

## **Accelerated Partial Breast Irradiation (APBI) in clinical practice**

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## **Abstract**

Accelerated partial breast irradiation (APBI) has been under clinical investigation for more than 15 years. There are several technical approaches which are clinically established e.g. brachytherapy, intraoperative radiotherapy (IORT) or external beam radiotherapy. The understanding of the underlying biology, optimal technical procedures, patient selection criteria and imaging changes during follow-up has increased enormously. After completion of several phase III trials using brachytherapy or IORT, APBI is currently increasingly used either in phase IV studies, registries or in selected patients outside of clinical studies. Consensus statements about suitable patients are available from several national societies like ASTRO, ESTRO and DEGRO. One may expect that 15 – 25% of patients undergoing breast conserving surgery may qualify for APBI i.e. patients with small ductal-invasive breast cancer without clinical involvement of lymph nodes.

**Key Words:** breast cancer, radiotherapy, partial breast irradiation, intraoperative radiotherapy

## **Background**

Radiotherapy plays a substantial role after breast conserving surgery in order to reduce local recurrences in the conserved breast and by this improving cancer specific and overall survival [1]. After establishing the clinical value of fractionated whole breast radiotherapy to a total dose of 50 Gy about 30 years ago, recent efforts have concentrated on tailoring radiotherapy to the individual risk of the patient. Several studies have tried to identify patients who need no radiotherapy at all [2]. However, none of the prospective randomized trials was successful in identifying a low-risk cohort of patients, in whom local recurrence rates were identical to patients undergoing radiotherapy. Trials designed on the analysis of local relapse patterns [3] according to the initial histology have focussed on reducing the dose and the volume in appropriately selected patients. Irradiation of a smaller volume, in this case the tumor bed with a safety margin only, allows to increase the daily dose without excessively increasing the rate of late toxicity. This development was supported by novel insights into breast cancer tumor biology. The concept of accelerated partial breast irradiation (APBI) was rigorously tested in several large scale clinical studies [4-7], and has now entered clinical guidelines (for summary see [8,9]. The current article reviews some of the underlying biological concepts, summarizes the results of the practice changing clinical trials and tries to give an overview on the current status of ongoing additional clinical studies.

## **Biological rationale [10-13]**

Fractionation, i.e. the prescription of total doses and daily single doses in radiation oncology, has been dominated for decades by knowledge gained from in vitro studies, animal experiments with fast growing squamous cell carcinoma and clinical data mainly from head and neck tumors. It is well established that a reduction in the daily fraction size must be compensated by an increase of the total dose to achieve the same biological effect. The way different tumor and normal tissues react to changes in the daily fraction size is usually characterized by a parameter known as the  $\alpha/\beta$  ratio. Classical radiobiological thinking suggests that tumor cells and acutely reacting tissues like skin, mucous membranes and the bone marrow have a high  $\alpha/\beta$  ratio in the range of 10 Gy, whereas late reacting tissues e.g. breast, brain and lung have low  $\alpha/\beta$  values in the range of 2 – 5 Gy with different shapes of the cell survival curves in vitro (see figure 1). Fractionated radiotherapy with single doses of 2 – 3 Gy yield a differential effect in the sense of normal tissue sparing in late reacting tissue compared to tumor cells, whereas higher single doses would reverse this leading to higher rates of clinical late damage. Based on this dogma, higher single doses were strictly avoided in curative radiation oncology for decades.

New clinical data especially derived from clinical studies in patients with adeno-carcinoma of the prostate [14] and the breast [15,16] have led to a re-thinking of the classical concepts.

Several analyses suggest that the  $\alpha/\beta$  ratio for breast cancer is in the range of 3-4 Gy. Whenever there is no difference in  $\alpha/\beta$  values between tumor and the surrounding normal tissue, there will be no clinical gain regarding normal tissue sparing in giving radiotherapy in small fractions as has been demonstrated by several clinical trials.

However, as has been known from stereotactic radiosurgery (SRS) series applying very high single doses to brain metastases, there is a strong relationship between the size of the high dose volume and the risk of radiation induced late damage [17]. Thus higher doses can be given to a tumor if the volume of normal tissue in the high-dose field is kept small. The successful concept of radiosurgery was recently modified and refined and can now be applied in the form of stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) to primary or secondary tumors in the body e.g. lung, liver, adrenals, and bones with impressive clinical results regarding local control (for review see [18,19]).

