PHASE III MULTICENTER TRIAL

INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

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0 General information

0.1 Statement of the Study Leading Committee

In January 1997 the International Conference on Harmonization passed the ‘Note for Guidance on Good Clinical Practice’ (ICH-GCP). The planning, execution and analysis of this trial is based on the GCP-Guidelines. Furthermore this study is based on the Declaration of Helsinki (Appendix I).

The Study Leading Committee commits itself to adhere to the Declaration of Helsinki and the GCP-Guidelines. The participating centers commit themselves with their Declaration of participation on the study (Appendix II) to comply with these guidelines.

Financial support to run the trial will be applied from the German Cancer Aid.

The Study Leading Committee commits itself to publish the results after the final analysis.

Signatures:

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Erlangen, April 22, 2004
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0.3 Synopsis

0.3.1 Rationale

Accelerated partial breast irradiation (APBI) leads to an equivalent local control rate with lower toxicity as external beam irradiation (EBI) after breast conserving surgery (BCS) in a highly selected subgroup of patients with low risk invasive carcinoma and low risk duct carcinoma in-situ (DCIS).

0.3.2 End Points

Primary objective
To assess the role of brachytherapy alone compared to whole breast irradiation in a defined low-risk group of invasive breast cancer or ductal carcinoma in situ concerning local failure (all ipsilateral local recurrences) to affirm the hypothesis that local control rates in each arm are equivalent.

Secondary objectives
- To assess incidence and severity of acute and late side effects of brachytherapy alone compared to whole breast irradiation.
- To assess the differences in cosmetic results of brachytherapy alone compared to whole breast irradiation.
- To assess distant metastases free survival (DMFS).
- To assess survival rates (Overall Survival: OS, Disease-free Survival: DFS).
- To assess the contralateral breast cancer rate.
- To assess QoL (Quality-of-Life) of patients treated with BT alone compared with WBRT.

0.3.3 Entry Criteria

Inclusion criteria
- Stage 0, I or II breast cancer.
- Invasive ductal, papillary, mucinous, tubular, medullary or lobular carcinoma.
- Ductal carcinoma in situ (DCIS) alone.
- No lymph invasion (L0) and no hemangiosis (V0).
- Lesions of \( \leq 3 \) cm diameter, histopathologically assured.
- pN0/pNmi (a minimum of 6 nodes in specimen, or a negative sentinel node is acceptable); in the case of DCIS alone axillary staging (e.g. sentinel lymph node biopsy) is optional.
- M0.
- Clear resection margins at least 2 mm in any direction; by lobular histology or DCIS histology only the resection margins must be clear at least 5 mm.
- For DCIS only: lesions must be classified as low or intermediate risk group (Van Nuys Prognostic Index <8, see Appendix XIV).
- Unifocal and unicentric DCIS or breast cancer.
- Age \( \geq 40 \) years.
- Time interval from final definitive breast surgical procedure to the start of external beam therapy or to brachytherapy is less than 12 weeks (84 days). If patients receive chemotherapy the radiotherapy can be started before systemic treatment (within 12 weeks). The radiation therapy can be also given in the interval between the chemotherapy courses. It is also possible to start radiation therapy after chemotherapy is completed according local protocols as soon as possible within 4 weeks after chemotherapy.
- Signed study-specific consent form prior to randomization.

Exclusion criteria
- Stage III or IV breast cancer.
- Surgical margins that cannot be microscopically assessed.
- Extensive intraductal component (EIC).
- Paget’s disease or pathological skin involvement.
- Synchronous or previous breast cancer.
- Prior malignancy (\( \leq 5 \) years prior to enrollment in study) except non-melanoma skin cancer or cervical carcinoma FIGO 0 and I if patient is continuously disease-free.
- Pregnant or lactating women.
- Collagen vascular disease.
- The presence of congenital diseases with increased radiation sensitivity, for example Ataxia telangiectatica or similar.
- Psychiatric disorders.
- Patient with breast deemed technically unsatisfactory for brachytherapy.

0.3.4 Projected accrual

Based on the assumed scenario 530 patients per group are required in the final analysis. To account for dropout (non-valid cases) estimated to be 10%, altogether 1170 patients should be recruited for the study.

0.3.5 Outline

The comparative therapeutic study is designed as a prospective, randomized, multicentric phase III-trial. The primary outcome is local recurrence. Randomization of patients will be stratified (balanced) with respect to center, invasive vs. non-invasive disease, and pre- vs. post-menopausal status.

Patients are randomized to one of two treatment arms:

Arm I (Standard treatment): Whole breast radiotherapy (WBRT)
Arm II (Investigational Treatment): Accelerated partial breast irradiation (APBI)

0.3.6 Treatment Modalities

Accelerated partial breast irradiation (APBI)

The target volume of the brachytherapy arm consists of the tumor bed with a safety margin of 2-3 cm in all directions. Minimal distance between implant and underlying ribs should be ≥ 5 mm and between implant and skin ≥ 5-7 mm to protect the skin from telangiectasia. The volume enclosed by the reference isodose surface (calculated analogue Paris-System, see protocol for details) depends on the tumor size and on the size of the resection margins (size of the PTV) - mostly about 40-150 cm³. A volume over 150 cm³ should be exceeded only in justified cases. The dose distribution is seen as sufficiently homogeneous, if the DNR is < 0.35 (preferably < 0.30).

Following dose concepts are recommended (Dref):

HDR: 32.0 Gy/8 fractions (8 x 4 Gy, 2 x daily) or 30.3 Gy/7 fractions (7 x 4.3 Gy, 2 x daily)
PDR: 0.60 - 0.80 Gy/hour to 50 Gy (1 pulse/hour, 24 hours/day)

Notice: The dose distribution is seen as sufficiently homogeneous, if the DNR is < 0.35 (preferably < 0.30).

Whole breast radiotherapy (WBRT)

All patients randomized to the external radiation treatment arm shall receive a total dose of 50.4 Gy to the entire breast in 1.8 Gy fractions x 28 fractions and afterwards a dose of 10 Gy in 2 Gy fractions x 5 fractions to the tumor bed as boost with appropriate electron beam, OR a total dose of 50.0 Gy in 2 Gy fractions x 25 fractions and afterwards a dose of 10 Gy in 2 Gy fractions x 5 fractions to the tumor bed as boost with appropriate electron beam.

Radiation treatment will be delivered in uniform daily doses through standard tangent photon and electron boost fields from Monday to Friday for 6-7 weeks.

Notice: In the WBRT-arm interstitial brachytherapy boost is not allowed.
0.3.7 Treatment Schedule

Time interval from final definitive breast surgical procedure to the start of external beam therapy or to brachytherapy is less than 12 weeks (84 days). If patients receive chemotherapy the radiotherapy can be started before systemic treatment (within 12 weeks). The radiation therapy can be also given in the interval between the chemotherapy courses. It is also possible to start radiation therapy after chemotherapy is completed according local protocols as soon as possible within 4 weeks after chemotherapy.

0.3.8 Follow-up

Patients are followed as shown in the table below:

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<tr>
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<td>Documentation of cosmetic results</td>
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<td>Digital Photographs</td>
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<tr>
<td>Documentation of QoL</td>
<td>X</td>
</tr>
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</table>

* = facultative
0.4 Zusammenfassung

0.4.1 Rationale

Die akzelerierte Teilbrustbestrahlung mittels HDR-/PDR-Multikatheter Brachytherapie führt in einer hoch selektionierten Patientinnen gruppe mit low-risk invasivem Mammakarzinom oder low-risk duktalem Carcinoma in situ (DCIS) zu äquivalenten lokalen Kontrollraten bei geringerer Toxizität.

0.4.2 Endpunkte

Primärer Endpunkt

 Sekundäre Endpunkte
- Auftreten und Schweregrad von akuten und chronischen Nebenwirkungen der alleinigen Brachytherapie verglichen mit der WBRT.
- Unterschiede im kosmetischen Ergebnis zwischen APBI und WBRT.
- Fernmetastasen-freies Überleben (DMFS).
- Gesamtüberleben (OS), Krankheitsfreies Überleben (DFS).
- Rate an kontralateralen Mammakarzinomen in beiden Armen.
- Unterschiede in der Lebensqualität (QoL) zwischen APBI und WBRT.

0.4.3 Eingangskriterien

Einschlusskriterien
- Stadium 0, I oder II Mammakarzinom.
- Invasives duktales, papilläres, muzinöses, tubuläres, medulläres oder lobuläres Karzinom.
- Duktales Carcinoma in situ (DCIS).
- Keine Lymphangiosis (L0) und keine Hämangiosis carcinomatosa (V0).
- Läsionen ≤ 3 cm Durchmesser, histopathologisch gesichert.
- pN0/ pNmi (minimal 6 dissezierte Achsellymphknoten oder ein negativer Sentinel-Lymphknoten sind akzeptabel); im Falle eines alleinigen DCIS ist das Axilla-Staging (z.B. mittels Sentinel-Lymphknoten Biopsie) optional.
- Fernmetastasenfreiheit (M0).
- Karzinomfreie Resektatbränder (R0) mit einem minimalen Sicherheitsabstand von 2 mm in alle Richtungen; im Falle eines invasiv-lobulären Karzinoms oder eines alleinigen DCIS ist ein minimaler Sicherheitssaum von 5 mm erforderlich.
- Bei alleinigem DCIS: die Läsionen müssen mit einem Van Nuys Prognostic Index < 8 classifiziert werden (von 12 möglichen Punkten).
- Unifokales und unizentrisches invasives Karzinom oder DCIS.
- Alter ≥ 40 Jahre.
- Das Zeitintervall zwischen brusterhaltender Operation und dem Beginn der adjuvanten Strahlentherapie (APBI oder EBI) darf maximal 12 Wochen (84 Tage) betragen. Bei Patientinnen mit Chemotherapie kann die Strahlentherapie vorher (APBI oder EBI), im Falle von Anthrazyklinhaltiger Chemotherapie auch im Intervall zwischen den Kursen (nur APBI) sowie nach Abschluss der adjuvanten Chemotherapie (APBI oder WBRT), jedoch so schnell als möglich mit einem maximalen Intervall von 4 Wochen (28 Tage), appliziert werden.
- Unterschriebene studienspezifische Einwilligungserklärung vor der Randomisierung.

 Ausschlusskriterien
- Stadium III oder IV Mammakarzinom.
- Schnittträder des Resektats können mikroskopisch nicht beurteilt werden.
- Extensive intraduktale Komponente (EIC).
- Morbus Paget oder pathologische Hautinfiltration.
- Früheres oder zeitgleich auftretendes (synchrones) Mammakarzinom.
• Früheres Malignom (≤ 5 Jahre vor der Rekrutierung für diese Studie) mit Ausnahme von non-melanoma Hautkrebs oder Zervixkarzinom im Stadium FIGO I soweit die Patientin anhaltend krankheitsfrei ist.
• Schwangere oder stillende Frauen.
• Bindegeweberkrankung.
• Patientinnen mit Krankheiten mit genetischer Prädisposition für eine erhöhte Radiosensitivität, wie zum Beispiel Ataxia telangiectatica oder ähnliches.
• Psychiatische Erkrankungen mit verminderter Compliance der Patientin.
• Patientinnen deren Mamma die Anwendung der alleinigen APBI aus technischen/anatomischen Gründen nicht zulässt.

0.4.4 Fallzahlenschätzung

Basierend auf den Annahmen zu den Therapieeffekten muss die Anzahl der Patientinnen pro Behandlungsarm 530 betragen. Bei einer geschätzten Rate von 10% nicht gültiger Fälle (Dropouts) sollten somit insgesamt 1170 Patientinnen rekrutiert werden.

0.4.5 Outline

Diese vergleichende therapeutische Untersuchung ist als prospektive, randomisierte, multizentrische Phase III-Studie konzipiert. Primärer Endpunkt ist die lokale Kontrolle. Die Randomisation der Patientinnen erfolgt stratifiziert nach Zentrum, invasivem vs. non-invasivem Karzinom und Menopausalstatus (prä- vs. post-menopausal).

Die Patientinnen werden in einen der folgenden Behandlungsarme randomisiert:

Arm I  (Standard Arm):  Konventionelle Ganz-Brust-Bestrahlung (WBRT)
Arm II  (Prüf-Arm):  Alleinige akzelerierte interstitielle Multikatheter-HDR/PDR-Brachytherapie (APBI)

0.4.6 Behandlungsmodalitäten

Alleinige interstitielle Multikatheter-HDR/PDR-Brachytherapie (APBI)

Das Zielvolumen der alleinigen Brachytherapie umfasst das Tumorbett mit einem Sicherheitssaum von 2-3 cm in alle Richtungen. Der kleinste Abstand zwischen dem Implantat und den drunter liegenden Rippen sollte 5 mm nicht unterschreiten, der kleinste Abstand zwischen dem Implantat und der Haut sollte 5-7 mm nicht unterschreiten, um der Bildung von Teleangiektasien vorzubeugen. Das durch die Referenzisodose umschlossene Volumen (PTV, kalkuliert analog Paris-System, siehe Protokoll für Details) wird durch die Größe des Tumors und die Größe der in-sano resezierten Sicherheitssäume beeinflusst – zumeist resultiert ein Volumen von 40-150 cm³. Ein höheres Volumen (> 150 cm³) sollte nur in ausgewählten Fällen vorkommen und muss schlüssig begründet werden können. Die Dosisverteilung wird als ausreichend homogen betrachtet wenn die DNR (Dose Non-Uniformity Ratio) < 0.35, bevorzugt < 0.30, ist.

Die folgenden Dosiskonzepte (Referenzdosis) werden als studienkonform angeboten:

HDR:  
32.0 Gy/8 Fraktionen (8 x 4 Gy, 2 x täglich) oder
30.3 Gy/7 Fraktionen (7 x 4.3 Gy, 2 x täglich)

PDR:  
0.60 - 0.80 Gy/Stunde bis 50 Gy (1 Puls/Stunde, 24 Stunden/Tag)

Konventionelle Ganz-Brust-Bestrahlung (WBRT)

Alle Patientinnen, die in diesen Arm randomisiert wurden, sollen eine Gesamtdosis von 50,40 Gy bzw. 50 Gy auf die gesamte Brust in 28 bzw. 25 Fraktionen (Einzelfraktionsdosis 1,8 Gy bzw. 2,0 Gy). Unmittelbar anschließend erhalten sie einen kleinvolumigen Boost mit individuell angepassten schnellen Elektronen auf das Tumorbett (10 Gy in 2 Gy Fraktionen, 5 Fraktionen).

Die Strahlenbehandlung erfolgt mit täglich gleichen Fraktionsdosen mit Standard-Photon-Tangentenfeldern und Elektronen-Boost-Feldern von Montag bis Freitag für die Dauer von 6-7 Wochen.
Hinweis: In diesem Arm ist ein interstitieller Boost nicht erlaubt!

