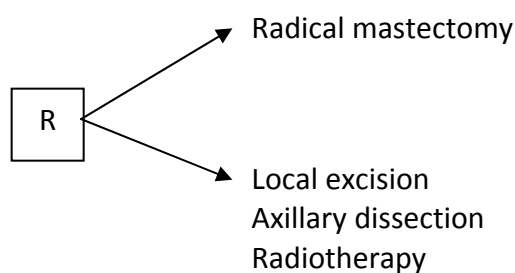


# EORTC BREAST CANCER COOPERATIVE GROUP

## PROTOCOL 10801

### OPERABLE BREAST CANCER

## RANDOMIZED CLINICAL TRIAL TO ASSESS THE VALUE OF BREAST- CONSERVING PROCEDURES



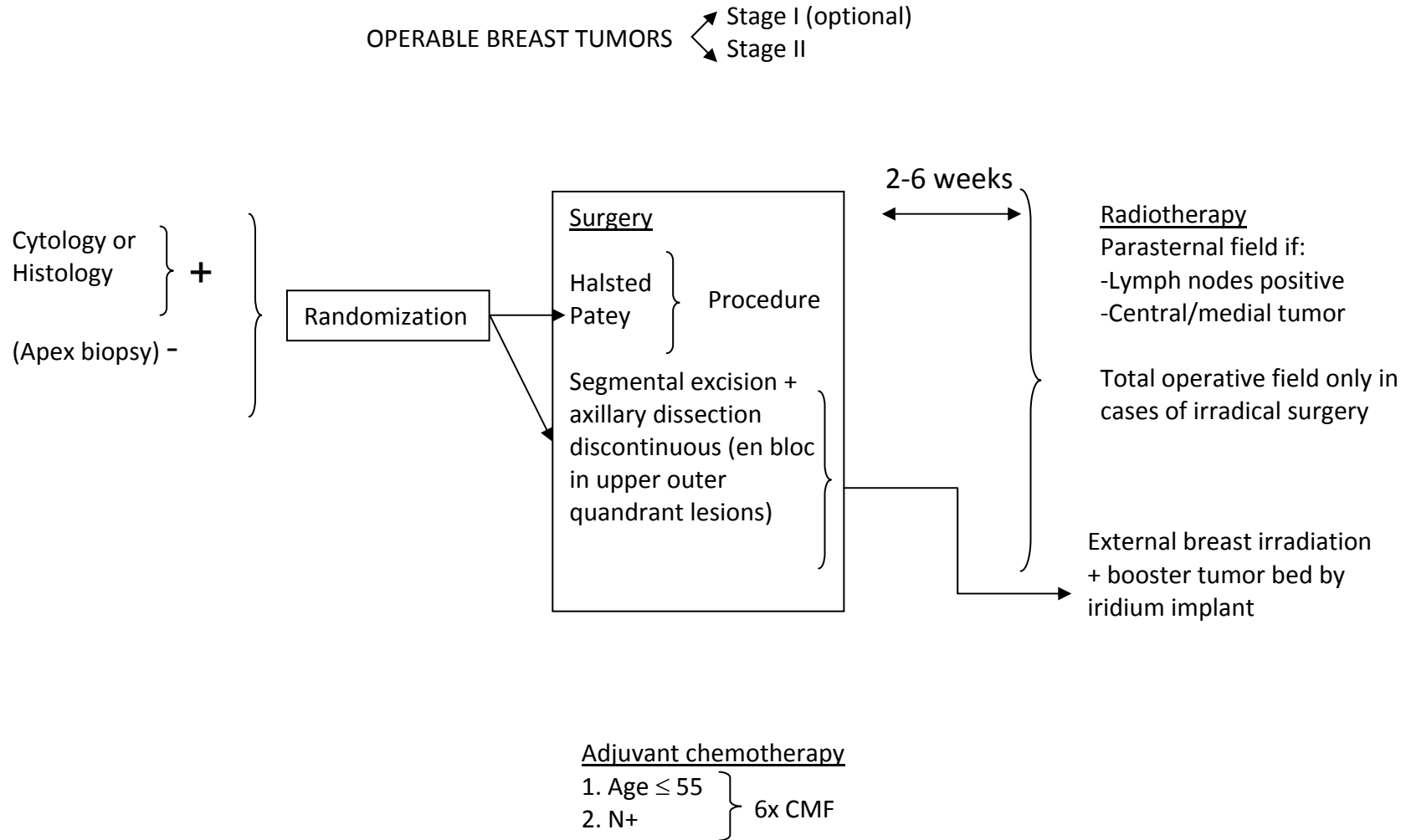
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TRIAL DESIGN



