Multiple Technology Appraisal (MTA)
INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer

1 List of Abbreviations

APBI	Accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
BCCT.core	Breast Cancer Conservative Treatment.cosmetic results (Software program)
BCS	Breast conserving surgery
CI	Confidence interval
CT	Computed Tomography
DCIS	Ductal Carcinoma in Situ
DIMDI	Deutsches Institut für medizinische Dokumentation und Information
DVH	Dose Volume Histogram
EBRT	External Breast Radiation Therapy
EG	Excellent and good
EORCT	European Organisation for Research and Treatment of Cancer
ER/PR	Estrogen receptor / progesterone receptor
FP	Fair and poor
Gy	Gray
Her2/neu	Human epidermal growth factor receptor 2, erb-B2, c-erbB2
IQR	Interquartile range
IORT	Intraoperative radiation therapy
kV	Kilo Volt
LENT-SOMA	Late Effects in Normal Tissues-subjective, objective, management, and analytic
LR	Local Recurrence
NR	Not reported
OAR	Organ at risk
PBI	Partial Breast Irradiation
PPBCT	Persistent pain after breast cancer treatment
RTOG	Radiation therapy oncology group
QLQ	Quality of life questionnaire
RCT	Randomized Clinical Trial
SD	Standard Deviation
TARGIT	***TARG***eted ***I***ntraoperative radiotherapy
TLD	Thermoluminiscent dosimeter
US	United States of America
WBRT	Whole breast radiation therapy

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3 Executive Summary

3.1 Brand name

INTRABEAM ® Radiotherapy System

3.2 Intended use / Indication for use

The INTRABEAM system is a radiotherapy system.

3.3 Recommended course of treatment

There is no recommended course of treatment indicated by the manufacturer.

3.4 Key clinical evidence

Clinical evidences presented are based on publications on the outcome of clinical trials. One major clinical trial, the TARGIT-A trial, is a prospective, randomized study. At the time of this evaluation, results from 5-year follow up were published. Numerous other publications are presented. It must be kept in mind that some of these other publications sum up results obtained either by assessment of sub-groups of the TARGIT-A trial or by assessment of results obtained from patients that were not included in the TARGIT-A trial. These assessments are based on non-randomized patients. Nevertheless, the results are included and presented as we believe that the non-randomized data substantiate the main results or give evidence for conclusions not investigated by the TARGIT-A trial. Besides, poster abstracts are also included, although not representing scientific literature, they were included as they were also considered as helping to draw the picture.

3.5 Presentation of main results

IORT using the INTRABEAM Radiotherapy System is described in the context of two different treatment protocols

1) IORT given as the single method or treatment, preferably at the time of lumpectomy

2) IORT given as a boost during surgery followed by EBRT

3.5.1 IORT as the single method of treatment

Results showing the clinical effectiveness of IORT given as a single method of treatment were obtained through the so called “TARGIT-A trial”, a prospective randomized clinical trial conducted with nearly 3500 patients in 33 centres in 11 different countries. [1] In principle, patients were treated either with IORT as single method of treatment (TARGIT) or with conventional EBRT. Results obtained after 5-year follow-up gave evidence that TARGIT is not inferior to conventional EBRT. Although the local recurrences were slightly higher in the TARGIT group when compared with EBRT, significantly less non-cancer related deaths were observed in the TARGIT group. This outcome can be explained by fewer deaths from cardiovascular causes and other cancers. The overall mortality for the TARGIT group was less than for the EBRT group. The outcome for 2298 patients in the pre-pathology strata (when TARGIT is given concurrently with lumpectomy) was much the same as EBRT. There is an increase of 1% in local recurrence along with a potential decrease of overall mortality of 2-3% at five years. It could be shown that the dose given at the time of surgery is essential., The outcome for the 1153 patients in whom IORT was given only after the final pathology results were available, i.e. about one month after lumpectomy, showed much less favourable results than in the patients who received IORT during lumpectomy. Consequently, the

authors clearly support TARGIT immediately during surgery. Thus our economic model is based on the results of the pre-pathology stratum with 2298 patients.

Other clinical trials, although not randomized, underline the results presented above and show that IORT given as a single method of treatment leads to favourable results [**Deneve et. al (2011)** [2], USA, n=42 treatments, no local recurrence after 3 months follow-up; **Grobmyer et al. (2013)**, [3], USA, n=80 breasts treated in n=78 patients, no local recurrence with a follow-up of 23 months]

Considerations were made with regard to toxicities and cosmetic outcome after TARGIT. As an outcome of the already mentioned TARGIT-A trial [1] no increased toxicity with TARGIT were observed and radiotherapy-related local toxic side-effects were slightly reduced when compared with EBRT. Other studies also give evidence that the treatment protocol of TARGIT is well tolerated:

Elliott et al (2012) (USA) [4]	n=67 breasts treated	post-operative cosmesis acceptable
Deneve et al.(2012) (USA) [2]	n=42 breasts treated	related toxicity acceptable
Grobmyer et al. (2013) (USA) [3]	n=80 breast in n=78 women treated	majority of patients had good to excellent cosmesis, procedure was well tolerated and toxicities appeared to be low;
Tuschy et al. (2013) (Germany) [5]	patients treated in the TARGIT trial, n=147 women treated with IORT as a boost and n=61 patients treated with IORT as a single method of treatment	no severe postoperative complications, observed acute toxicity after IORT was low, no differences with regard to short term complications between the two groups were observed;
Merdad et al. (2013) (Saudi Arabia) [6]	n=45 patients treated (IORT alone or IOER followed by EBRT)	none of the patients developed clinically significant complications, cosmetic outcome was at least acceptable in all patients;
Keshtgar et al. (2013) [7]	subgroup of patients included in TARGIT trial	superior cosmetic outcome for TARGIT patients when compared with patients treated with EBRT, differences between IORT and EBRT patients more significant at the beginning of the follow-up
Kolberg et al. (Germany) [8]	n=200 patients treated	satisfaction with cosmetic outcome 92% (patients) and 95% (physicians);
Jankiewicz et al. (Poland) [9]	Treatment with IORT alone (n=19) or IORT followed by EBRT (n=61)	No serious complications prolonging hospitalization; 5-year overall and disease free survival 100% in IORT group and 95,1% and 96,7%, respectively, in the IORT plus EBRT group, excellent and good aesthetic outcome in 90% of the patients
Steiner et al. (2013) (Israel) [10]	n=400 patients treated	Mild to moderate local complications in 14,5% Major complications in 6,2% Ipsilateral breast failures in 1,7% Systemic disease in 1%

The data presented above give evidence that IORT as a single method of treatment is non-inferior to EBRT (TARGIT-A trial) with a trend to a better overall survival and significant fewer non-breast cancer death. Moreover, it can be seen hat beside the TARGIT-A trial, several other patients in different centres all over the world have been successfully treated. The results show that in general, recurrences rates are low and the cosmetic outcome is at least satisfying, if not even good to excellent.

3.5.2 IORT given as a boost followed by EBRT

Besides of TARGIT as the sole method of treatment, the INTRABEAM Radiotherapy System can also be used in treatment protocols in which IORT is given intraoperative as a tumour bed boost followed by EBRT. Results published in literature demonstrate that this treatment protocol leads to good results. In higher risk patients overall survival rates of 87% and local (in-breast) relapse-free survival rates of 98,5% are reported [11] together with very low rates of local failure and toxicity. Another study also reports on very few severe surgical complications (10%) and breast wound infections (15%) and no case of recurrence or death after a follow-up of 21 months (range, 3-36months). [12] Other authors even point out that results obtained for 5-year recurrence rates in the EORTC study which can be considered as benchmark are inferior to results obtained with IORT boost treatment followed by EBRT. [13] The results are supported by the outcome of a matched pair analysis conducted in n=53 pairs of patients which showed a strong tendency towards better survival rates for IORT boost treatments followed by EBRT than for EBRT with external boost (90,2% versus 62,3%). [14] Moreover, a tendency of a significant reduction of non-breast cancer mortality in patients receiving TARGIT followed by EBRT when compared with patients receiving EBRT alone (0 out of 218 patients treated with IORT boost followed by EBRT versus 24 out of 892 patients treated with EBRT alone) was presented as a poster abstract. [15] As a further perspective, the successful application of an IORT boost followed by EBRT in conjunction with oncoplastic breast conserving surgery [16] , underlining the usefulness of IORT boost treatment.

3.6 Economic evaluation

The attached economic evaluation shows that INTRABEAM® used as a single dose radiation treatment instead of 3-6 weeks EBRT is very cost effective. The model was based on costs per treatment and utility rates. Travel costs to the radiotherapy center for the 3-6 weeks EBRT as it is standard practice in the UK were not considered. In the Base Case Analysis INTRABEAM® yielded higher QALYs at a lower cost than the standard treatment of breast cancer using EBRT. Discounted EBRT and IORT costs for the time horizon of 20 years were £ 20, 926 and £ 14, 461 respectively. Discounted incremental QALY gained by use of IORT was 0.0069 QALY. Model results were robust to parameter uncertainty and probabilistic results were similar to the deterministic results. Probabilistic results are based on mean of 1000 simulations . Application of the net monetary benefits (NMB) framework show higher NMB for INTRABEAM® in all Monte Carlo simulations. Cost effectiveness acceptability curves show that INTRABEAM® is cost effective at various thresholds of willingness to pay (WTP). INTRABEAM® is therefore a cost effective strategy to treat early breast cancer patients in the UK. The model was calculated very conservative based on costs per treatment with standard EBRT not considering tariffs for more expensive newer EBRT (IMRT) techniques. Also the travel expenses to the radiation center and the possibilities of the IORT boost treatment with the same equipment were not included. Including those variables into the model would make the treatment with INTRABEAM® even more cost effective. Implementation of this treatment could save valuable NHS resources in comparison to the current practice of EBRT in these patients.

Section A: Decision problem

A.1. Description of technology under assessment

The core piece of the INTRABEAM system is the XRS miniature x-ray source equipped with an x-ray probe 10cm in length and 3.2cm in diameter. This x-ray probe delivers a high dose of low energy radiation to the tumour bed.

In addition, electrons along the x-ray probe are accelerated using a maximum acceleration voltage of 50kV. At the tip of the e-x-ray probe, they encounter a target object, and this process creates the x-ray beam. The effective emitted x-ray energy in approx. 20keV or less. The dose quickly drops in soft tissue because of the low energy of the x-ray (~$1/r^3$).This way the treated lesion can shield the healthy tissue against injuries. The Technical Specification brochure was sent via mail to NICE.

A.2. Context

The use of INTRABEAM is related to many treatment options in radiation therapy (e. g. brain, spine, abdomen, skin). Nevertheless till now, it is used most often in the treatment protocol of breast cancer. Most publications describing the use of INTRABEAM either in case reports or clinical trials are related to the treatment of breast cancer.

In principle there are two different ways of treatment intended to be performed using INTRABEAM

a) IORT given with INTRABEAM as the sole treatment

The methodology of IORT as the sole treatment is in contrast with EBRT. The IORT with INTRABEAM is given as one single fraction with a high dose directly to the tumour bed and possibly remaining tumour cells. In case of EBRT, the whole breast is irradiated administering the prescribed dose in small fractions over a period of several weeks, starting some weeks after lumpectomy. The EBRT treatment is finished with a boost given in small fractions (but higher doses than during WBRT) focused on the region of the tumour bed. In case IORT is given as the sole treatment, no EBRT is given avoiding 5-7 weeks of treatment (in the UK 3-6 weeks).

b) IORT given with INTRABEAM as a boost treatment followed by EBRT

In case IORT is given as a boost treatment the intraoperative boost radiotherapy is given with INTRABEAM and the treatment is followed by EBRT (normally 25-30 fractions are administered some weeks after lumpectomy). No further external boost (normally about 5-10 fractions) is given in that treatment protocol, avoiding two further weeks of treatment.

A.3. Equity and equality

We are not aware of any equity or equality issues.

A.4. Statement of the decision problem

To assess the clinical and cost effectiveness of the INTRABEAM ® Radiotherapy System for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Section B: Clinical and cost effectiveness

B 1 Clinical Evidence

B 1.1 Identification of studies

A systematic literature search following a search protocol (defined search terms) was conducted. The search was performed in the following databases.

- Pubmed
- Cochrane
- DIMDI

The selection of the above mentioned databases was made based on the conviction that these databases reliably cover the most important and relevant journals and publications.

B 1.2 Study selection

The following search terms were being used:

> [(breast cancer) OR (breast tumor) OR (breast carcinoma)] **AND** [(("radiotherapy") OR "radiation therapy")) AND ("intraoperative")) OR (intraoperative radiotherapy) OR (IORT)]

The literature search was conducted in September 2013 and repeated for update reasons in December 2013.

B 1.3 Inclusion and exclusion criteria

Literature related to the subject to be evaluated were included in this evaluation.

Literature published before the year of 2007 was not respected as it is believed that such literature can hardly cover the current state of the art. The technology was used beginning with the year 2000 in a few centres. We assumed that substantial follow up experience (for more than 5 years) is available after 2007 only. Studies reported in full were included in the review; studies that were reported in abstract form were included if a new population from new sites were investigated. Studies that reported results for sub-groups of patients with additional data or sub-analyses from the primary studies were also included.

B 1.4 Multiple publications

Multiple publications with the same study population were included only when the article reported additional data to the primary publication.

B 1.5 Relevant RCT

Several publication dealing with the application and the outcome of treatment with the INTRABEAM system are available. Nevertheless, real randomized controlled studies are rare and most publications are either case reports or analysis of subgroups of the randomized trial. However, results of non-randomized trials are also presented here as we believe that they support our point of view.

Section 1: Literature related to IORT given as a single dose

1.1 Results of randomized trials with regard to recurrence and survival rates

A randomized trial including nearly 3.500 patients in two arms was conducted and is known under the name of “TARGIT-A“. [1] The aim of the study was to evaluate the hypothesis that in case of low-risk patients and early cancer IORT as the sole treatment (TARGIT) administered with INTRABEAM is not inferior to the treatment option EBRT. The concept and the TARGIT technique allows the patient to receive all required radiation intraoperatively (in one fraction) and before she wakes up from anesthesia. The surface of the tumor bed is irradiated with a dose of typically 20Gy, a dose that attenuates to 5-7Gy in 1cm tissue depth.

The 5-year follow-up results were published just recently (Nov. 2013). The investigator initiated trial was designed using two different arms:

- Arm A Treatment with IORT alone
- Arm B Treatment with EBRT (whole breast radiotherapy)

Patients were randomized to the treatment groups. For patients in both groups, pathology was made and the further treatment of patients in Arm A was decided on with respect to the outcome of pathology. In case pathology gave hints of risk factors, the patient received EBRT in addition to TARGIT. In case no risk factors were found IORT was the only treatment the patient received. Further distinction was made per protocol amendment – in some centres the method of treatment was changed and instead of radiation included in the initial surgery centres, neighbouring centres were allowed to administer IORT as a second intervention after evaluation of final pathology (“post-pathology”). The dose of radiation was administered during a second surgery by opening of the wound and administration of radiation, medium time 37 days after the first surgery along with a completely separate randomisation table for such patients. This protocol amendment lead to separate strata, equivalent to two trials run in parallel.

Basis data of the trial

The trial was conducted in 33 centres in 11 countries in the period between March 2000 and June 2012. In total, n=3451 patients were recruited in the period between March 24th 2000 to June 25th 2012. N=1721 patients were randomly allocated to TARGIT and n=1730 to EBRT. N=2298 patients were randomized before lumpectomy (pre-pathology) and n=1135 were randomized after lumpectomy (post-pathology). It is described that among those patients receiving TARGIT, n=239 out of 1571 (15,2%) received both IORT and EBRT in the pre-pathology stratum, and n=20 patients in the post-pathology stratum (3,6%) received both IORT and EBRT. The numbers of patients in the respective groups are summarized in *table 1*:

Total number of patients recruited	n=3451
Number of patients randomized before lumpectomy (“prepathology group”):	n=2298
Number of patients randomized after lumpectomy (“post pathology group”)	n=1153
Number of patients randomly allocated to TARGIT arm	n=1721
Number of patients randomly allocated to EBRT arm	n=1730
Patient drop-out in TARGIT A arm	n=150

Table 1: Number of patients in the respective trial groups

Number of patients in TARGIT A arm, prepathology group	n=1012
Number of patients in TARGIT A arm, postpathology group	n=559
Number of patients in TARGIT A arm that received both IORT and EBRT	n=239
Number of patients in TARGIT A arm, prepathology stratum, with IORT and EBRT	n=219
Number of patients in TARGIT A arm, postpathology stratum, with IORT and EBRT	n=20

Table 1: Number of patients in the respective trial groups (continued)

The core protocol defined three features when EBRT would be recommended to supplement TARGIT within the experimental group:

a) Tumour free margin smaller than 1mm
b) Extensive in-situ component
c) Unexpected invasive lobular carcinoma

Patient and tumour characteristic are presented in *Appendix 1, table 1*:

Inclusion criteria for patients

Patients aged 45 years or older and suitable for wide local excision for invasive ductal carcinoma found unifocal on conventional examination and imaging were considered as eligible.

Method of randomization

Patients were randomly assigned in a 1:1 ratio to receive either risk-adapted approach using single-dose TARGIT or EBRT as per standard schedule over several weeks. In case final pathology report showed unpredicted prespecified adverse features, then EBRT to be added to TARGIT in which case TARGIT served as the tumour bed boost.

Initially it was planned that randomization to either TARGIT or EBRT will be done before lumpectomy (i.e. pre-pathology). Nevertheless, the protocol was amended in 2004 and allowed intraoperative radiotherapy as a second procedure, i.e. by reopening the wound (i.e. post-pathology stratum). Results were analysed separately (pre-pathology versus post-pathology).

Primary outcome

Primary outcome measure was the absolute difference in local recurrence in the conserved breast (patients receiving BCS), the initial recruitment goal was a total of n=2232 patients.

