Hypofractionated Whole-Breast Irradiation preceded by Intra-Operative Radiotherapy with Electrons as anticipated Boost

HIOB

A new Option in Breast-Conserving Treatment for Operated Breast Cancer Stages I/II

Prospective one-armed multi-center-trial

ISIORT 01

ClinicalTrials.gov Identifier: NCT01343459

Principal Investigator: Univ. Prof. Dr. F. Sedlmayer
Co-Principal Investigator: Priv.-Doz. Dr. G. Fastner

Study Site Salzburg**: **Co-Investigators
Radio-Oncology:
Dr. M. Kopp
Dr. W.Iglseder
Dr. A. Vaszi
Priv.-Doz. Dr. F.Wolf, PhD
Priv.-Doz. Dr. F.Zehentmayr, MSc
Dr. C.Fussl
Dr. R.Konstantinovic
Dr. J.Kaiser
Dr. K. Dagn
Dr. S. Windischbauer

Special Gynegology:
Prof .Dr. R. Reitsamer
Dr. A. Sir

Principal-Investigator Italy: Dr. A. Ciabattoni,
Principal-Investigator Germany: Prof. Dr. W. Budach

Biostatistician:
PD Dr.W.Hitzl
Dr. P.Kopp

Study Coordinator: Protocol Office

Data management
M. Kaiser, MSc
Sponsor Intraop Medical, Krebshilfe Salzburg

INDEX

7.3.1 IOERT
7.3.2 WBRT
a. Time factors
b. Technical prerequisites
c. Radiation techniques / portal design
d. Dosage and Duration
e. Dose modification and treatment breaks
f. HIOB QA protocol
7.3.3 RT to regional lymphatics

4) Diagnostic measurements during treatment

5) Follow-up diagnostics

7.5.1 Mammography7.5.2 Screening for metastases
7.5.3 Evaluation of Toxicity
7.54. Cosmetic evaluation
7.5 5.Photographic documentation
7.5.6 Report of SAE/SUSAR

6) Final examination

6.1 Finally report at study-end /end of study participation

8.0 Study variables

1) Primary endpoint

2) Secondary endpoints

3) Tertiary endpoints

4) Definition of terms

9.0 Statistical Methods

10.0 Flow Chart

11.0 Summary

12.0 References

Appendix I: Registry

AppendixII: Inclusion/exclusion (Histology/IOERT protocol)

Appendix III: Week 1 WBRT/ Cosmesis-evaluation pre WBRT – Start

Appendix IV: End of WBRT/Evaluation of acute side effects along CTC-Scoring-System

Appendix V: Follow-up 4 weeks after WBRT-End/ Evaluation of acute side effects along CTC-Scoring-System

Appendix VI: Follow-up 4-5 months after WBRT-End/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Appendix VII: Follow-up 13 months after WBRT-End/ first mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Appendix VIII-XII: Follow-up 2-6 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Appendix XIII: Finally report at study-end / end of study participation

SAE/SUSAR - Report

Scoring-Systems

APPENDIX I – XIII: web-based electronic data acquisition, *see Flow chart*

1.0 Clinical Rationale:

Breast cancer is the most common cause of malignant disease in women worldwide. During one decade local therapeutic strategies have changed from radical surgery, i.e. mastectomy of the involved breast, to a multimodality treatment, consisting of breast conserving surgery, followed by whole breast irradiation.

1.1: Breast conserving treatment (BCT)

Many randomised prospective clinical trials proved the equality of therapeutic outcome comparing radical surgery with breast conserving treatment (NSABP-06 Fisher et al. NEJM 2002 (1); MILAN I Veronesi et al NEJM 2002(2)). Local control and overall survival are not comprised when breast conserving surgery is followed by whole breast irradiation (MILAN III Ann Oncol 2001 (3); NSABP B21 Fisher et al JCO 2002 (4), Analyses by van de Steene et al 2000 und 2004 Radioth.& Oncol (5,6), Uppsala-Orebro Studie Liljegren et al (7)) During WBRT, cumulative doses in the range between 50 – 54 Gy in single fractional doses of 1,8 – 2 Gy, 5 Fx/week, are commonly used to sterilize sublinical clonogenic tumorcells in order to decrease the probability of local-recurrence. WBRT is almost exclusively performed on linear accelerators with photons (energy 4 – 8 MV) on the basis of individual CT-based 3- D - plannings.

1.2 Boost irradiation to the tumor bed:

Pathological analyses revealed that the greatest subclinical tumor cell density (90%) is confined to an area of 4 cm surrounding the macroscopic tumor border (Holland et al Cancer 1985 (9)). Therefore, the tumor bed itself represents a region with the highest probability of local tumor recurrences in a dimension of about 65-80% of all events (Van Limbergen et al Radioth. & Oncology 1987 (10).

In respect to the fact that the probability of tumor control is a directly exponentional function of the applied dose, retrospective clinical trials showed a lower local recurrence rate if the dose is escalated by adding a `Boost`, defined as a limited irradiation to the former tumor bed. This was confirmed by prospective randomised trials: By the additional use of an electron boost of 10 – 16 Gy (5 to 8 x 2 Gy) or, alternatively, interstitial implants (HDR-brachytherapy) it is possible to halven the local recurrence rates in comparison to WBRT-only *(Romestaing et al Lyon trial JCO 1997(11); Bartelink et al EORTC 22881 NEJM 2001(12),*

Antonini et al Radioth.& Oncology 2007[13]). This effect could be observed in all age-classes whereas the absolut gain was greatest in the group below 45 years (*Antonini et al Radioth.& Oncology 2007[13]).*

1.3 Intraoperative Boost with electrons (IOERT):

Since 1998, an innovative intraoperative boost – strategy was implemented into clinical routine in Salzburg. In contrast to conventional boost techniques, which are usually applied after finishing WBRT; this booster dose is delivered intraoperatively to the tumor-bed prior to WBRT by the use of a high single dose (10 Gy) with electrons of a linac during the breast conserving operation. This approach has some evident advantages: direct visualisation excludes the danger of a geographic miss, exposes the area at highest risk to a highly effective single dose, while completely sparing the skin as one of the most important organs at risk for cosmetic late effects (teleangiectasia). Moreover, total treatment irradiation time is shortened in the dimension of 1 to 2 weeks. In addition, new primary reconstructive oncoplastic surgery became more popular in order to improve cosmetic results. This new surgical approach has a potential to mask the true position of the tumor bed, hence bearing an additional risk of misinterpretation of its location. IOERT is performed prior to oncoplastic intervention.

Until 7/2009, 1560 patients have been treated by boost IOERT in Salzburg as part of a multimodality treatment concept. All these patients are prospectively observed and their follow-up results on locoregional control repeatedly published. To date, every interims analysis showed lower local recurrence rates than standard treatment schedules *(Sedlmayer et al Strahlenth. und Onkologie Dez. 2007[14], Reitsamer et al Int. J. Cancer 2006 [15], Reitsamer et al Eu J Cancer 2002[16]).*

1.4 Local Recurrence Rates following IOERT plus WBRT with 50 Gy

In order to compare these results with other institutions, which share the same clinical expertise with IOERT during a comparable time-period, the International Society of Intraoperative Radio-Therapy (ISIORT) decided to initiate a pooled analysis between six European institutions in 2005, delegating data evaluation to the University Clinic of Radiooncology of Salzburg. The cumulative study cohort consists of 1031 analysable patients, who have been treated by a 10 Gy Boost plus 50-54 Gy WBRT in standard fractionation of 1,8-2 Gy. This cohort was repeatedly evaluated between 2006 and 2009. The most recent work-up dated July 2009 shows a cumulative local recurrence rate of 1% after a median

follow up of about 6 years (med. FU 71,53 mths, range 0,8 – 129 mths.), corresponding to an annual rate of 0,2 %, respectively.As a consequence of these outstanding clinical results, the intraoperative boost to the tumor bed with IOERT followed by WBRT is considered as best-practice standard in the radiooncological community in growing extent.

1.5. Optimal Dosage of WBRT: Standard- versus Hypofractionation (HypFx)

An internationally accepted standard fractionation schedule for WBRT consists of 25 sessions (5x/per week) with a single dose of 2 Gy, resulting in a cumulative dose of 50 Gy to the whole breast. Hypofractionation is defined as a fractionated radiotherapy with higher doses per fraction than 2 Gy, thus providing a shortened treatment time. The radiobiological considerations are elaborated in Chapter 2. Since the mid of the nineties, first clinical trials were conducted, revealing that hypofractionated irradiation schedules are able to provide an equal outcome in local control and cosmesis in comparison to conventional fractionation (Yamada et al IJROBP 1999 Abstr.(17), Olivotto et al Radioth.&Oncology 1996 (18), Shelley et al IJROBP 2000 (19), Clark et al J Natl.Can.Inst 1996 (20), Ash et al Clin.Oncol. 1995 Abstr. (21)). As a consequence, prospective randomised clinical trials were initiated by Canadian and British investigators in order to confirm these findings. In summary, 6483 patients were treated within these trials, 4159 of them in hypofractionated arms. The applied doses per fraction in the experimental arms ranged between 2,6 – 3,3 Gy, and resulted in cumulative total doses between 39 – 42,9 Gy. The comparing standard schedule was always represented by 2 Gy per fraction up to a total dose of 50 Gy (table 1).

Table 1. Randomised prospective clinical trials dealing with hypofractionated postoperative whole breast irradiation. BCT: Number of patients treated by breast conserving therapy within the respective trial.

Author/ Publication	Schedule	Dosage	Selection	n Pat (BCT*)
Whelan	**Standard**	**25 x 2 Gy**	**T1-2, N0 only; BCT only**	**612**
CONSORT	**HYPO**	**16 x 2,66 Gy**		**622**
JNCI 2002				
Owen	**Standard**	**25 x 2 Gy**	**T1-3; N-/(+ max 1 LK), BCT only**	**470**
RMH / GOC	**HYPO**	**13 x 3,3 Gy**		**466**
Lancet Oncol 2006	**HYPO**	**13 x 3 Gy**		**474**
Bentzen / Yarnold	**Standard**	**25 x 2 Gy**	**T1-3; N-/+, R0 (>1mm); BCT and MI**	**749 (631)**
START A	**HYPO**	**13 x 3,2 Gy**		**750 (641)**
Lancet Oncol 2008	**HYPO**	**13 x 3 Gy**		**737 (628)**
Bentzen / Yarnold	**Standard**	**25 x 2 Gy**	**T1-3; N-/+, R0 (>1mm); BCT and MI**	**1105 (1020)**
START B	**HYPO**	**15 x 2,66 Gy**		**1110 (1018)**
2008				

1.5.1 Local Recurrence Rates following Hypofractionation

In hypofractionated arms, local recurrence rates at 5 and 10 years were reported in the range of 2,2% - 3,6 % and 9,1 – 14,8 % , respectively.

In comparison to standard treatment, showing in-breast recurrence rates after 5 and 10 years of 3% - 3,6 % and 12,1% respectively, study cohorts in the experimental arms were superior, while maintaing equal long-term cosmetic results(*Whelan et al J Natl Canc. Inst.2002 (22), Owen et al Lancet Oncol 2006 (23), Yarnold et al Radioth. &Oncology 2005 (24), START A trial Bentzen et al Lancet Oncol 2008 (25), START B trial Bentzen et al Lancet 2008 (26), Whelan et al Semin. in Radiation Oncol. 2008 (27)). Recent long term data can confirm this data (T. Whelan et al NEJM 2010; 362:513-20(22a))*

The only hypofractionation schedule, tested during START A, which turned out to be inferior to standard arms was identified with 3 Gy per fraction to a cumulative dose of 39 Gy, with LR rates after 5 and 10 years of 5,2% and 14,8%, respectively.

1.5.2. Cosmesis following Hypofractionation:

The Canadian study published by Wheelan et al 2002 (CONSORT) detected no difference in cosmetic outcome after a hypofractionated schedule of 16 x 2,66 Gy. Cosmesis analyses reported by Yarnold et al (*Yarnold et al Radiotherapy & Oncology 2005 (28))* showed better results with a dose regimens of 3 Gy x 13 in comparison to 3,3 Gy per fraction (Fx 13) and the conventional standard fractionation of 2 Gy per fraction (Fx 25). The experimental hypofractionated arm with 3,3 Gy per fraction developed worst results.

1.6. Local recurrence rates after BCT: *best published evidence*

The success of a locoregional treatment in course of breast conserving therapy can be characterized by the annual local recurrence rate. Risk factors, which are frequently associated with the development of in breast-recurrences, are young patients' age, the presence of excessive intraductal (in-situ) components (EIC), multifocal invasive spread, high grade, negative receptor status, lymphovascular/- vascular invasion and positive axillary lymph node status. A recent meta-analysis of the EBCTG data described cumulative local recurrence rates following BCT after 5 years of 7%, resulting in annual rates of 1,5% *(Lancet 2005 Clarke M., Collins R, Darby S. et al (8)).* In case of R0- resection of an unicentric tumor without EIC, an annual local recurrence of 0,8% can be expected. The recent best published results amount to annual LRRs of 0,4 % (Bentzen et al START B trial (25)).

In the majority of publications, age was identified to be one of the strongest predictors for the developement of an In-breast Recurrence after BCT. Due to their different risk of local relapse, patients are frequently analyzed along three different age groups :

- ***a. > 50 a***
- **b. *41-50 a***
- **c. *35-40 a.***

1.7 **Local Recurrence Rates in BCT: Influence of patients' age**

Stratified for age as mentioned above, the following ranges have been published for in-breast recurrence rates in major trials:

- ***EBCTCG** Clark et al (8) **Metaanalysis***

7300 patients for BCT, no absolute numbers for age-related subgroups.

Radiotherapy : whole-breast-RT 50 Gy standard, Boost optional, no analysis of LRR regarding Boost.