## 1. BACKGROUND AND INTRODUCTION

It is becoming increasingly probable that certain operable breast tumours can be treated by breast-conserving techniques and orthodox treatment with equal results. Especially the newer techniques in radiotherapy with special booster techniques reveal possibilities of non-mutilating kinds of treatment. Treatment in which radiotherapy plays a more important part than formerly has been designed long ago, e.g. by Baclesse (1960) and Mustakillio (1972). More recently this kind of treatment has been designed and perfected in several French centres (Calle, 1978; Pierquin, 1978) and in the USA by the group of Hellman (1979) and of Fletcher (1979).

In these centres patients with small breast tumours are now more or less systematically treated by radiotherapy only, or by radiotherapy after lumpectomy and axillary dissection. The interpretation of the results is difficult, but they seem to be promising. It is urgent to have proof that these methods are as effective as a radical mastectomy.

Only a few randomized studies on breast-conserving therapy have been initiated. In the London Guy's Hospital trial (Hayward, 1978) compared orthodox surgery to wide local excision plus radiotherapy of the breast and regional fields, in all operable cases. In cases with clinically involved nodes the results were better with orthodox treatment and even in the cases without suspicious nodes this seems to be the case. For many patients, the cosmetic effect was only moderately acceptable. The main point raised against this trial is the low radiation dosage when compared to present day standards. Most of the recurrences were located in the axilla.

In Paris (Institut Gustave Roussy) orthodox treatment is compared to local excision and axillary dissection combined with radiotherapy of the breast, in the smaller operable tumours ( T<sub>1</sub> N<sub>0</sub> N<sub>1a</sub> N<sub>1b</sub> cases). Up to now the results in both groups are similar although the number of patients is still rather small and the follow-up period is short (Sarrazin, 1979).

In Milan only smaller tumours without suspicious nodes are studied (T<sub>1</sub> N<sub>0</sub> N<sub>1a</sub>). The Halsted type of mastectomy is compared with quadrantectomy and axillary dissection combined with radiotherapy of the breast. The number of patients in this study is large (1979: 603 cases in study) but only 50 patients have had a long term follow-up of 5 years or more. Until now the results in both groups are similar (Banfi, 1979).

Considering the promising possibilities shown by Pierquin and Calle for the bigger tumours as well, the EORTC breast Cancer Group proposed a randomized study to compare orthodox surgery to breast-conserving treatment in TNM Stage I and Stage II patients\*.

The breast-conserving treatment is as follows:

- Local excision of the tumour
- Dissection of the axilla

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\* For staging: see point 13.

- Irradiation of the breast with high doses, including booster techniques with Iridium implantation.

Since some centres already consider that lumpectomy and axillary dissection plus radiotherapy as the ideal treatment for very small tumours with “negative” axilla, centres may take the decision to either include or exclude TNM stage I patients (0-2 cm tumour without suspicious lymph nodes in the axilla).

For very big tumours, the cosmetic result after local excision even with a small margin is poor. Therefore no operable T3 tumours (> 5 cm in diameter) are included. The reasons to treat the axilla surgically are as follows:

- a. Patients with all nodal situations (provided “operable”) can be included in this study. It is generally thought that patients with clinically involved nodes cannot be treated by radiation only (risk of recurrence, even after high dosage radiotherapy, especially if salvage surgery is necessary later).
- b. Information on axillary node status is of importance for the prognosis.

Although there is no definite proof of the long term value of adjuvant chemotherapy, the results until now strongly suggest that adjuvant chemotherapy is effective in pre-menopausal patients with high risk of recurrence after radical mastectomy. Therefore patients younger than 56 years in this study who have axillary node metastases will receive adjuvant treatment. For practical reasons the groups are divided by age (55 years).

Three questions should be answered by this trial:

1. Is ultimate survival the same in both groups?
2. Is the local situation better in the study group (complication-edema of the arm, functional tests of the arm, recurrence rate in the breast, possibility of salvage therapy, complications after salvage therapy)?
3. Are there differences in psychological respect between the two groups?