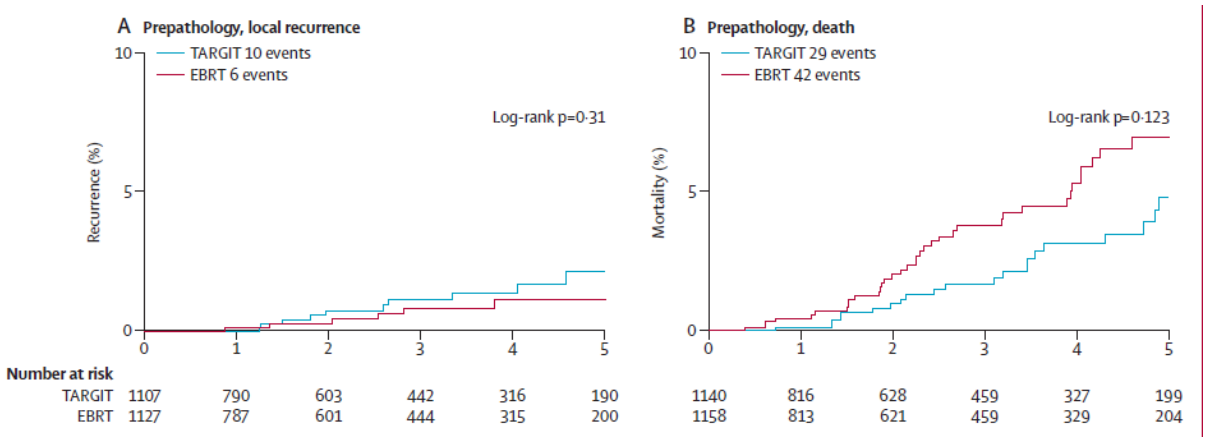
Secondary outcome

The secondary outcome were toxicity and overall survival, including breast cancer deaths as well as non- breast cancer deaths.

Results obtained

The risk of local recurrence with TARGIT turned out to be non-inferior to EBRT when all patients were analysed together. The analysis of the two strata according to timing of delivery of TARGIT confirmed that TARGIT was much as the same as EBRT when TARGIT was delivered concurrently with lumpectomy (i.e. pre-pathology), but not in the post-pathology stratum in which TARGIT was given as a second procedure after surgery with reopening of the wound). The local recurrence in the pre-pathology was 2.1 % (TARGIT) vs 1.1 % (EBRT) and the mortality was 4.6 % (TARGIT) vs. 6.9 % (EBRT).

Figure 1: Kaplan-Meier analysis of local recurrence in the conserved breast and death for the pre-pathology strata as per timing of randomisation and delivery of TARGIT. Local recurrence was the primary outcome, death was a secondary outcome. Pre-pathology (n=2298), randomised before lumpectomy and TARGIT given concurrently with lumpectomy:



Analysing the two strata together, the 5-year risk for local recurrence in the conserved breast for was 3,3% (TARGIT) versus 1,3% (EBRT), but breast cancer mortality was the same in both groups (2,5% for TARGIT versus 1,9% for EBRT). Significantly fewer cases of non-cancer deaths in the TARGIT group than in the EBRT group (1,4% in the TARGIT group versus 3,5% in the EBRT group) are reported. The overall mortality was 3,9% for the TARGIT group versus 5,3% for the EBRT group. Thus, whereas the local recurrence rate is slightly higher in the TARGIT group the overall mortality is lower. At 5-year follow-up, the risk of local recurrence with TARGIT was non-inferior to EBRT when all patients were analysed together. Analysing the two strata according to timing, TARGIT given concurrently with lumpectomy as performed in the pre-pathology stratum of the TARGIT group can be seen as good as EBRT. Therefore in view of the present results the authors wished to exercise caution and only support the use of TARGIT concurrent with lumpectomy. The post-pathology is not recommended any further.

As an overall aspect it could be shown that breast cancer mortality has been much the same for TARGIT and for EBRT. Significantly less non-breast cancer deaths have occurred in the TARGIT group than in the EBRT group (fewer death from cardiovascular causes and other cancers). Wound-related complications were much the same between the two groups. Significantly fewer grade 3 and 4 radiotherapy-related complications with TARGIT than with EBRT were detected. Results are summarized in *table 3*:

Event: 5-year cumulative risk (95% CI)			
	TARGIT	**EBRT**	**Absolute difference*)**
All patients			
Local recurrence (n=3375)	23; 3,3% (2,1 to 5,1)	11; 1,3% (0,7 to 2,5)	12 (2,0%)
Any other recurrence (n=3375)	46; 4,9% (3,5 to 6,9)	37; 4,4 % (3,0 to 6,4%)	9 (0,5%)
Death (n=3451)	37; 3,9% (2,7 to 5,8)	51; 5,3% (3,9- to 7,3%)	-14 (-1,4%)
Prepathology			
Local recurrence (n=2234)	10; 2,1% (1,1 to 4,2)	6; 1,1% (0,5 to 2,5)	4 (1,0%)
Any other recurrence (n=2234)	29; 4,8% (3,1 to 7,3)	25; 4,7% (3,0 to 7,4)	4 (0,1%)
Death (n=2298)	29; 4,6 (1,8 to 6,0)	42; 6,9% (4,3 to 9,6)	-13 (-2,3)

Postpathology			
Local recurrence (n=1141)	13; 5,4% (3,0 to 9,7)	5; 1,7% (0,6 to 4,9)	8 (3,7%)
Any other recurrence (n=1141)	17; 5,2% (3,0 to 8,8)	12; 3,7% (1,9 to 7,0)	5 (1,5%)
Death (n=1153)	8; 2,8% (1,3 to 5,9)	9; 2,3% (1,0 to 5,2)	-1 (0,5%)

*) in Kaplan-Meier point estimates at 5 years (TARGIT minus EBRT)

Table 2: Events, 5 years cumulative risk (95% CI)

Table 3 gives an overview of causes of death other than breast cancer

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
- Cardiac	2	8 (including 1 sudden death at home)
- Stroke	0	2
- Ischemic bowel	0	1
Other	7 Diabetes: 2 Renal failure: 1 Liver failure: 1 Sepsis : 1 Alzheimer Disease : 1 Unknown : 1	8 Myelopathy: 1 Perforated bowel: 1 Pneumonia: 1 Old age: 1 Unknown: 4
Total	17	35

Table 3: Causes of death other than breast cancer

The aim of the trial was to complete the treatment in the TARGIT group with only one radiation treatment delivered at the time of surgery. In case subsequent pathology suggested adverse histological features, the treatment was continued by EBRT, but without a tumour bed radiation boost. This scenario did happen in about 15% of the cases.

Results obtained from pre- and post-pathology group were compared and evaluated, and length of follow-up between the pre- and post-pathology was nearly the same. They differed by about one month, although randomization in the post-pathology stratum started later, as only about 5%of the patients could be recruited within the first few years before the post-pathology stratum was started. Results of an unplanned post-hoc exploratory non-randomised comparison of tumour characteristics and primary and secondary outcome as per treatment received amongst those who were randomized to TARGIT and received the allocated treatment is presented in *table 4*:

	Prepathology patients who received TARGIT Alone N=793	Prepathology patients who received TARGIT+EBRT N=219	Postpathology patients who received TARGIT Alone N=539
T size			
≤1cm	36% (256/703)	24% (47/199)	52% (269/515)
1-2cm	52% (366/703)	49% (98/199)	43% (223/515)
>2cm	12% (81/703)	27% (54/199)	5% (23/515)
Grade			
Grade 1	27% (188/707)	19% (38/200)	59% (285/486)
Grade 2	54% (380/707)	60,5% (121/200)	38% (182/486
Grade 3	20% (139/707)	20,5% (41/200)	4% (19/486)
Lymph node positivity			
Node negative	85% (604/712)	63% (126/201)	95% (492/519)
1-3 nodes involved	13% (94/712)	29% (59/201)	5% (27/519)
>3 nodes involved	2% (14/712)	8% 816/201)	0 (0/519)
5-year local recurrence in the conserved breast (95% CI)	2,7 (1,3-5,5)	0,9 (0,1-6,1)	5,9 (3,3-10,5)
5-year risk of breast cancer death (95% CI)	1,8 (0,7-4,6)	8,0 (3,5-17,5)	0,6 (0,2-2,5)
5-year risk of deaths from other causes (95% CI)	1,9 0,9-4,0)	0	1,5 (0,6-4,3)

Table 4: Unplanned post-hoc exploratory non-randomised comparison of tumour characteristics and primary and secondary outcome as per treatment received amongst those who were randomized to TARGIT and received the allocated treatment. Percentages are of the known values (continued)

The post-pathology group had the same or even less risk factors than the pre-pathology group, thus the difference in the results are not related to a variance in the patient population. The difference can be explained by the delayed application of radiotherapy. No increased toxicity with TARGIT were observed and radiotherapy-related local toxic side-effects were slightly reduced. Differences in the non-breast cancer related deaths between the EBRT groups in the pre- and post-pathology strata were statistically not significant. Cause-specific deaths were also much the same in the two groups, nevertheless, significantly fewer non-breast cancer deaths in the TARGIT group are described. Results are summarized in *table 5*:

	TARGIT	EBRT
Wound related complication		
Haematoma / Seroma requiring more than 3 aspirations or surgery	4	2
Wound infection requiring intraveneous antibiotics or surgery	12	9
Skin breakdown / Delayed wound healing	3	5
Total	19 (1,1%)	16 (0,9%)
	p=0,599	
Radiotherapy related complications		
Radiation therapy oncology group (RTOG) Grade 3 or 4 radiotherapy toxicity	4 (0,2%)	13 (0,8%)
	p=0,029	

Table 5: Complication 6 months after randomisation

The results show that when TARGIT is given concurrently with lumpectomy there is an increase of 1% in local recurrence along with a potential decrease of overall mortality of 2-3% at five years. The authors conclude that TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative external beam breast radiotherapy.

Preliminary results (4-years follow-up) were already published before, but are not presented here as the more recent data are available. It is believed that the newer data include the 4-year follow-up data. [17]

1.2 Literature related to side effects and cosmetic outcome after IORT as a single treatment

Initial experiences using the INTRABEAM system and results obtained in a study conducted in patients that were enrolled in the period between 2004 and 2008 were published by **Elliott et al.** in **2011**. [4]

Basis data of the study

The prospective study was conducted in the period between 2004 and 2008. The procedure was performed in n=67 postmenopausal patients, and the IORT procedures was done as part of the original segmental mastectomy procedure in n=61 patients, while in the other six patients it was done after excision of the primary tumour with re-exploration of the segmental mastectomy site. Due to the final histopathology report, n=4 patients later had total mastectomy and n=11 patients went on to have total breast external beam radiation. Patients' data and tumour characteristics are presented in Appendix 1, *table 2.*

Inclusion criteria

Patients with invasive ductal carcinoma <3,5cm in diameter in breast were included. Surgeons confirmed that there were at least 1cm from the surgical margin to the skin and wall chest.

Method of randomization

No randomization was executed, patients did not agree to be randomized in study groups and wanted to avoid WRT.

Method of treatment

The prescribed dose was 5Gy at 10mm from the surface of the applicator (dose as in the TARGIT-A trial). IORT as part of the original segmental mastectomy procedure in n=61 patients, and in n=6 patients it was done after excision of the primary tumour with re-exploration of the segmental mastectomy site. Due to results of the final pathology status (positive surgical margins, tumour biology, and nodal status) n=4 patients later had total mastectomy, and n=11 patients went on to have WBRT.

Follow-up

Cosmetic outcome were evaluated at three months, six months and annually.

Results obtained

The INTRABEAM IORT procedure was performed in n=67 patients. Very few serious surgical or radiation complications are described. Post-operative seroma was proven in all patients by ultrasound. Seroma were symptomatic (pain and swelling) in n=17 patients (25%) and were managed by aspiration. Usually three aspirations were necessary to resolve the seroma within six weeks, but in one patient chronic seroma developing a draining sinus requiring excision.

Table 6 gives an overview of the adverse events:

Adverse events		Number of patients
Significant wound problems	Radiation fibrosis	1
	Recurring lymphangitis	1
	Radiation fibrosis	1
Recurrences	Local	0
	Distant / systemic	2
Deaths	Cardiac disease (no evidence of cancer)	1
	Systemic recurrence without local recurrence	1

Table 6. Adverse events

Post-operative cosmetic outcomes were considered as acceptable, no patient had a serious surgical deformity, but all patients developed some induration at the operative site. Severe fibrosis and fat necrosis were found in n=1 patient, requiring excision at 18 months. In n=1 patient, mild increased pigmentation of the skin at the surgery site secondary to radiation was found and n=2 patients had very minimal telangiectasia.

Results of cosmetic outcome based on the Harvard criteria are presented in *table 7*:

Outcome	[n]	[%]
Excellent to good results	n=57 out of 67	(85%)
Fair to poor results	n=10 out of 67	(15%)

Table 7: Presentation of cosmetic outcomes (no indication at which follow-up the data were obtained)

No serious systemic effects or other toxicities were detected. Till publication date there have been no local failures. The authors conclude that IORT with the Intrabeam System is feasible, with few complications, good cosmetic results, great patient acceptance and that it is practical and excellent for breast IORT in the community setting.

The INTRABEAM device and its use were described in a review article published by **Deneve et al.** [2] in **2012**. The authors describe their results obtained by a study using the INTRABEAM system with INTRABEAM Spherical Applicators of a suitable size.

Basic data

The results presented are derived from a single institution study performed on a prospectively maintained database on patients who underwent IORT at the time of the initial surgery for early-stage breast cancers. A total of n=42 patients were treated with targeted IORT using the INTRABEAM system at the time of breast conserving surgery. Patients' characteristics are presented in *table* 3 in *Appendix 1*.

Inclusion criteria

Eligibility criteria included postmenopausal women older than 60 years with oestrogen receptor positive tumours with invasive ductal histology. Primary clinical tumour size was less than 3,1cm, were clinically node negative. The patients had received no prior neoadjuvant treatment. Invasive tumours with limited lymphovascular invasion and/or HER2-positive disease on core needle biopsy were considered acceptable.

Method of treatment

All patients underwent breast conserving surgery with sentinel lymph node biopsy followed by IORT using the INTRABEAM device. A dose of 20Gy was delivered to the lumpectomy cavity. The skin-to-surface of applicator of at least 1cm was determined by intraoperative ultrasound. All patients underwent unilateral digital mammography and focused breast ultrasound of the lumpectomy site at about 6 months follow-up. The development of new calcifications or the presence of a seroma was noted by the interpreting radiologist. A total of n = 42 patients underwent targeted IORT with the INTRABEAM system at the time of breast conserving surgery. An IORT dose of 20Gy was delivered to all patients for a median IORT duration of 25 minutes. Adjuvant whole breast irradiation was given in n = 8 patients (19%).

Follow-up

No detailed data with regard to follow-up procedures are given.

Results obtained

At a median of 15 days to first postoperative examination the following side effects were found:

Side effect	No. of patients	[%]
Evidence for IORT-related hyperemia/erythema (without requiring antibiotics)	n=15	(12%)
Palpable seroma	n=14	(33%)
Cellulitis (one requiring surgical drainage 9 days post-operative)	n=2	(5%)

Table 8: Side effects

The following post-operative complications were detected:

Postoperative complication	n=5	(12%)
Abscess requiring drainage	n=1	
Cellulitis	n=2	
Infected seroma requiring aspiration	n=1	
Hematoma	n=1	

Table 9: Postoperative complications

At six-month physical examination the following findings were obtained:

Non-infectious localized hyperemia	n=4	
Asymptomatic palpable seroma	n=5	
Scar retraction	n=1	
Cellulitis	n=1	

Table 10: Results of six-month following

With a median follow-up of three months (range, 1 to 13 months) there were no local recurrences. Authors mention that the complete procedure of application of IORT did not lengthen the entire duration of the operation significantly and it would compare favourably as far as overall time and cost savings when considering that a typical 6-week postoperative radiotherapy course involves 6 to 7 hours of radiotherapy room time with 30 to 60 hours of patient time. According to the authors IORT-related toxicity is acceptable and avoids the time inconvenience of a 5- to 6-week postoperative course of whole breast irradiation, making it an attractive treatment alternative for a significant group of patients.

In **2013**, results from a systematic and objective assessment of the cosmetic outcome after targeted intraoperative radiotherapy were published by Keshtgar et al. [7] The results were obtained from a patient subgroup who were taking part in the TARGIT-A trial [1] The background of their study was the consideration that cosmesis would represent an increasingly important outcome of breast conserving treatment, and radiotherapy treatment contributes to this outcome.

Basis data of the study

The study was performed based on patients taking part in the TARGIT-A trial. Cosmetic outcome of n=342 patients that were enrolled and treated in the TARGIT-A trial were assessed for cosmetic outcome using objective criteria and measuring methodologies. For assessing frontal digital photographs were taken before TARGIT and EBRT, and yearly thereafter for up to 5 years. Patients' data and tumour characteristics are presented in Appendix 1, *table 4*.

Inclusion criteria for patients

Patients participating in the TARGIT-A trial from two centres were enrolled. Consequently, the inclusion criteria mentioned there were applied.

Method of randomization

As part of the TARGIT-A trial where the patients were taken from, patients were 1:1 randomized to the IORT arm (BCS followed by treatment with IORT alone, as long as no risk factors were found in pathology) or to the EBRT arm (BCS followed by EBRT).

Treatment

Patients underwent breast conserving surgery and radiotherapy, and were randomized to receive either IORT (20Gy to the surface of the tumor bed equivalent to 5-6Gy at depth of 1cm from the surface of the applicator) or conventional 3-5 weeks external beam radiotherapy. For IORT treatment, the TARGIT technique delivering the entire radiation therapy in a single fraction at the time of surgery following the removal of the tumor was used. TARGIT can be given either pre-pathology (i.e. before results from pathology are available) or post-pathology (i.e. after results from pathology are available and as a second surgical intervention. All patients in the IORT group in this study were in the post-pathology cohort.

Follow-up

For patients involved in the study digital photographs for cosmetic study were taken at baseline and yearly thereafter for up to 5 years.