0.4.7 Behandlungsablauf

Das Intervall zwischen dem letzten definitiven chirurgischen Eingriff im Rahmen der brusterhaltenden Operation (BCS) und dem Beginn der jeweiligen Strahlentherapie (WBRT oder APBI) beträgt maximal 12 Wochen (84 Tage). Wenn eine adjuvante Chemotherapie geplant ist, kann die Strahlenbehandlung (WBRT oder APBI) auch vorher erfolgen (innerhalb von maximal 12 Wochen nach BCS). Die Strahlenbehandlung (APBI) kann auch im Intervall zwischen zwei Chemotherapiezyklen erfolgen. Es ist ebenso zulässig, die Strahlenbehandlung schnellstmöglich nach Beendigung lokaler Chemotherapieprotokolle (auch 12 Wochen nach BCS, jedoch spätestens 4 Wochen nach Abschluss der Chemotherapie) durchzuführen.

0.4.8 Nachsorge

Nachsorgeplan und –untersuchungen:

<table>
<thead>
<tr>
<th>Nachsorge-untersuchungen</th>
<th>Monate nach Abschluss der Strahlentherapie</th>
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<tr>
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</tbody>
</table>

*= fakultativ
Breast Conserving Surgery (BCS) -> Stratified Randomization

- Tumor bed brachytherapy alone (APBI)
  - Follow-up
- Whole Breast Radiotherapy (WBRT)
  - Follow-up
0.6 Listing of abbreviations

APBI accelerated partial breast irradiation
BCS breast conserving surgery
BCT breast conserving therapy
BT brachytherapy
Cl coverage index
COIN conformity index
CT computer tomography
DCIS ductal carcinoma in situ
DHI dose homogeneity index
DNR dose non-uniformity ratio
EBI external beam irradiation
EIC extensive intraductal carcinoma
ELE electrons
EORTC European Organization for Research and Treatment of Cancer
ER estrogen receptor
FUP follow-up period
GEC-ESTRO Groupe Européen de Curiethérapie – European Society for Therapeutic Radiology and Oncology
Gy Gray
HDR high-dose-rate
HG histological grade
HI homogeneity index
IDC infiltrating ductal carcinoma
ILC infiltrating lobular carcinoma
IORT intraoperative radiotherapy
Ir Iridium
LDR low-dose-rate
LF local-field
LR local recurrence
LTC local tumour control
LVI lympho-vascular invasion
MAST mastectomy
MCD mean central dose
MM marginal miss
MTD minimal target dose
MV megavolt
NR not reported
NS not significant
NSABP National Surgical Adjuvant Breast and Bowel Project
PBI partial breast irradiation
PDR pulse-dose-rate
PR progesterone receptor
PTV planning target volume
QA quality assurance
RR relative risk
RT radiotherapy
RTOG Radiation Therapy Oncology Group
SMS surgical margin status
TR tumor bed recurrence
VNPI Van Nuys Prognostic Index
WBRT whole breast radiotherapy
WF wide-field
3D three-dimensional
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1 Introduction

Breast conserving surgery (BCS) and radiotherapy (RT) of the conserved breast became widely accepted over the last 3 decades for the treatment of early breast cancer [1-5]. Numerous studies have established that there is no subgroup of patients, in which irradiation could be safely omitted [1-2, 6-7]. The standard technique of RT after BCS is to treat the entire breast up to a total dose of 45-50 Gy with or without a tumor bed boost [8-12]. The main advantage of breast conserving therapy (BCT) is superior cosmetic outcome with less psycho-emotional trauma compared with mastectomy. The major disadvantage of standard BCT is the prolonged treatment time of 5 to 7 weeks, which means a possible barrier for the general acceptance of this treatment method. Despite the well documented equivalence of BCT compared to mastectomy, it has been reported that up to 60% of patients who are clinically eligible for breast conservation still undergo breast amputation [13-14]. In other series, 15-30% of women treated with BCS failed to receive RT [15-17]. Reasons for the under utilization of this treatment approach include patient convenience, physician preference, and logistical problems [14-16]. Accelerated, limited field RT is an attractive treatment approach to shorten the standard 5-7 weeks course of whole breast RT to 4-5 days. Acceleration of RT would eliminate some disadvantages of extended treatment period, especially for elderly patients, working women, and those who live at a significant distance from radiation treatment facility.

Furthermore, the majority of local recurrences occur in close proximity to the tumor bed [1, 7, 18, 63]. Thus, the necessity of whole breast RT has been questioned, and several centers have evaluated the feasibility and efficacy of tumor bed irradiation alone [19-54]. Evolving number of prospective phase I/II-studies using interstitial brachytherapy (BT) have been reported suggesting that equivalent 5 to 6 year local tumor control (LTC) could be achieved with partial breast BT as with conventional external beam irradiation (EBI) [20, 29, 31-32, 35, 40-42, 50]. These results are strong level III evidences, supporting the concept of accelerated partial breast irradiation (APBI) using appropriate patient selection and quality assurance (QA). The only way to get higher level evidences is to initiate phase III trials evaluating the efficacy of partial breast BT compared to whole breast RT.
2 Background

2.1 Pathological and clinical basis for APBI

In the classical pathological study of Holland et al [55], mastectomy specimens of patients with T1-2 breast cancers were evaluated to assess where residual tumor was located after simulated tumor excision. If tumors were removed with a margin of 2, 3, and 4 cm, 42%, 17%, and 10% of the patients would have had residual tumor foci in the remaining breast, respectively. These observations supported the routine use of whole breast RT, since residual tumor foci were present outside the tumor bearing quadrant in at least 10% of the cases. However, in a later study of the Nijmegen group, only 2% of patients whose specimen contained no extensive intraductal component (EIC), had prominent intraductal carcinoma 2 or more cm from the edge of the primary tumor [56].

In a similar investigation of Gump [57] invasive lobular carcinomas and EIC positive ductal cancers were excluded. The incidence of cancer foci at a distance of more than 2 cm from the gross margins of the tumor was only 12% for tumors ≤ 2 cm. The author concluded that it was no longer necessary to treat the entire breast in every patient.

Contrary to Holland’s data, other publications applying more sophisticated pathologic processing of breast specimens reveal that the microscopic extension of malignant cells is unlikely to be beyond 1 cm for appropriately selected cases [58-62]. Recently, Faverly et al [62] reported that 53% of their patients had breast carcinoma of limited extent in which, by pathological definition, no additional foci of tumor were found beyond 1 cm from the edge of the dominant mass. They also found that the accuracy of identifying this group of cancers, by applying state-of-the-art mammography and pathology may be as high as 90%.

In contradiction to the theoretical relevance of multifocality, results of large well controlled studies have proved that 67-100% of postlumpectomy breast recurrences occurred in the vicinity of the tumor bed [1, 7, 18, 63]. The rate of elsewhere breast failures after breast conservation have been reported in the range of 0 to 3.8%, and was not affected by whole breast RT (Table 1) [1-2, 29, 34, 39, 49, 64-66]. These results suggest that RT exerts its maximal effect on residual tumor foci in the tumor bearing quadrant. Thus, RT limited to the tumor bed with a reasonable safety margin may provide similar local control in properly selected patients as whole breast RT.

It is also to be noted, that a significant portion of patients who experience ipsilateral breast tumor relapse following BCS and RT have new primary tumors as opposed to true recurrence [67-68]. In the study of Smith et al [68], 51% of all intrabreast relapses were classified as new primary tumors, and 71% of these relapses were in the remote areas of the breast. These data also imply that the majority of elsewhere breast failures occur after initial treatment. Thus, whole breast RT (as a part of primary treatment) may have only limited efficacy in preventing these recurrences.
Table 1. Incidence of elsewhere breast failures in selected patients according to treatment.

<table>
<thead>
<tr>
<th>Study / Author</th>
<th>BCS</th>
<th>BCS + WBRT</th>
<th>BCS + APBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>NSABP-B-06 [2]</td>
<td>2.7</td>
<td>17/636</td>
<td>3.8</td>
</tr>
<tr>
<td>Ontario [1]</td>
<td>3.6</td>
<td>15/421</td>
<td>1.0</td>
</tr>
<tr>
<td>Milan III [66]</td>
<td>1.5</td>
<td>4/273</td>
<td>0</td>
</tr>
<tr>
<td>W Beaumont [35, 50]**</td>
<td>3.3</td>
<td>13/400</td>
<td>0.6</td>
</tr>
<tr>
<td>Ochsner Clinic [29]</td>
<td>-</td>
<td>-</td>
<td>3.2</td>
</tr>
<tr>
<td>Polgár et al [40, 64-65]**</td>
<td>0.9</td>
<td>1/106</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range:</td>
<td>0.9-3.6</td>
<td>0-3.8</td>
<td>0-3.1</td>
</tr>
</tbody>
</table>

BCS = breast conserving surgery; WBRT = whole breast radiotherapy; PBI = partial breast irradiation; *n = number of elsewhere breast failures/number of patients treated; ** updated results.

2.2 Published results of APBI-studies

2.2.1 APBI with suboptimal QA and patient selection

To date, three groups have reported their results with sole tumor bed RT for unselected patients treated with BCS (Table 2.) [23-24, 34, 43]. In the Christie Hospital's phase III trial, patients were randomly assigned to receive either 40 Gy electron beam irradiation to the tumor bed only (limited field (LF) group), or 40 Gy whole breast plus regional RT (wide field (WF) group). The actuarial local recurrence rate at 8 years was significantly higher in the LF group than in the WF group (25% vs. 13%) [34, 43]. The average field size used in the LF arm was 6 x 8 cm, and no attempt was made to localize the excision cavity by means of surgical clips or CT-based treatment planning. Of note, the majority of recurrences were in the treated quadrant of the breast. Patients with tumors up to 4 cm in diameter were enrolled on the study, and axillary dissection was omitted. The recurrence rate for patients treated with sole tumor bed RT for invasive lobular cancers was as high as 43%. The authors concluded that with improved patient selection and refinement of technique, RT restricted to the tumor bed may be an adequate local treatment [34].

The first BT trial, using 55 Gy of low dose rate (LDR) iridium implants as the sole radiation treatment, was conducted at Guy's Hospital, in London [24]. Ten out of 27 patients (37%) experienced recurrence in the treated breast. The possible reasons for the unacceptably high local failure rate were the lack of systematic QA procedure, and proper eligibility criteria. The surgical margins were involved in 56% of the cases, and 41% of the primary tumors were EIC positive. Neither T2, nor N1 patients were excluded.

In the Royal Devon and Exeter Hospital pilot study, fractionated high dose rate (HDR) interstitial BT was used to treat the quadrant after tumor excision [23]. The local failure rate was 15.6% at 18 months. However, this study was also limited by the surgical techniques and pathological reports used: routine axillary dissection was not performed, and in many cases detailed histology was not available.

The results of these earlier studies proves that RT confined to the surgical bed is not an appropriate treatment for unselected patients, and justify the necessity for meticulous QA.
Table 2. Design, patient selection, and results of studies evaluating the efficacy of APBI with suboptimal QA and patient selection.

<table>
<thead>
<tr>
<th>Institute</th>
<th>Technique</th>
<th>Dose [Gy]</th>
<th>Tumor size/ pN-category</th>
<th>SMS</th>
<th>FUP [years]</th>
<th>Crude LR % (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie Hosp [34,43]</td>
<td>EBI</td>
<td>40-42.5</td>
<td>≤ 4 cm/Nx</td>
<td>clear/involved</td>
<td>8</td>
<td>19.5 (69/353)</td>
</tr>
<tr>
<td>Guy’s Hosp [24]</td>
<td>LDR</td>
<td>55</td>
<td>≤ 4 cm/N0-1</td>
<td>clear/involved</td>
<td>6</td>
<td>37 (10/27)</td>
</tr>
<tr>
<td>Royal Devon [23]</td>
<td>HDR</td>
<td>20-32</td>
<td>≤ 4 cm/Nx</td>
<td>clear/close**</td>
<td>1.5</td>
<td>15.6 (7/45)</td>
</tr>
</tbody>
</table>

SMS = surgical margin status; FUP = follow-up period; LR = local recurrence; *n = number of intra-breast relapses/number of patients treated; EBI = external beam irradiation; LDR = low dose rate; HDR = high dose rate; **detailed histology was not available in many cases.

2.2.2 APBI with appropriate QA and patient selection

Based on the controversial results of earlier studies, strict patient selection criteria and systematic QA procedures were involved in later clinical trials using BT with various dose rates as the sole radiation treatment [19, 21-22, 25-33, 35-42, 44-54]. To date, twelve working groups reported encouraging early results with 0 to 1.5% annual local recurrence rate, and good to excellent cosmetic results (Table 3).

Kuske et al [31] reported the ten year experience of the Ochsner Clinic. One hundred and fifty selected patients with Tis, T1-2 non-lobular tumors have been treated with LDR (n = 50) or HDR (n = 100) BT in 3 prospective phase I-II trials. Selection criteria included tumor size ≤ 4 cm, excision with negative margins, and ≤ 3 metastatic axillary lymph nodes. Patients with multicentric or EIC positive tumor were excluded, and negative postlumpectomy mammogram was also required if disease presented with microcalcifications. The target volume was defined as the clipped excision cavity with at least 2 cm margin. LDR patients received 45 Gy, while HDR patients had either 32 Gy in 8 fractions or 34 Gy in 10 fractions over 4-5 days. At a median follow-up of 3.8 years, there have been 2 breast (1.3%) and 4 regional (2.6%) recurrences. Both local recurrences occurred outside the target volume, and patients were salvaged successfully. The cosmetic results were scored good/excellent in 75%. Grade III toxicities requiring surgical intervention occurred in 4 patients (2.7%).

The encouraging results of the William Beaumont Hospital’s study were published very recently [35, 49]. One hundred and ninety-nine women were treated with 50 Gy LDR (n = 120) or 32-34 Gy HDR (n = 79) implant alone. Patient selection was similar to the criteria used in the Ochsner series. However, only invasive carcinomas up to 3 cm in largest diameter were eligible for this trial. Women with age less than 40 years were also excluded. At a median follow-up of 5.4 years, five patients (2.5%) have experienced local failure. The actuarial 5-year cause-specific survival was 97%. Cosmetic outcome was judged good or excellent in 93%, and no adverse sequelae were noted.

Both American and the Budapest groups performed matched-pair analyses to determine whether RT restricted to the tumor bed resulted LTC and cosmesis equivalent to those achieved with conventional whole breast RT [29, 35, 42, 49-50]. No statistically significant differences in LTC, overall survival, or cosmetic results were noted. Thus, the authors suggested multicentric randomized trials comparing sole BT to whole breast RT.

Several other groups have also addressed the issue of sole BT after BCS for properly selected patients (Table 3) [19-20, 27, 29-30, 33, 35, 38, 41-42, 44-45, 50, 53-54]. Initial findings of these trials are also promising with crude local recurrence rates of 0 to 6.7%, and good/excellent cosmesis in 75% to 100%. Wazer et al. [61] recently reported a high rate (27%) of clinically evident fat necroses in women treated with HDR BT alone which was significantly associated with the overall implant volume. However, all patients were successfully treated with conservative management. On the contrary, others reported lower rates (0 to 12%) of clinical fat necrosis [21, 27, 29-30, 38, 39, 41, 50].
Early results of the RTOG 95-17 and the German-Austrian multicentric phase II trials also showed excellent reproducibility and QA results with acceptable acute toxicity rates [45, 69]. In the German-Austrian study more than 160 patients were treated successfully with PDR or HDR interstitial BT alone. Outcome results of this study are pending as additional follow-up is needed; however to date only low acute, mild late toxicity rate and excellent cosmetic results have been reported by the authors (Table 3.) [45].