< 50 a (no further subgroups):
5-a-LRR: with RT 11% vs. 33% without.
Annual LRR: 2,2% with RTX vs. 6,6% without

> 50 (-60) a:
5-a- LRR: With RT 7% vs. 23% without
Annual LRR: 1,4% with RT vs 4,6%.

> 60 (- 69) a:
5-a-LRR: 4% vs. 16%.
Annual LRR: 0,8% vs. 3,2%.

>70 a
5-a LRR: 3 % vs 13%
Annual LRR: 0,6% vs. 2,6%.

- ***EORTC trial 22881-10882** Antonini et al (13)*

Standard- Whole-Breast RT 50 Gy; randomised Boost 16 Gy vs no Boost :

5569 pts.; Boostgroup 2661
FUP: Median 77,4 months (range 0 – 147,6)
Boost: 8x2 Gy (16 Gy) external electrons or tangential photons; or Ir 192 ; 10Gy/24h
Tumor stages: T1-2 N0-1

Cumulative LRR (Boost and no Boost):

< 40 a: 5-a-LRR: 14,5 %; **annual 2,9%.**
41-50 a: 5-a-LRR: 7,24%; **annual 1,44%**
51-60 a: 5-a-LRR: 3,75%; **annual 0,75%**
60 a: 5-a-LRR: 3,22%; **annual 0,64%**

Assumed LR-Rates for the Boost-Group

Boost all Pts. **< 35 J**, **n=3%**, after 5 a: 6,4%; **annual: 1,28%**
< 40 J, n=8%, after 5 a 6,1%**; annual:: 1,22%**
< 50 J, n=33%, after 5 a: 5,1%; **annual: 1,02%**
< 60J, n= 67% after 5 a: 4,4%; **annual: 0,88%**
< 70J, n=100% after 5 a: 3,8%; **annual: 0,76%**

- ***EORTC trial 22881-10882*** *Bartelink et al (12)*

Earlier publication of the same cohorts, better analysis regarding age:

LRR Boostgroup:		**percentage of patients**
<= 40 a: after 5a:	10,2%; **annual: 2,04%**	< 35 a: 3,1%
41-50 a:	5,8%; **annual: 1,16%**	36-40 a: 5,2%
51-60 a:	3,4%; **annual: 0,68%**	41-50 a: 25,1%
>60 a:	2,5%; annual: 0,5%	51-60 a: 32,3%
		> 60 a: 34,2%

- ***START A*** *Bentzen et al (26)* ***randomised hypofractionated WBRT-regimen vs. Standard-RT****:*

2236 Patients;
FUP (of surviving pts.): Median 5, 1a (range: 4,4 – 6,0)
Standard Schedule: 25x2Gy (50 Gy)
Hypofract Schedule I:13 x 3,2 (41,6 Gy)
Hypofract Schedule II:13 x 3 Gy (39Gy)
Accrual into WBRT-groups: 50Gy: 749; 41,6 Gy: 750; 39 Gy: 737;
Boost: Randomisiered in subgroups Standard, I and II:5x2 Gy (10 Gy) ext. electrons
Tumor stages: pT1-3a pN0-1 M0

NO age-related LRR sub group analysis
NO boost-stratified LRR sub group analysis

Group I: 41,6 Gy: 5-a-LRR: 3,5%; **annual 0,7%**

Relative number of patients: 20-29 a: 0,5 %, 30-39 a: 5,3%; 40-49 a: 18,1%; 50-59a: 37,7 60-69 a: 25,6%; 70-79 a: 11,3%; > 80 a 1,3%;
I.e.: < 50 a: 23,9%, > 50 a: 76,1%

Group II: 39 Gy: 5-a-LRR: 5,2%; **annual 1,04%**
Relative number of patients : 20-29 a: 0,4 %, 30-39 a: 5,2%; 40-49 a: 17,5%; 50-59 a: 38,8 60-69 a: 26,3%; 70-79 a: 10,6%; > 80 a 1,2%;
I.e.: < 50J: 23,1%, > 50 J: 76,9%

Standard Group: 50 Gy: : 5-a-LRR: 3,6 %; **annual 0,72 %**

Relative number of patients: 20-29 a: 0,7 %, 30-39 a: 5,1%; 40-49 a: 15,5%; 50-59a: 37,4 60-69 a 28,7%; 70-79 a: 11,6%; > 80 a 1,1%;
I.e.: < 50J: 21,3%, > 50 J: 78,7%

Breast sizes: acc. START B

- ***START B** Bentzen et al (25) **randomised hypofract. WBRT vs. Standard- WBRT**:*

2215 patients;
FUP (of surviving pts.): Median 6,0 a (range: 5,0 – 6,2);
Standard Schedule: 25x2Gy (50 Gy)
Hypofract Schedule I: 15x 2,66 (40Gy)
Accrual into WBRT-groups: 50Gy: 1105; 40 Gy: 1110;
Boost: Randomised in both WBRT subgroups:5x2 Gy (10 Gy) ext. electrons
Tumor stages: pT1-3a pN0-1 M0
NO age-related LRR sub group analysis
NO boost-stratified LRR sub group analysis

Group 40 Gy: 5-a-LRR: 2,2%; **annual 0,4%**

Relative numbers of patients in age groups 20-29 a: 0 %, 30-39 a: 3,5%; 40-49 a: 15,3%; 50-59a 40,3% ; 60-69 a: 29,5%; 70-79 a: 10,7%; > 80 a 0,7%;
I.e.: < 50a: 18,8%, > 50 a: 81,2%

Group 50 Gy: 5-a-LRR: 3,3%; **annual 0,66%**
Relative numbers of patients in age groups 20-29 a: 0,6 %, 30-39 a: 5,6%; 40-49 a: 16,2%; 50-59 a: 38,6% ;60-69 a 27,5%; 70-79 a: 10,6%; > 80 a 0,8%;
I.e.: < 50J: 22,4%, > 50 J: 77,6%

Breast size: was not mentioned as exclusion criteria. Definition along sizes „small, medium, large“, no scoring system for allocation.

- ***Clark et al (20) randomised hypofractionated RT vs no RT:***

837 patients;
FUP: Median 7,6 a (max. > 11 a).
Accrual: No RTX: 421; hfRT: 416;
Hypofract. WBRT:16 x 2,5Gy (40 Gy)
Boost: 5x2,5 Gy (12,5 Gy) electrons
Tumor stages: pT1- 2 (<= 4 cm) pN0 M0

No age-related sub-group analysis, in COX regression-Analysis sign. predictors for LRR: age<50, Tumor size >2 cm, Nuclear Grading;

RT Group: In-Quadrant-LRR after med. 7,6 a: 6,3%; **annual 0,8%**
Any – Quadrant- LRR after med.7,6 Jahren: 11,3%; **annual 1,5%**

No-RT-Group: IQ-LRR: 18,8%; **annual 2,4%**
Any-Q-LRR 35,2%; **annual 4,6%**
Breast size: not mentioned

- ***Ivaldi et al (29) Phase II hypofractionated WBRT plus IOERT- Boost:***

837 patients;
FUP: Median 9 mths FUP
Age: All < 49a, median 42 a
WBRT 13 x 2,85 Gy (37 Gy) + intraop. E-Boost
Boost: 12 Gy IOERT
Tumor stages: cT1- 2 N0 M0
LR: none
Breast size: no exclusion criterion

- ***Whelan et al (22) randomised hypofractionated vs Standard WBRT:***

1234 Patients
FUP: Median 69 mths
Accrual 42,4 Gy: 622 pts; 50 Gy:612 pts
Standard: 25x2Gy (50Gy**)**
Hypofraktionated: 16 x 2,65 Gy (42,4 Gy)
Boost: None
Tumor stages: T1-2 N0

Age group LR-Analysis :

HF-Arm:			**Conventional. Arm:**	
25 % < 50 a: 5a- LRR: 3,6%	**annualLRR:**	**0,72%**	**annualLRR:**	**1,44%**
30% 50-60a:	2,9% annualLRR:	0,58%	annualLRR:	0,52%
29% 60-69a:	3,1% annualLRR:	0,62%	annualLRR:	0,2%
16%>- 70a:	1,0% annualLRR:	0,2%	annualLRR:	0,58%

Breast size: excluded " > 25 cm diameter"

- ***Owen et al (23) randomised hypofract Schedules vs. Standard WBRT:***

1410 pts.
FUP (of surviving pts.): Median 9,7 a (range: 7,8 – 11,8).
Accrual 50Gy: 470 pts; 42,9 Gy: 466 pts; 39 Gy: 474 pts;
Standard : 25x2Gy (50 Gy)
Hypofract. I:13x3,3 (42,9 Gy)
Hypofract II:13 x 3 Gy (39Gy)
Boost: Randomised within subgroups Standard, I and II: ext. electrons 7x2 Gy
Tumor stages: cT1-3 cN0-1 M0
LRR after 10 years:

Standard :	12,1 %;	**annual 1,21%**
Hypo I:	9,1 %;	**annual 0,9%**
Hypo II:	14,8%;	**annual 1,5%**

NO age- or boost-related LRR analysis

Breast size: no explicit exclusion criterion. Virtual size scale along „small, medium, large“: co-60 allowed for small/medium.

- ***Bollet et al** (13a) Observation Study**:***

209 Patients;
Age: Median 37 a (23 – 39 a); 32% (66 pts) <= 35 a; 65% (143) >35 a.
Standard-WBRT: median 54 Gy (45-63)
Boost: 53% of pts.; Median Dose 15 Gy (2-25 Gy), positive margins 20 Gy ; close margins, G3, neg. HR). 12 Gy
Chemotherapy: 30% of pts..
FUP: Med. 12 a (1-20).
Tumor stages: cT1-2 cN0-1 M0

LRR of patients < 40 a (med. FU 12 a):

In-Breast Recurrences 70 (33,5%) , i.e. annual LRR 2,8%
True IQ Lokal Recurrences 51 (24,4%); annual LRR 2%

- ***Truong et al** (13 b) Observation Study*

5688 pts.;
Age: Median 37 a (23 – 39 a); 32% (66 pts) <= 35 a; 65% (143) >35 a.
Therapie: BCT, no informations about RT-details.
FUP: Med. 8,6 a (0,25 – 16,5).
Tumor stages: T1/2 N0-3 M0

.**LRR after 10a-FU :**
all N0 vs.N+: 5,8% (N+) vs 5,1% (N0);
annual LRR: 0,6% (N+) vs. 0,5% (N0).
Stratified along age only N+
< 50 years: after 10 a FU LRR 7,8 % : annual 0,8%
≥ 50 years: after 10 a FU LRR 4,7% : annual 0,5 %

- ***E. Touboul et al** (13 c) **retrospective study :***

528 pts;
Age: Median 52,5 a (range:26 – 86)**:** <= 50: 45,5 %; <= 40: 12,5%, >50: 55%
RTX: WBRT with Co 60, 4 MV, 6 MV: Mean total dose 45 Gy (40-50 Gy)
Boost: Ir 192: 15,2 Gy, Elektronen: 14,8 Gy (5-20 Gy) mit 2,5 Gy/d mit 4 Fx./W.
FUP: Median 87,5 months (7,5 – 233).
Tumor stages: T1/2 N0-2 M0

Local Recurrence Rates
Total: 5 a: 6,8% , 10 a: 14% ; ca. ***annual: 1,4%***

Age stratified:

<= 40 a: 5 a: 25%+-5%; 10 a: 35% +- 6,7%; annual 4,25 %
> 40 a: 5 a: 4% +- 1%; 10 a: 10 %+- 2%; annual 0,9%
<= 52 a: 5 a: 10% +- 2 %; 10 a: 19% +- 2,9%; annual:1,9%
> 52 a: 5 a: 3% +- 1,1 %; 10 a: 8,7% +- 2,5%; annual 0,75%

- ***I. Gage et al** (13 d) **retrospective study***

1870 pts;
Age: Median 51a (range:25 – 88 a)
Age stratification: none
Therapy: BCT.
RTX: WBRT: Median total dose 46 Gy
Boost: Ir 192 , e-; x; ; median total dose to tumor bed 64,7 Gy (60-84 Gy)..
FUP: Median 116 months (3 – 175).
Tumor stages: Stage I-II

LRR:
Total:
5 a: 7,4% , 10 a 13.3% ; annual ***1,4%***
True LR/marginal miss:
*5 a: 5,7%, 10 a: 9,3%**; annual 1%***
Out Quadrant:
*5 a: 0.9%, 10 a: 2,8%; **annual 0,24%***
Skin/ not classified:
*5 a: 0,8%, 10 a: 1,2%; **annual: ca. 0,14%***

- ***P.H.M. Elkhuizen et al** (13 e) **retrospective study***

1360 pats;
Age: Median 52 a (range: 24 – 88)
Age stratification: <= 50: 46% %; > 50: 54 %
Therapy: BCT.
RTX: WBRT 50 Gy (25 x 2 Gy)
Boost: Electrons, Photons, Ir 192:. 14 – 16 Gy
FUP: Median 52 months (7,5 – 233).
Tumor stages: pT1/2 N0-1 M0
LRR:

Total:
5 a: 8% , 10 a: 12%; annual***: 1,4%***
Age stratification:
<= 45a: 5 a: 12%; 10 a 19%; **annual 2,15 %**
> 45 - 65 a: 5 a: 7% ; 10 a: 11 % **annual 1,25%**
> 65a: 5 a: 3%; 10 a: 4% ; **annual 0,5 %**

- ***Adri C. Voogd et al*** *(13 f)* ***randomised Study:***

1772 pats;
Randomised: 879 BCT; 893 ME
Age: Median 52 a (range:24 – 88)
Age stratification: <= 50: 46% %; > 50: 54 %
Therapy: BCT.
RTX: WBRT: 50 Gy (25 x 2 Gy)
Boost: e-: 10-25 Gy; Ir 192: 20 – 25 Gy
FUP: Median 9,8 a .
Tumor stages: Stage I,II

LRR for BCT-Cohort

Total
10 a: 10%; ca. ***annual. 1,0%***

Age stratification:

<= 35a:	10 a	35%;	**annual 3,5 %**
36 – 40a:	10 a	9% ;	**annual 0,9%**
41 – 50a:	10 a	9% ;	**annual 0,9 %**
51 – 60a:	10 a	11%;	**annual 1,1%**
> 60a:	10 a	7%;	**annual 0,7%**

- ***T.E. Smith et al*** *(13 g)* ***retrospective Study:***

1152 pats;
Age: Mean 56 Jahre +- 0,38
Age stratification: <=35: 11% ; 36-49: 38 %;>50: 51%
Therapy: BCT.
RTX: WBRT: 48 Gy (24 x 2 Gy)
Boost: electrons; median total dose to tumor bed: 64 Gy
FUP: Mean 14,2 a
Tumor stages: T 1-3 N0-N+

LRR:
Total
10 a: 11,8%; ***annual 1,2%***
15 years : true local recurrences (IQ) 6,8% (annual 0,5%), 15 years Out-Quadrant LR: 13,1% (annual0,9%).
Age stratification::

Out-Quadrant LR: Median age 56,2a
True LR (In-Quadrant): Median age 58,2 a

<40 a:

36% Out Quadrant LR, 25% true LR.