Results obtained

Results were obtained using the BCCT.core software allowing a user-independent evaluation of results produced by automatic localization of fiducial points such as nipples, breast contour and sternal notch). Asymmetry, colour changes and scars were also evaluated, and cosmetic outcome was dichotomised into “excellent and good (EG)” and “fair and poor (FP)”. The results obtained by the objective evaluation indicate that the cosmetic outcome of patients treated with IORT if given as a second procedure (post pathology) in selected patients with low-risk breast cancer is significantly better than those treated with EBRT. Differences can be seen within the first year and continues to into the second year. From the third year onwards the EBRT group catches up with the IORT (TARGIT) group, which tends to remain at baseline levels. Patients in the EBRT group tended to significant breast asymmetries which probably is a consequence of a higher degree of fibrosis related to the larger volume of tissue in EBRT when compared with the focal nature of IORT. Changes in colour in the IORT group appeared as minimal, and colour differences between IORT and EBRT were more obvious one year following treatment and gradually decreased until year four when differences disappear. EBRT reaches non-significant difference to IORT in scar appearance following year two. Following a totally objective assessment in a randomised setting, the aesthetic outcome of patients demonstrated that those treated with TARGIT have a superior cosmetic result to those patients who received conventional external beam radiotherapy.

In the year **2013**, results from a single-center study using the INTRABEAM system were published by **Grobmyer et al.** [3] This study is claimed to be the largest single centre study reporting experiences with the INTRABEAM device in the US.

Basis data of the study

In total, n=78 patients with n=80 treatments (two cases of bilateral breast cancer) were included. Data including clinical presentation, diagnosis, stage, treatment details and recurrence were collected in the period between Nov. 2010 and Oct. 2012. Patient characteristics are shown in Appendix1, *table5*.

Inclusion criteria

Patients’ characteristics are presented in Appendix 1, *table 5*. No inclusion or exclusion criteria are mentioned.

Method of treatment

In all patients of the study, INTRABEAM IORT was planned immediately after lumpectomy. In patients where axillary lymph node metastasis, histologically positive lumpectomy margins, or lymphovascular invasion of in the lumpectomy specimen, adjuvant WBRT was recommended, and IORT was judged as the boost. Some patients then preferred mastectomy instead of margin re-excision and WBRT.

The prescribed dose was 20Gy to the surface of the applicator in all patients. Dose at 1cm from the surface ranged from 5Gy p 7Gy. Adequate skin spacing between the applicator and the skin was defined to be ≥1cm and ensured by intraoperative ultrasound.

Intraoperative ultrasound was performed with the applicator in place. N=68 (85%) did not require additional surgery after initial surgery and radiotherapy with INTRABEAM. N=12 (15%) patients underwent additional surgery, mastectomy (n=4) and margin re-excision (n=8).

Follow-up

Patients were evaluated beginning with 1 week postoperatively and assessment for any acute toxicity and postoperative complication was made. Then patients were assessed every six months for ongoing monitoring of cosmetic results and disease status, complications were evaluated using the “Radiation Therapy Oncology Group Toxicity Scoring System” based on Common Terminology Criteria for Adverse Events.

Results obtained

Post-treatment cosmesis was assessed based on achieved patient photographs using the Harvard breast cosmesis score, and available photographs were assessed by four independent observers.

The majority of complications and acute toxicities were either grade 1 or 2 (Radiation Therapy Oncology Group Toxicity Scoring System). No grade 3 complications and only 1 grade 4 complication were observed.

Seroma development in several patients during the early post-operative period was observed. Most of the seroma were asymptomatic and did resolve within 4 to 6 months, and only n=4 (5%) of the patients required one aspiration of seroma for symptomatic relief. Multiple aspiration of breast seroma was not required. Three cases of breast cellulitis (4%) that could be managed with antibiotics were found, and two patients had some mild erythema of the skin of the breast at their initial follow-up evaluation. It resolved without additional treatment within six weeks of their surgery.

A grade 4 complication was found in a patient who was noted to have ulceration of the skin of the breast three weeks after lumpectomy and radiotherapy treatment. Ulceration resolved within five weeks after radiotherapy treatment without additional intervention.

Results are summarized in *table 11*:

Complications		n	%
Seroma	Grade 1	20	25
	Grade 2	6	7,5
Dermatitis	Grade 1	3	3,7
	Grade 4	1	1
Infection	Grade 1	2	2,5
	Grade 2	2	2,5
Fibrosis	Grade 1	1	1

Table 11: Complication (Radiation Therapy Oncology Group Toxicity Scoring) in patients in series

After a medium follow-up of 12,5 months no local or regional recurrences were observed. In one patient, metastatic diseases to the bones had developed, (within 1 year of diagnosis).

Cosmesis has been assessed at each follow-up visit by assessing photographs of at least two different time periods. N=31 patients were considered as eligible, and assessment was performed on the basis of the Havard Cosmesis Scale. The majority of the patients had good to excellent cosmesis at all time-points, and cosmesis tended to improve with increasing follow-up time from lumpectomy and radiotherapy treatment.

A summary of the cosmetic outcome is given in table 12:

Assessment	1 month, %, (n=32)	6 months, % (n=34)	12 months, %, (n=17)	18 months, % (n=4)
Excellent, n	24	44	59	81
Good, n	49	43	33	19
Fair, n	20	8	4	0
Poor, n	5	4	4	0

Table 12: Results of cosmesis assessment

The use of INTRABEAM was associated with no local recurrences with a follow-up to 23 months. Radiation therapy with INTRABEAM was well-tolerated and is described as a safe technique for delivering radiation therapy to the tumor bed after breast conserving surgery, and toxicities appear to be low. Seroma rates were very low, particularly when compared with other techniques. The overall toxicity profile observed in the study is described as to be in contrast to other published data (e.g. balloon brachytherapy APBI techniques), data that would have demonstrated increased complication rates with other forms of partial breast irradiation. Results obtained from a comparison of the data obtained in that study with results achieved in the TARGIT-A trial (IORT arm) are presented in *table 18* show low toxicity and complication rates as already shown in TARGIT-A and seem to be even better than in the international TARGIT-A trial:

	TARGIT A IORT arm (n=1113)		Current series (n=80)	
	n	[%]	n	[%]
Hematoma needing surgical evacuation	11	1,0	0	0
Seroma needing 3 aspirations	23	2,1	0	0
Infection needing IV antibiotics or surgical intervention	20	1,8	2	2,5
Skin breakdown or delayed wound healing	31	2,8	1	1
RTOG toxicity grade 3 or 4	6	0,5	1	1
Major toxicity *)	37	3,3	1	1

*) Major toxicity defined as skin breakdown or delayed wound healing and RTOG toxicity grade 3 or 4

Table 13: Comparison of current series with the Intraoperative Radiation Therapy Arm of TARGIT-A

The authors conclude that although follow-up for patients in this series is relatively short (up to 23 months), there have been no local recurrences to date and have demonstrated good to excellent cosmetic results associated with the use of IB.

In **2012** results from a group in Denmark reflecting on persistent pain after breast cancer treatment (PPBCT) were published by **Andersen et al.** [18] The background of this publication was the consideration that EBRT has been shown to be a risk factor for PPBCT and the question whether IORT using a smaller field of radiation may reduce the development of PPBCT.

Basis data of the study

The result were obtained through a retrospective questionnaire based study based on patients included in the TARGIT-A trial.

Inclusion criteria

Patients identified in the local TARGIT A trial database from March 2007 to January 2010 were examined for eligibility. Inclusion criteria were postmenopausal women with primary unifocal and unilateral breast cancer age 50 or older, T1, N0 (N0)i+) and N1(mi), M0, oestrogen receptor positive confirmed by cytological or histological examination, suitable for BCS. Patients included must be available for regular follow-up for at least ten years. Exclusion criteria were bilateral cancer at the time of diagnosis, previous cancer in and / or irradiation to ipsilateral breast, patients known to have BRCA2 gene mutation, lobular cancer or extensive intraductal component, patients undergoing primary medical treatments (hormone or chemotherapy). Patients with previous contralateral breast surgery, local recurrence, metastatic disease, other cancer or axillary lymph node dissection, other cancer or axillary lymph node dissection were also excluded.

Method of treatment

Patients were treated following the TARGIT-A trial protocol

Follow-up

No details on follow-up given, questionnaire based analysis.

Results obtained

Prevalence of pain was 33,9% in the EBRT group and 24,6% in the IORT group. Pain localization was similar in the two groups. Pain intensity was low and not different between the two groups for most of the patients. In the EBRT group, 71% of the pain patients and 77% of the pain patients in the IORT group had scoring of 3 or lower on the rating scale (0=no pain, 10=worst imaginable pain). 86,8% of the pain patients in the EBRT group reported on pain on a weekly basis or more often, versus 64,5% of the IORT group patients. Prevalence of pain elsewhere (i.e. outside the treatment area) were found to be larger in the IORT group than in the EBRT group (40,7% versus 26,4%), but the authors point out that there is no pathophysiological explanation that IORT should give more pain in general. Prevalence of sensory disturbances was similar.

. The results of the comparison of IORT and EBRT in terms of the risk developing PPBCT as a sub-analysis of the randomized TARGIT-A study showed, that IORT does not increase risk of developing PPBCT compared with EBRT, but with a tendency towards a positive effect of TARGIT with regard to prevalence and frequency of PPBCT.

Whereas results with regard to long-term toxicities are well available in literature, considerations on immediate postoperative complications were published just recently by **Tuschy et al.** [5]

Basis data of the study

Results were obtained through a retrospective analysis of n=147 women in whom IORT was applied as a boost irradiation and n=61 patients who received IORT without additional boost. Both patient groups were part of the patients included in the TARGIT-A trial, treatment was performed in the period between Feb.2002 and April 2007.

Inclusion criteria

Patients were included and randomized following the criteria described in the TARGIT-A trial.

Method of treatment

Patients were treated as described in the TARGIT-A trial.

Follow-up

No details of follow-up given

Results obtained

In general, no severe postoperative complications were observed, and the observed acute toxicity after IORT were low (no grade 3/4 acute toxicity. The most frequent side-effects observed were haematoma/suggilation (in 24% of the patients in the breast, in 10,6% of the patients in the axilla), and palpable seroma (17,3%). 13,5% of the patients developed a seroma located in the axilla, and in 3,8% palpable seroma emerged in the breast. Needle aspiration was necessary in 25% of the cases with breast seroma and in 78,6% of the cases with seroma located in the axillary. Erythema grade I-II developed in 13% of the women, but none of them were classified as grade III or IV.

No differences between the patients in which only IORT was applied and patients treated with additional EBRT with regard to short-term complications were observed within the first post-operative week.

Also just recently results obtained in prospective phase II study on the use of IORT in early breast cancer conduced in Saudi Arabia have been published by **Merdad et al.** [6] It is one of the earliest reports on IORT using the INTRABEAM system in the Middle East.

Basis data of the trial

Data were obtained through a prospective phase II study carried out in the Kingdom of Saudi Arabia in the period between Dec.2010 and Nov.2012. N=45 patients were included in the study.

Inclusion criteria

All women with biopsy proven invasive duct carcinoma (IDC) and clinical mass of ≤3,cm, unifocal, unicentric based on radiological data and eligible for BCS were included.

Method of treatment

A radiation dose of 20Gy to the surface of the tumour bed (typically attenuating to 5.7Gy at one centimetre depth) was administered. In n=29 patients (64%) received IORT as the sole treatment, in n=16 patients (36%) EBRT was administered after IORT.

Follow-up

Median follow up:18 months (range,2-24 months); no further details given

Results obtained

Due to socio-economic factors the enrolled patients had a more advanced disease at diagnosis and had significant differences regarding patients and tumour characteristics between the study and TARGIT-A trial. None of the patients developed clinically significant complications [e.g. skin breakdown, delayed wound healing, infection needing intravenous antibiotics or surgical intervention, seroma needing aspiration, or hematoma needing surgical evacuation except for n=1 patient who developed RTOG grade 3 toxicity (moderate to severe skin erythema)]. N=12 patients proved to have fat necrosis. N=7 patients developed late radiotherapy skin effects such as skin thickening. Due to the small number of patients, no correlation between the incidence of late toxicities and EBRT, IORT applicator size, or tumour size could be evaluated. With a follow-up of 18 months (median, range, 2-24 months) none of the patients developed local or distant relapses. All patients achieved at least acceptable cosmetic outcome according to the patient or physician judgement.

The results listed above are also supported by results presented as poster abstracts. Although they cannot be considered as high quality literature, they are included here as they help to draw the picture.

Kolberg et al [8] presented data reflecting the satisfaction of patients and gynaecologists with the cosmetic results after completion of WBRT. Data were collected from the first 200 patients treated with INTRABEAM during BCS and were obtained in Bottrop (Germany).

Results are presented in *table 14*:

	Excellent	Good	Satisfying	Acceptable	Poor	Inacceptable
Patients	6%	63 %	23%	6%	2%	0%
Gynecologists	9%	59%	27%	2%	3%	0%

Table 14: Satisfaction with the cosmetic results after completion of the whole breast irradiation

The satisfaction of 92% (patients) and 95% (physicians) with the cosmetic results shows that IORT does not lead to a compromise in the oncoplastic approach

Results obtained in a study conducted in Lublin (Poland) including n=85 female patients were presented as poster abstract by **Jankiewicz et al.** [9] Patients were treated either with IORT alone (n=19) or with IORT followed by EBRT (n=61). Early complication occurred in 20% of the patients, but no serious complications prolonging hospitalisation appeared. Most frequent complications were prolonged wound healing (20%), inflammation of the tumour bed (14,1%), and breast inflammation (7,1%). Early radiation toxicity was observed in 15,3% of the patients, and the most frequent late complication was grade 2 fibrosis limited to the treated quadrant. No grade 3 or 4 fibrosis was detected in a 48-month follow-up, but seroma was detected in 37,7% of the patients. One case of local recurrence was detected in the IORT group, and no local recurrence was observed in the IORT plus EBRT group. 5-year overall and disease specific survival was 100% in the IORT group and 95,1% and 96,7%, respectively, in the IORT plus EBRT group. Excellent and good aesthetic outcome was achieved in about 90% of the patients. The results underline that IORT, combined with BCS in early breast cancer is a well-tolerated and safe method with low rates of complications. In the 5-years follow-up it provided good local control.

Results presented as a poster at the ASCO Annual Meeting in **2013** show the results of a study conducted in Israel by **Steiner et al.** [10] Results are based on the outcome of treatment of n=400 patients with low-risk early stage breast cancer. INTRABEAM was used to administer a dose of 20Gy to the surface of the surgical cavity. 14,5% showed mild to moderate local complications (6,5% wound infection, 5,8% complicated seromas, 1,7% bleeding or haematoma, 0,5% small skin necrosis. Major complications were observed in 6,2% of the patients (2,5% requiring surgical intervention, 2% late healing, 1% requiring intravenous antibiotics, 0,7% grade III RTOG fibrosis). Ipsilateral breast failures are reported for 1,7%, and one case of axillary recurrence. Systemic disease was observed in 1% of the patients, one of them with simultaneous breast recurrence and one of them with contralateral breast cancer.

Looking at the data presented, evidence was given that IORT as a single method of treatment has shown to be non-inferior to EBRT (TARGIT-A trial). Moreover, it can be stated that beside the TARGIT-A trial, several other patients in different centres all over the world have been treated. The results published show that in general, recurrences rates are low and the cosmetic outcome is at least satisfying, if not even good to excellent.

1.3 Literature related to radiotherapy in cases where EBRT is not recommended

In **2007**, an article reporting on the single centre experiences of IORT treatment during excision of recurrent breast cancer in the previously irradiated breast was published by **Kraus-Tiefenbacher et al.** [19] The objective of their study was to evaluate whether a second radiotherapy in the form of IORT can be administered to patients suffering from recurrences and who were previously treated with EBRT, as for such patients, normally mastectomy would be preferred.

The approach described in the publication is to treat patients after re-resection of the recurrent tumour with partial breast irradiation (PBI). The hypothesis is the following: re-irradiation of a limited volume will be efficient on the one hand, but on the other hand side effects related to the irradiation will be within an acceptable range.

Basis data of the study

Patients considered in this investigation were treated in the period between April 2002 and November 2006. N=15 patients were treated for breast-cancer recurrences at a medium of 10 years after previous external breast radiotherapy (EBRT). N=2 additional patients were selected for IORT with new primary breast cancer after previous partial breast EBRT for treatment of Hodgkin's disease years before. Among these 17 patients, 10 recurrences were in the initial tumour bed, 3 elsewhere in-breast failure and 2 invasive recurrences after previous Ductal Carcinoma in Situ (DCIS).

Reason for previous irradiation are summarized in *table 19*, reasons for recurrences are presented in *table 15.*

Median age	65,8 years (48,3-86,9)
Previous EBRT to the breast	n=17 (100%)
Primary breast cancer	n=13
DCIS	n=2
EBRT of mediastinal and axillary lymph nodes because of Hodgkin's disease:	n=2

Table 15: Reasons for previous radiotherapy

Recurrences	n out of total
Same histology and tumour localization as before (same quadrant, true in-breast tumour recurrence)	n=10 out of 17
Recurrences with a different histology, but the same location (categorized as secondary cancer)	n=3 out of 17
Previous EBRT due to DCIS, developed invasive recurrence during further follow-up	n=2 out of 17
Invasive breast cancer after treatment of Hogdkin's disease years before	n=2 out of 17

Table 16: Reasons for recurrences

Method of treatment

IORT was administered in a single dose, median dose at surface applicator surface: 20Gy (14.7 to 20Gy 50kV-X-ray at the applicator surface).

Follow up

Median follow-up time was 26 months (1 to 60 months). All patients underwent a prospective, predefined follow-up including clinical examination, and breast-ultrasound at 6 monthly and mammographies at yearly intervals.

Results obtained

After a median follow-up time of 26 months (1 to 60), n=16 of the n=17 patients were still alive. N=1 patient with secondary breast cancer died due to pulmonary metastases that were diagnosed 19 months after treatment for recurrence.

Acute toxicity was evaluated and judged as mild (no Grade 3/4 toxicities were observed and there was no delay in wound healing nor was wound infection to be observed. N=6 patients (35.3%) showed a limited induration of the tumour bed, for n=3 (17.6%) the induration was judged as moderate to severe. Cosmetic outcome after the median follow-up of 26 months is described as satisfactory (n=7 patients: excellent, n=7 patients good, and n=3 patients fair,

respectively). No unexpected toxicities were observed during a median follow-up of more than 2 years.