In the past decade, new interest in the biological effects of high single doses was stimulated by the technical development and clinical establishment of SRS and SBRT. Certain biological effects on tumor cells (seed) and from the surrounding microenvironment (soil) can only be observed, when single doses above certain thresholds around 3 - 5 Gy and around 8 - 10 Gy are given. Local tumor cell kill may be potentiated by a saturation of the repair machinery and by additional effects on the vasculature [13]. In addition non-target effects may lead to an increased cell kill in the vicinity of the macroscopic tumor [20], and abscopal effects mediated by the immune system may lead to distant tumor cell kill [21].

### **Results from Clinical Studies**

Three prospective randomized clinical studies establishing the role of APBI in clinical practice have been published up to now.

#### **Hungarian PBI Trial**

Ten year data have been reported from a Hungarian single center trial comparing whole breast radiotherapy (n=130, 50 Gy) with partial breast radiotherapy (n=88, multi-catheter brachytherapy 7 x 5.2 Gy, n=40, electrons 50 Gy) in small (pT1 pN0-1mi) non-lobular (G1-2, no EIC) breast cancers. The ten-year actuarial rate of local recurrence was between 5 - 6% in both arms with higher excellent – good cosmetic outcome (81% vs. 63%) after PBI [4].

#### **TARGeted Intraoperative radioTherapy (Targit) A(lone) Trial**

The TARGIT-A trial was a prospective, randomized multicentric trial. It included patients with unifocal small breast cancer with non-lobular histology and tested the concept of single dose intraoperative radiotherapy (IORT, see figure 2) during breast conserving surgery which was followed by external beam whole breast radiotherapy only in patients with additional risk

factors. Five year data on local control and overall survival were recently published demonstrating the non-inferiority of the experimental arm regarding the primary endpoint of ipsilateral in-breast tumor recurrence in the range of 1-3%. There was a trend for better overall survival and significantly less breast and arm symptoms after IORT only treatment with 20 Gy using a miniature X-ray generator (Intrabeam, Carl Zeiss Meditec, Oberkochen/Germany) [5,6,22].

### **Electron IntraOperative radioTherapy (ELIOT)**

A randomized single center study was performed at the European Institute for Oncology (EIO) at Milano/Italy. Patients were either randomized to a single dose of 21 Gy intraoperative electron radiotherapy (ELIOT or IOERT) or to standard whole breast radiotherapy. Inclusion criteria were broader than in the TARGIT A trial and no additional whole breast radiotherapy was given for patients with risk factors. The local recurrence rate was slightly higher in the experimental arm (about 4% vs. 1 %), however, in patients without risk factors like ESTRO consensus or ASTRO consensus „APBI suitable“ criteria, there were identical local recurrence rates in both arms[7].

### **Ongoing Clinical Studies with APBI as single modality**

#### **TARGIT E(Ilderly)**

Elderly patients with small, ductal invasive breast cancer were included into the prospective TARGIT E trial (NCT01299987). The rationale of this non-randomized single arm study was to compare in a sequential manner at predefined time points local recurrence rates after risk adapted IORT with recurrence rates derived from randomized clinical studies with and without whole breast radiotherapy after breast conserving surgery [23]. More than 500 patients were recruited from 29 national and international centers in less than 4 years. The first preplanned safety analysis (n=80, med follow-up 20.5 months) demonstrated the low complication rate of this approach [23]. Data on local recurrence rates and quality of life will be available in the near future.

#### **TARGIT C(onsolidation)**

In order to consolidate the results from single dose APBI further, a prospective phase IV study (NCT02290782) [25] was initiated including patients starting at the age of 50 years (see figure 3). It is a non-randomized single arm study using the experimental arm of the TARGIT A study and prospectively compares the local control rates with the best published results from clinical trials using external beam whole breast radiotherapy. 351 evaluable patients are planned. The expected local relapse rates are 0.825 and 1.375% after 3 and 5

years, respectively. Discontinuation of the trial is scheduled if local relapse rates rise to 1.55, 2.4 or 4% after 1, 3 or 5 years. Power calculations result in 387 patients with a calculated dropout and loss to follow-up rate of 10%, an alpha of 0.05 and a beta of 0.10.

### **NSABP B-39/RTOG 0413**

This randomized phase III study compares conventional whole breast irradiation with partial breast irradiation for women with Stage 0, I, or II breast cancer [26]. Several APBI techniques are allowed i.e. external beam, mammosite brachytherapy or multi-catheter brachytherapy. The primary goal is to determine whether irradiation limited to the region of the tumor bed following lumpectomy provides equivalent local tumor control in the breast compared to conventional whole breast irradiation. No results on outcome have been reported up to now.