- ***A. de la Rochefordiere et al** (13 h)**retrospective Study***

1703 pats;
Age: Mean 44 a (range 23 – 55), premenopausal.
Age stratification Group I: <= 33: 100;Group II: 34 – 40: 356;Group III: 41 – 55: 1247;
Therapy: BCT: 1317 (77%); ME: 386 (23%);
BCT: 622 (36 %) OP + RT; 729 (43%): RT alone (Co-60).
RTX: Mean dose WBRT 58,8 Gy (50 –67,6);
Primary RT: in case of complete or partial response 548 pts received a tumor bed boost up to a mean dose of 76,6 Gy (range: 60 – 90 Gy) without OP.
In147 Pats with partial responde after 58 Gy a wide excision was performed
In 34 Pats with insufficient response to RT after 58 Gy a mastectomy was performed
Primary Mastektomie: 352 (21%), post-ME RT in 169 (48%) pats.
Boost: no specifcations to technique and boost doses.
FUP: Med. 82 mths. (range 4 – 132) .
Tumorstages: Clinical stage I – III (T0 – 1 – T4 N0 –N2).

LRR:

Analysed as relative risk in dependency of age

Total annual risk for LR: 0,96 %
This relative risk was 2,2 times higher (p < 0,02) for Group I (<= 33 a) compared to Group III (40 – 55 a) and 1,5 fold higher (p < 0,0001) in Group II (34 – 40 a) than in Group III (40-55 a), respectively.
For rising age, the risk for a local recurrence was reduced with every additional year.

SUMMARY:

In the vast majority of prospective as well as retrospective trials of the last two decades, annual local recurrence rates following BCT showed a clear dependency of patient age within the following boundaries (primary references):

AGE:	Reference	LR per anno	LR after 5 years
Age > 50:	Bartelink	0,7%	3,5%
	START B	0,4 %	2,0%
Age 41-50:	Bartelink	1,2%	6,0%
	Whelan	0,72%	3,6%
Age ≥ 35-40	Bartelink	2%	10%
	Whelan	0,72%	3,6%

New therapeutic regimen have to show at least iso-efficacy or superiority in comparison to these „best evidence“ reports, which were derived from trials which have been sufficiently powered in terms of patient numbers as well as follow-up periods.

However, in contrast to the high published number of BC patients at ages 40 to 70 years, there are limitations for younger age groups, where literature is much scarcer.

1.8. IOERT as anticipated Boost-strategy with consecutive hypofractionated WBRT:

So far, all clinical trials investigating the effect of hypofrationated schedules, did not take into account the benefit of an additional tumor bed boost. A boost dosage was either in general not given (Whelan et al (27)), only used in an optional way (START A), or was randomised (START B (26), Owen et al (23)), however without being separately analysed with regard to its effect on local control.

To date, the only one published clinical trial which investigated hypofrationated WBRT in combination with IOERT was initiated by *Ivaldi, Veronesi et al (IJROBP 2008 (29)).* In a phase II concept, the authors reported about this treatment strategy to be principally feasible. Treatment consisted of IOERT with 12 Gy followed by a hypofractionated WBRT of 13 x 2,85 Gy. After a median FUP of 12 months, acceptable cosmesis and low toxicity was observed. This new irradiation concept combines advantages of hypofractionated WBRT as well as boost – IOERT, which seems to be superior to other boost strategies in terms of local tumor control. Nevertheless, there is no study evidence proving the superiority of hypofractionation combined with IOERT in comparison to established treatment schedules.

HIOB is defined as hypofractionated WBRT (40,5 Gy in 2,7 Gy per fraction) preceded by an Intra-Operative Boost to the tumor bed (-11,1 Gy D max IOERT).

The HIOB study concept is supposed to test this hypothesis whether such a combined schedule is superior or iso-effective towards standard RT in terms of local control and cosmetic outcome.

Benchmarking will be performed against the best published results following `Golden Standard`RT, usually defined as conventionally fractionated WBRT with 50 Gy (25 x2) plus external tumor bed boost with 10-16 Gy electrons (5-8x2Gy).

2.0 Radiobiological Background:

2.1 α/β-Modell

The biological effect of irradiation, which is mediated by ionizing molecular interactions, is determined by its influence on the tumor as well as its toxicity in normal tissue, the latter usually being more sensitive to higher single doses. Both effects can be modulated by changes in fractionation - size, cumulative total dosage and overall treatment time.
The most popular model to describe biological effects of irradiation on tissue or its cellular system is the `linear – quadratic- model` which was established in the seventies. It specifies the correlation between dose per fraction (d), cumulative dose (D) and biological effective dose (BED) on the basis of the `tissue constant` so-called `alpha-beta value`.

$$BED = D \times (1 + d/ \alpha/\beta)$$

Regarding the `mechanistic model`, this alpha-beta value consists of two forms of cell-death. Alpha stands for the `multitarget single hit ` part of the cell-death, indicating not-reparable cell-damages. In contrast, Beta stands for the `multitarget multihit` part of the cell-death, leaving damages where repair is in principle possible. The ratio between both values characterizes the sensitivity of tissues on changes in fractionation. A low value (<4) means high and a high value (>8) means low sensitivity towards fraction size modifications. The biological background of these different kinds of tissue-effects can be explained by the different portion of cycling cells. The lower this part, the lower the alpha/beta value (Brenner 2003)[1].

2.2. Estimation of the value of higher single doses to the tumor

Usually low values around 2-3 are calculated for late reacting tissues, e.g. neuronal tissue, and high values around 10 for fast reacting tissues, which become noticeable as acute side effects during radiotherapy (e.g. skin). For tumors, also high alpha/beta values are estimated.
In 1989, Fowler postulated an alpha/beta ratio of 4 for breast cancer as its best approximation (Fowler JF: The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62:679-694). The radiosensitivity of breast cancer seems to be completely different

[1] Moreover the intrinsic cell specific capacity for repair mechanisms influences the α/β-value.

from squamous cell carcinoma, which usually are evaluated with an estimated ratio of 10. A lower ratio results in higher sensitivity towards higher doses per fraction. As a consequence, the higher the dose per fraction, the lower the necessary total dose for the equal effects on tumor cells.

Table 2 depicts a comparative calculation of the iso-effectiveness of different WBRT fractionation schedules as a function of increasing single doses and decreasing number of fractions in comparison to the standard treatment of 50 Gy (25 x 2 Gy). Their respective biological effects (BED, biological equivalent dose) are calculated depending on the estimated tissue-reactions, which are characterized by the alpha/beta ratio.

Tab. 2

Doses per fraction (Gy)	BED 10	BED 3	n Fx Isoeffect on Tumor (a/b 4) to 25 x 2 Gy	Calculated cumulative dosage	BED 4	2 Gy Äquivalent
2	**60**	**83,3**	**25**	**50**	**75**	**50**
2,3	59	85	21	48	75,6	50,4
2,4	59	86	20	48	76,8	51,2
2,5	56	82	18	45	73,1	48,8
2,6	55	82	17	44	72,6	48,4
2,7	55	82	16	43	72	48
2,8	54	81	15	42	72,4	47,6

The same mechanism can be observed in tissue with `late reaction` and hence, lower alpha/beta values. With increasing doses per fraction, a decreasing tolerance by an unchanged cumulative dose must be assumed.

When however decreasing the total dose, improvement in normal tissue tolerance becomes possible. The estimation of late side effects depends on dose per fraction and cumulative dose, kind of tissue and alpha/beta ratio. It is quantified by the calculation of the BED (biological equivalent dose, Tab.2).

Clinical trials dealing with hypofractionated WBRT estimated an alpha/beta value for the tumor effect in the wide range of 1,8 – 6,0 (Owen 2006: 1,8 und 6; Whelan 2002: 4; Yarnold 2005: 3,6), only two trials still calculated with a value of 10 (Ivaldi 2007, Freedman 2007).

2.3. Estimation of the value of higher single doses per fraction on normal tissue (cosmesis).

Following RT, cosmetic results are influenced by reactions of skin and as well as mixed connective tissue. Reactive patterns of the stratum basale of the epidermic layer cause acute-side effects like erythema and desquamation, vascular-induced damages of the endothelial-cell capillary surfaces cause teleangiectasia and contribute to fibrosis development as the main late –side effect. Cosmesis is mostly influenced by late-side effects which can be observed over the years after WBRT.

In order to estimate acute – side effects, experiments in animals revealed an alpha/beta ratio between 9 and 12,5 (Douglas 1976, Joiner 1983, Moulder 1976; Steel 2002). In clinical trials, values between 8,8 (erythema, Turesson 1989) and 11,2 (desquamation, Turesson 1989) have been described. Alpha/beta ratios triggering late-effects of skin are reported between 1,7 (fibrosis) and 2,8 (Teleangiectasia, Turesson 1989 and Bentzen 1991), generally derived from clinical trials.

The following linear approximation is accepted to calculate the toxicity of acute and late effects (Steel 2002) [1]:

$$EQD_{2,T} = EQ_{2,t} - (T - t) \times D_{prolif}$$

$EQD_{2,T}$	equivalent dose of standard treatment (50 Gy)
$EQ_{2,t}$	equivalent dose of the experimental treatment regarding the shortended overall treatment time (to calculate)
T	overall treatment time of standard treatment (35 d)
t	overall treatment time of the experimental arm (21 d)
D_{prolif}	dosage, which is necessary to compensate any increasing cell proliferation if the treatment time between two treament schedules will differ (for skin: 0,12)

[1] If two comparable treatment-schedules differ in more than one week treatment time, the calculation of BED regarding D_{prolif} is questionable. D_{prolif} is assumed with 0 if we focus on late reactions (Steel 2002).

In the recent literature, the following alpha/beta values stand for the estimation of acute and chronic normal tissue reaction including effects on the tumor.

Acute reaction of skin/subcutaneous tissue: 8 – 12

Late reaction of skin: 2,2

Late reaction of subcutaneous tissue (fibrosis): 3

Tumor-effect: 2-6

In our clinical trial we will use following values, which now are assumed in the majority of publications: Acute reaction 10, late reaction 3, effect on tumor 4.

With respect to all currently accepted radiobiological formulas, calculated values and isoeffect - models, we expect no increased acute or late toxicity with our new dose regimen(Tab.2).Taking into account the fact that due to acute toxicity, desquamation of the the skin will lead to worse clinical effects than erythema, we calculate with an Alpha/Beta value of 11,2 (Desquamation, Turesson 1989)[2] . Using this alpha/beta ratio we end up at a BED of 50 Gy in the investigated arm, compared to 61 Gy in a standard regimen.

Because of late reactions of the skin, like teleangiectasia and fibrosis, which are essential for cosmetic results after years of follow-up, we calculated with an estimated alpha/beta value of 2,25 (Turesson 1989 und Bentzen 1991) a BED of 89 for the experimental arm (40,5 Gy/15 Fx) compared to a BED of 94 for the standard treatment (50 gy/25 Fx). Even when most extreme values currently published are applicable, we don`t expect any increasing toxicity during or after WBRT with the HIOB-schedule (Tab.3).

Tab. 3. The maximal expected values of acute and chronic normal tissues' side effects after WBRT with standard treatment and HIOB fractionations, respectively.

	Single dose	**Fx**	BED α/β **11,2** ***Desquamation***	BED α/β **2,25** ***Fibrosis/Teleangiectasia***
Standard regimen	**2**	**25**	**61**	**94**
Experimental arm	**2,7**	**15**	**50**	**89**

Nonetheless, these calculations are only approximations, therefore, one has to take into consideration that during clinical trials adjustments might be necessary. However, it is

remarkable that all clinical observations concerning fractionation and cumulative dosage were consistent with radiobiological expectations, especially regarding tumor control and reactions in normal-tissue, both being a strong hint for the reliability of the linearquadratic model (Table 4).

Tab. 4. Comparison of calculated BED`s depending in different hypofractionation.

	ED	**Fx**	**d**	**D (Gy)**	**BED Tumor 4**	**BED Skin acute 11,2**	**BED Skin late 2,25**	**BED Fibrosis 3,1**
Standard	**2**	**25**	**35**	**50**	**75**	**61**	**94**	**83,3**
Whelan	2,66	16	22	42,56	71	52,7	93	79
START A	3	13	35	39	68	49,4	91	77
	3,3	13	35	42,9	78	55,5	106	88,5
START B	2,67	15	21	40,05	67	49,6	88	74,5

An intended total treatment time of three weeks (15 Fx) at single doses of 2,7 Gy results in a nominal cumulative dose of 40,5 Gy, corresponding to a BED of 68 for tumor response using an alpha/beta value of 4 (in comparison, a cumulative dose of 50 Gy in 2 Gy per fraction is equivalent to a BED of 75). Adding an IOERT-Boost of 10 Gy (90% reference isodose), a total BED of 103 in the very tumor bed is achieved. The standard schedule with 50 Gy/25Fx WBRT and following tumor bed-Boost of 5 x 2 Gy electrons result in a BED of 90 in the tumor bed (Table 5).