In Budapest, 290 selected patients were enrolled into two prospective clinical studies evaluating the efficacy of tumor bed RT alone [39-42]. The planning target volume was defined as the clipped excision cavity with a margin of 2 cm – if it was anatomically possible. However, a smaller (1-1.5 cm) safety margin could be obtained in such cases when excision cavity was close to the skin surface or chest wall. In the phase I-II part, 45 women were treated with 30.3-36.4 Gy sole HDR BT in seven fractions over 4 days. Further 245 patients were randomized to receive either 50 Gy whole breast RT (n = 125) or tumor bed RT alone (n = 120). Eligibility criteria were the same as for the phase I-II study. However, patients with breast unsuitable for an interstitial implant were not excluded. In the tumor bed RT arm, 84 out of 120 women received 36.4 Gy sole HDR BT, and the other 36 women were treated with 8 to 16 MeV electrons up to a total dose of 50 Gy.

In phase I-II study, at a median follow-up of 6 years 3 local (6.7%), 3 axillary (6.7%), and 4 distant (8.9%) failures were observed. To date only 3 patients (6.7%) died of breast cancer. Local relapses were detected in the remote areas of the breast (outside the implanted volume), and they were successfully salvaged with lumpectomy, followed by a full course (46-50 Gy) 6 MV photon beam RT to the entire breast. The 5-year probability of cancer-specific, and local recurrence-free survival was 93.1% and 95.6%, respectively. The cosmetic results were judged to be excellent in 41 patients (91.1%). Only one patient (2.2%) developed symptomatic fat necrosis which required surgery.

To date, the Budapest phase III trial is the first randomized study comparing the efficacy and side effects of interstitial BT alone to whole breast RT. At a median follow-up of 2.5 years tumor bed RT alone is similar to whole breast RT with respect to local control, cancer-specific survival, skin and parenchymal side effects (Table 3.) [40-42]. The interim results of this ongoing phase III trial certainly support the initiation of further randomized trials. If such a clinical study were performed, accrual of at least 1000 patients would be needed to detect a statistically significant difference of 5% in LTC between the two treatment arms. Thus, an ideal phase III trial would require international cooperation and should be conducted as a multicentric study.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Clinical Trials Group’s phase III trial will be opened for accrual in 2004 to evaluate the equivalence of APBI to standard whole breast RT [70]. In addition to the well established technique of interstitial BT, other recently developed methods of APBI (e.g. MammoSite balloon brachytherapy, 3D conformal EBI) will be used in this study [22, 28, 70]. Two other randomized trials (Milan and London) are currently being conducted using single fraction intra-operative radiotherapy (IORT) [26, 46-48]. However, there is no available mature European data (with at least 5-year follow-up) to support the use of the latter novel techniques of APBI in a phase III trial.

Five to six year results are available only with interstitial BT, proving that multicatheter BT can be used with adequate reproducibility, low toxicity, and appropriate local tumor control. As a consequence, the GEC-ESTRO Breast Cancer Working Group will support only the use of interstitial HDR/PDR BT for this phase III trial of APBI.
Table 3. Results of studies evaluating the efficacy of APBI with appropriate QA and patient selection.

<table>
<thead>
<tr>
<th>Institute</th>
<th>Technique</th>
<th>Total Dose [Gy]</th>
<th>FUP [years]</th>
<th>LR [%]</th>
<th>Excellent/Good Cosmesis [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Beaumont [35,49]</td>
<td>LDR/HDR</td>
<td>50/32-34</td>
<td>5.4</td>
<td>2.5</td>
<td>5/199</td>
</tr>
<tr>
<td>Ochsner Clinic [29]</td>
<td>LDR/HDR</td>
<td>45/32-34</td>
<td>6.5</td>
<td>2</td>
<td>1/51</td>
</tr>
<tr>
<td>Budapest I [41,42]</td>
<td>HDR</td>
<td>30.3-36.4</td>
<td>6</td>
<td>6.7</td>
<td>3/45</td>
</tr>
<tr>
<td>Budapest II [41,42]</td>
<td>HDR/ELE</td>
<td>36.4/50</td>
<td>2.5</td>
<td>2.5</td>
<td>3/120</td>
</tr>
<tr>
<td>Virginia Univ. [19,20]</td>
<td>LDR/HDR</td>
<td>45/34</td>
<td>3.5</td>
<td>0</td>
<td>0/44</td>
</tr>
<tr>
<td>Tufts Univ. [53,54]</td>
<td>HDR</td>
<td>34</td>
<td>2.8</td>
<td>3</td>
<td>1/32</td>
</tr>
<tr>
<td>Uppsala [27]</td>
<td>PDR</td>
<td>50</td>
<td>2.8</td>
<td>2.3</td>
<td>1/43</td>
</tr>
<tr>
<td>Massachusetts [33]</td>
<td>LDR</td>
<td>50-60</td>
<td>4</td>
<td>0</td>
<td>0/48</td>
</tr>
<tr>
<td>Kansas Univ. [30]</td>
<td>LDR</td>
<td>20-25</td>
<td>3.9</td>
<td>0</td>
<td>0/24</td>
</tr>
<tr>
<td>London Reg. Ca C [38]</td>
<td>HDR</td>
<td>37.2</td>
<td>1.7</td>
<td>2.6</td>
<td>1/39</td>
</tr>
<tr>
<td>German/Austrian [45]*</td>
<td>PDR/HDR</td>
<td>49.8/32</td>
<td>1.1</td>
<td>0.5</td>
<td>1/201</td>
</tr>
<tr>
<td>Ninewells Hosp [44]</td>
<td>LDR</td>
<td>46-55</td>
<td>5.6</td>
<td>0</td>
<td>0/11</td>
</tr>
</tbody>
</table>

FUP = follow-up period; LR = local recurrence; n = number of intra-breast relapses/number of patients treated; ELE = electrons; LDR = low dose rate; HDR = high dose rate; PDR = pulse dose rate; * = data updated.

2.3 Patients selection for APBI – identification of a low-risk subset of patients

As a consequence of previous pathological findings, and results of prospective clinical studies, it is highly important to identify a low risk subset of breast cancer patients for whom tumor bed RT alone might be a sufficient treatment after BCS.

2.3.1 Patient age

Young age, as a prognostic factor for local breast recurrence, has been widely disputed in the literature [12, 63, 65, 68, 71-79]. Most series reported an increased breast failure rate using a variety of different age cutoffs. The EORTC boost trial demonstrated that young age was the most important prognostic factor for local recurrence [78]. The largest clinical benefit from boost was seen in patients younger than 40 years: at 5 years their local recurrence rate was reduced from 19.5% to 10.2%. In the Budapest boost trial, age less than 40 years was also found to be an independent prognostic factor for local recurrence [12, 65, 79]. The actuarial 5-year local failure rate was 30% for younger women, and 7.3% for patients above 40 years (p < 0.0001; RR: 5.25).

These results suggest that there is a distinct biological difference in breast carcinoma presenting in young women that predisposes them to local recurrence. Based on these considerations, patients below the age of 40 years should not be candidates for APBI.

2.3.2 Surgical margin status (SMS)

There is also a strong evidence to support that women with involved margins of resection are also ineligible for RT restricted to the lumpectomy site [24, 34]. At least 2 mm tumor free margin was deemed necessary in some APBI trials, but others also treated patients with close margins successfully by sole BT [21, 29, 39, 41, 50, 54].
Positive margin status have been accepted as a major risk factor for local recurrence after BCS and RT (Table 4.). Furthermore, the number of positive margins, as well as the width of clear surgical margin have influence on LTC [65, 79, 84-85].

Table 4. Local recurrence rate according to surgical margin status after BCS and RT

<table>
<thead>
<tr>
<th>Author</th>
<th>Local recurrence [%]</th>
<th>Tumor bed dose [Gy]</th>
<th>Follow-up [years]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMS + SMS -</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mansfield [80]</td>
<td>16/8</td>
<td>60-65</td>
<td>10</td>
</tr>
<tr>
<td>Smitt [81]</td>
<td>18/2</td>
<td>44-79</td>
<td>10</td>
</tr>
<tr>
<td>Spivack [82]</td>
<td>18.2/3.7</td>
<td>45-66.4</td>
<td>4</td>
</tr>
<tr>
<td>Anscher [83]</td>
<td>10/2</td>
<td>42-71</td>
<td>5</td>
</tr>
<tr>
<td>DiBiase [84]</td>
<td>14/6</td>
<td>60-65</td>
<td>5</td>
</tr>
<tr>
<td>Polgár [65,79]</td>
<td>34.7/9.5</td>
<td>50-66</td>
<td>5</td>
</tr>
<tr>
<td>Van Limbergen [63]</td>
<td>20.2/10</td>
<td>45-85</td>
<td>5</td>
</tr>
</tbody>
</table>

BCS: breast conserving surgery; RT: radiotherapy; SMS: surgical margin status.

However, the pathologists’ examination of margins is far from uniform, and many clinical series report the status of the margins, without describing how the margins were determined [85]. There is a consensus among pathologists that the use of the "India ink method" is essential to adequately assess margin status [85-86]. The specimen should be oriented with sutures, and delivered unfixed and intact to the pathologist. Based on the guidelines of EORTC Breast Cancer Cooperative Group, it seems to be a reasonable compromise to assess specimen margins in 6-8 blocks [86]. A complete cross-section through the largest diameter of the tumor should be sampled, including periphery and closest surgical edges, if necessary in more than one block. At least 3 additional blocks including nearest margins and tumor should be also sampled.

In the Schnitt et al. [87] study, the 5-year breast failure rate was 0%, 4%, 6% and 21% with clear, close, focally positive, and diffusely positive surgical margins, respectively. In the Budapest boost trial the respective rate with clear, close (≤ 2mm), and positive margins was 8.2%, 30.0%, and 34.7% [88].

2.3.3 Extensive intraductal component (EIC)

EIC is usually reported when 25% or more of an invasive ductal cancer consist of intraductal carcinoma, and ductal carcinoma in situ is also present in adjacent breast tissue. Holland et al [55, 89] reported that patients with EIC were more likely to have residual tumor outside the reference tumor than without EIC (74% versus 42%). The amount of residual tumor was also correlated with the presence of EIC. These findings explain why EIC positive patients were more likely to fail locally after BCS and RT (Table 5.). As a consequence, EIC is also viewed by most authors as a contraindication for APBI [27, 29-30, 39-41, 44, 50, 53-54].
Table 5. Local recurrence rate according to EIC after BCS and RT

<table>
<thead>
<tr>
<th>Author</th>
<th>Local recurrence [EIC +] [%]</th>
<th>Local recurrence [EIC -] [%]</th>
<th>Tumor bed dose [Gy]</th>
<th>Follow-up [years]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazer [90]</td>
<td>12</td>
<td>3</td>
<td>50-70.4</td>
<td>7</td>
</tr>
<tr>
<td>Fowble [91]</td>
<td>22</td>
<td>4</td>
<td>60-70</td>
<td>10</td>
</tr>
<tr>
<td>Eberlein [92]</td>
<td>27</td>
<td>7</td>
<td>&gt; 60</td>
<td>10</td>
</tr>
<tr>
<td>Krishnan [93]</td>
<td>9.1</td>
<td>5.2</td>
<td>60-70</td>
<td>10</td>
</tr>
<tr>
<td>Fodor [72]</td>
<td>27.2</td>
<td>7.2</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Polgár [88]</td>
<td>16.2</td>
<td>9.8</td>
<td>50-66</td>
<td>5</td>
</tr>
</tbody>
</table>

EIC: extensive intraductal component; BCS: breast conserving surgery; RT: radiotherapy.

2.3.4 Invasive lobular carcinoma (ILC)

ILC was thought to be a relative contraindication for breast conservation for decades, due to its multifocality and diffuse pattern of spreading [109]. However, long-term results from the nineties proved that adequate surgery and RT for ILC maintained similar LTC as seen for ductal cancers [72, 104, 110-116] (Table 6). These studies also reported that multicentric lesions were not significantly more frequent in ILC than in non-lobular infiltrating carcinoma [110]. The site of in-breast failure relative to the location of the original tumor was also not significantly different between lobular and non-lobular carcinomas [111, 113-115] (Table 6.).

In the Christie Hospital study, the local recurrence rate for patients treated with sole tumor bed RT for invasive lobular cancers was as high as 43% [34]. One could however argue that many of the patients treated in this trial were not acceptable candidates for BCT in general (e.g. positive/unknown margins in 19%).

On the other hand, in current APBI-studies using careful pathologic assessment of margin status, tumor bed brachytherapy alone maintained adequate local control also for patients with ILC [19, 27, 45].

Based on these data, one can conclude that the presence of ILC should not influence decisions regarding local therapy, and patients with ILC can be successfully treated with BCS and APBI.

Table 6. Incidence and site of local recurrence following BCS for lobular and non-lobular carcinomas

<table>
<thead>
<tr>
<th>Author</th>
<th>FUP [years]</th>
<th>LR [%]</th>
<th>TR + MM [%]</th>
<th>LR [%]</th>
<th>TR + MM [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastre-Garau [110]</td>
<td>10</td>
<td>20</td>
<td>NR</td>
<td>22</td>
<td>NR</td>
</tr>
<tr>
<td>Peiro [111]</td>
<td>10</td>
<td>15</td>
<td>86</td>
<td>13</td>
<td>78</td>
</tr>
<tr>
<td>Warneke [112]</td>
<td>5</td>
<td>3</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weiss [113]</td>
<td>5</td>
<td>9</td>
<td>100</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>Schnitt [114]</td>
<td>6.25</td>
<td>14</td>
<td>100</td>
<td>12</td>
<td>80</td>
</tr>
<tr>
<td>Fodor [115]</td>
<td>15</td>
<td>13</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Silverstein [116]</td>
<td>6.6</td>
<td>5</td>
<td>NR</td>
<td>5</td>
<td>NR</td>
</tr>
</tbody>
</table>

FUP: Follow-up period; ILC: infiltrating lobular carcinoma; IDC: infiltrating ductal carcinoma; LR: local recurrence; TR: tumor bed recurrence; MM: marginal miss; NR: not reported.
2.3.5 **Ductal carcinoma in situ (DCIS)**

Treatment of women with ductal carcinoma in situ (DCIS) by sole tumor bed RT is also controversial, since a large proportion of these tumors are widely spread in the breast [55-56]. However, small, unifocal DCIS that is excised with adequate margins is considered acceptable by some radiation oncologists [20, 29, 32]. Unifocal, low-risk DCIS – excluding patients with young age (Van Nuys Score ≤ 2), large tumors (Van Nuys Score ≤ 2), high-grade lesions (Van Nuys Score ≤ 2), and positive/close margins (Van Nuys Score ≤ 2) – may be appropriately treated with APBI.