### **GEC-ESTRO (Groupe Européen de Curietherapie – European Society of Therapeutic Radiology and Oncology)**

The Breast Cancer Working Group of GEC-ESTRO deals with clinical and technical issues of breast brachytherapy. In the last decade, several groups have implemented multi-catheter brachytherapy technique and 3-D CT based brachytherapy treatment planning for the management of breast cancer. One of the most important projects was the development and conduction of the first European multicentric breast brachytherapy trial comparing the efficacy of multi-catheter APBI to conventional whole breast irradiation. The study included 1233 patients up to the year 2009 in 16 centers from 7 European countries. No clinical results on outcome of the phase III trial have been reported up to now although results from the phase II trial appear promising [27,28].

### **Ongoing Clinical Studies APBI combined with external beam whole breast radiotherapy**

#### **TARGIT B(oost)**

Temporal and geographic miss are a potential disadvantage of applying the external beam boost following oncoplastic surgery, months of chemotherapy and weeks of external beam whole breast radiotherapy. For theoretical reasons, i.e. lack of geographic and temporal miss **[Womens Health]**, applying the boost already during surgery using IORT, i.e. optimal location, optimal timing, may be superior to the standard of care usually applied as an external beam boost [29-32]. In order to test the superiority of a TARGIT IORT boost compared to an external beam boost, the multicentric, prospective, randomized TARGIT B

study was initiated. More than 20 centres have already started recruiting and 1800 young or high-risk patients will be included.

### **Hypofractionated WBI preceded by intraoperative electron boost (HIOB)**

In an attempt to further reduce overall treatment duration without compromising local control rates, the multi-centre HIOB trial was started in January 2011 as an ISORT investigator initiated study. In this trial, the intraoperative boost with electrons (IOERT) of 10 Gy is combined with hypofractionated WBRT (15 x 2.7 Gy) for stage I/II breast cancer. A similar concept of IOERT plus short-term WBRT was tested in a phase II design by the Milano Group [33]. The HIOB trial design follows a sequential probability ratio test (SPRT), defining annual in-breast recurrence rates as benchmarks for successful treatment. Superiority of the intervention is defined by falling below the best published evidence in non-IORT cohorts. Beside tumor-related endpoints, major emphasis is made on treatment tolerance and cosmetic outcome [34].

As of August 2014, within ten active institutions 645 patients have been recruited, 481 of them already in follow-up and analyzed by March 2015. Perioperatively, no major complications were observed. Four weeks after the end of WBI and 479 evaluated patients, 177 (37%) showed no reactions at all (CTC 0), 277 (58%) presented with faint (CTC 1) and 24 (5%) with moderate to brisk erythema (CTC 2), respectively. G0-I late reactions (LENT-SOMA) occurred in a mean frequency of 97%, 96%, 98% and 96% after 4-5 months, 1, 2 and 3 years follow-up, respectively. Cosmesis was repeatedly assessed and referenced against the baseline appearance prior to WBI, which was scored as sufficient (excellent and good) in 69%/74% of 614 subjective/447 objective evaluations. Respective results at 4-5 months, one, two and three years post RT were 87%/75% of 418/378, 89%/77% of 306/164, 83%/75% of 132/107 and 84%/87.5% of 31/24 ratings. At a median follow-up period of 12.6 months (range 0.5-37), three patients were metastasized, two died, no in-breast recurrence was noted.

In sum, tolerance of a combined IOERT / hypofractionated WBI regimen was excellent, acute reactions were moderate and late reactions insignificant in short-term assessment. With regard to postoperative appearance, early cosmetic results are not impaired by this regimen. Both tumor control and cosmetic outcome have to be evaluated on long-term follow-up.

### **Imaging changes after APBI**

Since establishment of BCS structural changes like parenchymal scarring, local edema, fat necroses and dystrophic calcification have been described to occur at the original tumour site. Mammography is recommended as the leading method for radiological follow-up after

BCS, with ultrasound as an additional option in selected cases. In case of uncertain or suspect findings further diagnostic procedures like magnification mammography, MRI and needle biopsy have to be considered.

Increased structural changes in the tumour bed after IORT have been reported [35], although these are typically not associated with symptoms or cosmetic changes (see figure 4). Distinct post-operative changes can be found in more than 50% of patients. IORT is associated with a high incidence of fluid wound cavities, fat necroses and oil cysts. However, distinct postoperative changes on mammography after IORT are not necessarily associated with a relevant diagnostic uncertainty [36]. Additional procedures due to unclear findings in the tumour bed became necessary in a study by Wasser et al in 7% (IORT) vs. 8% (control group) of the patients.