Tab. 5: Cumulative comparison of the radiobiological values between the standard schedule of postoperative radiotherapy and HIOB
Standard schedule: 50 Gy WBRT plus tumor bed boost of 10 Gy (2Gy single dose)
HIOB: IOERT 10 Gy plus 40,5 Gy WBRT (ED 2,7 Gy).

Single-dose	BED 10 (skin acute)	BED 3 (fibrosis)	Nominal calculated cumulative dose	BED 4 (antitumor effect)
Standard-XRT				
Standard-WBRT: 2 Gy	60	83,3	50	75
Boost 10 Gy (2 Gy ED)	12	16,7	10	15
Cumulative BEDs after Standard-RT*	72	100	60*	90
HIOB -Schedule				
IOERT:10 Gy	0**	43,3	10	35
HIOB- WBRT:2,7	51,4	77	40,5	68
Cumulative BEDs in HIOB-Trial*	51,4	120,3	50,5	103

* in a small volume, in the region of the tumorbed

**absence of skin-exposure during IOERT

Regarding skin-reactions, HIOB-schedule is superior to the standard treatment, due to complete skin protection during IOERT. As to fibrosis in the tumor bed, one realizes a higher BED in the HIOB protocol than in the standard arm. However, this effect is possibly relativized by the fact that the treated boost volumes are much smaller in the HIOB protocol compared with external Boost strategies. In many postoperative situations, the tumor bed will be distended in comparison with an intraoperatively treated situs, due to the development of hematoseromas (Nairz et al Strahlenther Onkol 06/2006). Dealing with the fact that normal-tissue tolerance depends not only on size of single fraction or cumulative dosage, but also on the treated volume, the effect of a higher BED in the tumorbed should be compensated by an smaller target volume for the boost.

3. STUDY AIM

Primary endpoint is the proof of superiority (or iso-effectiveness) **of the experimental treatment schedule in terms of local (in-breast) tumor control rates** by benchmarking with best published results after 'gold standard' RT.

The investigated HIOB schedule consists from a combination of an IOERT to the tumor bed with -11,1 Gy D max, followed by WBRT of 15 x 2,7 Gy in 3 weeks.

Standard RT is defined as WBRT with 50 Gy (25 x 2 Gy) plus external beam tumor bed boost 10 – 16 Gy.

Secondary endpoints: Assessment of

1) Acute and late toxicity (LENT-SOMA Score)

2) Cosmetic results (*5 Point Scoring System (29,30)*)

3) Disease free Survival

4) Overall Survival

4.0 STUDY DESIGN

Multicentric prospective one-armed superiority study;

5.0 STUDY POPULATION

5.1 Inclusion Criteria

a. Histological proven invasive breast carcinoma

b. Age: ≥ 35 years

c. Tumorstage T1-2

d. Nodal status: N0-1

e. Freedom of surgical margins: R0, that means no ink on tumors (invasive or in situ) (ago-online.de)

f. Also multifocal disease within the same quadrant with a maximum distance of < 5 cm

g. All grades G1-G3

h. Hormonal receptor and Her-2 status: no limitations

i. Informed and undersigned consent

5.2. Exclusion criteria

a. In-situ Carcinoma without invasive component

b. Age < 35

c. Tumorstage T3,4

d. Nodal status >N1

e. If irradiation of regional lymphatics is required

f. R1

g. Re-excision after IOERT

h. Immediately secondary mastectomy (not due to recurrence).

i. Multicentricity according to international definition: > 5 cm distance to each other

j. previous radiotherapy to the involved breast

k. Karnofsky Index < 70%

l. Mixed connective tissue diseases including rheumatoid Polyarthritis, Thrombangitis obliterans

m. Chronic pre-existent lung disease (Lungfibrosis, Pneumokoniosis, late-type Allergies like Farmer lung; Asthma bronchiale, severe Emphysema, COPD III *)

n. Cardiac Co-Morbidity: clinically positive coronary vessel disease, St.p. myocardial infarction, pacemakers and/or defibrillators)

o. Distant metastases

p. Breast size (PTV) > 2500 ml

q. Missing written consent

r. Observed pregnancy

s. Bilateral breast cancer

***5.3 premature abort of the study*:**

a) individual drop-out:

- withdrawal of consent
- death
- Protocol violation, that means:
    - > 1 week break during WBRT
    - WBRT delay over 56 days from date of OP (and > 9 months in case of adj. CTX)
    - revoked consent to be treated according to protocol schedule (i.e 15x2.7 Gy)

- refusing of any further follow-up
- Lost to follow-up for unknown reasons

-Postoperative complications causing a WBRT delay over 56 days from date of OP necessitating an interruption > one week or stop of WBRT

- observed pregnancy

b) Break of the study:

- New aspects regarding side effects (e.g. unexpectedly high rates of G3 acute and /or chronic reactions)
- Crossing of statistical stopping rules

5.4 Co-morbidities:

If not mentioned under exclusion criteria, all co-morbidities must be medically controlled.

5.5 Co-medication:

Any, if not mentioned under exclusion criteria.

6.0 REGISTRY

Study registry is carried out after proof or exclusion, respectively, of the criteria listed in point 5.0.Following written informed consent which has to be done before OP and IOERT registration . Screening failures have to marked on WEB-site with yes or no., a study code is provided consisting from the patient's inials, a sequential number and an institutional code.

Definitive study entry is only possible after:

- **final histopathologic exam and**
- **regular IOERT without subsequent re-excision.**

Registry and initial investigation form have to be completed and submitted to the study office electronically via study WEB-platform .Confirmation is provided by WEB.

Update of patient information including omission of study has to be documented electronically according to the flow sheet checkpoints. The study end (regular or premature

abort [point 5.3.a]) has to be documented respectively (Appendix XIII). If an additional patient insurance has to be contracted, is to be clarified and provided by the participating center.

7.0 STUDY PROCEDURES

7.1. Diagnostics:

Histology including proof of the lesion's invasive nature has to be provided by biopsy (preferably prior to OP). Mammography is obligate for documentation of tumor size and unicentricity, optionally, MRIs and Breast sonography may be necessary.

Prior to study inclusion, definitive histopathology must be awaited to confirm inclusion criteria.

The dimension of investigations for metastases-screening- (e.g chest X-ray, abdominal sonography, CTs of chest and/or abdomen, labanalysis-and bone scintigraphy etc.) is left to the discretion of the participating center -, However, freedom of metastases (M 0) has to be confirmed prior to operation.

In case of doubt, postmenopausal status has to be confirmed by hormonal lab analyses.

7.2.1 Operation:

Lumpectomy / segmentectomy / tumorectomy with sufficient safety margins (see 5.1.e).

Lymph node assessment must follow a sentinel node concept.

According to recently published data , an axillary dissection of Level I and II might be omitted in case of a sentinel micrometastases only (13i, 13 j) up to 2mm.Perioperative antibiotic prophylaxis is mandatory in order to avoid wound-infection. After the IOERT- maneuver, it should be strongly pursued to mark the tumorbed with radio-opaque clips.

7.2.2: Systematic histopathologic analysis:

Histopathologic work-up of excised breast tissues and (sentinel-) lymphnodes have to follow the guidelines of either the AGO (Gynecologic Oncology working gruop; ago-online.de) or equivalent national pathologic societies' guidelines of the respective participating center.

7.2.3. Chemotherapy and antihormonal treatment:

Neoadjuvant CT or antihormonal treatment: Allowed. There are no limitations either for special substances (chemotherapeutical, antihormonal and other molecular targeted therapies) or defined treatment schedules.

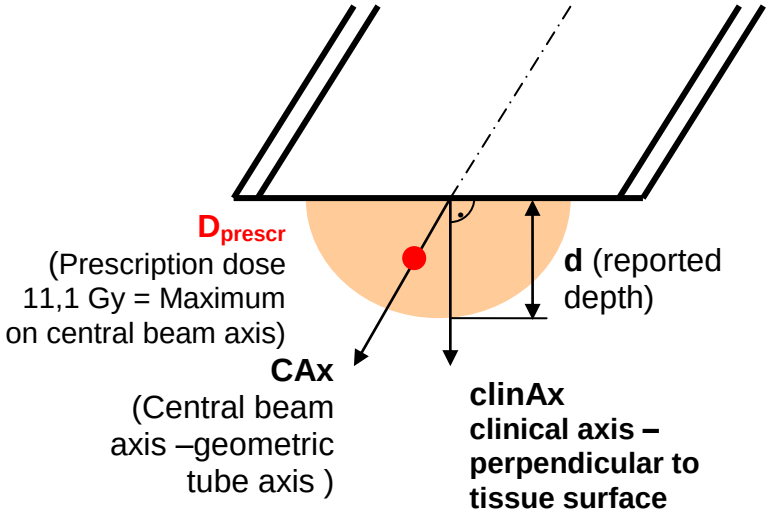
Adjuvant CT or antihormonal treatment: Patients have to be referred to WBRT within 9 months after IOERT. There are no limitations either for special substances (chemotherapeutical, antihormonal and other molecular targeted therapies) or defined treatment schedules.

7.3 Radiotherapy:

7.3.1. IOERT

- IOERT is performed on mobile or fixed linacs with variable electron energies in the minimum range of 4-12 MeV.

IOERT Dose (11.1 Gy) is specified at the point of maximum dose on the central axis depth dose curve. (Figure 1) The PTV should be encompassed by 90% of the prescribed dose (i.e. 10 Gy). A dose inhomogeneity of -10% within the target volume is acceptable. In the beam entrance region, small volumes of underdosage down to 80% are acceptable.
The depth of the 90%-isodose (10 Gy) has to be reported. In case of bevelled angles the depth is specified along the clinical axis (see diagram below “reported depth”).



PTV is defined as a 3D volume of at least 2 cm beyond the former macroscopic tumor edge (excluding skin, limit to anterior rib surface: 5-7 Gy)

- The choice of electron energy as well as of tube size has to account for minimum PTV requirements.
- Optionally, additional thoracic wall protection by lead shielding can be performed
- Tissue depth measurement has to be documented, preferably by intraoperative sonography or (mobile) CT. Mere probe measurements should be performed only occasionally.

7.3.2. WBRT

a. Time factors:

Must start not before day 36 postoperatively until day 56 p.o. in case of adjuvant hormonal treatment (or no further tumor specific medication). In case of adjuvant chemotherapy, a time – gap between IOERT and WBRT up to 9 months is allowed. After completion of the last chemotherapy cycle,WBRT has to be started within three weeks. If the patient is premenpausal, potential pregnancy has to be excluded with a typically pregnancy test, before radiotherapy will start.

b.Technical prerequisites:

3D-Planning must be performed on basis of individual CT-slices (real or virtual simulation) . The defined PTV should include the whole gland of breast and the adjacent chest-wall.

WBRT-treatment is delivered by photons –with a minimum energy of 4 MV on Linacs. If higher photon-energies are used, special care for sufficient dosage of superficial breast-tissue has to be taken

Weekly verification films of all portals are mandatory.

c. treatment technique :

WBRT is performed usually by tangential wedged fields. IMRT techniques are allowed.

d. dosage and duration of WBRT

- Single reference dose per fraction: 2,7 Gy (ICRU)
- Dose constraints : DVH calculation of lung and heart are mandatory
    - V20 (i.e. not more than 20% of ipsilateral lung volume) receives 20 Gy (or more) (28a)
    - Heart: < 50% of prescribed dose: not more than 5% of heart volume (29).
- Number of fractions: 15
- Number of fractions per week: 5
- Regular RT-breaks: Weekend/Feast days (not exceeding 7 days break, see above).

e.Dose modification for breaks during WBRT:

If < 7 days, none

f. HIOB QA protocol:

Participation in the HIOB trial requires control of dose delivery through a dosimetric quality assurance (QA) program. The Goal of the QA program is to assure the dose delivery to reference point within +/- 2% and the dose distribution according to the study protocol.

1) Electron and x-ray dosimetry is to be performed according to a protocol based on absorbed dose to water equivalent per IAEA TRS 398, TG 51, OeNORM S5234-3 or DIN 6800-2. Each participating institution will certify which calibration protocol is used, for both electron IOERT boost and the high energy x-ray EBRT treatments.

2) Monitor calibration should initially be verified by transfer dosimetry (such as TLD or external calibration of institutional dosimeters) in cooperation with an accredited dosimetry

laboratory, preferably a Primary Standard Dosimetry Lab (PSDL) or a Secondary Standard Dosimetry Lab (SSDL). Participants from the United States are encouraged to use the TLD service of the Radiological Physics Center (RPC).

3) If a mobile accelerator system is used to deliver the IOERT treatment, the following daily dosimetric QA should be performed:

a) Output measurement using an ion chamber in a solid phantom to assure precision of dose to the reference point within less than +/-3% at every treatment, per the recommendations of AAPM TG72.

Or for high dose-per-pulse mobile units only:

b) Real-time, in vivo detectors, such as Mosfet detectors, may be used to determine the dose actually delivered. If this technique is used, it is recommended that the treatment be split into two parts to allow adjustment of monitor units to be delivered if needed.

4) If a stationary accelerator system is used to deliver the IOERT treatment, the output calibration can be validated weekly using an ion chamber in a solid phantom.

5) For the EBRT treatment, the x-ray output of the energy used shall be validated weekly to assure precision of dose to the reference point within less than +/- 2 %.

6) If a mobile accelerator system is used to deliver the IOERT treatment, the energy constancy shall be checked at least monthly to assure that the depth dose beyond the 90% point is within 2 mm of the initial value. The method of determining the energy constancy shall be left to the discretion of each participating institution.