2.3.6 **Lympho-vascular invasion (LVI)**

Peritumoral LVI has also been reported by numerous authors as a risk factor for local recurrence after BCS [73, 103, 106]. In the Budapest boost-trial endolymphatic spread caused a 2-fold higher risk for intrabreast relapse (5-year LTC: 12.5% vs. 6.2%; p = 0.03) (personal communication, C. Polgár). Extrapolating from the assumption, that in the presence of LVI malignant cells can spread widely in the breast via lympho-vascular spaces, it seems appropriate to be conservative and only enroll women without LVI into APBI-studies.

2.3.7 **Histological grade (HG)**

The value of HG as a prognostic factor for local recurrence is controversial, too. It is difficult to compare the results of different series, because of the variety of grading systems and the difficulty in grading of breast carcinomas [108]. Clarke [37] found that high grade was a strong predictor for both local-regional relapse and for breast alone relapse. Van Limbergen et al. [63] noted 5-year control rates of 95% for grade I, 90% for grade II, and 84% for grade III tumors, but this did not reach statistical significance (p = 0.12) and was in a multivariate analysis lined to young age. In the Budapest series, HG did not have significant impact either on LTC [12, 65, 88]. However, the average time to local recurrence was shorter for grade III tumors (20 months; range: 10-34), than for grade I-II carcinomas (38 months; range: 28-50) [88].

These data suggest, that poorly differentiated malignant cells remaining in the breast following BCS tend to regrow more rapidly than low-grade tumors. However, there is no evidence proving that high-grade tumors would spread more widely in the ductal tree compared to low-grade carcinomas. Based on these considerations, in most APBI-studies tumors with any histological grade were enrolled and treated with adequate LTC [20, 29, 31-32, 35, 49-54].

2.3.8 **Hormone receptor status**

Despite the large body of literature supporting the routine use of estrogen receptor (ER) and progesterone receptor (PR) status in clinical decision making for systemic management, the role of the hormone receptors as prognostic factors for local relapse is relatively weak and unexplored [94]. Some studies are summarized in Table 7.
Table 7. Local recurrence rate according to hormone receptor status

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Pts</th>
<th>Surgery</th>
<th>RT</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng [95]</td>
<td>83</td>
<td>MAST</td>
<td>-</td>
<td>Negative ER correlated with LR, LR: 31% vs. 11%, p = 0.02.</td>
</tr>
<tr>
<td>Sundquist [96]</td>
<td>629</td>
<td>MAST</td>
<td>+/-</td>
<td>Trend towards higher LR rate with negative ER status (12.7% vs. 6.3%, p = 0.12).</td>
</tr>
<tr>
<td>Zellars [97]</td>
<td>1530</td>
<td>MAST</td>
<td>+/-</td>
<td>Higher LR rate in ER negative (16.4% vs. 12.0%, p = 0.04) in no-RT group, but no correlation in irradiated group.</td>
</tr>
<tr>
<td>Silvestrini [99]</td>
<td>1800</td>
<td>MAST/BCS</td>
<td>+/-</td>
<td>No correlation between ER status and LR rate.</td>
</tr>
<tr>
<td>Elkhuizen [100]</td>
<td>195</td>
<td>BCS</td>
<td>+</td>
<td>Higher frequency of PR-negative tumors in patients with LR (75% vs. 60%, p = 0.03).</td>
</tr>
<tr>
<td>Polgár [65]</td>
<td>190</td>
<td>BCS</td>
<td>+</td>
<td>No significant difference in LR rate according to ER-status (13.4% vs. 7.9%, p = NS).</td>
</tr>
</tbody>
</table>

RT: radiotherapy; MAST: mastectomy; BCS: breast-conserving surgery; ER: estrogen receptor; PR: progesterone receptor; LR: local recurrence; NS: not significant.

In the study of Fisher et al [98] both ER and PR correlated with local relapse, however the combination of ER and PR negativity was highly predictive of local recurrence.

In multivariate analysis only positive margin status and the combination of negative ER and PR status were significant for local relapse. Several other studies have failed to show any correlation between ipsilateral breast tumor recurrence and hormone receptor status [101-102]. Collectively, these data suggests that the value of hormonal receptor status in local tumor control is not as strong as its value in systemic disease.

To date, only the German-Austrian phase II study did not enroll patients with ER and PR negative tumors [45]. In all other successful European and American phase I-II trials ER and/or PR negativity was not a contraindication for APBI [19-22, 25-33, 35-42, 44, 46-54]. Based on these data, to date there is no existing evidence suggesting that patients with hormone receptor negative tumors would be ineligible for APBI.

2.3.9 Tumor size

In most series tumor size itself did not significantly affect LTC following BCT [63-65, 72, 88, 92, 103-104]. However, in the NSABP-B-06 trial, patients with T2 tumors were more likely to develop local recurrence following BCS without RT [105].

In earlier APBI-studies, tumors up to a diameter of 4-4.5 cm were treated by tumor bed RT alone [29, 31-32, 38-39]. In the Ochsner series, up to 19 catheters were used to implant the tumor bed for such cases [32]. At almost half of the patients (47%) had one or more grade 2-3 toxicities, including twelve (24%) fat necroses, of which two required surgery [32]. Others also found implant volume to be associated significantly with fat necrosis [54]. We have the impression that patients with tumors > 3 cm
might not be candidates for BT alone, because of the high risk of fat necrosis caused by large volume implants.

2.3.10 Axillary nodal status

The treatment of node-positive patients with tumor bed RT alone is controversial, too. Women with less than 4 involved axillary lymph nodes without extracapsular extension were also considered for BT alone in the American series [20-22, 29, 31-32, 35, 51-54]. Other groups (including successful European studies) selected only patients with negative or not more than microscopically involved lymph nodes [30, 33, 39-42, 44-45]. As we have no strong evidence to exclude the possible survival benefit of RT in patients with 1-3 positive nodes, it seems to be safe to exclude patients with macroscopically (> 2mm) involved axillary lymph nodes from a phase III APBI-study.

2.4 What should be the target volume for sole tumor bed RT?

If sole tumor bed RT is considered as an acceptable treatment modality for selected early breast cancer, another important issue should be the definition of the clinical (CTV) and the planning target volume (PTV) to be treated. Based on pathological considerations, at least 2 cm breast tissue margin around the primary tumor would be required to eliminate residual tumor foci in the remaining breast [55-62]. The authors feel that according to Holland's data [55-56] a 2 cm breast tissue margin measured from the edge of the primary tumor mass is acceptable. On the other hand, in the clinical practice, such a large safety margin usually results a target volume going beyond the breast tissue. For such cases, the boundaries of the PTV for BT should be redefined as 5 mm below the skin surface, and 5 mm above the underlying ribs [122].

Accurate tumor bed delineation should be also an important goal of treatment planning. In the past, the only available landmarks to localize the excision cavity were palpation, mammograms, surgical reports, and scars. Nowadays, several techniques exist to maintain better coverage of the target volume [40, 117]. Some authors used ultrasound for localization of the excision cavity [29, 51, 54, 117]. The majority of authors suggested that the best orientation was given by titanium marker clips implanted by the surgeon intraoperatively [21, 37, 51, 54, 117-119]. The nowadays recommended approach is to place 6 clips into the walls of the excision cavity according to its latero-medial, antero-posterior, and cranio-caudal dimensions. However, the irregular 3 dimensional (3D) shape of the excision cavity and the normal tissue structures can only be localized correctly on the visual information obtained from cross-sectional imaging [119-121]. The use of surgical clips and CT together seems to be the best method to determine the target volume, since both titanium clips and borders of the excision cavity can be visualized exactly from slice to slice. Some authors deliver sole BT using iridium-192 implants at the time of surgery [29-30, 37-38, 44, 51, 54]. The advantage of the intraoperative implantation is that it is possible to place the afterloading catheters more accurately in the tumor bed. In addition, the implant can be loaded within 48 hours after the surgery and the overall treatment time is also shortened. However, limitation of this procedure is that at the time of implantation there is lack of detailed histological information about whether sole BT is indicated at all. Furthermore, intraoperative implantation require good collaboration and time management between the surgeons and radiation oncologists, and is therefore not recommended/allowed in this trial.
3 Objectives - End Points

3.1 Primary objective

To assess the role of brachytherapy alone compared to whole breast irradiation in a defined low-risk group of invasive breast cancer or ductal carcinoma in situ concerning local failure (all ipsilateral local recurrences) and to affirm the hypothesis that local control rates in each arm are equivalent.

3.2 Secondary objectives

- To assess incidence and severity of acute and late side effects of brachytherapy alone compared to whole breast irradiation.
- To assess the differences in cosmetic results of brachytherapy alone compared to whole breast irradiation.
- To assess distant metastases free survival (DMFS).
- To assess survival rates (Overall Survival: OS, Disease-free Survival: DFS).
- To assess the contralateral breast cancer rate.
- To assess QoL (quality-of-life) of patients treated with BT alone compared with WBRT.
4 Study Summary

4.1 Design

It is a prospective, randomized, multicentric phase III trial. The primary objective is local recurrence.

4.2 Randomization

Prior to the recruitment of patients investigators must be registered. Each investigator or group of investigators at every clinical site must obtain local ethic committee approval for this protocol before they can enroll patients. Patients can be registered only after pre-treatment evaluation is completed, all pertinent documents are approved and on file and eligibility criteria are met.

Randomization of patients will be stratified according to center, disease stage and menopausal status. To assure balanced sample sizes in the two therapeutic groups randomization will use a block size of 10.

In each participating center, a log book will be kept, including all patients fulfilling the inclusion criteria (data necessary for inclusion is represented in Appendix XIII). For each patient, information on whether she participated or not, and possible reasons for decline, will be recorded. Furthermore, the patient ID will be generated and noted here according to a SOP. The patient ID will contain a unique number given at registration, initials, date of birth and sex. Hence, the log book kept by the local study physician or study nurse will be the link between individual records and the anonymized CRF.

Randomization of all patients who (i) fulfill the inclusion criteria and (ii) have given written informed consent to participate will be provided centrally by the biometrical study center. Randomization will be stratified (balanced) with respect to center, invasive vs. non-invasive disease, and pre- vs. post-menopausal status. In each stratum, a block size of 10 will be used. In practice, for each eligible patient willing to participate, the treatment modality is requested via e-mail or fax by the respective study center. On the mail/fax form, all inclusion criteria are listed (and checked by the biometrical center on that occasion), together with the patient ID. During working days, the treatment will be indicated within 24 hours. Before allocation to either treatment is revealed both to the physician in charge and the patient, the consent to participate and the result of randomization must be determined definitely.

Blinding of physicians performing treatments and of patients is not possible for technical reasons. However, the physicians performing the follow-up and the statistician shall be blind to the mode of treatment.

The randomization will be done via E-MAIL or FAX directly to:

W. Uter,
Institute for Medical Informatics, Biometry and Epidemiology
University Erlangen-Nuremberg
Waldstr. 6
91054 Erlangen
Tel.: 0049 9131 8522720
Fax.: 0049 9131 8522721
E-mail: apbi.study@imbe.imes.uni-erlangen.de

4.3 Study duration

Start of the study: March 2004
Duration of patient recruiting: 4 years
Duration of therapy: 4-5 days (brachytherapy) or 6 weeks (external beam therapy)
Follow-up: max. 5 years
End of study: 2011
4.4 Participating centers

This is a multicenter study. Beside the already mentioned members of the study group the participation of other centers is possible and planned. Each investigator (study center) must be registered.

Each investigator or group of investigators must obtain local ethic committee approval for this protocol before they can enroll patients.

Further it must be guaranteed, that the participating center can recruit at least 20 patients per year, can ensure appropriate quality assurance and also make possible for members of the study group to control it, if necessary.

The responsibilities of the investigator are summarized in Appendix XVII.
5 Patients

5.1 Number

A total of 1170 patients should be recruited for the trial (see 12.5). To account for dropout (non-valid cases) estimated to be 10%, altogether 1170 patients should be recruited.

5.2 Inclusion criteria

- stage 0, I or II breast cancer.*
- Invasive ductal, papillary, mucinous, tubular, medullary or lobular carcinoma.
- ductal carcinoma in situ (DCIS) alone.
- No lymph invasion (L0) and no hemangiosis (V0).*
- Lesions of ≤ 3 cm diameter, histopathologically assured.
- pN0/pNmi * (a minimum of 6 nodes in specimen, or a negative sentinel node is acceptable); in the case of DCIS alone axillary staging (e.g. sentinel lymph node biopsy ) is optional.
- M0 *.
- Clear resection margins and safety margins of at least 2 mm in any direction; in case of lobular histology or DCIS histology only the resection margins must be clear by at least 5 mm.
- For DCIS only: Lesions must be classified as low or intermediate risk group (Van Nuys Prognostic Index <8, see Appendix XIV).
- Unifocal and unicentric DCIS or breast cancer.
- Age ≥ 40 years.
- Time interval from final definitive breast surgical procedure to the start of external beam therapy or to brachytherapy is less than 12 weeks (84 days). If patients receive chemotherapy the radiotherapy can be started before systemic treatment (within 12 weeks). The radiation therapy can be also given in the interval between the chemotherapy courses. It is also possible to start radiation therapy after chemotherapy is completed according local protocols as soon as possible within 4 weeks after chemotherapy.
- Signed study-specific consent form prior to randomization.


5.3 Exclusion criteria

- Stage III or IV breast cancer.
- Safety margins that cannot be microscopically assessed.
- Extensive intraductal component (EIC).
- Paget’s disease or pathological skin involvement.
- Synchronous or previous ipsilateral or contralateral breast cancer.
- Prior malignancy (≤ 5 years prior to enrollment in study) except non-melanoma skin cancer or cervical carcinoma FIGO I if patient is continuously disease-free.
- Pregnant or lactating women.
- Collagen vascular disease.
- The presence of congenital diseases with increased radiation sensitivity, for example Ataxia telangiectatica or similar.
- Psychiatric disorders.
- Patient with breast deemed technically unsatisfactory for brachytherapy.
6 Therapy

6.1 Radiation therapy

Time interval from final definitive breast surgical procedure to the start of external beam therapy or brachytherapy is less than 12 weeks (84 days). If patients receive chemotherapy the radiotherapy can be started before systemic treatment (within 12 weeks). The radiation therapy can be also given in the interval between the chemotherapy courses. It is also possible to start radiation therapy after chemotherapy is completed according local protocols as soon as possible within 4 weeks after chemotherapy.

6.2 Brachytherapy

Important remark: If a patient is randomized to the brachytherapy arm and tumor bed clip markers are not present and in preimplant-CT it is not possible to identify the tumor bed, the patient has to be withdrawn from the study (see also 11.2). This decision has to be forwarded immediately to the data center.