In the year **2010** results of a study intended to determine safety and efficacy of targeted IORT in cases where EBRT is not feasible were published by **Keshtgar et al.** [31]

Basis data of the study

Experiences were obtained in three centres (Australia, Germany, United Kingdom) in the period between 1999 and 2008. N= 80 patients received the TARGIT protocol treatment alone as treatment of breast cancer. N=3 out of these n=80 patients received "percutaneous radiotherapy" alone, using the INTRABEAM under local anesthetic, and these patients had considerable comorbid conditions. N=21 patients treated with IORT were treated with EBRT in the past (N=18 for breast cancer in the same breast, n=3 had received mantle radiotherapy for treatment of Hodgkin's disease).

Inclusion criteria

The selected patients treated with IORT in this study were not eligible for the TARGIT trial, but were offered IORT outside the randomized clinical trial. Inclusion was agreed on for selected patients after careful considerations. Patients were not eligible for TARGIT trial due to in acceptability to be randomized to the EBRT arm. Nevertheless, the patients had compiling indications for BCS and refusal to accept mastectomy as an option. Reasons for treating off trial are presented in *table 17*, patients and tumour characteristics are shown in Appendix 1, *table 6*.

Reasons for TARGIT	No. of patients	Age (IQR) [years]	Follow-up (IQR) [months]	LR*)
Previous EBRT	21	60 (53-70)	42 (28-66)	0
Clinical reasons including comorbidity	31	69 (61-79)	29 (18-49)	1
Compelling personal reasons	28	67 (53-76)	45 (25-60)	1
Total	80	67 (56-76)	38(24-57)	2

*) *LR = number of local recurrences*

Table 17: Reasons for treating breast cancer with TARGIT off-trial

Method of treatment

A single radiation dose of 20Gy to the breast tissue (6Gy at 1cm distance from the applicator) were given after tumour excision.

Follow-up

Median follow-up of the patients was 38 months (IQR, 24-57; range , 3-105 months). None of the patients were lost to follow-up

Results obtained

The annual local recurrence rate was 0,75% (95% CI, 0.09% - 2,70%). During follow-up period, n=14 of the n=80 patients (17,5%) died of various causes, without any local disease recurrence.

There were no reports on clinically significant radiation toxicity in any of the cases treated. However, the authors mention that giving IORT after previous EBRT increases the risk of fibrosis (255 vs. 15%), but they also mention that this effect has already been reported in literature.

Acute toxicity after IORT were mild, with no grade 3 or 4 toxicities, and no delay in wound healing or wound infections were detected, except for one patient. Two cases of local

recurrence were detected at the time of the publication. No unexpected toxicity were observed and the results obtained correlated well with other series of BCS which have found a low acceptable local recurrence rate. The patients tolerated the treatment well without any evidence of radiation toxicity and, no excess dermatological side-effects.

Section 2: Literature related to IORT as boost followed by EBRT

2.1 Literature related to recurrence and survival rates when IORT is given as a boost followed by EBRT

Results describing the outcome of treatment of women with IORT, given as a boost and followed by EBRT were published by **Wenz et al.** in **2010**. [11] The report is on the outcome of the first 5 years after introduction of the approach to deliver IORT as a tumour bed boost during BCS for breast cancer, followed by EBRT.

Basis data of the study

The analysis was conducted as a single centre study in the period between 2002 and 2007. The analysis includes n=155 breasts of n=154 women. IORT as a boost, followed by EBRT, was applied. Patients' characteristics are shown in Appendix 1, *table 7*.

Inclusion criteria for patients

No information with regard to patients inclusion criteria are given.

Method of treatment

After wide tumour excision of the breast cancer, a single dose was given. The first 8 cases received 14,7 to 17,6Gy during dose finding, and later only 2 cases received less than 20Gy. The radiation doses were described at the surface of the applicator, and the INTRABEAM system was used as source of radiation. Duration of treatment was between 7,5 to 51,1 minutes.

After completion of wound healing, EBRT to the breast was initiated. (median interval between IORT and EBRT 40 days, range 13-226 days). EBRT was done applying a dose of 46Gy in 2Gy fractions was prescribed.

In n=26 cases, a dose of 50Gy was given to the breast and the supra/infraclaviar lymph nodes.

Follow-up

Patients were recalled every 6 to 12 months for follow-up visits. Median follow-up was 34 months (max. 80 months, 1 patient lost during follow-up). N=79 patients were evaluated at three year follow-up for late toxicity.

Results obtained

Clinical late toxicity at 3 years was scored by the treating radiation oncologists (modified LENT – SOMA scoring system) in all 79 cases having a 3-years follow-up with an intact breast. In total, a number of n=10 deaths, n=8 distant metastases developed, and n=2 in – breast recurrences were observed. The overall survival rate (5 years) was 87% and the local (in-breast) relapse-free survival rate was 98,5%.

Chronic toxicity after 3 years was mild in n=79 evaluable patients, and approximately two third of the patients had no or only barely palpable breast fibrosis. 4 out of 79 patients (5%) had a marked increase in density. 8% of the patients had a breast edema. Skin toxicity was mild, including telangiectases (6%) and hyperpigementation (6%)

Chronic toxicity after 3 years was mild in n=79 evaluated patients. Results are presented in *table 18:*

Toxicitiy	Grade 1	Grade 2	Grade 3	Grade 4
Fibrosis	43%	22%	30%	5%
Telangiectasia	94%	6%		
Breast edema	92%	5%	3%	
Retraction	81%	19%		
Ulceration	100%	0%		
Hyperpigmentation	94%	5%	1%	
Pain	80%	10%	9%	1%
Lymphedema	93%	6%	0%	1%

Table 18: Late radiation toxicity scored using the LENT-SOMA scale after 36 months of follow-up, values are percentage

The study shows that an IORT boost using low-kilovoltage X-rays followed by EBRT yields very low rates of local failure and toxicity. This is especially important considering that 35% were T2 tumors, 30% were node positive, and 22% of patients were aged <50 years. The European Organization for Research and Treatment of Cancer (EORTC) boost trial had approximately half T2 tumors, approximately one fifth node-positive patients, and one third of the patients were aged <50 years. The local recurrence rate after 5 years in the EORTC multicentre trial was 4.3%, as compared with 1.5% in the presented cohort.

In the year **2010**, results obtained by a single center study dealing with local recurrence and chronic toxicities were published by **Blank et al.** [20] However, when looking at the data presented, it becomes obvious that they are very likely to be derived from more or less the same study population as results published in **2010** by **Wenz et al.** [11]. The results published by Wenz et al. were taken from a total of n=249 cases of breast cancer treated in the period between Feb.2002 and Dec.2007 at the University Medical Center Mannheim. The results published by **Blank et al.** [20] are derived from a total of n=314 breasts treated in the period between Feb.2002 and Dec. 2008 at the University Medical Center Mannheim, so it can be assumed that data in both publications are derived to at least a large extend from the same study and the same population.

In the year **2011**, results obtained from a study including a total of 300 cancers (in 299 unselected patients, one patient with bilateral cancer) treated in the period between July 1998 and August 2005 and considerations on the effects of IORT as a boost treatment were published by **Vaidya et al.** [13] The study was dealing with feasibility, safety, and long-term efficacy of targeted intraoperative radiotherapy (TARGIT) using the INTRABEAM device.

Basic data of the study

Consecutive patients of any age at different centres, diagnosed with invasive breast cancer and found suitable for BCS were approached and informed consent was obtained. Patients included were claimed by the authors to be “clearly not a selected good-prognosis cohort”.

Tumours in the study were unifocal on mammography, none of the tumours was >4cm in diameter. There was no restriction in tumour type, tumour grade, receptor status, or axillary lymph node involvement. Patients and tumour characteristics are presented in Appendix 1, *table 8*.

Inclusion criteria

Unselected patients undergoing BCS, no restriction with regard to tumour type, tumour grade, receptor status, or axillary lymph node involvement.

Method of treatment

Each patient had her breast conserving surgery following the local protocol, typically a wide local excision of the primary tumour and axillary surgery. Intraoperative radiotherapy (INTRABEAM) was delivered immediately after surgical excision (during the same anaesthesia), except for nine patients (Australian cohort) in which the intraoperative radiotherapy was performed in a second operation within a few weeks.

Radiation dose received by the tumour bed was between 18Gy to 20Gy at the surface of the applicator, and 5-7Gy at 1cm into surrounding tissue. All patients received external beam radiotherapy to the whole breast, typically 45-50Gy in 25 fractions over a period of 5 weeks).

Follow-up

Patients were followed up with at least a 6-month clinical examination and annual mammogram. The median follow-up is 60,5 months (range: 10-122 months)

Results obtained

The first patient was treated in 1998 and was alive and well at the time of the publication (2011). Results reported are summarized in *table 19*.

Ipsilateral breast tumour cancer	n=8
5-year Kaplan Meier estimate for recurrence	1,73% (SE 0,77)
Recurrence in the tumour bed	n=5 out of 8
5-year Kaplan Meier estimate for recurrence in tumour bed	1,04% (SE 0,59)
Development of contralateral breast cancer	n=7

Table 19: Summary of results reported

There were no problems with wound healing, even in such patients who needed to have subsequent surgery (re-excision, mastectomy for diffusely positive margins).

As a benchmark, results obtained through this study are compared to results received in the EORTC study and the START-B study. Both studies report on results of 5-years recurrence in boosted patients and it turned out that results of the EORTC boost study are inferior with regard to recurrence rates at 5 years when compared with the TARGIT boost data. Patients' data and recurrence rates are summarized in *table 20*:

High risk factors	EORTC boost	START-B trial	TARGIT boost
Young age	33% were ≤50	21% were ≤50	32% were ≤50
% >1cm	75 %	86%	78%
% Grade 3	Not available	23%	29%
% Node +	21%	23,6%	29%
Recurrence rate at 5years	4,3%	2,8%	1,73%

Table 20: High risk factors compared with EORTC and START-B trial

Besides the literature presented, poster abstracts underlining the statements made before. To compare the overall survival rates between patients treated with IORT followed by EBRT and of patients treated with EBRT after BCS, a matched pair analysis was done by **Sperk et al.** [14] Although results were only published as a poster so far, results are presented here as

they can support the hypotheses made. From a total of n=370 patients treated for breast cancer, a matched pair analysis could be done for n=53 pairs of patients. It could be shown that there is a strong tendency towards better overall survival after IORT boost (i.e. IORT followed by EBRT) than for EBRT plus external EBRT boost (90,2% versus 62,3% overall survival). One local recurrence is reported for each group after a follow-up of 15 months (EBRT group, local recurrence free survival 95%) and 12 months, respectively (IORT plus EBRT group, local recurrence free survival,98,1%)

Poster abstracts by **Vaidya et al.** [15] show the same tendency. A significant reduction in non-breast cancer mortality of the patients receiving TARGIT plus EBRT as pre-specified in the protocol in the TARGIT-Arm (i.e. treatment with IORT as a boost followed by EBRT) when compared with the EBRT group is reported. The non-breast-cancer deaths were in TARGIT (boost) +EBRT: 0/218 vs. in the EBRT arm: 24/892.

2.2 Literature related to side effects and cosmetic outcome when IORT is given as a boost followed by EBRT

In **2009**, results obtained from a study dealing with the question of seroma formation (frequency and volume) after breast conserving surgery followed by intraoperative radiotherapy were published by **Kraus-Tiefenbacher et al.** [21]

Basis data of the study

The data of presented in this study (retrospective study) were obtained in the period between 2005 and 2007. In total, n=73 breast of n=71 patients were treated with breast conserving surgery and IORT (INTRABEAM system, “IORT group”). In the same period, n=88 breast tumours in n=86 patients were treated with breast conserving surgery without IORT (“NO-IORT group”) and were evaluated accordingly.

Patients’ characteristics are presented in Appendix 1, *table 9:*

Both patient groups were equally distributed with respect to patient age, height, weight, tumour size and tumour localisation. Characteristics of the two groups are shown in *table 21*

Variable	IORT	NO-IORT	p
Cases/Breasts	73	88	
Age [year]	63,3	63,8	0,66
Height [cm]	163	164	0,99
Weight [kg]	72	65	0,08
BMI [kg/cm^3]	27,3	24,9	0,02
Breast volume [mL]	1263,9	1088,6	0,004
Tumour size [cm]	1,8	1,7	0,41
Interval BCS to CT [days]	33	41,5	0,04

Table 21: Descriptive statistics regarding the two patient groups

Inclusion criteria for patients

No details describing the inclusion criteria are given.

Method of treatment

For IORT Group: 20Gy 50kV X-rays were prescribed at the surface of the applicator for tumour bed boost irradiation (no further details given).

Results obtained

All n=157 patients (n=161 breasts) underwent a CT scanning for external beam radiotherapy planning and the rate of seroma formation was documented and seroma volume was measured. Clinical palpalation of the breast was undertaken by an experienced radiation oncologist. Differentiation were made between

- No clinical finding
- Clinically palpable seroma
- Clinically palpable seroma requiring puncture

Results are presented in *table 22:*:

	IORT		NO-IORT		
Parameter	**n**	**%**	**n**	**%**	**n**
Clinical Examination					
No seroma palpable	56	77	68	77	124
Seroma palpable	14	19	10	11	24
Palpable and puncture required	3	4	10	11	13
CT-findings					
CT-seroma	59	81	46	52	105
No CT-seroma	14	19	42	48	56
CT-seroma but no clinical finding	42	58	26	20	68
No clinical or CT finding	14	20	42	49	56

Table 22: Summarized results for both groups regarding clinical palpation and CT evaluation

The interval between BCS and CT was significantly shorter in patients with clinically palpable seroma or CT-seroma compared with those with no palpable seroma. The volume of any CT-seroma decreased with time after BCS, but subanalysis of the two groups (IORT vs. NO-IORT) showed no significant difference in speed of seroma resorption. The incident of either clinical or CT-seroma was not associated with tumour localization or tumour size.

Results obtained from a single institutional study intended to evaluate the feasibility of intraoperative radiotherapy (IORT) to the primary tumour bed as tumour bed boost after whole breast irradiation were published in **2011** by **Chua et al.** [12] Moreover, acute toxicity of IORT delivered to primary tumour bed was evaluated.

Basis data of the trial

Results are obtained through a single arm prospective trial, single institutional, non-comparative study. A total of n=60 eligible patients were recruited between Feb. 2003 and May 2005. In n=1 patient the tumour could not be localized (surgery and IORT were abandoned), for n=1 patient mechanical problems with the device were observed, and n=58 with wide local excision of the primary tumour and IORT in their first surgical episode. Clinical characteristics of the patients included are shown in *Appendix 1, table 10.*

Inclusion criteria

Female patients aged 18 years or older with unifocal histologically proven non-metastatic invasive carcinoma of the breast ≥3cm and assessed to be suitable for BCS, including wide excision and postoperative WBI were included.

Exclusion criteria

Patients with tumours showing clinical or radiological evidence of skin involvement or chest wall invasion and tumour location <5mm from the skin surface on ultrasound examination were excluded from the study.

Method of randomization

No randomization was performed.

Primary outcome

The primary outcome of the study was the evaluation of the feasibility rate and surgical and radiation toxicities of IORT delivered by the INTRABEAM system followed by standard WBI in women with early breast cancer resected by BCS.

Secondary outcome

As a secondary outcome the assessment of cosmetic outcome and the assessment of local control rate of the protocol therapy were defined.

Method of treatment

N=58 of the n=60 registered patients had wide local excision of the primary tumour and IORT in their first surgical episode. Primary tumour could not be localized in n=1 patient (surgery and IORT were abandoned). Another patient had surgery without IORT due to a mechanical failure of the INTRABEAM device. Axillary surgery was performed in n=57 out of 58 patients (sentinel node biopsy: n=53; sentinel node biopsy and immediate axillary dissection: n=4; no axillary surgery: n=1). N=9 patients had a second surgical procedure consisting of axillary dissection only (n=5), re-excision of the breast only (n=2) , re-excision of the breast and axillary dissection (n=1), and wide local excision of the breast and sentinel node biopsy (n=1).

N=58 patients received IORT and n=55 patients completed both components of the protocol therapy of IORT and WBI.

In case of resection margins <1mm or positive a re-excision of applicable margin(s) was undertaken, no further IORT delivered in these cases. For primary tumour resected with negative margins of ≥1mm the standard post-operative external beam WBI was given. No external tumour bed boost was given.

For IORT, a dose of 5Gy at 10mm from the outer surface of the applicator was delivered to the target breast tissue. IORT was followed by standard WBI (50Gy in 25 fractions given as a rate of 2Gy per day, 5 days per week, for 5 weeks).

Follow-up

All study patients were reviewed at weeks 2, 4, and 8 after IORT. They were also reviewed during the fifth week of WBI and then at weeks 2 and 12 post WBI.

A review of all patients at weeks 2, 4, and 8 after IORT was made.

Results obtained

The results obtained are summarized in *table 23:*

Feasibility rates of IORT alone	97% (95% CI, 89-99%)
Feasibility rates of IORT and WBI	92% (95% CI, 83-97%)
Severe surgical complications	n=2
Haemotoma requiring open drainage	n=1
Abcess requiring open drainage	n=1
Haematoma	
None	n=48 (83%)
Not requiring drainage	n=9 (16%)
Requiring open drainage	n=1 (2%)
Ipsilateral breast infection	
None	n=51 (88%)
Cellulitis requiring antibiotics	n=6 (10%)
Abcess requiring open drainage	n=1 (2%)
Radiation dermitis	
Grade 0	n=3 (5%)
Grade 1	n=16 (28%)
Grade 2	n=35 (60%)
Grade 3	n=1 (2%)
Grade 4	n=3 (5%)
Pain due to radiation	
Grade 0	n=5 (9%)
Grade 1	n=44 (76%)
Grade 2	n=8 (14%)
Grade 3	n=1 (2%)
Grade 4	n=0 (0%)
Breast wound infections requiring antibiotics therapy	n=6
Recurrence or death at a median follow-up of 21 months (range 3-36 months)	none

Table 23: Results obtained (continued)

Severe surgical complications such as haematoma or abscess requiring open drainage or grade 3 or 4 acute radiation toxicity were identified in only a few cases (10%) of the patients treated with IORT. 15% of the patients had breast wound infections. No recurrence or death was observed at a median follow-up of 21 months (range 3-36 months).