7) If a stationary accelerator is used to deliver the IOERT treatment, the energy constancy shall be checked quarterly to assure that the depth dose beyond the 90% point is within 2 mm of the initial value. The method of determining the energy constancy shall be left to the discretion of each participating institution.

8) All centers will submit their first WBI radiotherapy treatment plans and portal images for analysis by the quality assurance team to ensure compliance with the protocol in terms of prescription point, dose homogeneity, and dose to organs at risk. The QA team will randomly review subsequent WBI treatment plans and portal images of all centers which have to be submitted on request. Depending on data compatibility an anonymized complete set of DICOM-files or alternatively PDF-files of relevant slices including CT information, structures, and dose distribution plus DVHs are to be provided.

9) The protocol defines the IOERT boost arrangement well. Additionally the volume irradiated to 10 Gy (i.e. volume of D_{90}) has to be specified.

7.3.3. Regional Lymphatics:

Indication for lymphatic irradiation is left to the discretion of the participating center. If RT of regional lymphatics (e.g supra/infraclavicular fossa, parasternal lymphatic pathway) is performed, patients have to be excluded from the HIOB protocol.

7.4 Diagnostics during WBRT:

- weekly clinical examination of the breast
- Additional diagnostic procedures (e.g labanalysis, imaging) are left to the discretion of the participating center

7.-5 Follow-up diagnostics

Follow-up starts at week 4 post completion of WBRT (i.e. week 13-15 after OP) and is continued in month 4-5 and 13 post WBRT- (i.e. -half-yearly during the first year post treatment). Afterwards, yearly exams are sufficient (Appendix V - XII)

7.5.1.Mammography
should be performed first within 13 months after operation and yearly henceforward. Additional or replacing breast MRI and Sonography are allowed.

7.5.2 Screening for metastases: The dimension of investigations for metastases-screening (e.g chest X-ray, abdominal sonography, CTs of chest and/or abdomen, labanalysis and bone scintigraphy etc.) is optionally and left to the discretion of the participating center.

7.5.3 . Toxicity assessment:

- Assessment of acute toxicity of WBRT according to CTC-toxicity Scoring-systems:

  -at the end of RT

  -at time of first follow-up investigation (week 8-10)

- Assessment of late toxicity according to LENT-SOMA scoring-systems at every further follow-up (i.e. once a year) (addendum).

- Assessment of fat necrosis according to a scoring system established by Lovey K et al [34] with year 3 after completed WBRT (App IX) – annually thereafter (App X-XII) (addendum).

7.5.4.Cosmetic evaluation

Assessment of cosmetic outcome according to 5-point- Scoring System (vanLimbergen)

before WBRT not earlier than 7 months after WBRT at yearly follow-up (addendum) (photodocumentation in standardized positions)

7.5 5. Photographic documentation have to be assessed

-prior to OP

-at each cosmetic evaluation (see above)

7.5.6 Report of SAE(„Serious adverse events“) and **SUSAR** (“Suspected unexpected seroius adverse reaction“):

SAE`s and SUSAR`s have to be reported along the respective web form to the study-center (University Clinic Salzburg). This report will be retranstmitted to the local ethics-commission in Salzburg immediatly.

Neverthelss, such reporting has also be performed to the local PI`s and national ethics-commission of the participating center.

University Clinic Salzburg:Prof. Dr. F. Sedlmayer +43/(0)662/4482/3904;

Germany: Prof. Dr. Budach, University Clinic Düsseldorf: +49/(0)211/81/17991; FAXNr.: +49/(0)211/81/18051
Italy: Dr.A.Ciabattoni, San-Felippo Neri Hospital, Rome
USA:Julie Reiland MD, Avera Regional Medcal Center,Sioux Falls.

7.6: Final exam at study-end:

The study ends regular by year 6 of follow-up (Appendix XII) and premature if point 5.3 a) is applicable.Both situations have to be documented electronically along the web-form Appendix XIII.

STUDY VARIABLES

8.1 Primary end parameter:

Histological proof of an In-breast Recurrence

8.2 Secundary end parameter:

detection of regional and/or distant failure

8.3 Tertiary end parameter:

- Assessment of acute toxicity of WBRT according to CTC-toxicity Scoring-systems:

-at the end of RT (Appendix IV)
-at time of first follow-up investigation (week 4 after WBRT) (Appendix V)

- Assessment of late toxicity according to LENT-SOMA scoring-systems (addendum) at every further follow-up (i.e. once a year) (Appendix VI - XII)

- Assessment of fat necrosis according to a scoring system established by Lovey K et al [34] with year 3 after completed WBRT (App IX) – annually thereafter (App X-XII) (addendum).

- Assessment of cosmetic outcome according to 5-point- Scoring System (vanLimbergen) has to be documented before WBRT 4-5 (Appendix VI) and 13 months (Appendix VII) after WBRT and once a yearl thereafter (addendum) (Appendix VII – XII) Photodocumentation in standardized positions has to be provided.

8.4 Definition of terms:

Local recurrence:

- In-Quadrant recurrences („true“ local recurrences, developed in the former index quadrant)

- Out-Quadrant recurrences: clearly distant from former tumor (Documentation according Appendix III – XII)

b) Lab tests:

All lab tests prior to study inclusion (Appendix I), during radiotherapy (Appendix III, IV) and follow – up visitations afterwards, are left to the discretion of the participating center.

For study documentation, a proof of recurrence has to be provided by radiological means and preferably, by positive biopsy

9. STATISTICAL METHODS

9.1 Comparison of the 5-year local recurrence rates

To analyze data the ‚Sequential Probability Ratio Test' *(Statistik, Lehr- und Handbuch der angewandten Statistik`, 15. Auflage, J. Hartung, Oldenbourg Verlag (32)*) will be applied.

To test whether the therapy of HIOB is equal/superior to the gold standard, 5-year in-breast-recurrence rates will be analyzed in 3 different age groups (see 1.7), in terms of an upper limit (in case of exceeding there is inferiority) and a lower limit (in case of undershooting there is superiority/equality) (see summary of the studies of Bartelink, Start B and Whlean). The H0 hypothesis states that HIOB is superior/equal to standard therapy and the H1-hypothesis is the negation of H0 hypothesis. For computation of the average number of subjects in the study and average duration of the study, the assumed 5-year local recurrence rates in the three age groups are as follows:

9.2 The following assumptions are met:

1a) 35-40 years: The 5-year local recurrence rate is 3.2% (i.e. if assumed that local recurrence rates are linear: 5 x local recurrence of 0.64%). This assumption is motivated on the basis of retrospective data.

1b) 40-50 years: The 5-year local recurrence rate is 1.7% (i.e. if assumed that local recurrence rates are linear: 5 x local recurrence of 0.34%). This assumption is again motivated on the basis of retrospective data.

1c) above 50 years: The 5-year local recurrence rate is 1.0% (i.e. if assumed that local recurrence rates are linear: 5 x local recurrence of 0.2%). This assumption is again motivated on the basis of retrospective data.

2) The age distribution consists of 6.3% subjects at the age of 35-40 years, 19.3% at the age of 41-50 year and 74.3% at the age above 50 years.

3) Scenario A: In summary, 200 subjects can be recruited yearly. Scenario B: 50 subjects aged 35-40 years can be recruited yearly, 100 subjects aged 40-50 years can be recruited yearly and 250 subjects with an age over 50 years can be recruited yearly.

9.3 Overview of the hypotheses in three age groups:

1. Subjects at the age of ***35 - 40 years:***

If one uses the above upper and lower limits (see summary of the studies of Bartelink, Start B and Whlean), the upper and lower limits for the hypotheses of the 5-year local recurrence rate p_5 are:

H0: p_5 <= 3.6% (= 5 x 0.72% (Whelan))
H1: p_5 > 3.6%

To test this hypothesis, the expected sample size is n = 62 subjects. The power of this hypothesis test is 90% in case that p_5 = 10% (= 5 x 2% (Bartelink)) or more.

2. Subjects at the age of ***41-50 years:***

In this age group, the hypothesis is:

H0: p_5 <= 3.6% (= 5 x 0.72% (Whelan))
H1: p_5 > 3.6%

For testing this hypothesis the expected sample size is n = 139 subjects. The power of this test is again 90% in case that p_5 = 6% (= 5 x 1.2% (Bartelink) or more.

3.Subjects older than ***50 years:***

The corresponding hypothesis is:

H0: p_5 <= 2% (= 5 x 0.4% (START B))
H1: p_5 > 2%

The expected sample size is n = 232 subjects and the power of the test is again 90%, if p_5 = 3.5% (= 5 x 0.7% (Bartelink) or more.

The type I error is 5% and the type II error is 10%.

The sample size is not fixed in advance, each subject is followed up to the 5-year follow-up exam and the information whether a local recurrence is occurred is used to decide between the H0 and H1 hypothesis. Subjects which cannot be followed-up to the 5-year exam due to various reasons will be excluded from the analysis. Hence, the observed 5-year local recurrence rate is the ratio of those subjects with a local recurrence within 5 years and all those subjects who were examined at the 5 year follow-up. Subjects with a local recurrence within 5-years who dropped out of the study for any reasons are still counted for estimating and testing the 5-year local recurrence rates.

Average duration of the study:

9.4.1 Scenario A: Recruitment of 200 subjects per year.

a) If the above assumptions are considered and the corresponding hypotheses are used, on average 12.6 subjects can be recruited in the age group of 35-40 years per year. This means that after 4.9 years all 62 subjects are in the study. If one adds up the 5-year follow-up, the average study duration is 9.9 years.

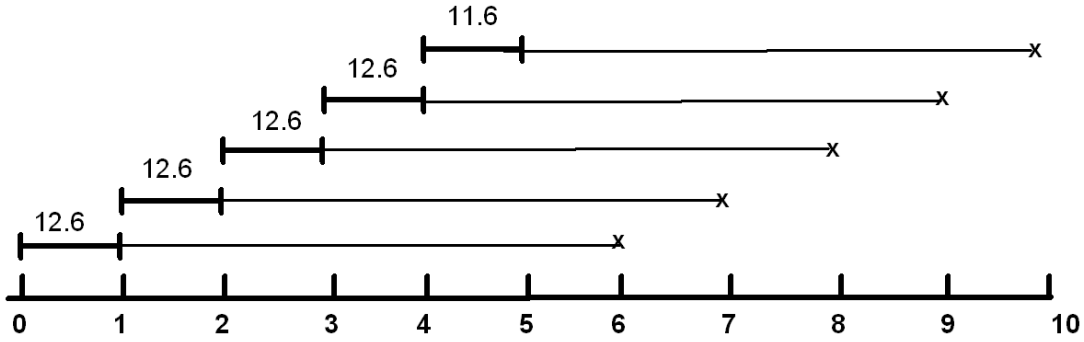
b) In the age group of 41-50 years on average 39 subjects will be recruited, i.e. it lasts 3.6 years until the 139 subjects are in the study. Again, adding up 5 years, the average study duration is 8.6 years.

c) In the age group of 50+ years, on average 149 subjects will be recruited, i.e. 1.42 years until 232 are in the study. The average study duration is 6.42 years.

The following graphs illustrate the average recruiting process and give an overview about the average study duration of the recruiting process for szenario A (200 subjects/year):

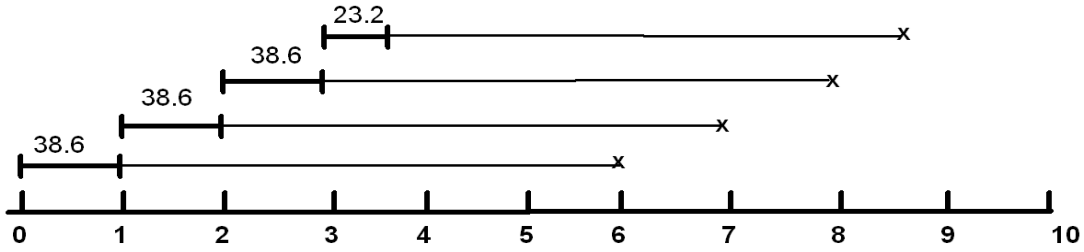
Subjects at the age of 35-40 years: estimations on average

At time 0, the first subject undergoes surgery. At the end of the first year, on average 12.6 subjects are recruited, at the end of the 5th year, in summary 63 subjects are recruited. The last subject receives its 5-year follow-up exam at 9.9 years.



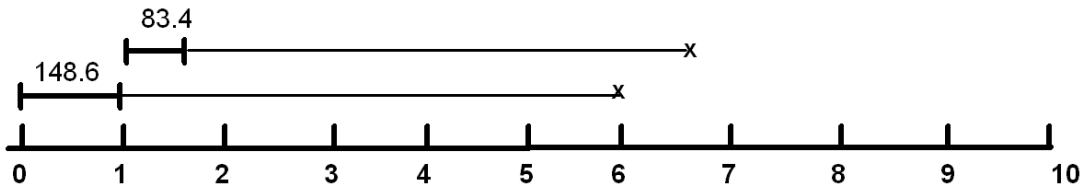
Subjects at the age of 41-50 years: estimation on average

The first subject undergoes surgery at time 0.
At the end of the first year, 38.6 subjects will be recruited on average. At 3.6 years in summary 139 subjects will be recruited.
Der last subject receives its 5 year follow-up exam at 8.6 years.



Subjects at the age of 50 years or above: estimation on average

At time 0 the first subject undergoes surgery. At the end of the first year 149 subjects will be recruited, at 1.42 Jahre 232 subjects will be recruited. The last subject receives its 5-year follow-up exam at 6.42 years.