6.2.1 Target definition

The target volume of the brachytherapy arm consists of the tumor bed with an adequate safety margin in all directions. The “clinical target volume” (CTV) is in this case identical with the “planning target volume” (PTV). In some cases restrictions have to be made in direction to the chest wall and skin, which is inevitable and unavoidable. For such cases, the boundaries of the PTV should be redefined as 5 mm below the skin surface, and 5 mm above the underlying ribs. The knowledge of the tumor-free margins is important, since the size of safety margins of implant volume depends on the size of these tumor-free resection margins. An obligatory precondition is the exact preparation of the resected breast tissue by the pathologists. The distance of the border of the PTV (safety margin) to the tumor surface (tumor margin) must be at least 20 mm, because this area contains 80% of the microscopic tumor extensions around the primary macroscopic tumor. From this results we conclude: >20 mm minus the minimum tumor-free resection margin (A) is the safety margin (B) included in the PTV. The larger the tumor-free resection margin, the smaller the safety margin for the PTV (Fig. 1): B = 20 - A (mm). Thus e.g. if the pathologist describes a minimum resection margin 12 mm lateral, 2 mm medial, 5 mm cranial, and 10 mm caudal, then the minimal safety margin should around the tumor cavity (surgical scar, clips) should be lateral >8 mm, medial >18 mm, cranial >15 mm and caudal >10 mm, depending on surgical techniques the safety margin in skin direction (anterior) and chest wall (posterior) should be defined also.
Fig. 1: Schematic representation of the target volume.

![Target Volume Diagram]

**tumor**

**resection volume**

**surgical margins**

A = minimal resection margin  
B = safety margin  
B = >20 mm minus A

Of course in most cases, these margins include a large amount of tissue in the lateral directions and especially in the direction to the nipple. Breast skin or thoracic wall are not the target volume for brachytherapy alone. The overlying skin is usually surgically removed with the superficially located tumors, and the residual skin does not need any treatment. Irradiation of the skin over 40 Gy (by conventionally fractionated WBRT (1.8-2.0 Gy per day) or by PDR-BT) should be carefully avoided to prevent skin teleangiectases. When a dose of 50 Gy is delivered to the skin vessels, teleangiectases may occur in 30% of the cases. Using brachytherapy the skin dose must not exceed 70% of the prescribed reference dose.

For the localization of the target volume any information source has to be taken in account, because the surgical scar alone is unsuitable for tumor bed localization.

The physician carries the responsibility for the planning of the implant and for the definition of the PTV. Before the implantation it is obligatory to know: mammography and ultrasound results, surgical report and written histological findings. In the histological findings the description of the tumor-free resection margins in mm in all dimensions is essential. Also the CT or MR investigation can be helpful. It is optimal, if the tumor bed is marked with six clips, indicating the cranio-caudal, medio-lateral and antero-posterior borders of the resected volume.
Depending on whether clips are present or not, the tumor bed has to be defined as follows:

6.2.1.1 Clip marking of the tumor bed is present

Under x-ray control, e.g. with the help of a conventional simulator or an Integrated Brachytherapy Unit (IBU) or a CT-unit the position of the clips and so the tumor bed are identified. Preimplant CT-scan and CT-based treatment planning is recommended. The optimal direction of the needles is determined and the appropriate point for insertion (entrance and exit points) of the needles at the skin is marked. As an alternative making a CT simulation on the basis of the same markings is acceptable. (Fig. 2). Post-implant CT-scan for documentation of implant quality is obligatory (but not obligatory for planning purposes).

Fig. 2: CT simulation of the tumor bed before the implantation: With the help of surgical clips entrance and exit points of the needles are marked (yellow triangles). The CT image permits the exact definition the length of active steps of the source within the needles (red arrow).

Recently the combination of surgical clips with CT- or IBU-localization during implantation procedure represents the most exact method of tumor bed localization.

6.2.1.2 Clip marking of the tumour bed is not present

Preimplant CT-scan for planning of the implant geometry, and postimplant CT-scan for treatment planning and documentation is mandatory.

CT-image based preplanning of implant geometry and PTV:
A CT-scan (with 3-5 mm slice reconstruction thickness) of the whole breast should be done with template on the breast (Fig. 3.). After contouring of the excision cavity in each slice, the PTV can be generated manually or automatically by adding an appropriate safety margin (see 7.2.1. and Fig. 1.) around the excision cavity. Then, the boundaries of the PTV should be modified (if necessary) to 5 mm below the skin surface, and 5 mm above the underlying ribs to avoid skin teleangiectasia and rib fracture. Following 3-D reconstruction of the PTV, position of implant needles can be defined using the needle-eye-view technique (Fig. 4.).
CT-image based treatment planning:
After implantation a CT-scan (with ≤ 3 mm slice thickness) of the implanted breast should be performed for evaluation of the PTV coverage. After contouring of the excision cavity, the PTV can be generated as described previously (Fig. 5.). The active source positions can be defined individually in each catheter.
Dose specification and prescription should be done according to the rules of the ICRU-report 58. Geometrical dose optimization is allowed. The dose is usually prescribed to 85% of the MCD.
DVH analysis should be used to confirm that 100% of the prescribed dose covering > 90% of the PTV (i.e. CI > 0.9). If adequate coverage can not be achieved, prescription of dose to a lower percentage isodose is allowed – keeping the DNR below 0.35. Otherwise the implant should be improved with the addition of new implant catheters.
An alternative way of dose prescription for CT-image based treatment planning is to automatically generate dose points on the surface of the 3D reconstructed PTV (Fig. 6.). Following the geometric optimization for volume implant, the dose can be prescribed to the “dose points on target” – keeping the DNR below 0.35. DVH analysis should be used to confirm that 100% of the prescribed dose...
covering > 90% of the PTV (Cl > 0.9). If adequate coverage with acceptable dose homogeneity can not be achieved, then the implant should be improved with the addition of new implant catheters. Reporting the value of MCD is mandatory and, if possible, MTD should be documented.

Fig. 5: Postimplant CT-image based definition of the PTV. Excision cavity (red); PTV (green).

Treatment parameters for CT-image based planning:

- DVH analysis of target coverage will confirm 100% of the prescribed dose covering > 90% of the PTV (Cl > 0.9).
- DNR < 0.35.
- Maximum skin dose < 70% of the PD.

- For reporting values of:
  - MCD,
  - volumes (D_ref, 1.5 x MCD, 1.5 x D_ref),
  - surface CI, DNR, DHI, COIN

should be also given (see Appendix XVIII).

Fig. 6: Dose prescription to „dose points on target“.
PTV (thick red line); dose points defined on the surface of the PTV (blue points);
100% isodose line (thin red line); 50% isodose line (green line).
Ultrasound-guided location of the PTV

PREVIOUS IMPLANTATION:
The tumor bed is well detectable with ultrasound in case of an open cavity remaining postsurgically. During the first four to six postsurgical weeks after surgery an echoless area may define the cavity, the distance to the skin and chest wall may appear very well also. Any pressure to the breast tissue has to be avoided in order to get no false distances. Additional to mammography, surgical report and palpation, ultrasound helps to locate the PTV. In case of a closed cavity ultrasound examination is not a reliable tool to locate the PTV.

DURING IMPLANTATION:
It is very useful to see the reference needle in the lower plane in real time. If it doesn’t meet the cavity, a correction can be done immediately to place the needle in the correct position. After complete implantation of the lower implant plane a further ultrasound examination helps to get the actual distance between needles and skin, in order to relocated the needles more superficially or to add another plane. With an ultrasound examination plastic tubes are well defined, too. After completion of the implant procedure the brachytherapist can judge the right coverage of the surgical cavity, with this maneuvers a better definition of PTV may be achieved.

6.2.2 Dose specification

When treating with a single stepping source the length of the source steps has to be determined in that way, that the reference isodose encloses the tumor bed with an adequate safety margin (PTV). The reference isodose corresponds the minimum target dose according ICRU 58 (in the ideal case congruently with the CTV). Several reference points according to ICRU 58 in the central implant plane must be defined, by calculating the average value of doses of all reference points we receive the so-called “mean central dose” (MCD).

The reference dose enclosing the target volume is usually defined within the range of 80-90% of the MCD (usually 85%) (Fig.7). A specification on isodoses smaller than 80% of the MCD has the consequence that the percentage of volume which is enclosed by larger isodoses (120-150%), increases. To avoid unwanted overdosing we advise against this procedure. If the prescription isodose is lower than 80%, the DNR must be < 0.35 (preferably < 0.30). If these dose prescription and homogeneity constraints are not fulfilled, it must be the consequence to implant additional needles/catheters. It is necessary therefore that during the implantation the target volume must be covered by a sufficient number of needles/catheters.

The volume enclosed by the reference isodose surface depends on the tumor size and on the size of the resection margins (size of the PTV) - mostly about 40 - 150 cm³. A volume over 150 cm³ should be exceeded only in justified cases. Smaller volumes mostly develop with a one-plane implant, which is not allowed in this study! As additional parameter for the quality of the implant the DNR (see Appendix XVIII) must be calculated. The dose distribution is regarded sufficiently homogeneous, if the DNR is < 0.35 (preferably < 0.30). If these criteria are not fulfilled, physician and physicist should clarify the causes and look for improvements for the further procedure on an individual basis.

Fig. 7: Dose distribution of a 2-plane implant. (reference dose volume 57 cm³, DNR = 0.18).
6.2.3 Prescription of dose, dose rate, fractionation

Following dose concepts are recommended ($D_{ref}$):

**HDR:**
- $32.0$ Gy/8 fractions ($8 \times 4$ Gy, $2 \times$ daily) or
- $30.3$ Gy/7 fractions ($7 \times 4.3$ Gy, $2 \times$ daily)

**PDR:**
- $0.60 - 0.80$ Gy/hour to $50$ Gy ($1$ pulse/hour, $24$ hours/day)

**Notice:** The dose distribution is regarded sufficiently homogeneous, if the DNR is $< 0.35$ (preferably $< 0.30$).

6.2.4 Technique

Breast implants can be carried out under general or local anesthesia and premedication with $2.5 - 5$ mg midazolam (Dormicum®) given $15 - 30$ min before implantation. Some centers prefer general anesthesia (Erlangen, Vienna, Linz etc.), some (Budapest, Leuven etc.) local anesthesia. For the implantation are needed: $16 - 20$ cm long implantation needles (Guide needles), templates in different sizes (with channels in square or triangular arrangement and with distances of the channels between $12$ and $20$ mm), lineal, stick, tweezers (Fig.8).

Preplanning of the implant geometry should be based on x-ray localization or CT-scans (if clips are not present). There are several well-established techniques for PTV-localization and implantation [9,40,41,122]. One of the possible implant procedures is described below:

The patient is placed in supine position with the ipsilateral arm in $90^\circ$ abduction. Once the tumor center is localized, and the three dimensions of the CTV and the PTV (length, width, and thickness) are defined and delineated on the patient's skin, implantation of the first needle follows, the so-called "guidance needle or reference needle" without or with template (Fig.9). The position of this needle has to be selected in such a manner, that this needle is placed under the deepest place of the tumor bed (the tumor) and in the center of the lowest level of the implant. It is important to consider both the position of the clips and the tumor position in the preoperative mammograms (the tumor distance from the thorax wall is represented only in the preoperative ultrasound and mammography pictures!).

To ensure, that the following needles will be implanted parallel and equally distant from each other a template of suitable size is placed over the guidance needle. Then the needles are implanted according to the rules of the Paris System. In most cases, they are inserted in a medio-lateral or crano-caudal direction. In the outer quadrants it is possible to implant with needles orientated in a $45^\circ$ angle. Usually two or three planes of needles are implanted. A single plane implant is not allowed. Number and spacing between needles (template size) is chosen to adequately cover the width and the thickness of the PTV. Seven to fourteen needles spaced $12 - 20$ mm are usually required. Guide needles must be replaced by plastic tubes immobilized by buttons at both sides of the breast (Fig.9).

The main advantage is that the therapy is better tolerated by the patient, but it is not possible to keep the optimal geometry. In case of sole HDR-brachytherapy we recommend the use of the Comfort Breast System (Nucletron) for higher treatment acceptance and comfort among the patients.

The next step is the verification of the positions of the plastic tubes with the help of a conventional localization with simulator or CT. First we should define the source length – active source steps (directly in the CT picture or with ruler at the simulator, Fig. 10). It is important to maintain a sufficient distance between the superficial implant tubes and the overlying skin. In the case of a CT-based planning this distance is directly visible and measurable.

Using the conventional localization a metal wire cross should be laid on the skin above the implant in a central position (Fig.11). Generally it is important, that the skin dose does not exceed $60\%$ of the prescribed dose. This dose is not exceeded, if the superficial plane is implanted at least $10$ mm from the skin.
Fig. 8: Instruments
Fig. 9: Implant procedure
Fig. 10: Determination of the active length within the catheters (tubes) with conventional localization. By the determination of the active length it is important to pay attention, that both the safety margin (85% isodose line) do not fall below 2-3 cm to the tumor bed (surgical scar, clips) and the minimum distance of the last source position to the skin do not fall below the value of 0.5 cm.

Fig. 11: „Cross“ for the determination of the skin dose, if only a conventional localization was accomplished.
6.2.5 Quality assurance

Quality assurance review will be based on the parameters stated below. These parameters may be modified as additional information from ongoing Phase II-trials becomes available.

All brachytherapy plans require filming on simulator or CT simulator units. Copies of preoperative mammography films, copies of simulator or CT films with calculated dose distribution including value of reference isodose in relation to the MCD and also volume of \( D_{\text{ref}} \), \( 1.5 \times \text{MCD} \) and \( 1.5 \times D_{\text{ref}} \) surface, skin dose values (at relevant skin points above the implant, at 5 mm depth of the entrance and exit points of the catheters and their maxima), documentation of clips position in relation to the implant, DNR (optionally DHI, CI, COIN in case of CT-based planning) values must be submitted to the reference center within one week after completion of brachytherapy for the first five patients in each study center.

- Catheters will be placed by the radiation oncologist following randomization.
- Image guided technique of placement to the physician preference.
- Treatment parameters:
  - Treatment target volume – Clinical Tumor volume (CTV) – defined as breast tissue volume around resection margins, guaranteed safety margins (see 2.2.1) of at least 2 cm.
  - Dose/fractionation: HDR: 32.0 Gy/8 fractions (8 x 4 Gy, 2 x daily) or 30.3 Gy/7 fractions (7 x 4.3 Gy, 2 x daily)
  - PDR: 0.60 - 0.80 Gy/hour to 50 Gy (1 pulse/hour, 24 hours /day)
- The dose distribution is seen as sufficiently homogeneous, if the DNR is < 0.35 (preferably < 0.30).
- Treatment parameters for CT-image based planning:
  - DVH analysis of target coverage will confirm 100% of the prescribed dose covering > 90% of the PTV (CI > 0.9).
  - DNR < 0.35.
  - Maximum skin dose < 70% of the PD.
  - For reporting values of volume of \( D_{\text{ref}} \), \( 1.5 \times \text{MCD} \), \( 1.5 \times D_{\text{ref}} \), surface CI, DNR, MCD, DHI, COIN should be also given (see Appendix XVIII)

6.3 External beam therapy

All patients randomized to the external radiation treatment arm shall receive a total dose of 50.0-50.4 Gy to the entire breast in 1.8-2.0 Gy fractions x 25-28 fractions and afterwards a dose of 10 Gy in 5x 2 Gy fractions to the tumor bed as boost with appropriate electron beam.