Accurate long term follow-up (until death) is essential in this study to register even very late recurrences! The risk of late recurrence is increased by leaving the irradiated breast in situ.

It is of great importance that in each centre the secondary treatment is uniform in both arms in cases when metastatic disease is discovered and that this secondary treatment is given following the last optimal therapy schedules. It is also essential that the guidelines in this protocol for therapy or for locally recurrent disease are followed to be able to compare the survival between the groups.

The feasibility of the techniques described in this protocol was studied in a pilot study. A total of 70 patients from the Netherlands Cancer Institute, Rotterdam Radiotherapy Institute, Institut Jules Bordet and Guy’s Hospital were treated in the proposed way and no serious problems were met; however, the ethical-psychological problems to be caused by randomisation are thought to be numerous and will probably increase as time goes by.

## 2. OBJECTIVES OF THE TRIAL

Assessment of the results of a breast-conserving therapy (radiotherapy + surgery) in patients with operable breast cancer with regard to:

1. survival (long term follow-up until death of the patient)
2. loco-regional control
3. disease-free period until moment of appearance of distant spread
4. cosmetic results
5. quality of life

## 3. SELECTION OF PATIENTS

Eligible: patients with breast cancer

1. Stage I and Stage II (0-5 cm tumours and N<sub>0</sub>-N<sub>1a + b</sub>)
2. Breast carcinoma proven (cytologically or histologically)
3. Lymph node metastases in the axilla: absent or operable

Excluded:

1. Patients of 71 years and older
2. Tumour fixed to the muscles
3. Stage III and IV
4. Karnofsky performance index less than 80
5. Emotionally or psychologically unable to undergo treatment
6. Questionable operability (doubt as to interpretation of inoperability criteria)
7. Sarcoma of the breast or carcinoma in situ
8. Histologically proven lymph node metastases in the highest level of the axilla, if appec biopsy is used
9. Patients with other malignant tumours (except skin tumours, non-melanoma)
10. Excluded by possible surgical contra-indication for lumpectomy: large tumour in a small breast
11. Excluded by possible radiotherapeutical contra-indications: very large breast
12. Multiple suspicious lesions in the breast (by palpation or on mammogram)
13. Impossibility of strict follow-up
14. Inflammatory cancer
15. Concurrent pregnancy or lactation
16. Bilateral tumour

Note 1) Patients to be excluded for the above reasons should always be judged by both surgeon and radiotherapist.

Note 2) All excluded patients should be registered at the data centre.

Note 3) All patients who refuse to participate in this study, but who are otherwise eligible should also be registered.

#### 4. EVALUATION PRIOR TO THERAPY

Required clinical evaluation: prior to therapy a complete patient history, a physical examination and technical evaluation should be made, which must include the following items:

1. Date of birth
2. Date of first symptom of cancer
3. Menopausal status and approximate date of menopause, if applicable
4. Other chronic disease and associated medications
5. Family history regarding breast disease

#### Physical examination

At least the following points should be carried out:

1. Measurement of 2 largest perpendicular diameters of the tumour by 2 independent persons (surgeon and radiotherapist)
2. The status of the lymph nodes in the axilla
3. Clinical investigation to exclude metastases beyond the axilla
4. Performance scale (Karnofsky)
5. Measurement of shoulder/arm function
6. Psychological and social state

TNM-UICC  
classification

#### Required technical evaluation

- Haematology examinations, Hb., WBC, platelets
- Chemistry test: liver function tests, creatinine, electrolytes, calcium, alkaline phosphatase, CEA (optional)
- Isotopes: skeletal scanning (optional)  
Scan of internal mammary lymph nodes (optional)
- CT scan (optional) of chest wall and internal mammary lymph nodes (optional)
- Ultrasound of chest wall and internal mammary lymph nodes (optional)
- X-ray: lung  
breast (with measurement of 2 largest perpendicular diameters of the tumour)  
In case of suspicious skeletal scan, metastases should be excluded by skeletal X-ray and whenever possible by bone biopsy
- ER, PRR measurements in tumour tissue
- Photography of both breasts

## 5. TRIAL DESIGNS AND RANDOMIZATION

Patients with operable breast tumours (see 3.0) with histologically or cytologically proven carcinoma and a negative apex biopsy (if used as a selection criterion) will be randomized. Patients should be randomized prior to definite surgery (according to clinical findings). The randomization will be either radical mastectomy (Halsted or Patey procedure) or breast-conserving therapy (Local excision + axillary dissection with external irradiation and iridium implant).