9.4.2 Scenario B: recruitment of 400 subjects per year:

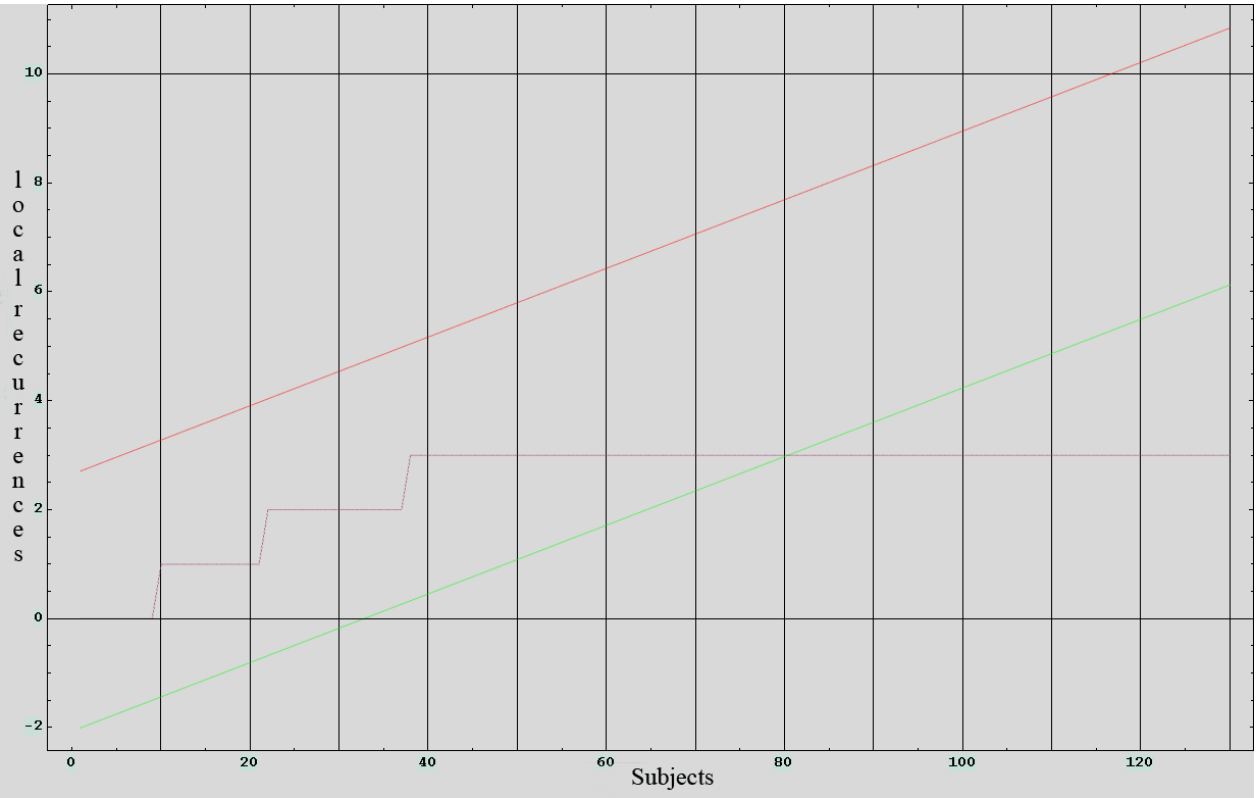
We assume to recruit 50 subjects/year in the 35-40 year age group, 100 subjects/year in the 40-50 year age group and 250 subjects/year in the age group with subjects older than 50 years.

The average duration of the study is 6.24 years for subjects at the age 35-40 years, for subjects at the age 40-50 years it is 6.4 years and 5.9 years for subjects older than 50 years.

9.5 Decision rules for the sequential probability ratio test:

In case of an occurrence of a local recurrence, the line is drawn one unit up and one unit to the right, otherwise it is drawn one unit to the right. For the first time, if the upper line is crossed by the stepped line, then a decision for H1 is made, if the stepped line crosses the lower line hypothesis H0 is accepted.

Here is an illustration for subjects at the age of 35-40 years:



In this case, the stepped line crosses the lower line when 80 subjects are examined at the 5 year follow-up exam. The hypothesis H0 is to be accepted.

9.6 Estimation of the yearly local recurrence rates

The yearly local recurrence rates will be estimated based on the Kaplan-Meier analysis together with 95% confidence intervals.

9.7 Premature stop of trial

To estimate the progress of the study within the first 5-years of follow-up, the 1-year recurrence rates are evaluated by a second SPR test. If too many 1-year relapses occur within a short period of time, the study has to be stopped. In order to quantify this statement, three hypotheses for the 1-year recurrence rates in the respective age groups are set up:

age group 35-40: H0: p1 <= 0.72% vs H1: p1 > 0.72% with p2 = 4,0%
age group 41-50: H0: p1 <= 0.72% vs H1: p1 > 0.72% with p2 = 2,4%

age group 51+: H0: p1 <= 0.4% vs H1: p1 > 0.4% with p2 = 1,4%
the trial has to be stopped (H1 has to be accepted) if …

age 35-40:
... up to the 18th patient or earlier 2 or more recurrences occur
... up to the 70th patient or earlier 3 or more recurrences occur
... up to the 122nd patient or earlier 4 or more recurrences occur
... up to the 174th patient or earlier 5 or more recurrences occur
... up to the 226th patient or earlier 6 or more recurrences occur
... up to the 278th patient or earlier 7 or more recurrences occur

age 41-50:
... up to the 45th patient or earlier 3 or more recurrences occur
... up to the 116th patient or earlier 4 or more recurrences occur
... up to the 188th patient or earlier 5 or more recurrences occur
... up to the 259th patient or earlier 6 or more recurrences occur
... up to the 331st patient or earlier 7 or more recurrences occur
... up to the 403rd patient or earlier 8 or more recurrences occur

age 51+:
... up to the 89th patient or earlier 3 or more recurrences occur
... up to the 214th patient or earlier 4 or more recurrences occur
... up to the 339th patient or earlier 5 or more recurrences occur
... up to the 464th patient or earlier 6 or more recurrences occur
... up to the 589th patient or earlier 7 or more recurrences occur

FLOW CHART:

	APP I		APP II	APP III		APP IV	APP V	APP VI	APP VII	APP VIII – XII
Week	**0-2 präop**	**OP/ IOERT**	**Up to wk 1- -pre-WBRT**	**WBRT *wk 1* (start wk 6-8 postop)**	**WBRT *wk 2***	**WBRT *wk 3***	**4 wk *post WBRT***	**4-5 Months (post WBRT)**	**13 Month (post WBRT**	**Year 2-6 once a Year (post WBRT)**
Written consent	x									
Anamnesis	x									
Screening for Study	x									
In-/exclusion			x							
Biopsy	x									
Breast Sonography *									x	X
Mammography **									x	X
Staging-imaging*	x								x	x
Lab analysis*	x			x		x	x	x	x	X
Operation		x								
Radiotherapy		10 Gy		2,7Gy x5	2,7Gyx5	2,7Gyx5				
Clinical investigation	x			x	x	x	x	x	x	X
Photographic documentation	x			x Prior to WBRT			x	x	x	x
Toxicity assessment						CTC (end of WBRT)	CTC	LENT-SOMA	LENT-SOMA	LENT-SOMA
Cosmetic Scoring				X Prior to WBRT				x	x	x
Fat necrosis										App IX-XII x
Surgical technique			x							

* optional investigations; ** to replace by ultrasound and or MRT if mammography is not possible

11.0 SUMMARY:

Title:

HIOB - Hypofractionated Whole-Breast Irradiation preceded by
Intra-**O**perative Radiotherapy with Electrons as anticipated **B**oost
ISIORT- 01

HIOB is defined as hypofractionated WBRT (40,5 Gy in 2,7 Gy per fraction) preceded by an Intra-Operative Boost to the tumor bed (90 % reference dose of 10 Gy, 11,1 Gy Dmax IOERT).

Primary endpoint is the proof of superiority of a new treatment regimen.

The HIOB study concept is supposed to test the hypothesis whether such a combined schedule is superior (or iso-effective) towards "standard" RT in terms of local control and cosmetic outcome.

In the vast majority of all publications, annual and 5 year in-breast recurrence rates following BCT showed a clear dependency on **patient age** within the following boundaries (primary references):

AGE:	Reference	LR per anno	LR after 5 years
Age > 50:	**Bartelink**	**0,7%**	**3,5%**
	START B	**0,4 %**	**2,0%**
Age 41-50:	**Bartelink**	**1,2%**	**6,0%**
	Whelan	**0,72%**	**3,6%**
Age ≥ 35-40	**Bartelink**	**2%**	**10%**
	Whelan	**0,72%**	**3,6%**

Along **these three different age groups,** benchmarking will be performed against the best published results following `Golden Standard`RT, usually defined as conventionally fractionated WBRT with 50 Gy (25 x2) plus external tumor bed boost with 10-16 Gy electrons (5-8x2Gy).

Superiority is defined as going below the lower limit of the estimated 5 year local recurrence rate within the respective age group

Inferiority is defined as crossing the respective upper limit.

Secondary endpoint:
Disease free survival

Tertiary endpoint: toxicity assessment (acute and late) including long term cosmetic evaluation

Study design and statistics:

- Prospective multi-center single-armed
- Sequential probability ratio test (SPRT)
- Separate analysis within three different age groups

Estimated Accrual time: strongly dependent on recruitement per year within the respective age group. Due to the statistical estimation of Szenario A and B the study will close after max. Time-period of 10 years in case of A or 6,4 years in case of B..

Principal investigators and study coordinators:

UC of Radiotherapy and Radio-Oncology
UC of Special Gynecology and Breast Cancer Center
Landeskrankenhaus Salzburg, Paracelsus University Clinics

Study population:
See Points5.1 und5.2 Inclusion/Exclusion criteria

Operation:

- Lumpectomy / segmentectomy / tumorectomy with sufficient safety margins (see above). Lymph node assessment must follow a sentinel node concept.
- Perioperative antibiotic prophylaxis is mandatory.
  After IORT, it should be strongly pursued to mark the tumorbed with radio-opaque clips

Chemotherapy and antihormonal treatment:

neoadjuvant: allowed
adjuvant: allowed.

There are no limitations either for special substances (chemotherapeutic, antihormonal and other molecular targeted therapies) or defined treatment schedules in neoadjvant and/or adjuvant sequence.

Radiotherapy:

IOERT

- IOERT is performed on mobile or fixed linacs
- Reference dose: 11 Gy specified as maximum dose, with a minimum target volume dose of 90% encompassing the PTV (i.e. 10 Gy).

WBRT

- must start within day 36- 56 postoperatively (week 6 – 8 p.o.) in case of adjuvant hormonal treatment (or no further tumor specific medication)
- In case of adjuvant chemotherapy, a time – gap between IOERT and WBRT up to 9 months is allowed (WBRT start within three weeks after the last chemotherapy cycle).
- Single reference dose per fraction: 2,7 Gy (ICRU)
- Number of fractions: 15, Number of fractions per week: 5
- Total WBRT dose: 40,5 Gy

RT of regional lymphatics: exclusion criterion

Diagnostics of Local recurrence:

- yearly mammographies,
- optional breast sonography, MRI
- LR has to be histologically confirmed

Follow-up screening for detection of metastases - investigations (e.g chest X-ray, abdominal sonography, CTs of chest and/or abdomen, labanalysis) are left to the discretion of the participating center.

Assessment of acute toxicity of WBRT according to CTC-toxicity Scoring-systems:

Assessment of late toxicity according to LENT-SOMA scoring-systems

Assessment of fat necrosis according to a scoring system established by Lovey K et al [34] with year 3 after completed WBRT (App IX) – annually thereafter (App X-XII) (addendum).

Assessment of cosmetic outcome according to 5-point- Scoring System (vanLimbergen) starting before WBRT, including photodocumentation in standardized positions

REFERENCES

1. B.Fisher, S.Anderson, J.Bryant, R.G. Margolese, M. Deutsch, E.R. Fisher, J-H Jeong and N.WolmarkTwenty year follow up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breastcancer NEJM Oct. 17, 2002: 347(16):1233-41

2. U. Veronesi, N. Cascinelli, L. Mariani, M. Greco, R. Saccozzi, A. Luini, M. Aguilar and E. Marubini. Twenty year follow up of a randomized study comparing breast-conserving surgery with radicalmastectomy for early breastcancer; NEJM Oct. 17, 2002:347(16):1227-1232

3. Veronesi U, Marubini E., Mariani L., Galimberti V., Veronesi P., Salvadori B., Zucali R.; Radiotherapy after breast conserving therapy in small breast carcinoma: Long term results of a randomized trial. Ann Oncol 2001, July; 12(7):997 - 1003

4. Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, Margolese RG, Nesbitt L, Paik S, Pisansky TM, Wolmark N,;Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less; , JCO Oct. 15 2002: 20(20): 4141-9

5. Van de Steene J, Soete G, Storme G Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link.Radiotheray and Oncology June 2000; Vol.55(3):263-72

6. Van de Steene J, Vinh-Hung V, Cutuli B, Storme G. Adjuvant radiotherapy for breast cancer: effects of longer follow-up. Radiotherapy and Oncology; July 2004; vol.72(1):35-43

7. Liljegren G., Holmberg L, Adami HO, Westman G, Graffman S, Bergh J. Sector resection with or without postoperative radiotherapy for stage I breast cancer: Five year results of a randomised trial. Uppsala-Orebro Breast Cancer study Group.

8. M. Clark,R.Collins,S.Darby, C.davies, P.Elphinstone, V. Evans, J. Godwin, R. Gray, C. Hicks, S. James, E. MacKinnon, P. McGale, T.mcHugh, R.Peto, C.Taylor, Y. Wang. Effects of radiotherapy an of differences in the extent of surgery for early breast cancer on local recurrence and 15.year survival : an overview of randomised trials. EarlBreast Cancer Trialists`Collaborative Group (EBCTCG); Lancet 2005, December 17; Vol 366:2087-2106.