Radiation treatment will be delivered in uniform daily doses through standard tangent photon and electron boost fields from Monday to Friday for 6-7 weeks.

Notice: In the WBRT-arm interstitial brachytherapy boost is not allowed.

6.3.1 Dose Specifications Factors

The prescription point (ICRU-50 reference point) is defined at the point of isocenter. If this point is not adequate then at the central CT slice, a line is drawn through the isocenter and perpendicular to the posterior border of the tangential fields. The prescription point is then placed along this line at the center between posterior field border and skin contour.

Electron boost dose is prescribed in point of Dmax on the beam axis, assuring that the 85%-isodose line encloses the PTV. Adequate field size, localization and electron energy should be defined with simulator or CT-scans.

Notice: The PTV for the electron boost has the same dimensions as for brachytherapy.
6.3.2 Technical Factors

Equipment must have nominal photon energies between 4-10 MV and nominal electron energies between 6-18 MeV. Compensators, wedges, or dynamic therapy must be used to keep the maximum PTV dose preferably within 15% of the prescription dose. The beam may be conformed to the shape, with a margin, to the shape of the breast if necessary with cerrobend-type blocking or by using a multi-leaf collimator. Fields will be designed using a simulator unit or CT simulator with appropriate patient immobilization for the daily setup accuracy.

6.3.3 Critical Structure Dose

Central lung distance (CLD) should not exceed 3 cm (preferably < 2 cm).

6.3.4 Supraclavicular Field

Regional nodal irradiation (supraclavicular and/or axillary and/or parasternal fields) should not be used.

6.3.5 Documentation

All treated fields (including electron boost field) require filming on simulator or CT simulator units. Portal verification must be done for all treated photon fields. Copies of both simulator and portal fields of the first 5 patients of each center must be submitted to the study coordinator within one week after completing the external beam therapy.

6.4 Drug therapy

Adjuvant sequential chemotherapy and/or hormonal therapy is allowed according to the local protocol of the treating center (keeping the time schedule defined in 7.1.).

6.5 Surgery

6.5.1 Breast-Conserving Surgery

Within the present trial lumpectomy, wide excision or quadrantectomy should be utilized for suspected or known malignancy. Lumpectomy and wide excision is defined as resection of a breast mass with a significant margin of breast tissue left attached to the mass in all axes. A 1-cm clearance grossly as the intended amount of non-malignant tissue that is left attached to the mass should be used. However, the minimum of clearance acceptable is at least above 2 mm of non-malignant tissue in all axes. Lesions that are superficial should be ellipsed with a segment of skin that affords gross clearance of at least 1 cm for the lesion. The part of the pectoralis fascia which is next to the lesion should be included, if indicated. The specimen is marked with different length sutures in order to tag at least three of the six axes of the mass for orientation purposes for the pathologist, who is asked for immediate evaluation of the margins. Clips are used to mark the tumour site for the radiotherapist.

6.5.2 Treatment of the axilla

Standard treatment of the axilla within this trial is a level I and II axillary dissection. At least 6 (preferably 10) lymph nodes should be dissected. However, sentinel lymph node biopsy alone or with axillary dissection is admissible.
6.6 Pathology

Good pathological reporting and precise histopathologic classification of the resected invasive carcinoma or ductal carcinoma in situ (DCIS) are essential prerequisites in order to decide whether a patient will be included in the present trial or not. The guidelines and procedures for a standardized pathological assessment in this study are summarized in appendix XV. It is also an aim of pathology in this trial to identify potential histopathological or molecular predictors of selective advantage for brachytherapy versus external beam radiation. For this purpose a central pathological review of selected patients is planned and will be organized during study. Representative H&E stained slides and/or paraffin blocks will then have to be sent in.
7 Data Management

7.1 Data collection and data management

Data collection will be done utilizing report forms in digital form and also as hard copy (Appendices IX-XIII). The digital report form, the original, is sent to the data center, the hard copy remains on site with the local department.

Digital report forms must be filled in carefully with a computer, pencil notes are not allowed. Data fields which cannot be filled in due to missing information on that item need to be commented on (so that the missing data can be distinguished from accidental omissions). The report forms must be filled in within due time after treatment and follow-up, respectively, checked, dated and signed by the physician in charge and sent to the data center via registered mail services.

In the biometrical study center report forms will be entered into database, using a custom programmed database and screen forms with plausibility checks (e.g., acceptable range of data values, consistency with other items). Data entry is performed by two independent persons into two different databases. After double data entry, errors are identified by procedures comparing data, linked via the patient ID and other appropriate variables as unique identifier and subsequently corrected. Correction proofs are stored together with the individual report form. Validated data are stored in a database (MS Access). After termination of the study and entry of all data, including possible corrections after validation checks, the database will be closed. This process will be documented. For data analysis, the following commercially available software packages will be used: SAS (in the current version; presently 8.2) and SPSS (in the current version, presently 11.5).

7.2 Data security

Personal data of patients remain in the local participating centers. Only anonymized data will be passed on to the study center via registered mail services. Access to the biometrical study center is restricted to authorized users. In addition, within these precincts, access to electronic data, including the study databases mentioned, is restricted to a user group explicitly authorized to have access to data. All these users sign a declaration that they will treat all data confidently. An electronic back-up of data is automatically compiled each weekday night, following a proprietary SOP.
8 Patient assessments

8.1 Clinical examinations

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

The following examinations are obligatory:

8.2 Prior to therapy

8.2.1 Patient eligibility and randomization form

Before treatment a patient eligibility and randomization form (see appendix) has to be sent to the documentation center in Erlangen. Eligibility and exclusion criteria will be checked and the result of the randomization communicated within 24 hours.

8.2.2 Cosmetic outcome

Documentation of bra cup size of the untreated breast (category A, B, C and D or larger, see appendix).

Digital photographs from ventral (see example).

Example:

Evaluation of the cosmetic result of the breast-conserving surgery (see appendix):


<table>
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<tbody>
<tr>
<td>Excellent (1)</td>
</tr>
<tr>
<td>Good (2)</td>
</tr>
<tr>
<td>Fair (3)</td>
</tr>
<tr>
<td>Poor (4)</td>
</tr>
</tbody>
</table>
8.2.3 Side effects

Documentation of surgery-related preexisting side effects with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE, Publish Date: June 10, 2003) and with the RTOG/EORTC Late Radiation Morbidity Scoring Schema. See tables below.

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

| RTOG/EORTC Late Radiation Morbidity Scoring Schema |
|---------------------------------------------------|-------------------------------------------------|-----------------|----------------|----------------|
| **ORGAN TISSUE**                                   | **SKIN**                                        | **Grade 1**     | **Grade 2**    | **Grade 3**    |
| Slight atrophy                                     | Slight atrophy; Pigmentation change. Slight teleangiectasia (< 1 cm²); Some hair loss. | Patch atrophy; Moderate teleangiectasia (1-4 cm²); Total hair loss. | Marked atrophy; Gross teleangiectasia (> 4 cm²). | Ulceration |
| **SUBCUTANEOUS TISSUE**                            | None                                           | Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction | Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement | Necrosis |
8.2.4 Quality of life (QoL)

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

References:


8.3 During therapy

8.3.1 Radiotherapy report form

Up to six weeks after the treatment the radiotherapy report form (see appendix) has to be sent to the documentation center in Erlangen. This form describes modality and quality of the performed radiotherapy as well as acute toxicity using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), Publish Date: June 10, 2003.

8.3.2 Cosmetic outcome

Digital photographs from ventral (see example above) taken at the first treatment day to document the interstitial implant or the external beam radiation fields, respectively.

8.3.3 Acute side effects

Documentation of radiotherapy-related acute side effects with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE, Publish Date: June 10, 2003). See table above.

8.3.4 Quality of life (QoL)

Immediately after the last fraction of interstitial or percutaneous radiotherapy patients are intended to fill out an QoL-questionnaire (EORTC QLQ-C30 including the Breast cancer module QLQ-BR23, see appendix).

8.4 Follow-up assessments

Follow-up investigations should be done every 3 months for 2 years after radiotherapy, every 6 months for the following 3 years and once a year for the next five years. Careful history-taking, inspection, palpation and mammography has to be performed as shown in the table below. QoL questionnaire and digital photos should be filled out before and after RT, than at 6 and 12 month FUP, and yearly thereafter (see table above). Further investigations (x-rays, scintigraphy, CT-scans etc.) are indicated if there are clinical signs for metastatic disease.

8.4.1 Follow-up form
After each follow-up investigation a follow-up form (see appendix) has to be sent to the documentation center in Erlangen. The follow-up form documents local and systemic control, patterns of recurrence, further therapies, cosmetic outcome, late effects and survival.

8.4.2 Cosmetic outcome

Digital photographs from ventral (see example above).
Evaluation of the cosmetic result (see appendix):


The results have to be documented on the follow-up form (see appendix).

8.4.3 Late side effects

Documentation of late side effects with the RTOG/EORTC Late Radiation Morbidity Scoring Schema. See table above. The result has to be documented on the follow-up form (see appendix).

8.4.4 Quality of life (QoL)

At every follow-up investigation patients are intended to fill out a QoL-questionnaire, at least at the 3-, 6-, 12-, 24-, 36-, 48-, 60-, 72-, 96- and 120-months follow-up investigation. (EORTC QLQ-C30 including the Breast cancer module QLQ-BR23, see appendix).
9 Determination of therapy safety

9.1 Collection, evaluation and reporting

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

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

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

All abnormal laboratory results must be appraised by the investigator as to clinical significance. For any laboratory abnormality considered as clinically significant, details must be provided regarding the action taken with respect to the test drug and the patient outcome.

9.2 Documentation of unexpected events

All serious or unexpected adverse events including death, which occurs on study or within 28 days subsequent to withdrawal from study, must be reported immediately to Mr. O. Ott, Mr. V. Strnad or Mr. C. Polgár by telephone or fax, regardless of presumed causal relationship.

Alternates:

<table>
<thead>
<tr>
<th>O. Ott, MD</th>
<th>V. Strnad, MD</th>
<th>C. Polgár, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Coordinator</td>
<td>Chairman</td>
<td>Chairman</td>
</tr>
<tr>
<td>Tel.: +49 9131 8532935</td>
<td>Tel.: +49 9131 8532976</td>
<td>Tel.: +36 1 2248600</td>
</tr>
<tr>
<td>Fax: +49 9131 8539335</td>
<td>Fax: +49 9131 8535969</td>
<td>Fax: +36 1 2248620</td>
</tr>
</tbody>
</table>

The local investigator should supply the following information:

1. Name and location of investigator.
2. Patient's initials.
3. Patient's age.
4. Nature, date of onset of event, and it's duration (date and cause of death if applicable).
5. Pre-existing conditions/concomitant medication including dose regime, route, and duration.
6. Relationship of AE to disease treated in study, concurrent disease, investigational or other drug in the investigator's opinion (yes/no/possibly).
7. Treatment for Adverse Event (none/symptomatic/supportive/intensive).
8. Outcome (recovered/still under treatment/alive with sequelae/died).
9. Relevant test/laboratory documentation.

9.3 Serious or unexpected events

Unexpected side effects are diseases, signs of disease or symptoms, that appear or aggravate after the patient was recruited to the trial.
The grading of an unexpected side effect will be performed with the Common Terminology Criteria for Adverse Events v3.0 (CTCAE, Publish Date: June 10, 2003). If grading with these criteria is not possible, side effects will be classified with the following classification:

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

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

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

Serious unexpected events are:

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

As all radiotherapy given in both arms is performed only immediately after recruitment and randomization, any interim analysis of the primary outcome, i.e., the 5-year event rates, could not affect accrual and study treatments given any more. Furthermore, according to existing evidence from phase II studies, medium term results, e.g., a 2-year local recurrence rate, with APBI are expected to be sufficiently favorable, compared to WBRT. Hence, secondary outcomes in terms of treatment safety are the only reasonable criteria for study abort. These outcomes will be analyzed at yearly intervals, starting 1 year after study initiation and will lead to a study abort in the following case:

A significantly higher rate of SAE in the APBI group than in the WBRT group is found.

Furthermore, an interim analysis could be motivated by the wish to recommend a change of treatment guidelines (in favor of the experimental treatment, if equivalent) as early as possible for the benefit of patients outside the study context. Thus, a single interim analysis after completion of follow-up of 50% of the patients, will be performed to possibly be able to reject the null hypothesis of inferiority. At this time, a decision will be made based on the alpha-spending principle according to O’Brien and Fleming.

Analyses for data inspection in terms of quality control are not regarded as interim analyses and will thus not affect the power of the study, because no decisions will be based on these analyses, but only a monitoring of data quality will be performed.
11 Criteria for assessment of therapy efficacy

11.1 Criteria for evaluability

- All patients who meet eligibility criteria and have received at least one fraction will be evaluated for toxicity.
- All patients who meet eligibility criteria and have been registered to the study will be considered evaluable for survival, even if they have not received the study therapy. Time to survival will be calculated from date of first treatment (definitive surgery) to date of death.
- Time to treatment failure will be calculated from the date of first treatment (definitive surgery) to date of progressive disease or relapse.

11.2 Withdrawal of patients

11.2.1 Reasons for withdrawal

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

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

A further special reason for withdrawal of patients in the APBI group has been described in section 6.2 (tumor bed cannot identified in preimplant-CT when no tumor bed clip markers are not present). Such a withdrawal takes place directly after randomization and will be handled by replacement, i.e., the withdrawn patient will be taken off when computing block sizes in stratified randomization.

11.2.2 Assessment of withdrawals

All withdrawals and reasons therefore will be included in the final report. All withdrawals due to side-effects will be included in the overall assessment of the regimen's efficacy and acceptability.
Statistics

11.3 End point and hypothesis

The primary endpoint for analysis is the diagnosis of a local recurrence as a first event within a 5-year-observation period. Secondary endpoints include survival time (death from breast cancer sequelae) and distant disease-free interval, defined to be the time from randomization to first diagnosis of distant metastases, as well as strata-specific event rates. Furthermore, therapy safety, cosmetic results and quality of life measures are considered as secondary end points.

The scientific hypothesis to be assessed and statistically tested (in a confirmative manner) is “non-relevant non-inferiority” of the experimental treatment with regard to the primary endpoint. Compared to the 5-year recurrence rate under standard therapy, an absolute increase of up to 3% under the experimental therapy is regarded as non-relevant non-inferior, e.g., 7% vs. 4%. This figure (4%) can be regarded as the low ceiling of event rates reported in recent studies using lumpectomy and total breast irradiation. This conservative figure has been used for calculation of patient number (see 12.5).

11.4 Patient group for analysis, stratification

The overall primary outcome is “non inferiority” of the experimental treatment in terms of an absolute increase of not more than 3% local recurrences within 5 years, irrespective of prognostic factor profiles (used for stratification). However, as secondary outcomes, strata-specific event rates will be calculated, among other analyses.

In the framework of a non-relevant non-inferiority trial the statistical analysis must not implement the “intention-to-treat” principle, because here this introduces bias towards “no difference” which would exaggerate estimates of equivalence. A “per protocol” analysis has to be done. Valid cases (see ICH-E9) will be included in the final confirmatory analysis.