Malter et al. presented results obtained through using IORT in combination with oncoplastic BCS. [16] A total of n=100 patients were treated with IORT as a boost, followed by WBRT. Resection defects were reconstructed after IORT boost treatment using predefined oncoplastic principles to achieve optimal aesthetic results after BCS. With a median follow-up of 7,6 months n=1 patient had a chronic skin toxicity with percutaneous fistula, n=2 patients developed liponecrosis and n=3 patients developed a seroma which was punctured. It could be shown that IORT as a tumour bed boost using low energy x-ray is clinically feasible with low toxicity and complication rates. IORT supports the close interdisciplinary between radiation therapy and breast surgery and can be combined with oncoplastic principles in BCS.

2.3 Literature related to quality of life when IORT is given as a boost followed by EBRT

Results obtained through a single centre cross-sectional analysis that focused on quality of life after treatment with INTRABEAM were published by **Welzel et al.** in **2013**. [26] Starting point was the authors explain that in the year 2000, the international randomized phase III trial TARGIT-A, which started in the year 2000.

Primary aim of the study published by Welzel et al. was to assess radiation-related quality of life parameters in the first n=123 women from a single centre participating in the TARGIT-A trial.

Secondary aim of the study was to compare TARGIT-A IORT EBRT patients with two non-randomized control groups of patients treated with

a) IORT as a tumour bed boost followed by EBRT outside of TARGIT-A (IORT boost)
b) EBRT followed by an external-beam boost to the tumour bed (EBRT boost)

Quality of life was assessed using two validated questionnaires of the EORTC – the quality of life questionnaire C30 (QLQ-C-30) and the Breast cancer module (QLQ-BR-23)

Basis data of the study

N=230 women with stage I–III breast cancer were entered in the study. A subgroup of n=87 women from the two arms of the randomized phase III trial TARGIT-A was analysed, and results were compared to a non-randomized control group (n=90) receiving IORT as a tumour bed boost followed by external beam whole breast radiotherapy (EBRT) outside the TARGIT trial and n=53 treated with EBRT followed by external-beam boost (EBRT boost).

Patients' basic data are shown in *table 35*:

Inclusion criteria

To qualify for the analysis, patients had to be randomized in the TARGIT-A trial between 2002 and 2009 from the University Medical Centre Mannheim

Primary endpoint

Primary endpoints were the global health status, restrictions in daily activities (role functioning) and general pain subscales from EORTC.

Method of randomization

Patients included in this analysis were randomized in the TARGIT-A trial between 2002 and 2009 (one centre).

Method of treatment

Patients of the control group outside the TARGIT-A trial were treated in the same centre. Patients received BCS and either a combination of 20Gy IORT and post-operative EBRT of 46Gy in 23 fractions ("IORT boost group") or postoperative EBRT of 50Gy in 25 fractions ("EBRT boost group"). EBRT was initiated after wound healing and/or chemo therapy.

N=46 patients were allocated to the IORT, and n=16 patients out of this group were allocated for EBRT. N=4 patients did not receive IORT and one patient refused EBRT. N=42 patients were treated with EBRT. A total of n=87 patients were analysed.

Follow-up

The follow-up time was 39,1 months (median 41 months, range, 8 to 64)

Results obtained

Quality of life was assessed on the basis of two validated questionnaires of the EORTC – one was the "quality of life questionnaire" (QLQ-C30) and the other was the Breast Cancer Module (QLQ-BR23).

a) Intention to treat analysis for randomized patients from TARGIT-A trial

In the intention to treat analysis patients allocated for IORT showed more professional and other daily activities and fewer general pain symptoms compared to patients allocated to EBRT.

Variable	Allocated to IORT			Allocated to EBRT			
	N[a)]	Mean	SD	N[a)]	Mean	SD	p
Global Health status[b)]	46	61,6	21,7	40	54,8	19,9	0,183
Restriction in daily activities[b)]	46	72,8	32,3	41	61,8	29,2	0,055
General pain[c)]	46	29,3	32,8	42	42,5	33,0	0,048
Breast symptoms[c)]	45	17,0	20,8	42	18,1	20,2	0,629
Arm symptoms[c)]	45	24,4	26,7	40	31,1	27,9	0,279

a) Number of valid assessments
b) Higher scores are equal to good functioning/good quality of life
c) Higher scores are equal to severe symptoms/worse quality of life

Table 24: Preselected QoL variables between TARGIT-A patients allocated to IORT versus EBRT

Patients treated with IORT alone reported more professional and other daily activities when compared with patients treated with EBRT. Mean scores for general pain, breast, and arm symptom scales were significantly lower in IORT patients than EBRT patients. Differences in breast-symptoms between IORT and IORT-EBRT patients were also significant. Results are shown in *table 25*:

Symptoms (moderate/sever)	TARGIT-A			EBRT-boost	
	IORT [%]	EBRT [%]	IORT-EBRT [%]	IORT-boost [%]	EBRT-boost [%]
Pain in area affected breast	4/0	11/4	25/13	20/9	11/8
Swelling in area of affected breast	0/0	4/2	7/7	7/10	11/2
Oversensitivity in area of affected breast	4/0	9/7	20/7	20/15	11/8
Skin problems on or in area of affected breast	4/4	9/4	13/6	11/2	4/7
Pain in arm or hand	8/8	18/23	33/20	21/15	26/8
Swelling in arm or hand	8/4	9/7	6/6	18/9	19/6
Difficulties in raising or moving arm sideways	20/0	24/12	13/7	16/10	11/8

Table 25: Frequencies of moderate or severe breast and arm symptoms reported by patients in each group

No differences between IORT-EBRT group and IORT-/EBRT-boost patients were found for any of the quality of life comparisons. The authors summarize that a single-centre subgroup of patients of the TARGIT- A trial treated with IORT alone were found to have significantly better radiation-related quality of life as those treated with EBRT. This statement is related to the assessment of restrictions in daily activities (role functioning), general pain, breast, and arm symptoms. Patients of the TARGIT-A trial treated with IORT-EBRT are described to have significantly more breast symptoms, and a trend to more general pain and arm symptoms when compared to patients that received IORT alone, but did not differ from

patients treated with an IORT boost or EBRT boost outside the TARGIT-A trial or EBRT without a boost.

2.4 Literature related to the preferences of patients

Results obtained through a preference study conducted to determine the trade-off results that women might make for the convenience of a single treatment delivery intraoperatively were published in **2013** by **Alvarado et al.**. [30] The purpose of the study was to explore and quantify preferences of patients using trade-off techniques if they were given a choice between IORT and EBRT.

Basic data of the study

Data from n=81 patients were collected; patients' data are shown in Appendix 1, *table 12*.

Inclusion criteria

Women who were current and past current candidates for radiation following BCS were considered as eligible. No further details are given.

Method of treatment

No real treatment was performed, patients were asked for preferences. Methodologies were presented to the patients in a three-part presentation on the computer :

a) Introductory educational section

   Comparison of EBRT with IORT in terms of procedures, cost to insurance, possible side effect were made for the patients

b) Preference elicitation section

   Patients were asked about their preferences of treatment. Additional accepted risks that patients would accept to undergo IORT instead of EBRT were asked and assessed.

c) Brief survey about medical and personal history

   Questions on the survey included age at diagnosis, time since diagnosis, race, highest education, working status (full- or part time) primary caregiver status, tumour grade, types of therapy received or anticipated, and receptor status for oestrogen receptor, progesterone receptor, and HER2/neu. Patients who already had received their radiotherapy were asked for time since diagnosis, ability to continue working, type of treatment received (IORT, EBRT or EBRT with boost), commute to radiation facilities and radiation tolerance.

Follow-up

No follow-up was undertaken

Results obtained

Patients preferred the IORT option at equivalent local recurrence risk. N=2 patients accepted even 34-39% additional risk with IORT. The median accepted additional risk of local recurrence was 2,3%, which falls into the non-inferior margin of an absolute difference of 2,5% for the TARGIT-A trial. Results are presented in *table 26:*

Acceptance of IORT at no additional risk	n=22
Acceptance of IORT with some additional risk of having local recurrence within 10 years	n=52
No acceptance of IORT if recurrence risk is equal to that of standard EBRT	n=7

Table 26: Outcome of acceptance study

Results from a cross-sectional study of patients' preferences and their determinants were presented as a poster abstract by **Corica et al.** [27] N=209 women participating in the Australian cohort of the TARGIT-A trial were evaluated by self-rated questionnaires. N=108 patients received IORT and n=101 received EBRT as the method of treatment. The following results were obtained:

Acceptance of 4%-6% increase of local recurrence for increased convenience of IORT	36%
No acceptance of IORT at all	22%
Acceptance of 4%-6% increase of local recurrence for increased convenience of IORT	60% of patients treated with IORT
	12% (patients treated with EBRT)
No acceptance of IORT	2% (patients treated with IORT)
	43% (patients treated with EBRT)

Table 27: Acceptance of IORT

Given the early results of the TARGIT trial however, it is unlikely that the clinical difference in LR between IORT and EBRT will exceed what patients will accept.

Section 3: Literature related to potential drawbacks, restrictions and other side effects

3.1 Risks for patients with cardiac pace makers

Concerns with regard of negative effects of radiation therapy in patients with pace makers were discussed by **Keshtgar et al.** in **2012**. [28] Background of their consideration were reports describing that ionizing radiation would interfere with modern cardiac pace makers. It is described that irradiation of cardiac pace makers can result to altered sensitivity, amplitude changing, telemetry and programming defects, adjustments or loss of functions for seconds, days or even permanently. Doses as low as 2Gy are mentioned as being able to result in significant functional changes. The hypothesis of the work presented here was that IORT could be an alternative to EBRT in patients with cardiac pacemakers.

Basis data of the study

Single case study in a 83 year old female with a 15mm suspicious lump in the breast. Diagnosis of DCIS was confirmed by biopsy. The patient had a cardiac pace maker located in a subcutaneous tissue pocket 9cm away from the primary tumour.

Inclusion criteria

No inclusion criteria for this single case study were mentioned.

Method of treatment

Intraoperative radiotherapy using the INTRABEAM device was performed after wide local excision and sentinel node biopsy. A three diameter dose to the pacemaker was measured using thermoluminiscent dosimeters (TLD), which were placed on the edge of the device closest to the x-ray source, and the distance between the applicator shaft of the INTRABEAM and the pacemaker were recorded.

Results obtained

The average reading of the TLDs was 0,08Gy, the procedure was well-tolerated by the patient. Moreover, the function of the pacemaker was tested by a cardiology team before and after the treatment and there was no malfunctions of the pacemaker during surgery or IORT.

3.2 Risk of ischemic heart diseases due to radiation therapy in breast cancer

In **2013**, results obtained from a study evaluating the risk of ischemic heart diseases related with radiotherapy for breast cancer were published by **Darby et al.** [29] Background of the study were considerations that radiotherapy for breast cancer often involve some incidental exposure of the heart to ionizing radiation. Therefore, the authors conducted a population-based case-control study of major coronary events such as myocardial infarction, coronary revascularization, or death from ischemic heart disease. The analysis was carried out in Sweden and Denmark.

Basic data of the study

In a population based case-controlled study, a total of n=2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 were evaluated and n=963 women with major coronary events were included in the study. N=1205 women served as control group. Mean radiation doses to the whole heart and to the left anterior descending coronary artery were estimated from patient's radiotherapy chart. Data from patients in Sweden and Denmark were evaluated. Data are presented in Appendix 1, *table 13*.

Inclusion criteria

Women who received external-beam radiotherapy for invasive breast cancer were included. The following events were defined as "major coronary event":

- Myocardial infarction
- Coronary revascularization
- Death from ischemic heart disease

Women whose primary diagnosis was a major coronary event that after a diagnosis of breast cancer but before any recurrence or diagnosis of a second cancer were classified as case patients.

Eligibility criteria differed slightly between the two countries.

In **Sweden**, all women living in Stockholm for whom data were recorded in the Swedish National Cancer Register were considered if

- they received a diagnosis of breast cancer between 1958 and 2001
- were younger than 70 years of age at the time of diagnosis
- had received radiotherapy

Information on radiotherapy were taken from hospital records.

In **Denmark**, all women for whom data were recorded in the Danish Breast Cancer Cooperative Group were considered if

- they received the diagnosis breast cancer between 1977 and 2000
- were younger than 75 years at the time of diagnosis
- received radiotherapy

Exclusion criteria

Patients with diagnosis of angina alone were not included (angina could not reliably be identified by the authors).

Women without histopathology confirmation of breast cancer, with bilateral or metastatic disease at the time of diagnosis or with a history of cancer (excluding nonmelanoma skin cancer) or previous radiotherapy to the thoracic area were excluded.

Method of treatment

Radiotherapy charts, including a diagram or a photography of the field of treatment and a dose plan from the patients, where available, were copied and evaluated. Each radiotherapy regimen was reconstructed on the CT-scan of a woman with typical anatomy. Virtual simulation and CT planning involved the reconstruction of radiotherapy fields on a CT scan, and radiation doses at structures of interest were estimated using a treatment-planning system.

Results obtained

As results it turned out that among the case-defining major coronary events (event resulting in inclusion in the study)

- 44% occurred less than 10 years after breast cancer was diagnosed
- 33% occurred 10 to 19 years after breast cancer was diagnosed
- 23% occurred 20 or more years after breast cancer was diagnosed

In 65% of the patients, the case-defining major coronary events could be confirmed by hospital cardiology or autopsy reports and were consistent with 9% of case population. For the remaining 26%, no relevant records could be found. For 54% of the patients it was known that they have died due to ischemic heart disease, either at the time of their case-defining event or subsequently.

Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast, but there was no other strong association between the rate of major coronary events and tumour characteristics or the cancer treatment administered in addition to the radiotherapy. The overall rate ratio for a major coronary event among women with a history of ischemic heart disease as compared with women with no such history was 6,67 (95% CI, 4,37 to 10,18). The ratio has been 13,43 (95% CI, 7,65 to 23,58) during the first 10 years after the cancer diagnosis as compared with 2,09 (95 % CI, 1,05 to 4,13) during later years.

Rates of major coronary events were also elevated among women with

- a history of other circulatory diseases
- diabetes
- chronic obstructive pulmonary diseases
- smoking
- high body mass index
- regular analgesic use

The overall average estimated doses of radiation of the heart has been 6,6Gy for women with tumours in the left breast, and 2,9Gy for women with tumours in the right breast, and 4,9Gy overall range. The rate of major coronary events increased by 7,4% for each 1Gy increased in the mean dose delivered to the heart.

Women were grouped in four categories related to the radiation dose of the heart: <2Gy, 2 to 4Gy, 5.9Gy and 19Gy or more. There was an increased risk of major coronary events related to the dose delivered to the heart when compared with an estimated dose of zero to the heart. The increase in risk is presented in *table 28:*

Radiation dose to the heart	Increase of rate of major coronary events
<2 Gy	10%
2 to 4 Gy	30%
5 to 9Gy	40%
10Gy or more	116%

Table 28: Increase in risk of major coronary events related to radiation dose to the heart

With regard to the increase per Gy there was no significant difference for any of the matching factors used in selection of controls, tumour characteristics (including whether the tumour was situated in the left or in the right breast) or cancer treatments in addition to radiotherapy. Although the rate of major coronary events was higher among women with cardiac risk factors than among those without such risk factors, the percentage increase in the rate of major coronary events per Gray was similar for women with and those without a cardiac risk factor at the time of breast-cancer diagnosis.

The increase in the rate of major coronary events per Gray of radiation according to the number of years since radiation were the following (*table 29*)

Time since radiotherapy	No. of case patients	No. of controls	Increase in rate of major coronary events (95% CI) [%increase/Gy]
0 to 4 years	206	328	16,3 (3,0 to 64,3)
5 to 9 years	216	296	15,5 (2,5 to 63,3)
10 to 19 years	323	388	1,2 (-2,2 to 8,5)
≥ 20 years	218	193	8,2 (0,4 to 26,6)
0 to ≥ 20 years	963	1205	7,4 (2,9 to 14,5)

Table 29. Percentage increase in the rate of major coronary events per Gray, according to time since radiotherapy

Estimated mean doses to the left anterior descending coronary artery and to the heart were correlated and the authors mention that the mean dose to the heart would be a better predictor for major coronary events than the mean dose to the left descending coronary artery. The mean dose of radiation to the heart remained much more significantly associated with major coronary events after the mean dose to the left anterior descending coronary artery was taken into account, but the mean dose applied to the left anterior descending coronary artery was not significantly associated with the rate of major coronary events after the mean dose to the heart was taken into account.

Current doses administered to the heart due to radiotherapy for breast cancer of the right breast are mentioned to be typically 1 to 2Gy, and doses for the treatment in left breast are described as “may be around 10Gy”. The mean doses among the n=2168 women included in the analysis ranged from 0,03Gy to 27,72Gy (overall average of mean dose of 4,9Gy).

The risk of a major coronary event increased linearly with the mean dose to the heart and the magnitude of the risk was 7,4% per Gy with no apparent threshold below which was no risk. The risk started to increase within the first 5 years after exposure and continued for at least 20 years. The absolute increases in risk for a given dose to the heart were larger for women with pre-existing cardiac risk factors. Therefore the authors conclude, that clinicians may wish to consider cardiac dose and cardiac risk factors as well as tumour control when making decisions about the use of radiotherapy for breast cancer.

3.3 Risk of secondary cancer due to radiation therapy in breast cancer

Considerations on the risk of radiation induced secondary cancers were published in **2011** by **Aziz et al.** [22]. The authors mention that radiation induced secondary cancer would be a rare, but severe late effect after breast conserving therapy, and they intended to estimate the secondary cancer risk after IORT when compared to other modalities of breast radiotherapy.

Computer tomography scans of an anthropomorphic phantom were acquired with an INTRABEAM IORT applicator in the outer quadrant of the breast. Data were transferred to a treatment planning system via DICOM, and ipsilateral breast, contralateral breast, ipsilateral lung, spine and heart were contoured.

Three different treatment modalities were evaluated – IORT using INTRABEAM (single dose of 20Gy prescribed at the applicator's surface), APBI applying accelerated partial breast irradiation with 34Gy in 10 fractions (5days x 2 x 3,4Gy, prescribed at 10mm depth from the Intrabeam applicator surface) and EBRT using standard three dimensional conformal radiotherapy with 50Gy in 25 fractions to the whole breast using two tangential fields of wedges.