9. R.Holland, S.H.J. Veling, M. Mravunac and J.H.C.L. Hendriks.Histologic Multifocality of Tis, T1 – 2 Breast Carcinomas. Implications for Clinical Trials of Breast-Conserving Surgery. Cancer 1985, September 1; Vol 56:979-990

10. Van Limbergen E., Van den Bogaert W., Van der Schueren E., Rijnders A.Tumor excision and radiotherapy as primary treatment of breast cancer. Analysis of patient and treatment parameters and local control. Radiotherapy and Oncology; January 1987; Vol.8(1):1-9

11. Romestaing P., Lehingue Y, Carrie C, et al;Role of a 10-Gy boost in the conservative treatment of a early breast cancer: Results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997 ; Vol. 15:963-8

12. H. Bartelink, J-C Horiot, P. Poortmans, H Struikmans, W. Van Den Bogaert, I. Barillot, A. Fourquet, J Borger, J. Jager, W. Hoogenraad, L. Collette, and M. Pierart. Recurrence Rates after Treatment of Breast Cancer with Standard Radiotherapy with or without Additional Radiation. EORTC 22881, NEJM 2001, November 8; Vol 345(19): 1378-1387.

13. N. Antonini, H. Jones, J.C. Horiot, P. Poortsmans, H. Struikmans, W. Van den Bogaert, I. Barillot, A. Fourquet, J. Jager, W. Hoogenraad, L. Collette, M. Pierart, G. Hart and H. Bartelink. Effect of age and radiation dose on local control after breast conserving treatment: EORTC 22881-10882;. Radiotherapy and Oncology 2007; Vol 82: 265-271.

13 a. Marc A. Bollett, B. Sigal-Zafrani, V. Mazeau, A. Savignoni, A. de la Rochefordiere,A.Vincent-Salomon, R. Salmon, F. Campana, Y.M. Kirova, R. Dendale, A. Fourquet. Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first. Radiotherapy and Oncology 82 (2007) 272-280.

13 b. P.T Truong M.D, C.M., F.R.C.P.C., S.O.Jones, B.Sc., H.A. Kader, M.D.,F.R.C.P.C., E.S. Wai, M.D., F.R.C.P.C, C.H.Speers, B.A., A.S.Alexander,M.D., F.R.C.P.C., and Ivo A. Olivotto, M.D., F.R.C.P.C. Patients with T1 to T2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy.Int.J.Radiation Oncology Biol. Phys., Vol. 73, No.2, pp. 357-364, 2009.

13 c. E. Touboul,M.D, L. Buffat, M.D, Y. Belkacemi, M.D, J-P Lefranc, M.D., S. Uzan, M.D., P Lhuillier, M.D.,C Faivre, M.D, J. Huart, M.D, J-P Lotz, M.D, M. Antoine, M.D, F. Pene, M.D., J. Blondon, M.D, V. Izrael, M.D, A. Laugier, M.D, M. Schlienger, M.D, and M. Housset, M.D. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer; Int. J. Radiation Oncology Biol. Phys., Vol. 43, No.1,pp. 25-38, 1999.

13 d. I. Gage, M.D, A. Recht, M.D, R. Gelman, Ph.D., A.J. Nixon, M.D., B. Silver, B.A, B.A. Bornstein, M.D. and J.R. Harris, M.D. Long-term outcome following bterast-conserving surgery and radiation therapy; Int.J. Radiation Oncology Biol. Phys., Vol. 33, No.2., pp. 245-251, 1995.

13 e. P.H.M. Elkhuizen, M.D., M.J. Van de Vijver, M.D., Ph.D., J. Hermanns, Ph.D., H.M. Zonderland, M.D, C.J.H. Van de Velde, M.D., Ph.D., and Jan-Willem H. Leer, M.D., Ph.D.; local recurrence after breast-conserving therapy for invasive breast cancer: High incidence in young patients and association with poor survival; Int. J. Radiation Oncology Biol. Phys., Vol. 40, No. 4, pp. 859-867, 1998.

13 f. A. C. Voogd, M. Nielsen, J.L.Peterse, M. Blichert-Toft, H. Bartelink, M. Overgaard, G. van Tienhoven, K.W. Andresen, R.J. Sylverster and J. A. van Dongen; Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: Pooled results of two large European randomized trials; Journal of Clinical Oncology,Vol 19, no 6 (March 15), 2001:pp 1688-1697;

13 g. T. E. Smith, M.D, D. Lee, M.D., B.C. Turner, M.D, D. Carter, M.D, and B.G. Haffty, M.D.; True recurrence vs. new primary ipsilateral breast tumor relapse: An analysis of clinical and patologic differences and their implications an natural history, prognoses and therpeutic management; Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 5, pp. 1281-1289, 2000.

13 h. A.de la Rochefordiere MD, F. Campana MD, J.Fenton MD, J.R. Vilcoq MD, A. Fourquet MD, B. Asselain MD, S.M. Scholl MD, Prof P. Pouillart MD, J.-C. Durand MD and H. Magdelenat PHD ; Age as prognostic factor in premenopausal breast carcinoma ; The Lancet, Volume 341, Issue 8852, 24 April 1993, pages 1039-1043.

13.i: Guiliano AE, McCall L., Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K; Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010 Sep;252(3):426-32;

13j: Guiliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M; Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis:A randomized clinical trial. JAMA 2011 Feb9;305(6):569-75

14. F.Sedlmayer,G. Fastner, F. Merz, H. Deutschmann, R. Reitsamer, C. Menzel, A. Ciabattoni, A. Petrucci, E. Hager, N. Willich, R. Orecchia, V. Valentini on behalf of the ISIORT Europe. IORT with Electrons as Boost Strategy during Breast Conserving Therapy in Limited Stage Breast Cancer: Results of an ISIORT Pooled Analysis. Strahlentherapie und Onkologie Dezember 2007;Vol 183 (Sondernr.2):32-4

15. R. Reitsamer, F. Sedlmayer, M.Kopp, G. Kametriser, C. Menzel, H. Deutschmann, O. Nairz, W. Hitzl and F. Peintinger.The Salzburg concept of intraoperative radiotherapy for breast cancer : Results and considerations. Int.J.Cancer 2006, December 27; Vol 118: 2882 - 2887

16. . R. Reitsamer, Peintinger F., Sedlmayer F., Kopp M., Menzel C., Cimpoca W., Glück S., Rahim H., Kopp P., Deutschmann H., Merz F., Brandis M and Kogelnik H Intraoperative radiotherapy given as a boost after Breast-conserving surgery in breast cancer patients.. Eu J Cancer August 2002 ; Vol 38 (12) :1607-1610

17. Y. Yamada, I. Ackerman, E. Franssen, R.G. MacKenzie and G. Thomas Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer ? Abstract : Int. J. of Radiation Oncology Biology Physics ; Vol. 44, Issue 1, 1 April 1999 : pp 99-104

18. I.A. Olivotto, L.M.Weir, C.Kim-Sing, C.D. Bajdik, C.H. Trevisan, C.M. Doll, W-Y. Lam, V.E. Basco, S.M. Jackson Late cosmetic results of short fractionation for breast conservation. Radiotherapy and Oncology 1996, Vol.41:7-13

19. W. Shelley, M. Brundage, C. Hayter, L. Paszat, S. Zhou and W. Mackillop A Shorter Fractionation Schedule For Postlumpectomy Breast Cancer Patients. Int. J. Radiation Biol. Phys ;2000, Vol. 47, No. 5 :1219-1228.

20. R.M. Clark, T. Whelan, M. Levine, R. Roberts, A. Willan, P. McCulloch, M. Lipa, R.H. Wilkinson, L.J. Mahoney.Randomized Clinical Trial of Breast Irradiation Following Lumpectomy and Axillary Dissection for Node-Negative Breast Cancer : an Update. Journal of the National Cancer Institute, Vol. 88, No. 22, November 20, 1996.

21. D.V. Ash, E :A. Benson, J:R Sainsbury, C.Round and C. Head. Seven - yearfollow-up on 334 patients treated by breast conserving surgery and short course radical postoperative radiotherapy : A report of the Yorkshire breast cancer group Clinical Oncology 1995; Volume 7, Issue 2, pages 93-96. Abstract

22. T. Whelan, R. MacKenzie, J.Julian, M. Levine, W. Shelley, L. Grimard, B. Lada, H. Lukka, F. Perera, A. Fyles, E. Laukkanen, S. Gulavita, V. Benk, B. Szetchman Randomized Trial of Breast Irradiation Schedules After Lumpectomy for Women With Lymph Node-negative Breast Cancer. Journal of the National Cancer Institute, Vol.94, N0. 15, August 7, 2002.

22a. T. Whelan, J.-P. Pignol, Mark N. Levine et al; Long-Term Results of hypofractiionated Radiation Therapy of Breast Cancer; NEJM 2010; 362:513-20

23. J.R. Owen, Anita Ashton, J.M. Bliss, J. Homewood, C. Harper, J. Hanson, J. Haviland, S.M. Bentzen and J.R. Yarnold.Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision : Long-term results of a randomised trial. Lancet Oncol 2006, May 17 ; Vol.7 :467-71.

24. John Yarnold, Anita Ashton, Judith Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Jo Haviland, Soren Bentzen and Roger Owen Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer : Long – term results of a randomised trial. Radiotherapy and Oncology 2005, Vol 75 : 9-17

25.S.M. Bentzen, RK Agrawal, Aird EG, Barret JM, Barret-Lee PJ,Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen, JR, Simmons S, Sumo G, Sydenham MA, Venables K and Yarnold JR.The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early braest cancer: a randomised trial. The Lancet 2008, March 29;Vol 371(9618):1098-1107

26. S.M. Bentzen, RK Agrawal, Aird EG, Barret JM, Barret-Lee PJ, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen, JR, Simmons S, Sumo G, Sydenham MA, Venables K and Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.Lancet Oncol, April 2008; 9(4): 331-341

27. T. J. Whelan, Do-Hoon Kim and J. Sussman Clinical Experience Using Hypofractionated Radiation Schedules in Breast Cancer.; Semin Radiat Oncol 2008; Vol 18:257-264.

28. J. Yarnold, A. Ashton, J. Bliss , J. Homewood, C. harper, J. hanson, J. haviland, s. Bentzen and R. Owen. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long term results of a randomised trial:

Radiotherapy and Oncology 2005; vol. 75: 9.17
28 a. Bhatnagar AK, Beriwal S, Heron DE et al. Initial outcomes analysis for large multicenter integrated cancer network implementation of intensity modulated radiation therapy for breast cancer. Breast J. 2009 Sep-Oct;15(5):468-74.

29. G:B Ivaldi, M:C: Leonardi, R. Orecchia, D. Zerini, A. Morra, V.Galimberti, G.Gatti, A. Luini, P. Veronesi, M. Ciocca, C. Sangalli, C. Fodor and U. Veronesi.Preliminary results of electron intraoperative therapy Boost and hypofractionated extrenal beam radiotherapy after breast-conserving surgery in premenopausal women. Int. J. Radiat. Oncol. Biol. Phys.; 1 oct. 2008; Vol 72(2):485-93

30. Van Limbergen, Van der Schueren E., Van Tongelen K. Radiotherapy an d Oncology; Cosmetic evaluation of breast conserving treatment for ammary cancer.1. Proposal of of a quantitative scoring system. Radiotherapy an d Oncology; November 1989; Vol.16(3):159-67

31.J.R. Harris, M.B. Levene, G. Svensson and S. Hellman; Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast;Int. J. Radiat. Oncol. Biol. Phys. Vol. 5, pp 257- 261, 2/1979).

32. J. Hartung, B. Elpelt, K. Klösener Statistik, Lehr- und Handbuch der angewandten Statistik`, 15. AuflageOldenbourg Verlag

33. Nairz O, Deutschmann H, Kopp M, Wurstbauer K, Kametriser G, Fastner G, Merz F, Reitsamer R, Menzel C, Sedlmayer F.A dosimetric comparison of IORT techniqies in limited-stage bbreast cancer. Strahlentherapie Onkologie, 2006 Jun.,182 (6), 342-8

34. Lovey K, Fodor J, Major T, Szabo E, Orosz Z, Sulyok Z, Janvary L, Frohlich G, Kasler M, Polgar C (2007) Fat necrosis after partial-breast irradiation with brachytherapy or electron irradiation versus standard whole-breast radiotherapy—4-year results of a randomized trial. Int J Radiat Oncol Biol Phys 69(3):724–731.

35. McCulley SJ, Macmillan RD. Therapeutic mammaplasty: analysis of 50 consecutive cases. Br J Plast Surg. 2005;58:902–7.

36. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol. 2010;17:1375-91.

Appendix I: Registry

Patienten ID:…….

Date of written consent YYYY/MM/DD:.....

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
other ():……

Additional staging imaging: yes () no ()
if yes; chest x-ray ()
abdominal sonography ()
bone scan ()
others:……..

M0-confirmation: ()

Positive biopsy/cytology: ()

Photo documentation: yes () no ()

Anamnesis: yes () no ()

Clinical investigation: yes () no ()

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix IIa: Inclusion/exclusion (Histology/IOERT protocol)

Histology:

IDC ()
ILC ()
mixed IDC+ILC ()
Tubular ()
Medullary ()
Metaplastic
Mucinous
mixed IDC+ tubular ()
mixed IDC+ mucinous ()
mixed Tubular + lobular ()
NST ()
mixed NST+ILC ()
mixed NST+tubular ()
mixed NST+mucinous ()

EIC pos./DCIS prominent : yes () no ()

Multifocality (same quadrant): yes () no ()

T – stage (0-2,x):…..

N-stage (0-1,x):…..

Grading (x,1-3):…..

Hormone receptor status: pos () neg ()

Estrogen receptor (ER): pos () neg ()

Progesteron receptor (PR): pos () neg ()

Her2-neu receptor: pos () neg ()

KI-76 %:….. not done ()

Resection status: R0 () R1 ()

Re-excision after IORT (if yes please comment): yes () no ()

Definitive free margins in mm:…..