11.5 Statistical considerations

The one confirmatory analysis will be to test for “non-inferiority” of the experimental treatment as detailed in 12.1, i.e., one-sided, with a significance level set to 0.05. The calculation of the number of patients required to yield a power of 80%, under the above assumption concerning baseline event rate and acceptable increase of this associated with the experimental treatment is given in 11.5.

11.6 Therapy safety

Concerning safety aspects, all patients who received at least one fraction will be considered. Descriptive, exploratory analyses will be done separately for each arm and will include adverse events (coded according Appendix IV), quality of life endpoints as well as relevant laboratory results possibly related to treatments. These results will be represented in a tabulated format or graphically, as appropriate. Confidence intervals will be supplemented to any point estimate.

11.7 Calculation of patient number

The calculation of patient number is based on the following assumptions and parameters, respectively:

- Primary outcome variable: 5-year rate of local recurrences, with 4% as reference value in the WBRT group.
- “non-relevant” increase of up to 3% of local recurrence rate.
- Significance level: 0.05, one-sided test (“non-relevant non-inferiority’ only)
To yield a power of 80%, the sample size for the analysis must be $2 \times 530$ patients, i.e., 1060. To account for dropout (non-valid cases) estimated to be 10%, altogether 1170 patients should be recruited. A graphical display of the statistical power as a function of sample size under these assumption is shown below.

11.8 Steps of analysis

A chart according to the Consort-Statement (http://www.consort-statement.org) will be presented in any publication to illustrate the flow of patients. As a next step, descriptive exploratory analyses will address patient characteristics, including the distribution of factors relevant for prognosis. The one confirmatory statistical analysis will be a test of non-relevant non-inferiority of the experimental vs. standard treatment as outlined above. Further exploratory tests will be performed as appropriate regarding secondary clinical endpoints and safety and QoL aspects, as outlined above.

11.9 Interim analysis

See chapter 10.
12 Administration

12.1 Patient's consent

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

The ethical principles for medical research involving human subjects written down in the WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (see Appendix I) are practiced in this clinical trial.

12.2 Ethical committee permission

The first evaluation of the protocol will be carried out by the ethical committee of the University of Erlangen.

It will be the responsibility of each local investigator to submit the proposed final protocol as well as the patient consent form (see appendix VIII) to the appropriate Ethics Committee before the study can be started.

Written verification of the Ethics Committee approval should be provided to the study-coordinator (O. Ott, MD).

It is the responsibility of each investigator to inform his Ethics Committee of serious, unexpected AEs, which arise during the course of the investigator's study whether or not the AE occurred in their own trial. This allows the Ethics Committee to re-evaluate the ethical aspects of the trial.

Written informed consent will be obtained for this study from all patients or their legal guardians. The investigator or his/her staff will explain the nature of the study and the risks involved to each patient prior to his/her treatment. The patient will also be informed that he/she is free to withdraw from the study at any time. The investigator should use the elements of consent outlined in Appendix III as a guideline to write his/her own informed consent. Original, signed informed consent forms will be kept at the investigator center.

The principal investigator(s) should ensure that the study is conducted in accordance with the principles of the "Declaration of Helsinki", as adopted by the 29th World Medical Assembly, Helsinki, Finland, 1964, and revised recently. A complete transcript of the "Declaration of Helsinki" is in Appendix I.

12.3 Observance of guidance of Good Clinical Practice (GCP)

The trial will be practiced along the GCP-guidelines. The treatment must be carried out exactly along the study protocol. Exceptions are allowed in case of emergency situations, if the security and the sanity of the patient is threatened and can be avoided with an alternative treatment. Every protocol deviation immediately has to be communicated to the data control center in Erlangen.

12.4 Protocol additions

Additions or changes of the protocol can only be made by the study chairmen and must be presented as an amendment to the protocol to each local ethical committee.
12.5 Monitoring of investigation

The chairmen of the study have to control the exact performance and compliance of each study center concerning the study protocol. On-site visits at all participating centers will be arranged during the initial study period for this reason. Furthermore, the biometrical study center will draw a random sample of study patients from each participating center. The CRF’s of these patients will be cross-checked against the original patient files at the participating center during the study visits (inspection and verification of study documentation according to GCP). The results of these investigations have to be documented and will be presented on study center meetings.

12.6 Qualification of the study-physicians

The chairman of the study as well as all other participating study-physicians have to proof at least two years experience in performing clinical trials according to the GCP-guidelines.

12.7 Study chairmen

V. Strnad, C. Polgár,
University Hospital of Erlangen National Institute of Oncology
Department of Radiation Oncology Budapest
Erlangen

Mr. Strnad is a senior physician for radiation oncology and chief of Section brachytherapy of Dept. of Radiation Oncology at the University hospital at Erlangen, Germany.

Mr. Strnad is the study chairman of a still ongoing phase II multicenter trial that examines the role of sole brachytherapy of the tumor bed after breast conserving surgery. More than 200 patients were recruited (mainly in Erlangen). Publication of first interim results will happen in the first half of 2004, two publication are in press.

Mr. Polgár is deputy head of the Department of Radiotherapy and head of Brachytherapy Section at the National Institute of Oncology, Budapest, Hungary.

Mr. Polgár was the study chairman of a phase II trial that evaluated the feasibility, side-effects and local control of sole HDR brachytherapy of the tumour bed following BCS. Forty-five patients were enrolled, and results (including 5-year results) were published in international journals [39-41]. He is also the study chairman of a still ongoing phase III trial evaluating the equivalence of APBI to standard whole breast RT. More than 245 patients were recruited. The first interim results have been published recently [41].

12.8 Archiving

Each study physician is obliged by law to keep copies of protocols, the patient identification list, original documentation of test results, drug disposal logs, the collected patient data (including original and follow-up forms), declaration of patient’s consent, the permission of the ethical committee, correspondence, records of informed consent and other documents pertaining to the conduct of the study for a period of at least 15 years after study was closed. This time interval remains unchanged even if the study-physician gives all the documents and duties to a successor. Should the investigator wish to assign the study records to another party or move the records to another location, the chairman of the study must be notified. The investigator must maintain independent records of the patient’s data at all times.

The responsibilities of the investigator are summarized in Appendix XVII.
12.9 Keeping a study file

The study coordinator Mr. O. Ott will collect all study-related documents and correspondence in a special study file.

12.10 Confidentiality

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

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

12.11 Patient insurance

According to German law for this investigation a patient insurance is not necessary (see Appendix VII). Because of the multicentricity of the trial each local study physician is responsible to check in consensus with the local ethical committee if a patient insurance is necessary. If yes, the study physician has to organize insurance covering for his recruited patients.

12.12 Final report/ Publications

After completion of the study the clinical results will written by the study chairmen and published in a scientific journal, which is listed in the "Current Contents". The sequence of the co-authors is determined by the number of recruited patients. For each study center one co-author will be listed, if the number of recruited patients counts more than 25.

12.13 Sponsoring

Nucletron B.V. (NL) provided 20.000 € as initial sponsoring for insurance purposes. The sponsoring to run the study will be applied for from the German Cancer Aid.
13 References


## Appendices

15.1 Appendix I: Declaration of Helsinki, Version 10/2000
15.2 Appendix II: Declaration of participation on the study for study-physician
15.3 Appendix III: Patient Consent form and Declaration of consent
15.4 Appendix IV: Toxicity Criteria
15.5 Appendix V: Cosmesis analysis criteria, report form
15.6 Appendix VI: Performance Status Scale (ECOG, Karnofsky)
15.7 Appendix VII: Patient insurance
15.8 Appendix VIII: Vote of ethic committee
15.9 Appendix IX: Report form for Serious Adverse Events
15.10 Appendix X: Brachytherapy Quality Report Form
15.11 Appendix XI: Patient Eligibility Check Form
15.12 Appendix XII: Patient Registration and Randomization Form
15.13 Appendix XIII: Patient Report Form - after end of therapy follow-up form
15.14 Appendix XIV: Classification of Ductal Carcinoma in Situ
15.15 Appendix XV: Pathologic evaluation
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14.1 Appendix I: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical
   principles to provide guidance to physicians and other participants in medical research involving
   human subjects. Medical research involving human subjects includes research on identifiable
   human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's
   knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words,
   "The health of my patient will be my first consideration," and the International Code of Medical
   Ethics declares that, "A physician shall act only in the patient's interest when providing medical
   care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation
   involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human
   subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic,
   diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of
   disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must
   continuously be challenged through research for their effectiveness, efficiency, accessibility and
   quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic
   procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and
   protect their health and rights. Some research populations are vulnerable and need special
   protection. The particular needs of the economically and medically disadvantaged must be
   recognized. Special attention is also required for those who cannot give or refuse consent for
   themselves, for those who may be subject to giving consent under duress, for those who will not
   benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for
   research on human subjects in their own countries as well as applicable international
   requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or
   eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of
   the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific
   principles, be based on a thorough knowledge of the scientific literature, other relevant sources of
   information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the
   environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be
   clearly formulated in an experimental protocol. This protocol should be submitted for
consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
14.2 Appendix II: Declaration of participation on the study

Declaration of participation on the study

(Date)

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

PHASE III MULTICENTER-TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

of the

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

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

The [institution’s name] confirms its commitment to contribute to this trial and to recruit and randomize at least 20 patients per year. Patient data will documented properly, follow-up data assessed regularly as lined out in the protocol. Data will be forwarded to the study data center in Erlangen in time.

on behalf of [organization]:

Name, Title: ___________________________________

Function/Job: ___________________________________

Signature: ____________________________________

(Stamp)
14.3 Appendix III: Patient consent form and declaration of consent

Patient Consent Form
1st Edition, June 15

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

Dear Patient!

You suffer from breast cancer/ductal carcinoma in situ (DCIS) - a malignant or potential malignant disease. The conventional treatment consists of breast-conserving surgery (BCS) and an obligatory irradiation of the whole breast (WBI) following surgery.

Together with other European radiotherapy clinics our hospital carries out an investigation to find out, if in the subgroup of women with breast cancer/DCIS with a very low risk of local recurrence the whole breast irradiation can be removed by a partial breast irradiation (PBI), restricted to the former tumor area. This kind of irradiation is performed by the implantation of small plastic tubes in general/local anesthesia in the so called tumor bed – the former cancer carrying area. Then a little radiation source is able to reach the tissue at risk via those tubes. With this so called interstitial radiotherapy (iRT) or brachytherapy (iBT) the radiation dose can be applied in only one week, in contrast to a 6 week lasting whole breast irradiation.

On the basis of the available scientific knowledge we expect in your favorable situation that partial breast irradiation leads to sufficient tumor control in the ipsilateral breast. A 100-percent-security is not reachable, but we can expect a very low percentage of local recurrences. The advantages of partial breast irradiation are a short treatment duration and a lower rate of side effects at the skin surface.

This Phase III treatment trial compares the effectiveness of PBI with that of WBI. It is a "randomized" trial, then you will be assigned at random (by computer) into the two study groups. You will either receive PBI over a treatment time of one week (inpatient), or WBI over a treatment time of six weeks (outpatient). Your chances of being placed in one of the two treatment groups are fifty percent.

If you are randomized to the WBI irradiation group (standard treatment) you will receive around thirty daily radiation fractions, five days a week.

Side effects

Possible side effects of PBI are:
Acute effects: hematoma, radiodermatitis, edema, implant infection, bleeding, pain.
Late effects: fibrosis of the skin and breast tissue, edema, lipoid necrosis, teleangectasia, pain.
Possible side effects of WBI are:
Acute effects: radiodermatitis, dry and moist desquamation, edema, inflammation, bleeding, pain.
Late effects: fibrosis of the skin and breast tissue, edema, lipoid necrosis, teleangectasia, pain.

Confidentiality

Your patient and treatment data will be only used anonymously for scientific evaluation. Your personal data will be kept confidential and never be published or given to third persons without removing your name.
Participant’s Rights

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

Contact Information

More information is available from the responsible physicians at your local hospital.

Local responsible physician:

Name and Address of Hospital
Name of Physician
Telephone Number
PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP.

Declaration of Consent
1st Edition, June 15

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

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

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

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

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

Patient's name:  ..............................................................

ID-Number:  ..............................................................

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

....................................................................................................................... Place, date and signature of the responsible physician
### Toxicity criteria

**PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.**

**EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis associated with radiation</td>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema</td>
<td>Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site</td>
<td>Death</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Minimal symptoms, invasive intervention not indicated</td>
<td>Minimally invasive evacuation or aspiration indicated</td>
<td>Transfusion, interventional radiology, or operative intervention indicated</td>
<td>Life-threatening consequences; major urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Infection (wound)</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life-threatening, disabling</td>
<td>Death</td>
</tr>
<tr>
<td>Intra-operative injury (breast)</td>
<td>repair of injured organ/structure indicated</td>
<td>Partial resection of injured organ/structure indicated</td>
<td>Complete resection or reconstruction of injured organ/structure indicated</td>
<td>Life threatening consequences; disabling</td>
<td>-</td>
</tr>
<tr>
<td>Pain (breast)</td>
<td>Mild pain not interfering with function</td>
<td>Moderate pain; pain or analgesics interfering with function, but not interfering with ADL</td>
<td>Severe pain; pain or analgesics severely interfering with ADL</td>
<td>Disabling</td>
<td>-</td>
</tr>
</tbody>
</table>

**RTOG/EORTC Late Radiation Morbidity Scoring Schema**

<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>SKIN</th>
<th>0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td></td>
<td>Slight atrophy</td>
<td>Patch atrophy; Moderate teleangiectasia (1-4 cm²); Total hair loss.</td>
<td>Marked atrophy; Gross teleangiectasia (&gt; 4 cm²).</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td></td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic Slight field contracture &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue. Field contracture &gt;10% linear measurement.</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>
Cosmetic outcome criteria

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP.


<table>
<thead>
<tr>
<th>Excellent (1)</th>
<th>perfect symmetry, no visible distortion or skin changes, and no visible catheter entry/exit sequelae.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (2)</td>
<td>slight skin distortion, retraction or edema, any visible telangiectasia, any visible catheter entry/exit scar, or mild hyperpigmentation.</td>
</tr>
<tr>
<td>Fair (3)</td>
<td>moderate distortion of the nipple or breast symmetry, moderate hyperpigmentation, or prominent skin retraction, edema, or telangiectasia.</td>
</tr>
<tr>
<td>Poor (4)</td>
<td>marked distortion, edema, fibrosis, or severe hyperpigmentation.</td>
</tr>
</tbody>
</table>

---
## 14.6 Appendix VI: Performance status criteria

### Performance Status Criteria

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP.

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td><strong>Descriptions</strong></td>
</tr>
<tr>
<td>0</td>
<td>Normal activity.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Symptoms, but ambulatory.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
14.7 Appendix VII: Patient insurance

Patient insurance

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

According to German law for this investigation a patient insurance is not necessary. Because of the multicentricity of the trial each local study physician is responsible to check in consensus with the local ethical committee if a patient insurance is necessary. If yes, the local study physician has to organize insurance covering for his recruited patients.
Ich komme gerne zu Ihnen in die Klinik, um die gesamte Versicherungsproblematik mit Ihnen zu besprechen.