- 5.1 In patients with high upper outer quadrant lesions, en bloc quadrantectomy and axillary dissection will be performed. If in these cases the breast tissue surrounding the excised specimen cannot be closed, the iridium implantation of the breast tissue will be technically more difficult. A booster with external irradiation must be given if iridium implantation is impossible (rare).
- 5.2 Because of the possibility of minor differences in selection and technique, randomization will be done "per institute" and patients will be stratified according to stage and menopausal status.
- 5.3 Registration and randomization by means of a telephone call to the EORTC Data Centre (tel. Brussels 538.65.3) from 9.00 a.m. to 6.00 p.m., Monday through Friday. The date of registration is the date this telephone call is made.

At this time the following information is requested:

1. Protocol number (10801)
2. Name of Institute
3. Stage I or II
4. Menopausal status
5. Patient's name
6. Physician's name
7. Caller's name

The patient eligibility (Section 3 "Selection of patients") should be verified prior to calling.

If registration by telephone is not possible, patients may also be registered by telex:

22773 EORTC DATA CENTRE  
Institut Jules Bordet  
Rue Héger-Bordet 1  
1000 BRUXELLES, Belgique

Informed consent: to be discussed by each centre. A pamphlet with information to the patient on the trial principles should be prepared in each participating centre.

## 6. SURGICAL GUIDELINES

6.1 Study Group: Patients included in the study will be stratified retrospectively according to whether an “en bloc” procedure was performed or not.

#### 6.1.1 Discontinuous treatment of tumour and axilla

##### 6.1.1.1 Local excision

A margin of normal looking breast tissue of approximately 1 cm (or more if no deformation is expected) is chosen. Careful closure (no dead space) is required. Suction drainage with drain entrance near the excision (distance less than 1 cm) can be used. Marking (clip) or exact documentation of the deepest point of excision bed is required. Preferably the radiotherapist who will do the implantation will assist at the excision.

##### 6.1.1.2 Axillary dissection

Total clearance of all axillary nodes with preservation of muscles and long thoracic nerve. The pectoralis minor muscle may be removed but the management of the pectoralis minor muscle should be the same as with the radical mastectomy (one method per institute). If necessary the thoracodorsal nerve and vessels can be removed. The axillary levels should be carefully marked. It should be possible to state the invasion by four levels (see point 8.2).

In all cases, nodes should be counted and the number of histologically examined nodes and positive nodes stated. The status of the nodes at the apex should be recorded separately. It is recommended that the operative surgeon marks the levels himself by coloured strings or any other suitable means, or separates them immediately after surgery.

To be sure that all low axillary nodes are removed the axillary tail of the breast is included in the specimen. All precautions should be taken to prevent tumour contamination from the local excision (careful closure of the wound; changing of instruments, drapes, etc.). After the axillary dissection the wound is carefully washed out with a cell killing solution e.g. Dakin’s solution.

#### 6.1.2 Tumours localised in the upper outer breast quadrant; en bloc procedure

These tumours should be removed “en bloc” with the axillary contents, for technical and oncological reasons. An en bloc procedure is mandatory when in a discontinuous setting the two operative fields might communicate.

With en bloc removal wider margins of normal breast tissue will be necessary. The margin should be at least 3 cms in the direction of the nipple to diminish the tumour implantation risk.

If necessary the thoracodorsal nerve and vessels can be removed.

For managing the m. pectoralis minor, for marking of axillary levels and for wound washing, see 6.1.1.2.



## 6.2 Control group

Radical mastectomy will be done by Halsted or Patey procedure. For managing of the m.pectoralis minor, for marking of axillary levels and for wound washing, see 6.1.1.2.

## 6.3 Salvage surgery

By complete removal of breast and underlying muscles.

Local recurrences should if possible be approached surgically, as radically as possible.

## 7. RADIOTHERAPY GUIDELINES

Radiotherapy should be started as soon as possible within 6 weeks after surgery.