Mean and maximal doses, dose volume histograms (DVHs) and volumes receiving more than 0,1Gy and 4Gy of Organ at risk (OAR) were calculated and compared.

Comparison of isodose distribution from three breast radiotherapy techniques showed large differences in the dose distribution and especially in the low dose regions delivered to the OAR. Results are presented in *table 30*:

Dose to organ	**IORT**		**APBI**		**EBRT**	
	Mean dose [Gy]	Max. dose [Gy]	Mean dose [Gy]	Max. dose [Gy]	Mean dose [Gy]	Max. dose [Gy]
Ipsilateral breast	2,2	20	10,4	102	49,0	55,3
Contralateral breast	--	<0,3	--	<0,56	1,1	10,4
Ipsilateral lung	0,03	1,8	0,13	7,4	3,4	53,0
Contralateral lung	--	<0,3	--	<0,56	0,24	1,0
Heart	0,01	1	0,06	3,8	1	2,8
Spine	--	<0,3	--	<0,56	0,24	0,5

Doses of <,5% of the prescribed dose cannot be shown by the planning system (---)

Tab. 30: Volumes of OAR receiving doses greater than 0,1Gy and 4Gy which doses considered to be relevant for induction of secondary cancer

Volumes of OAR receiving doses greater than 0.1Gy and 4Gy (doses) were also estimated. Such doses were considered as relevant for induction of secondary cancers. Results are shown in *table* 31:

Dose to organ	IORT		APBI		EBRT	
	% Vol >0,1Gy	% Vol <4Gy	% Vol >0,1Gy	% Vol <4Gy	% Vol >0,1Gy	% Vol <4Gy
Ipsilateral breast	84,5	18,1	88,2	54,4	99,9	99,9
Contralateral breast	<1	0	<1	0	97,7	1,3
Ipsilateral lung	4,5	0	5,0	1,3	98,8	10,1
Contralateral lung	<1	0	<1	0	87	0
Heart	1,8	0	4,2	0	98	0
Spine	<1	0	<1	0	92	0

Table 31: Volumes of OAR receiving doses greater than 0,1Gy and 4Gy (doses considered to be relevant for induction of secondary cancer)

As a summarizing result, the authors state that in comparison with APBI and EBRT, the calculated mean and maximal doses for OAR would be lower than for IORT as well as for high dose volumes (>4Gy). They state that this would suggest, that the risk of secondary cancer induction after IORT would be lower than after APBI or EBRT.

B 1.10 Interpretation of clinical evidence

NICE has responded to Sir Ian Kennedy's report 'Appraising the value of innovation'. As requested we want therefore respond to the following three questions in our submission:

- Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Yes, the technology is innovative and has an impact on health-related benefits like survival rates and side effects (see below).

- Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?

We have submitted an economic model including a QALY calculation.

- Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

The nature of data was presented above and will be interpreted below.

When evaluating the clinical evidence two different options have to be distinguished:

- IORT as single method of treatment
- IORT followed by a boost

The parameters intended to answer the above questions are

- Overall survival
- Local and regional recurrence after treatment with INTRABEAM
- Cosmetic outcome and toxicities
- Quality of life

General

The radiotherapy using INTRABEAM for IORT is related to advantages, independent of the treatment option [IORT as the sole method of treatment (single dose administered intraoperatively, "TARGIT") or IORT as a boost followed by EBRT]. One of the major advantages is related to the workflow of the treatment – in IORT the time between surgery and the administration of the prescribed dose is very short. As shown as a result of the comparison between the pre- and post-pathology strata of the TARGIT-A- trial [1] and *in-vitro* studies it seems to be quite beneficial with regards to recurrence rates if the radiation dose is given promptly after surgery. [23] Moreover, due to the intraoperative approach, the source of radiation is placed directly in the tumour cavity avoiding a "geographic miss"., Also the lack of tumor cell proliferation before and during radiotherapy and effects of high single doses on the microenvironment including the microvasculature or cytokine pattern seem to be benefical. [11] By directly placing the source of radiation into the region of interest, the surrounding tissue is irradiated sparing the other tissue. Furthermore the relative biological effectiveness (RBE) of different radiation energies used in IORT and in EBRT has different effects on cancer DNA. **Martinsen et al.** [32] found that cell lines were killed more efficiently by 50 kV photon radiation compared to 380 keV radiation and that 6 MV radiation was even less efficient. This effect can be explained by the higher LET (linear energy transfer) of the 50 kV photon radiation. The energy of 50 kV radiation is deposited more densely and is

therefore causing more irreparable radiation damages and thus higher RBE than the higher energies. [32] Moreover, the radiation of the tumour bed from “inside out” seems to result in more favourable cosmetic outcome, less toxicity and less pain for the patient. The use of INTRABEAM as source of radiation avoids handling of open radiation sources such as radiation seeds as used in conventional brachytherapy.

The results obtained through the TARGIT-A trial give evidence that the sole application of IORT as a sole treatment protocol is not inferior to EBRT. When looking at the data of the patients involved it can also be seen that the results obtained are not related to low-risk patients, a certain number of patients were younger than 70 years and in about one half of the patients treated in the IORT group tumour sizes were larger than 1cm. Despite the fact that about 30 % of the patients had substantial risk factors as compared to the ASTRO guidelines for suitable and cautionary risk patients, the results were as good as the 5-7 weeks EBRT (pre-pathogology).

The following hypotheses are to be underlined:

a) Overall survival and recurrence rates for IORT as the sole treatment are not significantly different when compared with EBRT (with a trend of better survival)
b) Overall survival and recurrence rates for IORT given as a boost followed by EBRT are not significantly different to EBRT
c) The timing at which IORT is administered makes a difference in the outcome
d) Cosmetic outcome is better for IORT than for EBRT, toxicities are lower
e) Side effects and impacts on critical organs are less in IORT than in EBRT
f) The quality of life for patients is higher for IORT than for EBRT
g) IORT can be administered to patients where EBRT is not advised
h) IORT can be used in patients wearing a cardiac pace maker
i) IORT has a low risk of inducing secondary cancer

a) Overall survival and recurrence rates for IORT as the sole treatment are not significantly different when compared with EBRT (with a trend of better survival)

Several studies describing the treatment protocol of IORT as sole treatment were presented, but only one randomized trial was discovered. [1] So probably the most remarkable study published is the “TARGIT-A trial”, which was a randomized study including nearly 3500 patients. Results from a 5-year follow-up period were published recently [1]. The results obtained in this study gave evidence that IORT with INTRABEAM as the only method of treatment is not inferior when compared with EBRT as an established treatment protocol. The criteria for defining non-inferiority were differences in local recurrences of 2,5%. [1]. Overall survival rates and recurrence rates can be derived from the 5-years follow-up rates determined through this trial. The results obtained show that IORT as the sole method of treatment in selected low-risk to intermediate-risk patients is not inferior when compared with EBRT.

TARGIT given concurrently with lumpectomy as performed in the pre-pathology stratum of the TARGIT group (prepathology, n=2298) had much the same results as EBRT: 2,1% (1,1–4·,) versus 1,1% (0·5–2·5; p=0·31). Breast-cancer mortality was 17 patients for TARGIT versus 15 patients for EBRT (3,3%, 1,9–5,8 vs 2,7%, 1,5–4,6; p=0,72), non-breast-cancer mortality was 12 patients for TARGIT versus 27 patients for EBRT (1,3%, 0,7–2,8% vs 4,4%, 2,8−6,9; p=0,016). Thus, in absolute terms, there were four additional local recurrences but 13 fewer deaths in the pre-pathology TARGIT stratum. Analysing the post- and pre pathology strata together the 5-year risk for local recurrence in the conserved breast for was 3,3% (TARGIT) versus 1,3% (EBRT), but breast cancer mortality was the same in both groups (2,5%

for TARGIT versus 1,9% for EBRT). Nevertheless, significantly fewer cases of non-cancer deaths in the TARGIT group than in the EBRT group (1,4% in the TARGIT group versus 3,5% in the EBRT group) are reported. The overall mortality was 3,9% for the TARGIT group versus 5,3% for the EBRT group. Thus, whereas the local recurrence rate is slightly higher in the TARGIT group the overall mortality is lower. At 5-year follow-up, the risk of local recurrence with TARGIT was non-inferior to EBRT when all patients were analysed together.

When evaluating the results a close look at the patients should be made – the patients included were not only low risk patients. About 85% of the patients randomized to the IORT group (IORT as the sole method of treatment) were younger than 70 years, and less than 40% of the patients in the IORT group had tumour sizes smaller or equal 1cm, all other tumours treated were either larger in volume or the size was unknown (10%). With regard to the tumour grade it must be considered that only 35% of the tumour treated with IORT were grade 1 tumours, and all the others were higher grades (60%) or unknown (11%). So it can be stated that the results obtained through the IORT group of the TARGIT-A trial were not related to low risk patients.

Preliminary results (data from 4-year follow up) obtained from the TARGIT trial were already published in **2010**. [17] As these data reflect the results obtained from a 4-year follow-up, they are expected to be included in the most recent publication dating from November 2013 and therefore are not respected here. Although the only randomized study dealing with a comparison of IORT as the sole method of treatment with EBRT as a method of treatment is the above mentioned TARGIT-A trial, other study groups outside the TARGIT-A protocol described the outcome of such treatment options. **Grobmeyr et al.** [3] published results obtained in the USA including n=78 patients and treatments of n=80 breasts. **Elliott et al.** published results obtained through a study including n=67 patients [4] in **2011**. Most recent results were obtained in a study conducted in Saudi Arabia [6], and results obtained in other centres are also available. **Deneve et al.** published results in **2012** obtained through a study in the USA including n=42 patients. [2] Besides publication as full paper, poster abstracts describing the use of IORT outside the TARGIT A-trial are also available and are mentioned here as they give helpful hints, although they are not considered as high quality literature. **Steiner et al.** published results of studies conducted in Israel including n=400 patients. [10]

The outcome of these trials, although not being randomized trials, underline the results obtained through the TARGIT-A trial with very good tolerability and low recurrence rates.

b) Overall survival and recurrence rates for IORT given as a boost followed by EBRT are not significantly different to EBRT

Besides the protocol of IORT as the sole method of treatment, IORT can also be administered intraoperatively to the tumour bed (boost treatment of the tumour bed) followed by EBRT for higher risk patients.

The use of INTRABEAM intended to deliver a boost intraoperatively, followed by WBI, is described in literature. As sub-analysis of a randomized trial, the treatment of patients with IORT as a boost to the tumour bed followed by EBRT is described in the TARGIT-A trial. [1] IORT as a tumour bed boost followed by EBRT was undertaken in case of unpredicted prespecified adverse outcome of histology after lumpectomy (risk adapted radiotherapy). The group of patients included in the IORT+EBRT showed significantly fewer non-breast cancer deaths than EBRT (p=0.012), Despite the poor prognostic factors for survival in the group selected to receive TARGIT plus EBRT, as shown by the increased breast cancer mortality (8·0%, 95% CI 3·5–17·5), local recurrence was low in that group (0·9%, 0·1–6·1), and did not differ from those who received TARGIT alone

Results from other publications describing the use of IORT as a boost followed by EBRT are available. Although the underlying studies were not randomized, they are included here to give evidence that the results obtained through the TARGIT-A trial is supported by data

obtained from centres and studies other that the TARGIT-A trial. Results are presented here to help to draw the picture, although some subgroups of the TARGIT-A trial are included. Results from Australia (**Chua et al, 2010**) underline the feasibility of the use of IORT (INTRABEAM) and IORT followed by WBI. [12] No recurrence or death was observed at a median follow-up of 21 months (range, 3-36 months).

Results published by **Vaidya et al.** in **2010** [13] intended to evaluate the feasibility, safety and long-term efficacy of IORT followed by EBRT. Within a median follow-up of 60,5 months (range 10-122 months), the five year Kaplan-Mayer estimate for ipsilateral recurrence was 1,73% , and for recurrence in the tumour bed 1,04%. Other groups published their results of a 5 years of experience using IORT as a boost followed by EBRT in **2010**. [11] The results based on the treatment of n=155 breast of n=154 women show that overall survival rate was 87% and the local (in-breast) relapse-free survival rate was 98,5%. With regards to late toxicity aspects it could be shown that IORT in combination with EBRT was well tolerated. The two posters (Sperk and Vaidya) comparing IORT boost with EBRT boost survival data show a trend that patients have a better survival with IORT boost. This underlines the hypotheses that avoiding the geographical miss with regular EBRT approximately 10 weeks after the surgery has a real benefit for the patient. The TARGIT B trial is therefore powered as a superiority trial.

Besides the results presented above, literature also mentions theoretic advantages using IORT as a tumour bed boost treatment at the time of surgery. Although these advantages are not supported by clinical data, they are worth being considered and presented here. In general three advantages are discussed in literature. [11,12]

1) The risk of geographic miss: In the case of application of a tumour bed boost in BCS the accurate localization is described as essential to avoid geographic miss [12]. Nevertheless, the accurate targeting of the boost can be difficult due to deformation and positional changes in the post-operative breast. [13]

Chua et al. [12] cite literature claiming geographic misses up to 80% of the treatments; other literature mentions crates of geographic misses of 50-80% [13]. The risk of geographic miss can be circumvented by administering the boost intraoperatively and directly to the tumour cavity margins following lumpectomy, i.e. as IORT. [11,12]

2) Giving the radiation boost intraoperatively (IORT as a boost) ensures that radiation is administered at the earliest possible time [11]. Delays may become biologically relevant, and the delay is named as “temporal miss”. [13] and a delay may reduce local control [11] Potential effects of the period between surgery and irradiation is discussed below in detail.

3) Administering the boost irradiation intraoperatively means administration of radiation from inside-out, resulting in lower skin doses and thus in better cosmetic results. [11]

Literature points out that the combination of IORT with EBRT is feasible and provides a well-timed and targeted boost dose that, when compared with other methods of partial breast irradiation, may not be achieved even with the most sophisticated three-dimensional planning. [13] It saves five to ten sessions and patient visits and ensures excellent conformation and dosimetry and reduces the risk of both “geographic miss” as well as “temporal miss”. [13] The risk of local recurrence in case of IORT given as a tumour bed boost during BCS is described as relatively low [11] and toxicity rates seem to be acceptable. [11] The hypothesis is raised that a TARGIT boost might be superior to conventional external beam boost [13], although this hypothesis clearly lacks of clinical evidence at the moment and TARGIT B has just started.

c) The timing at which IORT is administered makes a difference in the outcome

As part of the TARGIT-A study a subgroup of the IORT arm received IORT only after the final histological results were present ("post-pathology group"), i.e. with a delay of several weeks (mean 37 days) when compared with the group that received IORT as a part of the surgery, i.e. at the time before any pathological results were present ("Pre-Pathology group"). This treatment option was allowed due to a protocol amendment, but was not the original idea of the TARGIT-A trial. Nevertheless, results obtained through comparison of the pre-pathology group and the post-pathology group are interesting and worth to be looked at.

The results obtained give clear hints that the recurrence rate in the pre-pathology group was much the same when compared with the EBRT group (2.1% in the TARGIT pre-pathology group versus 1,1% for the EBRT group). The breast cancer mortality was 3,3% in the TARGIT pre-pathology group compared with 2,7% in the EBRT group, but non-breast cancer mortality was much lower in the TARGIT group (1,3%) when compared with the EBRT group (4,4%). Again, the recurrence rate in the TARGIT group turned out to be a little higher than in the EBRT group, but on the other hand there were fewer deaths in the pre-pathology group when compared with EBRT. When TARGIT is given concurrently with lumpectomy, there is a 1% increase in local recurrences (from 99% to 98% chance of being free from local recurrences) but a potential of 2-3% decrease in overall mortality (from 93.1% to 95,4% chance of being alive) in 5 years.

Nevertheless, there was a difference in results between the pre-pathology and the post-pathology group –the local recurrence rate was 5,4% in the TARGIT group (post pathology) versus 1,7% in the EBRT group. Breast cancer mortality was 1,2% in the TARGIT group versus 0,5% in the EBRT group, and non-breast cancer mortality was 1,58% in the TARGIT group versus 1,76% in the EBRT group. Thus the recurrence rate in the TARGIT post-pathology group was higher than in the EBRT group, but deaths were slightly fewer in the TARGIT group (post-pathology stratum) when compared with the EBRT group. Therefore, the results obtained unmask the disadvantages (i. e. potential cardiovascular side effects) of EBRT if applied without previous IORT treatment. The TARGIT-A trial group clearly points out that IORT, given as pre-pathology treatment, is their preferred treatment protocol. [1]

However, the results obtained did not confirm non-inferiority of IORT not administered concurrently with lumpectomy (post-pathology stratum of the TARGIT arm, IORT as a second procedure after reopening the wound) when compared with EBRT. On the other hand it can be concluded that following the original idea of the TARGIT-A trial (i.e. administration of the complete prescribed dose intraoperatively at the time of lumpectomy) leads to better results than post-pathology treatment. The time when the dose is administered seems to play a role with regard to the local recurrence rate (1,7% pre-pathology versus 5.4% post-pathology)

These outcomes are in line with considerations based on the results obtained through *in-vitro* tests, published in **2008** by **Belletti et al.** [23] The authors investigated whether TARGIT influences the responses of breast cancer cell lines after stimulation with surgical wound fluid in terms of proliferation, motility, and invasion. One of the aspects to be investigated was the question whether IORT may have an immediate effect on the local tumour microenvironment and whether it would be conceivable that IORT not only kills residual tumour cells but also alters the microenvironment, making it less favourable for tumour cell growth and invasion in humans. As results it is reported that wound fluid stimulates proliferation, migration, and invasion of breast cancer cell lines, but the stimulating effect was almost completely abrogated when wound fluids from patients that were treated with IORT were being used. Such fluids failed to properly stimulate the activation of some intracellular signal transduction pathways when compared with fluids taken from untreated patients.