The same is true for MR mammography during follow-up [37]. Persistent wound cavities have been reported in up to 80% of the patients, which were associated with a persisting rim of contrast enhancement. Knowing these imaging changes and the respective time course does not cause problems in the interpretation of the images or the differential diagnosis.

### **APBI in special clinical situations (patients with pacemakers or cardioverter-defibrillators)**

In parallel to the demographic changes of the total population, we also encounter an aging cohort of patients with breast cancer displaying more and more co-morbidities which may pose novel problems for the treating radiation oncologist. Modern cardiac implanted electronic devices (CIED; cardiac pacemakers (PM) and cardioverter-defibrillators (ICD)) are increasingly used and may pose a specific challenge to the treating physicians when radiotherapy for breast cancer is planned. Ionising radiation at doses of 2 – 10 Gy has been reported to interfere with modern devices, which are equipped with complementary metal oxide semiconductor circuitries (CMOS) and random access memories (RAM). Possible effects on the implanted devices include for example altered sensitivity, amplitude changes, telemetry and programming defects, or even loss of function. Guidelines e.g. from the German National Society of Cardiologists and the German Society for Radiation Oncology have been recently published highlighting this problem and suggesting adequate measures to avoid damage to implanted cardiac devices [38]. However, using external beam radiotherapy for breast cancer avoidance of relevant doses to the cardiac implanted electronic device (CIED) cannot always be achieved. Reasons for CIED –failures in radiotherapy are under investigation. Evidence points out that direct placement in the LINAC beam or scatter radiation with an uncertain threshold dose (somewhere > 2 Gy) will eventually harm electronic parts. Reported CIED failures point towards photon energies > 10MV that cause generation of photoneutrons and lead to failures in CIEDs that were located

even distant to the isocenter. APBI may be a valuable alternative in these cases because of low beam energy and steep dose gradients and there have been already clinical reports on successful application of IORT in the vicinity of pacemakers [39].

### **Conclusion and Future Directions**

Accelerated partial breast irradiation has been under clinical investigation for more than 15 years. The understanding of the underlying biology, optimal technical procedures, patient selection criteria and imaging changes during follow-up has increased enormously. After completion of several phase III trials with long term follow-up [40], APBI is currently increasingly used either in phase IV studies, registries or in selected patients in routine clinical practice outside of clinical studies. One may expect that 15 – 25% of patients undergoing breast conserving surgery may qualify for APBI alone and up to 60% for APBI as a boost followed by whole breast radiotherapy [9].