### 7.1 Parasternal lymph node region (both arms)

7.1.1 Indication: a: centrally or medially localized tumour  
b: lateral tumour and histologically proven axillary lymph node metastases

7.1.2 Technique: radiotherapy field of the homolateral lymph nodes: 2 cms above the sternal notch down to the fifth intercostal space with a field of 6 cm wide (1 cm hetero- and 5 cm homolaterally from the midline, also including the medial part of the supraclavicular fossa.

When the internal mammary node scan shows crossing over or extension outside the previously described field, the field should be adapted (in those centres where this scan is used).

7.1.3 Dose: 50 Gy in 5 weeks at 2 cm depth in 25 fractions with a daily dose of 2 Gy (according to the ICRU definition 1978).

In case of a pathologic lymph node scan and ultrasound and/or CT scan abnormalities a booster dose of 15 Gy should be given with electrons (only in those centres where these methods of investigation are used).

### 7.2 Complete operated area and regional node areas (both arms)

7.2.1 Indication: locally irradiated operation (microscopic or macroscopic)

7.2.2 Technique: the field should include sub- and supraclavicular regions, and the axilla (McWhirter fields)

In the control group also the thoracic wall.

7.2.3 Dose: 50 Gy in 5 weeks in 25 fractions with a daily dose of 2 Gy (ICRU def.).

### 7.3 Mammary gland (after breast-conserving surgery)

### 7.3.1 External irradiation

7.3.1.1 Technique: field: the whole breast should be included in the irradiated area. The treatment must be done by two tangential fields. No bolus on the skin should be used.

The tangential fields should overlap the parasternal irradiation field, but no more than  $\frac{1}{2}$  - 1 cm.

7.3.1.2 Dose: the standard minimum dose for the whole breast is 50 Gy in 5 weeks at the intersection of the central axis of the beams (according to the ICRU definition, 1978). If a split period was necessary the total dose should be corrected with the help of the TDF formula (Orthon and Ellis, 1973). The dose in the breast should not differ more than 15 %.

### 7.3.2 Booster therapy

Iridium implantation: within 2 to 6 weeks after the external irradiation, the iridium implantation should be done. If an iridium implantation is not possible (rare), the extra dose should be given with electrons (25 Gy/2½ weeks)

Target volume:

1. the whole excisional bed, with at least 1 cm margin. In case of microscopic irradicality of the lumpectomy, this margin should be at least 2 cm.
2. the implanted volume should include the efferent mammary ducts from the tumour bed to the nipple, positioning at least one iridium wire  $\frac{3}{4}$  cm behind the nipple.

7.3.2.1 Technique: the implantation should be done if possible in two planes. The lowest plane lies at the bottom of the excisional bed (on the pectoral muscle). The first needle should be brought in centrally in this plane. The second plane lies superficially, however the distance between the iridium wire and the skin should be at least 0.5 cm. The implantation will be guided by plastic plates placed on both sides of the breast.

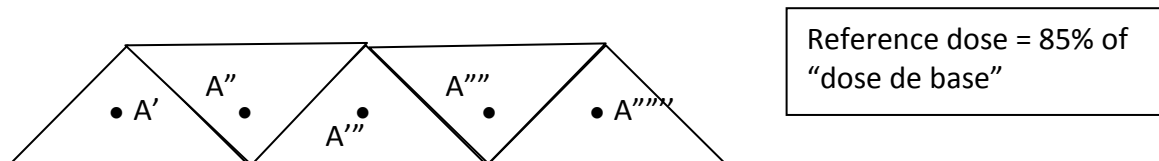
#### 7.3.2.2 Dose:

For the calculation of the dose the Paris system is used. The dose will be calculated in a transverse plane in the central axis of the implant. The centre of every triangle of the implant are the points A', A'', A''', etc.

The "dose de base" is the average of the doses in points A', A'', A''' etc. To define the final dose the "reference dose" should be used.

#### Dosage:

A reference dose of 25 Gy is necessary in 2-4 days.



7.4 Salvage radiotherapy in local recurrence. If a local recurrence cannot be treated medically radiotherapy with maximal tolerated dose will be given.

## 8. ADJUVANT THERAPY

Adjuvant chemotherapy will be given to all patients with histological proof of axillary node involvement and age  $\leq 55$  yrs. Treatment will be 6 cycles of CMF.