The hypothesis is much supported by the fact that the patients selected for IORT in the post-pathology stratum were highly selected for favourable pathological entry criteria – and yet

they show significant differences with regard to local recurrences (1,7% in the pre-pathological group versus 5,4% in the post-pathological group). [1] The results suggest that TARGIT is effective in reducing local recurrences when given concurrently with lumpectomy.

d) Cosmetic outcome is better for IORT than for EBRT, toxicities are low

With increasing survival of patients with breast cancer the aesthetic outcome is described to become an increasing important consideration. [7] Consequently, several investigations were made considering radiation related side effects, cosmetic outcome and toxicities. Again, the randomized TARGIT-A trial can be quoted leading to more or less direct comparison of the outcome of two different treatment protocols. Wound-related complications turned out to be much the same between the two trial groups, but significantly fewer grade 3 or 4 radiotherapy-related complications in the TARGIT-group than in the EBRT group are reported. [1] Wound related complications were much the same for the TARGIT and the EBRT group, but nevertheless there were significantly less cases of grade 3 or 4 radiotherapy related complications with TARGIT that with EBRT. [1] Other publications describing the results obtained through a systematic and objective assessment of cosmetic outcome (asymmetry of the breast, colour changes and scars) [7] indicate that patients treated with IORT given as post-pathology treatment in selected low risk patients is significantly better than for those treated with EBRT.

Results from studies conducted in the USA were published in **2013** by **Grobmyer et al.** [3] underline this outcome. Inclusion of n=78 patients lead to a number n=80 treatments and patients were treated either with IORT or IORT followed by EBRT of the whole breast. The assessment of the cosmetic outcome showed that the complications acute toxicities were either grade 1 or 2 and only 1 case of grade 4 complications. Seroma development was observed in several patients (32,5%), but was asymptomatic and resolved in most cases. Moreover, seroma rates are declared as very low, especially when compared with other methodologies. The majority of the patients had good to excellent cosmesis, and cosmesis tended to improve with increasing follow-up time from lumpectomy and radiotherapy treatment. The radiotherapy treatment with INTRABEAM was well-tolerated, and toxicities are described as “appear to be low”. Other publications also underline this picture and consider the cosmetic outcome after treatment of n=67 patients with IORT. [4] Seroma was proven in all patients, but cosmetic outcome was judged as acceptable in all patients. No serious systemic effects are described. The concept is also proven by the results published by **Deneve et al.** in **2012**. [2], (Number of patients involved n=42) describing that palpable seroma was found in 33% of the patients, whereas evidences for IORT-related hyperemia/erythema were observed in 12%. Postoperative complications were described for 12%, and cellulitis was reported in 5%.

Publications dealing with the outcome after IORT treatment followed by a boost are available. No problems with wound healing were mentioned by **Vaidya et al.** [13] as outcome of a study including n=299 patients and n=300 cancers. Treatment was IORT followed by EBRT (whole breast irradiation). **Chua et al** [12] reported in 2010 that severe surgical complications such as haematoma or abscess requiring open drainage or grade 3 or 4 acute radiation toxicity were identified in only a few cases (10%) of the patients treated with IORT. 15% of the patients had breast wound infections. Other publications [11] describing the outcome after IORT followed by EBRT mention that chronic toxicity after 3 years was judged as “mild” in all patients and for about two third no or only barely palpable breast fibrosis were discovered. Skin toxicities including telangiectases (6%) and hyperpigmentation (6%), did appear, but were considered as “mild”. Breast edema were found in 8% of the patients.

Publications directly dealing with the question of seroma formation after IORT treatment and treatment without IORT are also available. [21] The results obtained show seroma formation

in both groups,. The rate of palpable seroma was not different between the two groups, but fewer breasts required puncture in the IORT group. However, significantly more breasts showed CT seroma in the IORT group, and the volume of CT-seroma were higher in the IORT group than in the non-IORT group. No significant difference in speed of seroma resorption is mentioned

These results are supported both by the results published by **Wenz et al.** [11] and by the outcome of the TARGIT-A trial. [1] With regard to wound complications, the TARGIT-A trial mentions that 6 months after randomization, there were no significant differences in any protocol, but fewer grade 3 and 4 radiotherapy-related skin complications with TARGIT than with EBRT (4/1721 versus 13/1730) are reported.

The lower risk of geographic misses as described above may also contribute to the better cosmetic outcome, as well as the concept of irradiation of the tumour bed from “inside out”. Following this concept, the target tissue is irradiated, but due to the steep fall-off of the radiation ($1/r^3$) other tissue is not spared and skin is hit by large doses.

e) Side effects and impacts on critical organs are less in IORT than in EBRT

As one of the results obtained through the TARGIT-A trial it turned out that there were less non-breast cancer related deaths observed in the IORT group when compared with the EBRT group. It is stated that the fewer number of deaths in the TARGIT group is attributable to fewer deaths from cardiovascular causes and other complications [1]. This effect of fewer non-cancer related deaths may be related to less exposition of critical organs (e.g. heart) to radiation. This hypothesis is supported by data recently published in literature [29] It is described that the use of intraoperative radiation of the tumour bed from “inside out” results in less radiation induced ischemic heart diseases and other relevant major coronary events (myocardial infarction, coronary revascularization, or death from ischemic heart disease). The risk of major coronary events increases by 7,4% with each Gray administered to the heart. [29] The use of intraoperative methodologies such as IORT with INTRABEAM is likely to reduce the risk of major coronary events. On the one hand, external radiation has to pass the tissue from outside before reaching the region of interest. Due to the application of INTRABEAM as an intraoperative methodology the dose of radiation is applied directly to the tumour cavity sparing the non-involved tissue. Because of the steep fall-off ($1/r^3$) it is likely that the radiation received by critical organs such as the heart is lower than in cases EBRT which results in lower non-cancer related deaths

f) The quality of life for patients receiving IORT is better

The studies conducted with regard to quality of life were comparing the treatment protocols of IORT followed by EBRT with EBRT as treatment. It turned out that patients being treated with IORT alone reported more professional and other daily activities than patients who received EBRT without IORT. The mean scores for general pain, breast, and arm symptoms were significantly lower in IORT patients than in EBRT patients. Differences in breast-symptoms were also significant. [26]

Besides the direct outcome of better quality of life for patients being treated with IORT, an indirect increase of quality of life is mentioned in other publications. In case of BCS followed by WBI and a boost treatment, the administration of the boost may require about six weeks of additional period of treatment. It is mentioned in literature that many women are not able to attend these daily postoperative radiotherapy, especially when there is limited access to radiotherapy centre. [1,2] Thus, many of these women prefer mastectomy although BCS would be a suitable option. [1] Even in cases where the access to the radiotherapy centre is easy, the supplementary period of treatement can be stressful and inconvenient. [1,4,17] Avoiding the daily trips to a radiation centre therefore is very attractive to patients, especially those living far from the centre [3]], and shortened treatment courses from 5 to 6 weeks to 5

days or less may help patients who could not undergo conventional postoperative radiotherapy to avoid mastectomy. [2]

The higher quality of life seems to be highly appreciated by the patients. Studies dealing with the acceptance of increase in quality of life versus higher risk of recurrences showed that patients were willing to accept a slightly higher risk for higher quality of life. [30]

g) IORT can be administered to patients where EBRT is not advised

It is a general conviction that further radiotherapy in patients who already received irradiation is not possible, as the normal tissue tolerance does not permit a second full-dose course of radiotherapy to the entire breast after a second BCS. Therefore, in such cases mastectomy is recommended. [19,30]. Other circumstances besides recurrences in the same breast such as severe respiratory problems, collagen or autoimmune disorders, chronic lung disease with respiratory dysfunction or painful arthritis may question the application of post-operative EBRT. [30] Nevertheless, results obtained using the methodology of partial breast irradiation (PBI), an approach based on the hypothesis that the irradiation of a limited volume is acceptable with regard to side effects on the one hand and effective on the other. Data published in literature support this hypotheses – authors report that after a follow-up of 26 months (median) n=16 out of n=17 patients still were alive, and acute toxicities after IORT were mild (no grade 3/4 toxicities). No delay in wound healing or infections were reported. Cosmetic outcome was judged as satisfactory. [19] Other publications describing the treatment of patients that already received EBRT with IORT mention that no unexpected toxicities were observed. [31]

h) IORT can be used in patients wearing a cardiac pace maker

Literature describes potential drawbacks in radiotherapy in patients with a pace maker as components included in the cardiac pace maker may fail when receiving doses as low as 10Gy. [28] Significant functional failure is reported in case the cardiac pace maker receives doses even as low as 2Gy. Surgical movement of the cardiac pacemaker can be a solution if not withholding the radiotherapy treatment. Literature describes IORT as an alternative to EBRT in such cases, and doses measured at the edge of the pace maker were low (0,08Gy). The treatment was well tolerated and not hints of failure of the pace maker. Moreover, the use of INTRABEAM does not cause problems with regard to electromagnetic interferences, which are considerations in case linear accelerators are used. [28] The use of INTRABEAM is described as a good alternative for the treatment in patients with a cardiac pace maker.

i) Low risk of inducing secondary cancer

Literature mentions that there is a clear evidence for the association between radiation exposure and cancer induction, and the importance of secondary cancer risks after radiation therapy has been recognized by several international institutions [22] Estimations for secondary cancer risks, based on calculations of radiation doses given to several organs at risk were performed and dosimetric comparison of IORT (INTRABEAM) with selected other breast radiotherapy techniques were made. [22] It is concluded that in comparison with APBI and EBRT, the calculated mean and maximal doses for organs at risk are lower for IORT, as well as the high dose volumes (i.e. volumes receiving >4Gy). It is concluded that this would suggest that the risk of secondary cancer induction after IORT is lower than after APBI or EBRT. However, clinical data underlining this hypothesis are not presented.

In summary we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits. The INTRABEAM ® radiotherapy system might improve what patients expect from personalized treatment in either saving two weeks (boost treatment) or 6 weeks (single dose) of external EBRT with a trend of better survival. The health-related benefit can be shown in a QUALY calculation as shown in the economic

model. To our knowledge the data shown above enable the Appraisal Committee to take account of these benefits.

B 1.11 Cost effectiveness (Cost effectiveness is attached as an EXCEL sheet)

Background

Over the past 20 years, diagnostic and therapeutic medical interventions have evolved into more patient-focused, less invasive techniques. That statement holds true for patients diagnosed with breast cancer who undergo breast conserving surgery. Inclusive of the comprehensive breast program, the patient receives radiation therapy which is usually given in the UK over 3-6 weeks to the whole breast.

INTRABEAM Intraoperative Radiotherapy (IORT) is given as a single dose or as a boost internal radiation therapy performed during surgery after removal of the tumor. INTRABEAM delivers radiations directly into the tumour cavity irradiating the tumour bed.

The treatment was successfully introduced through an internationally randomized controlled clinical trial called TARGIT-A, which compared a single dose of radiation given intra-operatively to conventional external beam radiotherapy in women with early breast cancer. The eligible candidates for the INTRABEAM Radiation single-dose treatments include patients with early breast cancer.

Objective

The objective of this work was to determine the cost effectiveness of INTRABEAM in early breast cancer patients. In this model based economic evaluation INTRABEAM (new intervention) was compared with radiotherapy which is usually given in the UK over 3-6 weeks as whole breast external beam radiotherapy – EBRT (comparator).

Methods

The economic analysis used a state transition Markov model approach to simulate the treatment outcomes in breast cancer patients up to time horizon of 20 years post-surgery for early breast cancer. The primary outcome of interest was quality adjusted life years gained (QALY). The analysis was conducted from the NHS health care payer's perspective and to address decision uncertainty, probabilistic sensitivity analysis was performed. Probabilistic results were based on mean of 1000 simulations. PSA allows systematic propagation of uncertainty in all model parameters by assigning distributions to parameters and using a Monte Carlo simulation technique. A discount rate of 3.5% was applied to the future costs and effects.

Results

In the Base Case Analysis INTRABEAM was a dominant strategy yielding higher QALYs at a lower cost than the standard treatment of breast cancer using EBRT. Discounted EBRT and IORT costs for the time horizon of 20 years were £ 20, 926 and £ 14, 461 respectively. Discounted incremental QALY gained by use of IORT was 0.0069 QALY. Model results were robust to parameter uncertainty and probabilistic results were similar to the deterministic results. Application of the net monetary benefits (NMB) framework show higher NMB for INTRABEAM in all Monte Carlo simulations. Cost effectiveness acceptability curves show that INTRABEAM is cost effective at various thresholds of willingness to pay (WTP).

Conclusion

INTRABEAM® is a cost effective strategy to treat early breast cancer patients in the UK. Implementation of this treatment could improve quality of life in these patients and could save valuable NHS resources in comparison to the current practice of EBRT in these patients.

Appendix 1: Patients‘ data of the studies presented

***Table 1*:** **J.S. Vaidya, F. Wenz, M. Bulsara, J.S. Tobias, D.J. Joseph, M. Keshtgar, H.L. Flyger, S. Massarut, ;M. Alvarado, C. Saunder, W. Eiermann, M. Metaxas, E. Sperk, M. Sütterlin, D. Brown, L. Esserman, M. Roncandin, A. Thompson, J.A. Dewar, H.M.R. Holtweg, S. Pigorsch, M. Falzon, E. Harris, A. Matthews, C. Brew-Graves, I. Potyka, T. Corica, N.R. Williams, M. Baum**

“Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT –A randomised trial”

www.thelancet.com, Vol. 382, published online November 11, **2013**

	TARGIT (1721)		**EBRT (730)**		
Age [years]					p=0,274
≤50	150	9%	122	7%	
51-60	527	31%	548	32%	
61-70	781	45%	807	47%	
>70	263	15%	253	15%	
Pathological tumour size					p=0,273
≤1cm	611	39%	597	39%	
1,1-2cm	751	48%	726	48%	
>2cm	190	12%	207	14%	
Unknown	169	10%	200	12%	
Grade					p=0,394
1	528	35%	558	37%	
2	757	50%	720	48%	
3	232	15%	227	15%	
Unknown	194	11%	225	13%	
Lymphovascular invasion					p=0,224
Abscent	1348	87%	1343	88%	
Present	194	13%	178	12%	
Unknown	179	10%	209	12%	
Nodes involved					p=0,091
0	1307	83%	1303	85%	
1-3	219	14%	211	14%	
>3	43	3%	29	2%	
Unknown	152	9%	187	11%	

Table 1: Patient and tumour characteristics

	TARGIT (1721)		EBRT (730)		
ER status					p=0,090
ER +ve	1441	92%	1433	94%	
ER -ve	120	8%	99	7%	
ER Unknown	160	9%	198	12%	
PgR status					p=0,179
PgR +ve	1232	81%	1230	82	
PgR -ve	289	19%	265	18%	
PgR unknown	200	12%	235	14%	
HER 2 receptor					p=0,585
Positive	170	11%	178	12%	
Negative	1329	89%	1309	88%	
Unknown	222	13%	243	14%	

Table 1: Patient and tumour characteristics (continued) [

***Table 2*: R. Elliott, M. DeLand, J.F. Head, M.C. Elliott**

"Accelerated partial breast irradiation: initial experience with the Intrabeam system"

Surgical oncology **2011**, 20, 73-79.

Age	<50 year	n=10
	>50 years	n=57
	60 years	median
Tumour size	1,2 cm with T1 tumour	n=50
	1,2 cm with T2 tumours	n=10

Table 2: Patients' and tumour characteristics

Table 3: **J.L. Deneve, R.A. Hoefer jr, E.E.Harris, C. Laronga**

"Accelerated partial breast irradiation: a review and description of an early North American surgical experience with the intrabeam delivery system"

Cancer Control. **2012** Oct;19(4):295-308.

Variable	**N**	**Variable**	**N**
Age (median in years) (range)	71 (54-88)	Tumour classification	
Primary tumour location (quadrant)		Tis	1 (2%)
Central	6 (14%)	T1a	3 (7%)
Upper outer	28 (67%)	T1b	23 (55%)
Upper inner	4 (10%)	T1c	13 (31%)
Lower outer	3 (7%)	T2	2 (5%)
Lower inner	1 (2%)	Tumour grade	
Histology		Low	18% (43%)
Ductal carcinoma in situ	1 (2%)	Intermediate	23 (55%)
Invasive ductal carcinoma	38 (91%)	High	1 (2%)
Invasive lobular carcincoma	2 (5%)	Nodal status (n=40)	
Associated ductal carcinoma in situ	27 (64%)	NOi-	36 (86%)
Tumour size (median [cm], range)	1,0 (0,2-3,5)	N1	4 (10%)

Table 3: Demographic and histopathology for 42 patients undergoing intraoperative radiotherapy with INTRABEAM

Table 4: **M.R.S. Keshtgar, N.R. Williams, M. Bulsara, C. Saunders, H. Flyger, J.S. Cardoso, T. Corica, N.Bentzon, N.V. Michalopoulos, D.J. Joseph**

"Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial"

Breast Cancer Res. Treat **2013**, 140, 519-525.

Parameter		**TARGIT**	**EBRT**
Patient characteristics	Number of patients in this study	178	164
	From Perth (Australia)	51	53
	From Copenhagen (Denmark)	127	111
	Age at randomization (years), mean (SD)	63,6 (6,7)	63,2 (6,3)
	Height (cm) mean (SD)	166 (6,1)	165 (5,7)
	Weight (kg) mean (SD)	72,3 (12,8)	72,3 (14,3)
	Body Mass Index (kg/m^3) mean (SD)	26,4 (4,7)	26,7 (5,3)
Tumour characteristics	Specimen weight (g), mean (SD)	40,5 (25,1)	37,4 (19,7)
	Tumor size (mm) mean (SD)	10,3 (4,8)	10,6 (4,1)
	Laterality: right (%)	89 (50)	80 (49)
	Laterality: left (%)	89 (50)	84 (51)
	Screen detected: yes	123 (69)	110 (67)
	Screen detected: no	55 (31)	54 (33)
Tumour grade	1 (%)	118 (66)	106 (65)
	2 (%)	40 (23)	38 (23)
	3 (%)	3 (2)	6 (4)
	Unknown (%)	17 (10)	14 (9)
Treatment: Incision type	Circumferential (%)	113 (65)	93 (58)
	Transverse (5)	27 (16)	17 (11)
	Circumareolar (%)	7 (4)	11 (7)
	Radial (%)	27 (16)	38 (24)
Treatment: Chemotherapy	No (%)	178 (100)	164 (100)
Treatment: Adjuvant hormonal therapy	Yes (%)	72 (40)	74 (45)
	No (%)	106 (60)	90 (55)
Follow-up	Median Follow-up (years) (interquartile range)	2,0 (1,1-2,7)	2,0 (1,1-2,7)

Table 4: Patient, tumour and treatment characteristics

Table 5: S. Grobmyer, J.L. Lightsey, C.M.Bryant, C. Shaw, A. Yeung, N. Bhandare, B. Hithichingham, E.M. Copeland

"Low-kilovoltage, single –dose intraoperative radiation therapy for breast cancer: results and impact on a multidisciplinary breast cancer program"

J Am. Coll. Surg. **2013**, 216), 617-623.

