (not removed for study or previously removed).
- pN0 regional lymph node metastasis.
- pN1 metastasis in movable ipsilateral axillary node(s)
 - pN1a - Only micrometastasis (none larger than 0.2 cm)
 - pN1b - Metastasis in lymph node(s), any larger than 0.2 cm
 - pN1Bi Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension.
 - pN1bii Metastasis in 4 or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension.
 - pN1biii Extension of tumor beyond the capsule of a lymph node metastasis less than 2.0 cm in greatest dimension.
 - pN1biv Metastasis in a lymph node 2.0 cm or more in greatest dimension.
- pN2 Metastasis in ipsilateral axillary lymph nodes that are fixed to one another or to other structures.
- pN3 Metastasis to ipsilateral internal mammary lymph node(s).

pM - Distant Metastasis.

The pM categories correspond to the M categories.

Addendum 3: PATHOLOGY

Pathologic examination of excisional biopsy specimen.

Randomization in this trial relies heavily on careful microscopic examination of the excisional biopsy specimen. It is often not possible to orient these specimens without guidance from the surgeon; therefore, the surgeon should mark the specimen, for instance with long and short sutures at the nipple and basal side.

The pathologist is responsible for accurate microscopic assessment of the margins of excision. This is most easily accomplished by marking the margins with Indian ink, which adheres well to fresh tissue that has been blotted free of blood and moisture, or has been dipped for a minute in methanol. However, margins can only be inked reliably in intact, unliced specimens. In order not to interfere with frozen section and receptor studies, the specimen should be delivered immediately, unfixed and intact to the laboratory.

Once inked, the specimen should be lamellated in thin slices. If a gross identifiable tumor is present, the largest diameter, the shape of the tumor and the minimal distance from the nearest surgical edge should be recorded. After this, portions for receptor analysis and/or frozen section can be removed. Frozen section studies of margins should be discouraged unless the tumor seems to be close to a margin and intraoperative confirmation of this will have immediate impact on treatment.

Radiography of the lamellated specimen may be helpful in the assessment of margins; specimen radiography is especially indicated in cases with mammographical microcalcifications, in order to pinpoint the lesions in the excisional biopsy.

A complete cross section of the tumor, including periphery, surrounding tissue and closest surgical edges, should be sampled for microscopy, if necessary in more than one block. At least 3 additional blocks including nearest margins and tumor, should be sampled. Additional samples should be obtained on the basis of gross and/or radiological findings.

Tumor transected at an inked surface represents clearly involved margins; this applies equally to invasive carcinoma and ductal carcinoma in situ. Tumor foci within one high power field (40x) is regarded close to the margin. In this case the excision is still considered as complete.

An extensive ductal carcinoma in situ component is a risk factor for local recurrence. Therefore, the amount of ductal carcinoma in situ should be semi-quantitatively analysed. As rule of thumb the in situ component is regarded extensive if in the cross section more than 25% of the tumor area exists of ductal carcinoma in situ (usually more than 15 ducts are involved in these cases).

RECOMMENDED PROCEDURES FOR PATHOLOGIC EXAMINATION OF
EXCISIONAL BIOPSY

A. Sampling

- ask surgeon to deliver specimen intact, immediately and unfixed, and to mark nipple side with suture.
- record size of specimen in cm in three dimensions.
- mark surface with Indian ink.
- lamellate specimen in slices 0.3 - 0.5 cm.
- describe: - largest diameter of dominant lesion (DL).
- aspect margins DL.
- macroscopic completeness of excision.
- minimal distance (in cm) of the DL from the nearest surgical margin.
- obtain portions for receptor analysis and/or frozen sections, being careful to leave specimen margins intact.
- (optional: X-ray slices).
- sample for microscopy:
 - complete cross section DL including periphery and surrounding tissue (in addition to frozen section block !).
 - macroscopical nearest surgical edges; additional samples of margins if necessary on the basis of gross or radiological findings (at least 3 blocks).
 - all macroscopical and/or radiological abnormal tissue from remaining specimen.

B. Reporting

In order to be able to complete the on-study form, the local pathology report should include:

- the size of the excisional biopsy specimen in three dimensions
- the largest diameter of the dominant lesion (measured in the unfixed specimen, in mm)
- the histologic tumor type (according WHO criteria [Histologic typing of Breast Tumours, 2nd ed, p 21. Geneva, 1981])
- microscopic completeness of excision of invasive carcinoma
 - incomplete = tumor transected at surface
 - doubtful = tumor foci within one high power field (40x)
- minimal microscopic margin from invasive carcinoma in mm
- presence of in situ tumor adjacent to invasive carcinoma
classified as lobular and/or ductal carcinoma in situ

- the dominant type of ductal carcinoma in situ
classified as comedo/solid, cribriform, micropapillary or mixed
- the quantity of ductal carcinoma in situ adjacent to the invasive carcinoma
quantified as:
 - little = 2-3 ducts
 - moderate
 - extensive = more than 15 ducts, in the cross section more than
25% of the tumor area consists of DICS
- microscopic completeness of excision of ductal carcinoma in situ
- the presence of lymphatic invasion adjacent to the invasive carcinoma
tumor emboli should be seen in at least 2 endothelial lined vessels
- total number of axillary lymph nodes examined
- total number of positive axillary lymph nodes
- presence of extra nodal growth
= transverse growth through the lymph node capsule in the perinodal fat tissue

This trial includes a central histopathologic review by the EORTC Breast Group Pathology Panel to obtain uniform classification, grading, prognostic index and evaluation of risk factors of local recurrence.

All local pathologists are therefore kindly requested to send a copy of the pathology report and a set of slides of the complete cross section of the invasive carcinoma (HE stained or unstained, preferably tissue not subjected to frozen section studies) to:

Ms. Frances Godson, Radiotherapy Department, Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Plesmanlaan 121, 1066 CX Amsterdam.

Addendum 4: QUANTITATIVE ASSESSMENT OF RADIOFIBROSIS OF BREAST CONTOUR AND NIPPLE POSITION ASYMMETRY.

For the quantitative measurement photographs are needed with the patient in standing position and both arms besides the trunk. Marks on the skin have to be made at the incisura jugularis (+) and at the midline, 25 cm lower (+) to allow calculation of the correct magnification factor.

The following measurements will be made on the photographs centrally in Amsterdam:

On the ordinate:

- distance A from the incisura jugularis to the nipple level.
- distance I from the incisura jugularis to the projection of the inferior breast contour.

On the abscissa :

- distance M from the midline to the nipple.
- distance L from the midline to the projection of the lateral breast contour.

The distances A, I, M, L shall be measured in the treated breast whereas the distances A', I', M', L' of the untreated breast will serve as references. Differences (A'-A) and (I'-I) quantifies upside retraction of the nipple position and the inferior breast contour, whereas (M'-M) and (L'-L) measure asymmetry in the medio-lateral direction. These measurements correlate as well with cosmetic scorings results as with treatment parameters such as radiation dose and fractionation schedule (25). They can be carried out quickly and precisely using the digitiser of a treatment planning system.

SCORING SYSTEM FOR
MEASUREMENT OF BREAST CONTOUR AND NIPPLE ASYMMETRIES