### 8.1 Treatment schedule

Chemotherapy will be started within 4 weeks after completion of radiotherapy, as soon as skin reactions permit.

One course of CMF will be given every 4 weeks, for a total of 6 cycles.

### 8.2 Dose schedule

Cyclofosfamide	100 mg/m <sup>2</sup> ; p.o. day 1 to 14
Methotrexate	40 mg/m <sup>2</sup> ; i.v. day 1 and day 8
5-Fluorouracil	600 mg/m <sup>2</sup> ; i.v. day 1 and day 8

Next cycle will start at day 29.

### 8.3 Dose modification

WBC	Platelets	CMF dose
> 4 (x10 <sup>9</sup> /L)	> 100 (x10 <sup>9</sup> /L)	100%
2.4 – 4	75-100 (x10 <sup>9</sup> /L)	50%
< 2.5	< 75 (x10 <sup>9</sup> /L)	0

If dose reduction according to this scheme should be required at the beginning of the cycle, this cycle should be postponed for a maximum of 2 weeks. After 2 weeks the cycle can be started at a reduced dose if necessary.

- serum creatinine: over 110  $\mu\text{mol/l}$ : reduce MTX to 20 mg/m<sup>2</sup>  
Over 160  $\mu\text{mol/l}$ : discontinue MTX

#### 8.4 Side effects, apart from bone marrow suppression

5 FU, MTX: mucous membrane toxicity: stomatitis, conjunctivitis, gastrointestinal problems.

Cyclofosamide: nausea, hair loss, occasionally.

MTX: excessive toxicity possible with impaired renal function.

### 9. **PATHOLOGICAL GUIDELINES**

The following data should be clear from the pathology report.

1. tumour size: ... cm x ..... cm (two largest perpendicular diameters)
2. nodal status; at least 10 lymph nodes should be examined;
  - 4 levels described: lower level
  - middle level
  - upper level
  - apex nodes

The number of positive nodes/number of nodes per level should be noted, eventual rupture of the node capsule should be noted.

3. Type and differentiation grade
4. Microscopic radicality of lumpectomy

### 10. **GUIDELINES FOR MEASURING**

- a. cosmetic result
- b. quality of life

#### a. Cosmetic results:

A standard series of photographs of the breast preferably 2 yrs after the end of therapy will be judged by a panel of independent judges.

#### b. Quality of Life:

To the patients in both groups it will be explained that a psychological evaluation of the consequences of the treatment procedures is part of the study.

The patients will be requested to complete a complaint questionnaire 2 years after the end of the therapy.

### 11. **FOLLOW-UP**

#### 11.1 Frequency of control investigations at least:

First year: every 3 months

Second year: every 3 months

Third year: every 3 months  
 Fourth year: every 6 months  
 Fifth year: twice a year  
 Tenth year: once a year, until death

### 11.2 Procedure

Physical examination with regard to:

- a. Local regional control
  - b. Distant spread
  - c. Side effects of the treatment  
(fibrosis, oedema, teleangiectasia)
- } at every control visit

Technical evaluation:

- a. Haematological examinations: HB, E.S.R.
  - b. Chemistry test: liver functions  
Alkaline phosphatase  
CEA (optional)
  - c. X-ray of the lungs: 2x per year; after 4<sup>th</sup> year once yearly.
  - d. X-ray of the breast(s): every year, starting 3 months after the end of therapy
  - e. Shoulder function test, measurement of thickness of the arms (circumference 10 cm proximal and 12 cm distally of elbow: at every control visit in the first year. Thereafter once yearly.
  - f. Quality of Life questionnaire: two years after the end of therapy.
  - g. Cosmetic result photography: once at 2 years after the end of therapy in the breast-conserving therapy group.
- } at every control visit

NB: If schedules with more frequent follow-up are practised, the frequency should be equal in both arms.

## 12. FORMS AND PROCEDURES FOR COLLECTING DATA

All data concerning each registered patient should be mailed to the EORTC Data Centre. The required forms for recording the data and the time schedule are listed below:

1.	On study form	Within 2 weeks after randomization
2.	Radiotherapy form	After completion of surgery and radiotherapy
3.	Flow sheet	Nr.1 together with on study form, thereafter at least every 6 months
4.	Summary and Evaluation form	When patient is taken off study
5.	Complaint questionnaire	Two years after the end of therapy
6.	Cosmetic result	Two years after the of therapy in the breast-conserving group

The Summary and Evaluation Form should be used only when a patient is removed from the study. If the patient is taken off study for a reason other than death, careful documentation should be provided on the Summary and Evaluation form.