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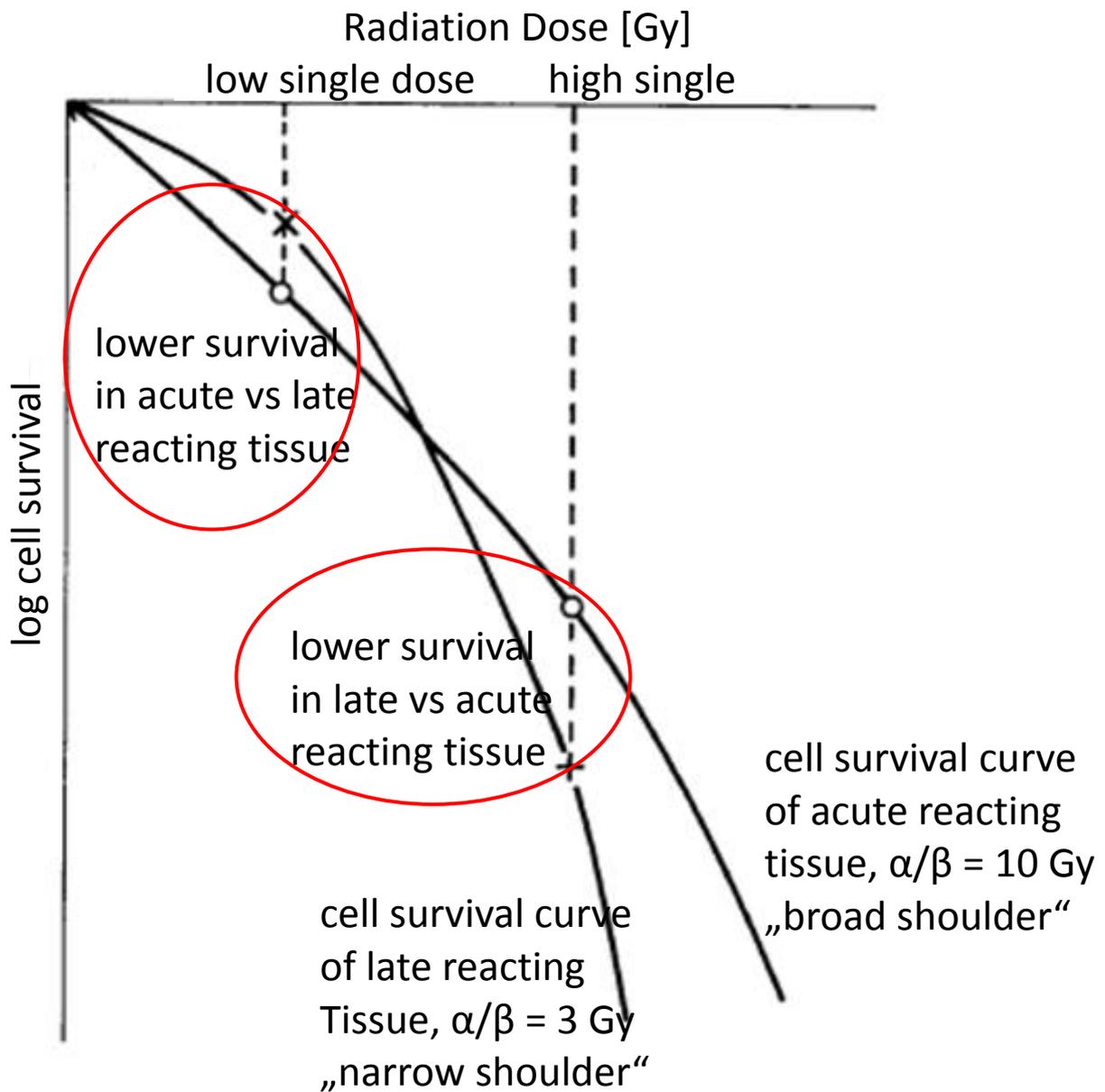
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**Figure Legends:**

Figure 1:



Cell survival curves in vitro. An increasing radiation dose leads to a lower cell survival.

Depending on the cell type, the survival curve may have a different shape which is mathematically characterized by the parameter  $\alpha/\beta$  given in Gray. A low value of  $\alpha/\beta$  implies a larger curvature (narrow shoulder), while a higher  $\alpha/\beta$  is associated with less curvature (broad shoulder, more linear slope at low doses).

It is well established that a reduction in the daily fraction size must be compensated by an increase of the total dose to achieve the same biological effect. The way different tumor and