Secondary mastectomy (immediately, NOT due to recurrence; if yes please comment):

yes () no ()

Appendix IIa:

Modality for depth calculation of Boost-Target-Tissue: Ultrasound ()
probe ()
CT ()
not done ()

IORT electron Energy (MeV):…..

Tube diameter (cm):…..

Tube length (cm):……

Volume of D90 (>10 Gy) ml:…..

Resected breast tissue [g]:……

d (depth of 90% = 10 Gy) in mm:…..

Bevel angle (°):…..

Lead shielding breast wall: yes () no ()

Date of operation YYYY/MM/DD:…….

Surgical technique: lumpectomy/segment resection: ()
OPS I: ()
OPS II: ()

Local complications (referring to operative procedure (hemorrhage,inflammation, fistula etc.) NOT toxicity due to WBRT; if yes: Description under comments):
yes () no ()

Hormonal therapy: yes () no ()

Planned chemotherapy: yes () no ()
if yes Type and number of cycles:

Study entry date YYYY/MM/DD:……..

Screening error (if yes please comment): yes () no ()

Appendix IIa:

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix IIb (neoadjuvant chemotherapy): Inclusion/exclusion (Histology/IOERT protocol)

Histology:

IDC ()
ILC ()
mixed IDC+ILC ()
Tubular ()
Medullary ()
Metaplastic
Mucinous
mixed IDC+ tubular ()
mixed IDC+ mucinous ()
mixed Tubular + lobular ()
NST ()
mixed NST+ILC ()
mixed NST+tubular ()
mixed NST+mucinous ()

EIC pos./DCIS dominant : yes () no ()

Multifokalität (gleicher Quadrant): yes () no ()

cT – Stage (0-2,x):…..

cN- Stage (0-1, x):…..

cGrading (1-3,x):…..

cCR: yes () no(), if no:
cPR ()
"no change" ()

ypT – Stage (0-2,x):…..

ypN- Stage (0-1, x):…..

yGrading (1-3,x):…..

pCR: yes () no (), if no:
pPR ()
"no change" ()

Hormone receptor status: pos () neg ()

Estrogen receptor (ER): pos () neg ()

Appendix IIb

Progesteron receptor (PR): pos () neg ()

Her2-neu receptor: pos () neg ()

KI-76 %:….. not done ()

Resection status: R0 () R1 ()

Re-excision after IORT (if yes please comment): yes () no ()

Definitive free margins in mm:…..

Secondary mastectomy (immediately, NOT due to recurrence; if yes please comment):

yes () no ()

Modality for depth calculation of Boost-Target-Tissue: Ultrasound ()
probe ()
CT ()
not done ()

IORT electron Energy (MeV):…..

Tube diameter (cm):…..

Tube length (cm):……

Volume of D90 (>10 Gy) ml:…..

Resected breast tissue [g]:…….

d (depth of 90% = 10 Gy) in mm:…..

Bevel angle (°):…..

Lead shielding breast wall: yes () no ()

Date of operation YYYY/MM/DD:……

Surgical technique: lumpectomy/segment resection: ()
OPS I: ()
OPS II: ()

Appendix IIb

Local complications (referring to operative procedure (hemorrhage,inflammation, fistula etc.) NOT toxicity due to WBRT; if yes: Description under comments):

yes () no ()

Hormonal therapy: yes () no ()

Planned chemotherapy: yes () no ()
if yes Type and number of cycles:

Study entry date YYYY/MM/DD:……..

Screening error (if yes please comment): yes () no ()

Neoadjuvant chemotherapy: no () yes(), if yes:
schedule, number of cycles:
……

Neoadjuvant antihormonal therapy: no() yes(), if yes:
substance and treatment duration:
……

Postop. Hormonal therapy: yes () no ()

Postop. chemotherapy: yes () no ()
if yes Type and number of cycles:

Study entry date YYYY/MM/DD:……..

Screening error (if yes please comment): yes () no ()

Appendix IIb

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix III: Week 1 WBRT/ Cosmesis-evaluation pre WBRT – Start

Date of follow up YY/MM/DD:

Lab analysis: yes () no ()
if yes: BC ()
others :……

Photodocumentation: yes () no ()

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Start WBRT YYYY/MM/DD:…….

Radiotherapy 5x2,7 Gy/week (∑40.5Gy) (if no please comment):yes () no ()
Alternative radiotherapy scheme:……./week (∑…….Gy)

Breast volume (ml):…..

Screening error (if yes please comment): yes () no ()

IMRT: yes () no ()

Chemotherapy pre-RT: yes () no ()
if yes Type and number of cycles:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Appendix III:

Clinical investigation: yes() no()

Status of death : died no ()

Yes (), if yes:

1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix IV: End of WBRT/Evaluation of acute side effects along CTC-Scoring-System

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
others :……

Clinical investigation: yes () no ()

Toxicity-CTC score:…..
0: None
1: Faint erythema, dry desquamation
2: Moderate to brisk erythema, moderate edema, moist desquamation (mostly confined to skin folds and creases).
3: Confluent moist desquamation > 1.5 cm and not confined to skin folds, pitting edema
4: Skin necrosis or ulceration of dermis (full thickness) may include bleeding not induced by trauma

Radiation break: yes () no ()
if yes please comment the reason and the exact duration: < 1 week ()
1 week < ()
Radiotherapy 5x2,7 Gy (if not please coment): yes () no ()

End of WBRT (dd/mm/yyyy):……

Clinical investigation: yes() no()

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Appendix IV:

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix V: Follow-up 4 weeks after WBRT-End/ Evaluation of acute side effects along CTC-Scoring-System

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
others :……

Photodocumentation: yes () no ()

Clinical investigation: yes() no()

Toxicity-CTC score:…..
0: None
1: Faint erythema, dry desquamation
2: Moderate to brisk erythema, moderate edema, moist desquamation (mostly confined to skin folds and creases).
3: Confluent moist desquamation > 1.5 cm and not confined to skin folds, pitting edema
4: Skin necrosis or ulceration of dermis (full thickness) may include bleeding not induced by trauma

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Appendix V:

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix VI: Follow-up 4-5 months after WBRT-End/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Post-RT chemotherapy: yes () no ()
if yes Type and number of cycles:

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others ……

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):……
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):……
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix VI:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix VII: Follow-up 13 months after WBRT-End/ first mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others
……

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix VII:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix VIII: Follow-up 2 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others……

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix VIII:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix IX: Follow-up 3 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others ……

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix IX:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix X: Follow-up 4 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others ……

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix X:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix XI: Follow-up 5 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others…….

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix XI:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix XII: Follow-up 6 years after WBRT-End/ mammography/ Evaluation of late side effects along LENT-SOMA-Scoring-System/Cosmesis-evaluation

Date of follow up YYYY/MM/DD:…….

Lab analysis: yes () no ()
if yes: BC ()
BC,GOT,GPT,GGT,CA 15/3,alkal. Phoshatase, Calcium, Creatinin, Postassium ()
others:…..……

Clinical investigation: yes () no ()

Photodocumentation: yes () no ()

Mammography (if no, please comment): yes () no ()

Additional breast imaging:
Ultrasound ()
MRT ()
others:…….
not done ()

Additional staging imaging:
chest x-ray ()
abdominal sonography ()
CT-chest/abdomen/pelvis ()
CT-brain ()
MRT-brain ()
others:…….
not done ()

Toxicity-LENT SOMA Score:

Cosmetic score subjective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Cosmetic score objective (E0-E4):…..
E0: Excellent:No visible therapy related sequelae
E1: Good: Minimal changes in pigmentation, visible scare, loc. teleangiectasia
E2: Moderate result: Clear deformation of Breast contour, nipple displacement, marked skin changes.
E3: Bad result: Severe retraction or fibrosis, severe teleangiectasia.
E4: Complications: Skin necrosis

Appendix XII:

Status:…..
1: Tumor free
2: local recurrence (in-quadrant)
3: local recurrence (in-quadrant)
4: Secondary tumor (Please comment histology)
5 Metastases
6:
6: regional recurrence (lymphnode-region: axillary/supraclavicular/parasternal)
0: no statement (unknown)

Status of death : died no ()
Yes (), if yes:
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Date of local recurrence YYYY/MM/DD:…….

Date of appearance of distant metastases YYYY/MM/DD:……..

Date of death YYYY/MM/DD:…….

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:…….

Appendix XIII: Finally report at study-end / end of study participation

Date of follow up YYYY/MM/DD:…….

Reasons for finishing follow-up:

End of clinical trial ()

Protocol violation, that means:

- > 1 week break during WBRT ()
- WBRT delay over 56 days from date of OP (and > 9 months in case of adj. CTX) ()
- revoked consent to be treated according to protocol schedule (i.e 15x2.7 Gy) ()
- refusing of any further follow-up ()
- Lost to follow-up for unknown reasons ()

Patient died ()

observed pregnancy ()

Date of death:……..

Status at time of death:…..

1
1 died of disease: ()
2 died of secondary cancer: ()
3 died of other reasons (please comment): ()
4 died of unknown reasons: ()

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:……..

SAE / SUSAR - Report:

SAE (“Serious adverse Event”), please comment: ()

SUSAR (“Suspected Unexpected Seroius Adverse reaction”), please comment: ()

Comments:

Correctness of all data confirmed by (name of the doctor):

Date:……..

Scoring-Systems

Early toxicity: CTC- Score

CTC Versio 2.0, publish Date: 30 April, 1999

GRADE

Adverse Event	0	1	2	3	4
Radiation dermatitis	none	Faint erythema or dry desquamation	Moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Confluent moist desquamation >1,5cm diameter and not confined to skin folds; pitting edema	Skin necrosis or ulceration of full thickness dermis; may include bleeding no induced by minor trauma or abrasion.

Correctness of all data confirmed by (name of the doctor):

Date:……..

Late toxicity: LENT-SOMA

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective pain	Occasional – minimal Hypersensation, Pruritus	Intermittend & tolerable	Persistent & intense	Refractory & excruciating
Objective Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Fibrosis/ Fat necrosis	Barely palpable increased Density	Definite increased density and firmness	Very marked density, retraction and fixation	
Teleangiectasia	<1/cm2	1/cm2 – 4/cm2	>4/cm2	
Lymphedema arm (circumference)	2 cm – 4 cm increase	>4 cm – 6 cm increase	> 6 cm increase	Useless arm, Angiosarcoma
Retraction/Atrophy	10%-25%	25% - 40%	40% - 75%	Whole breast
Ulcer	epidermal only,< 1 cm	Demal,> 1 c	Subcutaneous	Bone exposed,necrosis
Management Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Edema			Medical internention	Surgical intervention/ Mastectomy
Lymphedema arm		Elevate arm,elastic Stocking	Compression wrapping, Intensive physiotherapy	Surgical intervention Amputation
Atrophy				Surgical intervention Mastectomy
Ulcer		Medical intervention	Surgical intervention, Wound debridement	Surgical intervention/ mastectomy

Analytic Photographs	Assesment of skin changes as atrophy,retraction or fibrosis,ulcer Y/N Date:
Tape measure	Assesment of breast size and forearm diameter Y/N Date:
Mammogramm	Assesment of skin thickness and breast density Y/N Date:
CT/MRI	Assesment of breast size,fat atrophy,and fibrosis density Y/N Date:

SCORING: every aspect has to be scored with 1-4, 0 if no toxicity is observed
The sum is divided by 12 and accouts for the LENT-SOMA Score.

Correctness of all data confirmed by (name of the doctor):

Date:……..

Cosmesis :

Cosmesis - Scoring - System irradiated breast cancer patients (32,33)

Methods:

Evaluation is done by an five point-scale:

E0: Excellent aesthetic result.
At first sight no visible therapy related sequelae. Both breasts have a similar appearance.

E1: Good result:
Minimal changes in pigmentation, a visible scar, localized teleangiectasia.

E2: Moderate result:
Marked sequelae with a clear deformation of breast contour, nipple displacement, or marked skin changes, but yet `acceptable`.

E3: Bad result:
Severe retraction or fibrosis, severe teleangiectasia.

E4: C**omplications**: Skin necrosis.

The evaluation should be done by the patients themselves **(subjective evaluation)** and by the treating persons such as the radiation oncologist and the surgeon **(objective evaluation).**

Evaluation sheet Cosmesis		
E0	excellent	Def.: Both breasts symmetric,no visible. sequleae
E1	good	Def.. pigmentation,visible scare,localized teleangiectasia
E2	moderate	Def.: Deformation breast contur/mamille,skin edema/fibrosis
E3	bad	Def.: Svere teleangiectasia,clear fibrosis with retraction
E4	complication	Def.: skin - necrosis
result:		
E0,E1	satisfact. result	
E2	moderate	
E0,E1,E2	acceptable	
E3,E4	unacceptable	

Comment:For later statistical analysis we differentiate between:

- **Satisfactory results :** E0 , E1.
- **Moderate results:** E2.
- **Acceptable results:** E0, E1, E2.
- **Unacceptable results:** E3, E4.

WEB-Plattform: LENT-SOMA: Wahlmöglichkeit zur Klassifizierung mit 0.
Erinnerungs-POP-up für FUP.
Fotos zur Kosmesisbeurteilung elektronisch einspielen?.

Correctness of all data confirmed by (name of the doctor):

Date:……..

Assessment of fat necrosis:

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

Correctness of all data confirmed by (name of the doctor):

Date:……..

Surgical technique:

Lumpectomy/Segment resection: ()

OPS I: < 20 % des Brustvolumens wurden reseziert (“ecompasses dual-plane undermining, including the nipple-areola complex (NAC), NAC recentralization, no skin excision is required: ()

OPS II: 20-50% des Brostvolumens wurde reseziert (“encompasses more complex procedures derived from breast reduction techniques, involve extensive skin excision and breast reshaping”): ()

Correctness of all data confirmed by (name of the doctor):

Date:…….