### 13. STATISTICAL CONSIDERATIONS

Assuming an overall 10 years survival rate of 40% to 60% in the control group (radical mastectomy), 225 (100) eligible and evaluable patients must be entered on each treatment and followed for a minimum of 10 years in order to ensure with a probability of .80 that the upper 90% confidence limit for the true difference in the percentage of patients surviving 10 years on each treatment does not exceed 10 percent (15 percent).

If it is desired to compare the results separately in subgroups (Stage I, II, for example) then the following table gives the number of patients required on each treatment arm in each subgroup under various hypotheses:

#### SAMPLE SIZE REQUIREMENTS (per treatment arm)

<u>Difference no greater than 10%</u>	<u>True survival response at 5 yrs (both groups)</u>				
	60%	65%	70%	75%	80%
a. $\alpha=0.05$ (one sided) power = 80%	297	282	260	232	198
b. $\alpha=0.10$ (one sided) power = 80%	217	206	190	170	144
c. $\alpha=0.10$ (one sided) power = 90%	316	300	277	247	211
<u>Difference no greater than 15%</u>					
d. $\alpha=0.05$ (one sided) power = 80%	132	126	116	108	88
e. $\alpha=0.10$ (one sided) power = 80%	97	92	85	76	65
f. $\alpha=0.10$ (one sided) power = 90%	141	133	123	110	94

**14. STAGING DEFINITIONS: UICC, Geneva, 1978**

Stage I	T1a, T1b	N0, N1a	M0
Stage II	T1a, T1b	N1b	M0
	T2a, T2b	N0, N1a	M0
	T2a, T2b	N1b	M0
Stage IIIa	T3a, T3b	N0, N1	M0
	T1a,b,T2a,b	N2	M0
	T3a,b		
Stage IIIb	T1a,b,T2a,b	N2	M0
	T3a,b		
	T4a,b,c	Any N	M0
Stage IV	Any T	Any N	M1

## 15. LITERATURE

Baclesse F., Ennuyer A., and Cheguillaume J.

Est-on autorisé à pratiquer une tumorectomie simple suivie de radiothérapie en cas de tumeur mammaire ?

Journal Radiologie, 41 : 137-139, 1960.

Banfi A.

G.E.R. Meeting, September 1979, Helsinki.

Bonnadonna

Personal communication 1980 and data given at 2<sup>nd</sup> Breast Cancer Working Conference.

Calle R., Pilleron J.P., Schlienger P., Vilcoq J.R.

Conservative management of operable breast cancer.

Cancer 42: 2045-2053, 1978.

Haagensen C.D.

In: Diseases of the breast, W.B. Saunders Company, Philadelphia, 1971.

Harris J.R., Levene M.B., Hellman S.

Results of treating stage I and II carcinoma of the breast with primary radiation therapy.

Cancer Treat Rep 62(7): 985-991, 1978.

Harris J.R., Levene M.B., Svensson G., Hellman S.

Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast.

Int J Radiat Oncol Biol Phys 5: 257-261, 1979.

Hayward J.L.

The Guy's trial of treatment of "early breast cancer".

World J Surg 1/3: 314-316, 1977.

Hayward J.L.

Limited treatment in the management of early breast cancer.

Cancer Treat Rep 62(7): 983-984, 1978.

Montague E.D., Gutierrez A.E., Barker J.L., du V. Tapley N., Fletcher G.H.

Conservation surgery and irradiation for the treatment of favourable breast cancer.

Cancer 43: 1058-1061, 1979.

Mustakallio S.

Conservative treatment of breast carcinoma – review of 25 years follow-up.

Clin Radiol 23: 110-116, 1972.

Pierquin B, Mueller W., Baillet F., Maylin C., Raynal M., Otmezguine Y.



Radical radiation therapy for cancer of the breast. The experience of Créteil.  
Front Radiat Ther Oncol 12: 150-161, 1978.

Sarrazin D.

G.E.R. Meeting, September 1979, Helsinki.