Freundliche Grüße
Im Auftrag

Dr. Albrecht Bender
Justiziar
Vote of ethic committee

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST.

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

14.8 Appendix VIII: Vote of ethic committee

Antrag an die Ethik-Kommission/Beauftragte-Nr. 3080
Phas III Multicenter Trial: Interstitial brachytherapy alone versus external beam radiation therapy after breast conserving surgery for low risk invasive carcinoma and low risk duct carcinoma in-situ (DCIS) of the female breast.

Anlagen:

Sehr geehrter Herr Kollege Strnad,


Der Antrag wurde nunmehr zusammenstimmend bewertet. Die Ethik-Kommission regte an, die Empfehlung ihres Schreibens vom 02.04.2004 vollständig umzusetzen und nicht nur im Protokoll, sondern auch in der schriftlichen Information für die Patient/innen auf die Ausschlusskriterien Schwangerschaft/Stillzeit sowie die Notwendigkeit einer medizinisch anerkannten Kontrazeption während der Studienteilnahme hinzuweisen.

Auch bei einer positiven Beurteilung des Vorhabens durch die Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg verbleibt die ethische und juristische Verantwortung für die Durchführung des Projekts unvermindert bei Ihnen und Ihren Mitarbeiter/innen.


Mit freundlichen kollegialen Grüßen

(Prof. Dr. med. P. Retz)
Stellv. Vorsitzender der Ethik-Kommission

Anlage: Teilnehmerliste
14.9 Appendix IX: CRF – serious adverse events

Report form for serious adverse events

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Treatment or Follow-up status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Date:</td>
</tr>
<tr>
<td>First name:</td>
<td>Follow-Up:</td>
</tr>
<tr>
<td>Pat.-ID:</td>
<td>months</td>
</tr>
<tr>
<td>Date of birth:</td>
<td>Free of disease?</td>
</tr>
<tr>
<td>Study Center:</td>
<td>Status:</td>
</tr>
<tr>
<td></td>
<td>Date of death:</td>
</tr>
<tr>
<td></td>
<td>Cause of death:</td>
</tr>
</tbody>
</table>

| Serious adverse event:        | Remarks:                      |
| Specify details:              |                               |

| Signature:                    |                               |
| Datum:                        |                               |

Date

Signature of Study Physician
Basic data and treatment documentation form

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

Study Chairmen: V. Strnad (Erlangen), C. Polgár (Budapest)
Study Coordinator: O. Ott (Erlangen)

See attached CD-Rom documentation.
14.11 Appendix XI: CRF – eligibility check

Eligibility Check Form

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

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Study Chairmen: V. Strnad (Erlangen), C. Polgár (Budapest)
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See attached CD-Rom documentation.
Follow-up form

PHASE III MULTICENTER TRIAL: INTERSTITIAL BRACHYTHERAPY ALONE VERSUS EXTERNAL BEAM RADIATION THERAPY AFTER BREAST CONSERVING SURGERY FOR LOW RISK INVASIVE CARCINOMA AND LOW RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

EUROPEAN BRACHYTHERAPY BREAST CANCER GEC-ESTRO WORKING GROUP

Study Chairmen: V. Strnad (Erlangen), C. Polgár (Budapest)
Study Coordinator: O. Ott (Erlangen)

See attached CD-Rom documentation.
14.13 Appendix XIII: Classification of DCIS

Classification of ductal carcinoma in situ (DCIS)

A. Low grade nuclei (NG 1)

Appearance: Monotonous (monomorphic).
Size: 1.5-2.0 normal RBC or duct epithelial cell nucleus dimensions.
Features: Usually exhibit diffuse, finely dispersed chromatin, only occasional nucleoli and mitotic figures. Usually associated with polarization of constituent cells.
Cave at: The presence of nuclei that are of similar size but are pleomorphic precludes a low grade classification.

B. High-grade nuclei (NG 3)

Appearance: Markedly pleomorphic.
Size: Nuclei usually >2.5 RBC or duct epithelial cell nuclear dimensions.
Features: Usually vesicular and exhibit irregular chromatin distribution and prominent, often multiple nucleoli. Mitosis may be conspicuous.

C. Intermediate grade nuclei (NG 2)

Nuclei that are neither NG 1 nor NG 3.

Necrosis Quantification

Comedonecrosis: Any central zone necrosis within a duct, usually exhibiting a linear pattern within ducts if sectioned longitudinally.

Punctate: Non-zonal type necrosis (foci of individual cells necrosis visible under 10X, 40X is not needed).
14.14 Appendix XIV: Pathological evaluation

Pathological evaluation

Specimen Handling

The breast specimen should be grossly inspected for any orientation designed by the surgeon. Its size (in three dimensions) and weight should be measured. The oriented specimen should be inked. Multiple colors may be used to identify various margins of resection. Sectioning of the specimen should be performed by using a procedure which allows determination of tumor size and evaluation of the distance of the suspected tumor areas to the surgical margins. For a description of two different techniques to submit tissue from surgical margins the pathologist is referred to the procedures as described by Rosen (1997) and Decker et al. (1997). A radiograph of the tissue slices should be obtained if microcalcifications have been described mammographically.

The size of the axillary specimen should be measured (in three dimensions) and the specimen should be weighted. All identifiable nodes should be processed for histology.

Tissue sampling for histological examination

For relatively small specimens (less than 5 cm in diameter) all of the tissue specimen should be submitted for evaluation.

For specimens of more than 5 cm in diameter:
- *when a tumor mass is macroscopically visible*: A cross section of the suspected tumor mass at its greatest diameter should be completely embedded.
- *when no tumor mass is macroscopically visible and the mammographically suspected area is marked*: At least 3 tissue slices of the marked suspected area should be processed.
- *when no tumor mass is macroscopically visible and the suspected area has not been marked*: Thorough sampling is necessary: At least two thirds of the breast tissue exclusive of adipose tissue should be processed.

Resection margins

For each surgical margin (e.g. superior, inferior, medial, lateral, superficial and deep) at least one tissue section should be embedded. If pure DCIS or invasive carcinoma with extensive DCIS-component is present two or more tissue sections for each surgical margin should be processed.

Lymph nodes

Small nodes are submitted entirely. Nodes over 0.5 cm should become sliced. At least three serial sections should be obtained from every tissue block. Besides H&E stained tissue sections immunohistochemistry with anti-cytokeratin mAbs should be performed to identify isolated tumor cells if necessary.

The pathology report should include

Macroscopy
- Dimension and consistency of the specimen.
- Appearance of cut sections: number and size in three dimensions of the suspected tumor masses if these are macroscopically visible.
- Distance of the suspected tumor area to the resection margins (mm).
- Amount of fibrosis of the total specimen.
- Cysts and calcifications if visible.
Histology of Invasive breast cancer
- Histological typing according to the classification proposals of the World Health Organization (WHO 2003).
- Grading based on the assessment of tubule/gland formation, nuclear pleomorphism and mitotic counts by using the score system as proposed by Elston and Ellis (1991).
- Tumor size.
- Multicentricity and/or multifocality as defined by Faverly et al. (1994).
- Number of lymph nodes which have been examined by histology.
- Number of lymph nodes with histologically detectable metastases.
- pTNM classification (UICC 2002).
- Lymphatic invasion (L0, L1).
- Venous invasion (V0, V1).
- Distance of the invasive cancer to the resection margins (mm).

Ductal carcinoma in situ (DCIS)
- Size
- Grading (DIN 1C or DIN 2) according to the minimal criteria as established from the working group (WHO 2003). The criteria (nuclear grade, necrosis and architectural pattern) should always be documented in the report. Nuclear grade should be performed according to the criteria established on the Consensus Conference on the classification of ductal carcinoma in situ (Consensus Conference Committee 1997).
- Distance of the DCIS to the resection margins (mm)
- Van Nuys Prognostic Index (modified version as proposed by Silverstein in St. Gallen 2001):

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>&lt; 15mm</td>
<td>16-40mm</td>
<td>&gt;41mm</td>
</tr>
<tr>
<td>Margin width</td>
<td>&gt; 10mm</td>
<td>1-9mm</td>
<td>&lt; 1mm</td>
</tr>
<tr>
<td>Pathological classification</td>
<td>Non-high grade without necrosis</td>
<td>Non-high grade with necrosis</td>
<td>high grade</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60 years</td>
<td>40-60 years</td>
<td>&lt; 40 years</td>
</tr>
</tbody>
</table>

References
14.15 Appendix XV: QLQ – C30

Quality of Life Questionnaire EORTC QLQ- C30

**EORTC QLQ-C30 (version 3)**

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

Please fill in your initials: 

Your birthdate (Day, Month, Year): 

Today’s date (Day, Month, Year): 

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

**During the past week:**

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page.
During the past week:

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

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

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

<table>
<thead>
<tr>
<th>Rating</th>
<th>Very poor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Rating</th>
<th>Very poor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

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## 14.16 Appendix XVI: QLQ – BR23

### Quality of Life Questionnaire EORTC QLQ- BR23

**EORTC QLQ-BR23**

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

### During the past week:

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

### During the past four weeks:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. To what extent were you sexually active? (with or without intercourse)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Answer this question only if you have been sexually active. To what extent was sex enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page.
<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Did you have any pain in your arm or shoulder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Did you have a swollen arm or hand?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Was it difficult to raise your arm or to move it sideways?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had any pain in the area of your affected breast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Was the area of your affected breast swollen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Was the area of your affected breast oversensitive?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Have you had skin problems on or in the area of your affected breast (e.g. itchy, dry, flaky)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
14.17 Appendix XVII: Responsibilities of the investigator

Responsibilities of the investigator

Each principal investigator should undertake the following:

1. Provide retrospective data on numbers of patients who would have satisfied the proposed entrance criteria during preceding time periods in order to assure an agreed acceptable recruitment rate for the trial.

2. Ensure that he/she has sufficient time to conduct and complete the trial, has adequate staff and appropriate facilities (including laboratories) available for the duration of the trial, and to ensure that other trials do not divert essential subjects or facilities away from the agreed trial.

3. Provide an up to date Curriculum Vitae and a signed Form and CV of sub-investigators assisting in the clinical setting.

4. Agree the protocol with the chairmen and confirm in writing that he/she has read, understands and will work according to the protocol and Good Clinical Practice, accepting the oversight of the monitor and control procedures, and agree with the sponsor on a publication policy.

5. Agree and sign the contract pertaining to the agreed protocol.

6. Submit the protocol to the appropriate Ethics Committee, and provide a copy of the committee's written approval to the study-coordinator.

7. Provide a list of Ethics Committee members and their titles and affiliations.

8. Not make any changes to the protocol without prior discussion and written agreement with study-coordinator or chairmen except when necessary to eliminate an apparent immediate hazard to trial patients. If such an urgent change is made the investigator will inform the study-coordinator by phone within 24 hours.

9. Inform the Ethics Committee of: a) protocol changes made after their approval which are likely to affect the safety of subjects; and b) Serious Unexpected Adverse Events occurring (from any source) during the trial, in order for the committee to re-evaluate the ethical aspects of the trial.

10. Maintain all trial records.

11. Obtain informed consent, written, from trial subjects prior to their inclusion in the trial in accordance with the procedures laid down in the protocol.

12. Take responsibility for study supplies and drug accountability documentation and ensure that investigational compounds are only dispensed to trial subjects, and in accordance with the protocol.

13. Manage code procedures and documentation with great care, and ensure that the treatment code is only broken in accordance with the protocol and that the monitor is consulted/informed forthwith when this is done (prior to code breaking whenever possible).

14. Negotiate with other departments e.g. Pharmacy, Nursing, Pathology, over costings for additional work involved in the study.

15. Acquire the normal ranges for laboratory tests and a copy of the Laboratory Quality Assurance and Control Standards.

16. Ensure that all members of the team involved in the study are informed of the protocol, and that each fully understands the part for which they are responsible.

17. Report all serious, unexpected adverse events immediately to the study-coordinator or chairmen by phone or fax, and when applicable to the Ethics Committee. Complete a e AE form when required and return it to the study-coordinator within five working days.

18. Make all data available to the monitor and/or relevant authority (where required) for verification/audit/inspection purposes.

19. Ensure that the confidentiality of all information about subjects and the information supplied by study coordinator or chairmen is respected and maintained by all persons involved.

20. Observe the following in relation to patient care:

   - subjects enrolled in a trial should, whenever appropriate, be provided with a card bearing information identifying that he/she is in a trial. Contact addresses/telephone numbers should be given in case medical care is needed at another medical centre.

   - in the patient's medical records it should be clearly marked that the subject is participating in a clinical trial.

   - the family doctor should, with the subject's consent, normally be informed.

   - retain all study documentation and records for at least 15 years after the completion or discontinuation of the trial. Patient files and other course data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years (EC GCP Guidelines).
14.18 Appendix XVIII: Definitions of brachytherapy indices

Definitions of volumetric indices for brachytherapy

Volumes for all implants

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vref</td>
<td>volume receiving the reference dose (Dref), or more</td>
</tr>
<tr>
<td>V1.5 x ref</td>
<td>volume receiving 1.5 x Dref, or more</td>
</tr>
<tr>
<td>V1.5 x MCD</td>
<td>volume receiving 1.5 x MCD, or more (ICRU 58, high dose volume)</td>
</tr>
</tbody>
</table>

Volumes for CT-based implants (with PTV definition)

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPTV</td>
<td>volume of the PTV</td>
</tr>
<tr>
<td>PTVref</td>
<td>volume of the PTV receiving the Dref, or more</td>
</tr>
<tr>
<td>V90</td>
<td>fraction of the PTV receiving 90 % of the Dref, or more (ICRU 58, low dose volume = V90 x VPTV)</td>
</tr>
<tr>
<td>V100</td>
<td>fraction of the PTV receiving 100 % of the Dref, or more</td>
</tr>
<tr>
<td>V150</td>
<td>fraction of the PTV receiving 150 % of the Dref, or more</td>
</tr>
</tbody>
</table>

Index for all implants

<table>
<thead>
<tr>
<th>Term</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNR</td>
<td>DNR (dose-nonuniformity ratio) = V1.5xref/Vref</td>
</tr>
</tbody>
</table>

Indices for CT-based implants (with PTV definition)

<table>
<thead>
<tr>
<th>Term</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>CI (coverage index): fraction of the PTV receiving the Dref, or more (CI = V100)</td>
</tr>
<tr>
<td></td>
<td>CI = PTVref/VPTV</td>
</tr>
<tr>
<td>DHI</td>
<td>DHI (relative dose homogeneity index): fraction of the PTV receiving dose between 100 % and 150 % of the Dref</td>
</tr>
<tr>
<td></td>
<td>DHI = V100-V150</td>
</tr>
<tr>
<td>COIN</td>
<td>COIN (conformal index): COIN = c1 x c2, where c1 = CI and c2 = PTVref/Vref</td>
</tr>
</tbody>
</table>