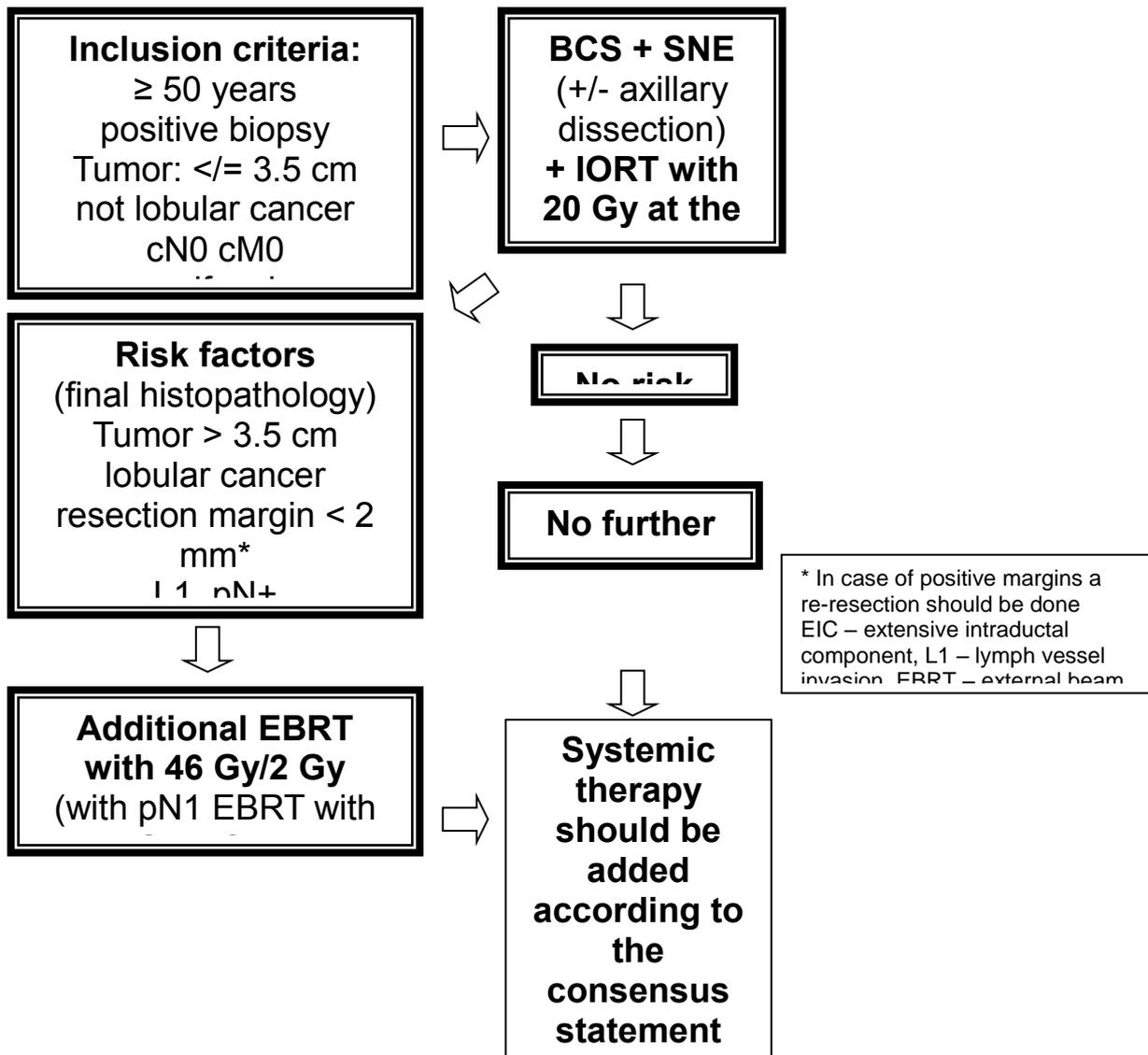
normal tissues react to changes in the daily fraction size is usually characterized by a parameter known as the  $\alpha/\beta$  ratio. The difference in  $\alpha/\beta$  values implies that late-reacting tissue is spared relative to tumor cells when the daily fraction size is reduced and the total dose is increased by the amount which will give the same rate of local tumor control. Conversely, increasing the size of the daily dose fraction would increase damage to the late-reacting normal tissue if the total dose were adjusted to keep the tumor control rate constant.

Figure 2:



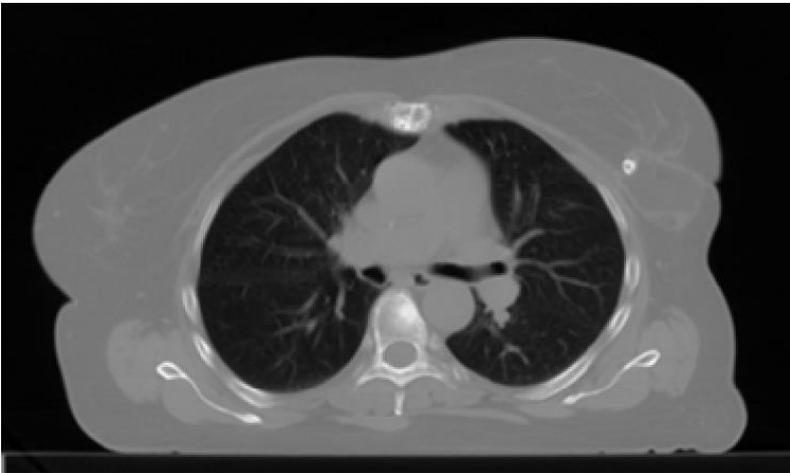
Intraoperative Radiotherapy during breast conserving surgery using the INTRABEAM system (Carl Zeiss Meditec, Oberkochen/Germany)

Figure 3:



Flow chart of the ongoing TARGIT C trial corresponding to the experimental arm of the TARGIT A study. The TARGIT E trial used basically the same approach using different entry criteria (70 years and older).

Figure 4:



Outcome three years after breast conserving surgery and IORT. Imaging changes like calcifications are typically more pronounced after APBI as compared to standard whole breast radiotherapy without compromising cosmesis.