Characteristics		n	%
Age [year]	Younger than 50	2	3
	50 to 59	18	23
	60 to 69	29	37
	70 or older	29	37
Ethnicity	White	64	82
	Black	6	7,7
	Hispanic	5	6,4
	Asian	1	1,4
	Other	2	2,6
Laterality	Left	42	52,5
	Right	38	47,5
Histology	DCIS	4	5
	Invasive Ductal	69	86
	Invasive lobular	3	4
	Other	4	5
Clinical stage	0	4	5
	IA	72	90
	IIA	3	3,7
	Recurrent	1	1
Pathological stage	0	4	5
	IA	61	76
	IB	3	4
	IIA	9	11
	Other *)	3	4
Hormone receptor status	ER/PR+	72	90
	ER/PR-	7	9
	NR	1	1
HER2/neu status	Positive	5	6,5
	Negative	67	88
	NR	4	5

*) *Stage IIB, 1; IIIA, 2, Table 5 : Patient characteristic*

Table 6: **M.R.S. Keshtgar, S. Tobias, F. Wenz, D. Joseph, C. Stacey, M.G. Metaxas, A. Keller, T. Corica, N.R. Williams, M. Baum M.**

"Targeted intraoperative radiotherapy for breast cancer in patients in whom external beam radiation is not possible"

Int J Radiation Oncology Biol Phys. **2011** 80(1), 31-38.

Characteristic		**Nonrecurrent breast cancer (n=62)**	**Recurrent breast cancer (n=18)*)**	**All (n=80)**
Age (at time of surgery	≤50	6	2	8
	>50	56	16	72
T size	<2cm	44	16	60
	2-5cm	17	2	19
	>5cm	0	0	0
	unknown	1	0	1
Grade	1	21	4	25
	2	28	9	37
	3	11	4	15
	unknown	2	1	3
Node status	Node negative	44	11	55
	Node positive	9	0	9
	Unknown	9	7	16

*) Patient and tumour characteristics at the time of IORT, not the initial surgery

Table 6: Patient and tumour characteristics

Table 7: **F. Wenz, G. Welzel, E. Blank, B. Hermann, V. Steil, M. Sütterlin, U. Kraus-Tiefenbacher**

Intraoperative radiotherapy as a boost during breast conserving surgery using low-kilovoltage experience: the first 5 years of experience with a novel approach

Int J Radiation Oncology Biol. Phys. **2010**, 77(5), 1309-1314.

Age	Median: 63 years (range, 30-83 years)
Tumour stage	
T1	n=100
T2	n=55
Nodal involvement	
N0	n=108
N1	n=34
N2	n=11
N3	n=2

Table 31: Patients characteristics

Table 8: **J.S. Vaidya, M. Baum, J.S. Tobias, F. Wenz, S. Massarut, M. Keshtgar, B. Hilaris, C. Saunders, N.R. Williams, C. Brew-Graves, T. Corica, M. Roncadin, U. Kraus-Tiefenbacher, M. Sütterlin, M. Bulsara, D. Joseph**

"Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery"

Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):1091-97.

Age		**Tumour grade**	
≤40	21	1	67
41-45	24	2	146
46-50	50	3	86
51-55	34	Unknown	
56-60	45	Lymph nodes	
61-65	44	Negative	204
66-70	40	Positive	87
71-75	27	Unknown	9
>75	14		
Pathological tumour size			
<1cm	63		
1-2cm	172		
2,1-3cm	52		
>3cm	9		
Unknown	4		

Table 8: Patients and tumour characteristics

Table 9 **U. Kraus-Tiefenbacher, G. Welzel, L. Brade, B. Hermann, K. Siebenlist, K.S. Wasser, F.S. Schneider, M. Sütterlin, F. Wenz**

„Postoperative seroma formation after intraoperative radiotherapy using low kilo-voltage X-ray given during breast conserving surgery"

Int. J. Radiation Oncology Biol. Phys. **2009**, 1-6

Characteristics	**IORT**	**NO-IORT**
n	n=71 (73 breasts treated)	n=86 (88 breasts treated)
Breast conserving surgery	n=73	n=88
Invasive cancer	n=73	n=75
Ductal carcinoma in situ	n=0	n=13
Median breast volume	1263,9ml	1088,6ml
Body mass index	27,3kg/cm^3 (median)	24,9kg/cm^3 (median)

Table 9: Patients' characteristics

Table 10: **B.H. Chua, M.A. Henderson, A.D.Milner**

"Intraoperative radiotherapy in women with early breast cancer treated by breast conserving therapy"

ANZ J Surg **2011**, 81, 65-69.

Characteristic	Category	Number	%
Age at registration [years]	Median	56,5	
	Range	39-83	
Menopausal status	Pre	19	32
	Post	41	68
	Yes	39	65
Tumour detected by mammography only	Yes	39	65
Laterality of tumour	Right	26	43
	Left	34	57
Location of tumour	Upper outer	27	45
	Lower outer	3	5
	Upper inner	12	20
	Lower inner	2	3
	Upper central	7	12
	Lower central	4	7
	Outer	4	7
	Unknown	1	2
Radiologic tumour size [mm]	Median	10	
	Range	1-35	
Clinical T stage	T1	55	92
	T2	5	8
Clinical N stage	N0	60	100
Diabetes	No	55	92
	Yes	5	8
Tobacco history	Never smoked	38	63
	Ex smoker	15	25
	Current smoker	7	12
Adjuvant chemotherapy	Yes	13	22
Adjuvant endocrine therapy	Yes	37	62

Table 10: Clinical characteristics of registered patients

Table 11: G. Welzel, A. Boch, E. Sperk, F. Hofmann, U. Kraus_Tiefenbacher, A. Gerhardt, M. Suetterlin, F. Wenz

„Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A

Radiation Oncology **2013**, 8:9

	TARGIT-A				EBRT + Boost		
	IORT (n=25)	EBRT (n=46)	IORT-EBRT (n=16)	p*	IORT Boost (n=90)	EBRT boost (n=53)	p**
Age [years]							
Mean	65,5	62,5	61,8	0,276	60,1	49,9	<0,001
SD	8,5	8,2	6,0		11,1	9,2	
Married /partnered	14 (58%)	22 (48%)	13 (81%)	0,006	58 (64%)	39 (76%)	0,191
Employed	4 (16%)	9 (20%)	0 (0%)	0,185	27 (31%)	31 (60%)	<0,001
Months since BCS							
Means	32,7	30,6	35,6	0,641	34,2	47,5	<0,001
SD	19,1	17,2	19,6		13,7	7,4	
Tumour size							
0-1cm	8 (32%)	14 (30%)	3 (19%)	0,376	13 (14%)	6 (11%)	0,414
1-2cm	16 (64%)	25 (34%)	9 (56%)		49 (54%)	23 (43%)	
>2cm	1 (4%)	7 (15%)	4 (25%)		28 (31%)	24 (45%)	
Nodal involvement							
N0	23 (92%)	36 (78%)	14 (88%)	0,622	66 (73%)	34 (65% [a)])	0,253
N1	2 (9%)	9 (20%)	2 (12%)		20 (22%)	11 (21%)	
>N1	0 (0%)	1 (2%)	0 (0%)		4 (4%)	7 (13%)	
ALND	4 (16%)	14 (30%)	4 (25%)	0,409	55 (61%)	41 (79% [a)])	<0,001
Chemotherapy	4 (17%)	5 (11%)	2 (12%)	0,908	18 (20%)	36 (68%)	<0,001
Endocrine therapy	23 (26%)	40 (93%)	13 (81%)	0,322	70 (78%)	36 (86%)	0,349
Radiotherapy of supra- and infra-clavicular nodes	0 (0%)	2 (4%)	0 (0%)	0,693	7 (8%)	10 (19%)	0,049
Medical comorbidities ≥2 [b)]	14 (56%)	37 (80%)	11 (69%)	0,091	49 (54%)	9 (17%)	<0,001

[a)] One patient without axillary assessment

[b)] Coexisting medical conditions were assessed by medical record review and by patient self-report. A medical comorbidity was defined s having two or more physical illness or injuries that needed long-term treatment

Table 11: Patient characteristic (as treated) (continued)

Table 12: **M.D. Alvarado, J. Conolly, C. Park, T. Sakata, A.J. Mohan, B.L. Harrison, M. Hayes, L.J. Esserman, E.M. Ozanne**

"Patients preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery"

Breast Cancer Res Treat **2013**

Characteristics	**Number of patients**	**Percentage of patients**
Age at diagnosis		
≤45	n=18	22,2%
46-60	n=43	53,1%
>60	n=20	24,7%
Tumour grade		
Low	n=15	18,5%
Intermediate	n=18	22,2%
High	n=6	7,41%
Unknown	n=42	51,9%
Previous radiation therapy	n=60	74%
Future radiation therapy planned	n=16	20%

Table 12: Selected patient data

***Table 13*: S.C. Darby, M. Ewertz, P. McGale, A.M. Bennet, U. Blom-Goldman, D. Brønnum, C. Correra, D. Cutter, G. Gagliardi, B. Gigante, M.-B. Jensen, A. Nisbet, R. Peto, K. Rahimi, C. Taylor, P. Hall**

"Risk of ischemic heart disease in women after radiotherapy for breast cancer"

N Engl J Med **2013** (386;11) 987-998.

Characteristic	Radiation dose to the heart [Gy]	Increase in rate of major coronary event (95% CI)	p-value for heterogeneity
Characteristics used for selection of matched controls			
Country			0,38
Sweden	5,4 ± 5,7	5,7 (1,2 to 13,7)	
Denmark	4,4 ± 2,7	11,2 (2,5 to 30,7)	
Age at diagnosis of breast cancer [year]	**-0,99**		
20-39	4,7 ± 4,8	-1,5 (< -25,3 to 616)	
40-49	4,9 ± 4,8	6,3 (-2,0 to 41,3)	
50-59	5,1 ±4,8	7,1 (0,4 to 22,2)	
60-69	4,8 ± 4,2	7,8 (1,7 to 19,7)	
70-74	4,9 ±3,1	9,7 (-2,9 to 116)	
Year of breast-cancer diagnosis			
1958-1969	3,7 ± 4,1	6,6 (-0,2 to 20,7)	
1970-1979	7,3 to 6,3	20,4 (5,4 to 79,2)	
1980-1989	4,9 ± 3,6	0,8 (-2,8 to 8,7)	
1990-2001	4,2 ± 2,7	11,8 (-0,1 to 56,2)	
Tumour characteristics			
Nodal status			0,26
Negative	4,8 ± 4,4	4,0 (-1,0 to 14,1)	
Positive	5,0 ± 4,3	11,8 (2,7 to 33,6)	
Size			0,24
<2cm	4,9 ± 4,2	20,4 (3,6 to 98,3)	
2-5cm	4,9 ±4,5	6,9 (1,1 to 18,0)	
Location			0,17
Outer quadrants	4,4 ± 2,8	10,0 (1,1 to 32,8)	
Inner quadrants	4,8 ± 3,5	- 2,1 (< -6,9 to 21,2)	
Laterality of breast cancer			0,88
Right	2,9 ± 2,5	5.0 (-2,2 to 22,5)	
Left	6,6 ± 4,9	4,1 (-0,4 to 13,8)	

Table 13: Characteristics of the women in the study at the time of breast cancer diagnosis and association between the characteristics and the subsequent rate of major coronary events

Characteristic	Radiation dose to the heart [Gy]	Increase in rate of major coronary event (95% CI)	p-value for heterogeneity
Cancer treatment			0,59
Surgery			
Mastectomy	5,1 ± 4,7	8,7 (3.2 to 18.0)	
Breast-conserving surgery	4,3 ± 3,1	14,9 (-0,1 to 77,6)	
Adjuvant hormonal therapy			0,55
No	5,0 ± 4,5	7,6 (2,9 to 15,2)	
Yes	4,6 ± 3,3	-0,4 (< 6,7 to 70,2)	
Ovarian ablation			0,94
No	4,9 ± 4,2	5,5 (1,1 to 12,9)	
Yes	4,3 ± 4,2	6,5 (< -3,6 to 77,7)	
Factors associated with subsequent major coronary events			
No	5,1 ± 4,7	7,4 (1,8 to 17,8)	
Yes	4,6 ± 4,1	7,4 (1,1 to 19,5)	
Other medications			0,58
No	4,8 ± 4,1	8,4 (1,9 to 21,3)	
Yes	4,7 ± 3,6	2,8 (- 4,3 to 47,3)	
Death of case patient from ischemic heart disease			0,81
No	4,9 ± 4,2	8,0 (2,3 to 17,2)	
Yes	4,9 ± 4,5	7,2 (2,4 to 14,9)	
Cardiology record of case patient reviewed			0,60
Yes	4,5 ± 3,1	9,2 (1,8 to 21,7)	
No	5,1 ± 4,8	7,0 (2,5 to 14,2)	
All women	4,9 ± 4,4	7,4 (2,9 to 14,5)	

Table 13: Characteristics of the women in the study at the time of breast cancer diagnosis and association between the characteristics and the subsequent rate of major coronary events (continued)

Appendix 2: References

[1] **J.S. Vaidya, F. Wenz, M. Bulsara, J.S. Tobias, D.J. Joseph, M. Keshtgar, H.L. Flyger, S. Massarut, ;M. Alvarado, C. Saunder, W. Eiermann, M. Metaxas, E. Sperk, M. Sütterlin, D. Brown, L. Esserman, M. Roncandin, A. Thompson, J.A. Dewar, H.M.R. Holtweg, S. Pigorsch, M. Falzon, E. Harris, A. Matthews, C. Brew-Graves, I. Potyka, T. Corica, N.R. Williams, M. Baum**

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"Accelerated partial breast irradiation: a review and description of an early North American surgical experience with the intrabeam delivery system"

Cancer Control. **2012,** *Oct;19(4)*:295-308.

[3] **S. Grobmyer, J.L. Lightsey, C.M. Bryant, C. Shaw, A. Yeung, N. Bhandare, B. Hithichingham, E.M. Copeland**

"Low-kilovoltage, single –dose intraoperative radiation therapy for breast cancer: results and impact on a multidisciplinary breast cancer program"

J Am. Coll. Surg. **2013**, *216*, 617-623.

[4] **R. Elliott, M. DeLand, J.F. Head, M.C. Elliott**
"Accelerated partial breast irradiation: initial experience with the Intrabeam system"

Surgical oncology **2011**, *20*, 73-79.

[5] **B. Tuschy, S.Berlit, S. Romero, E. Sperk, F. Wenz, S. Kehl, M.Sütterlin**

"Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays"

Radiation Oncology **2013**,*(8)*, 95

[6] **A.A. Merdad, Y.A.Bahadur,E.E. Fawzy, A.H.Hassouna, M.M.Eltaher, Z.K. Algaithy, F.K.Al-Thoubaity, C.T. Constantinescu**

"Phase II study on the use of intraoperative radiotherapy in early breast cancer"

Saudi Med.J. **2013**, *Nov; 34(11),* 1133-8.

[7] **M.R.S. Keshtgar, N.R. Williams, M. Bulsara, C. Saunders, H. Flyger, J.S. Cardoso, T. Corica, N.Bentzon, N.V. Michalopoulos, D.J. Joseph**

"Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial"

Breast Cancer Res. Treat **2013**, *140*, 519-525.

[8] H. Kolberg, M.Stephanou, L. Akplot-Basci,G. Lövey

"Intraoperative radiotherapy using INTRABEAM ® device as intraoperative boost in breast conserving therapy – a single institution experience after first 200 cases"

ECCO, ESMO, ESTRO congress Sept. **2013**, Abstract No. 2016

http://eccamsterdam2013.ecco-org.eu/Scientific-Programme/Abstract-search.aspx#

[9] M.Jankiewicz, A. Kurylcio, J.Romanek, L.Mielko, M.Lewicka, B. Cisel, W.P. Polkowski

"Targeted intraoperative radiotherapy using low-kilovoltage X-rays for early breast carcinoma: single centre case series with 5-years follow-up

ECCO, ESMO, ESTRO congress Sept. **2013**, Abstract No.2051

http://eccamsterdam2013.ecco-org.eu/Scientific-Programme/Abstract-search.aspx#

[10] M.Steiner, Leviov, A.Biterman, E. Shiloni, J.Goldman

"Intraoperative radiotherapy in early breast cancer: 400 consecutive patients in one institiution"

Clin Oncol 31, **2013** (suppl; abstr 1108)

Poster Abstract ASCO Annual Meeting **2013**, Abstract No. 1108

http://meetinglibrary.asco.org/content/113394-132

[11] F. Wenz, G. Welzel, E. Blank, B. Hermann, V. Steil, M. Sütterlin, U. Kraus-Tiefenbacher

"Intraoperative radiotherapy as a boost during breast conserving surgery using low-kilovoltage experience: the first 5 years of experience with a novel approach"

Int J Radiation Oncology Biol. Phys. **2010**, *77(5)*, 1309-1314.

[12] B.H. Chua, M.A. Henderson, A.D.Milner

"Intraoperative radiotherapy in women with early breast cancer treated by breast-conserving therapy"

ANZ J Surg **2011**, 65-69.

[13] J.S. Vaidya, M. Baum, J.S. Tobias, F. Wenz, S. Massarut, M. Keshtgar, B. Hilaris, C. Saunders, N.R. Williams, C. Brew-Graves, T. Corica, M.Roncadin, U. Kraus-Tiefenbacher, M. Sütterlin, M. Bulsara, D. Joseph

"Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery"

Int J Radiat Oncol Biol Phys. **2011** *Nov 15;81(4)*:1091-97.

[14] E. Sperk, D. Astor, G.Welzel, A.Gerhardt, M.Sütterlin, F. Wemz

„Intraoperative versus external beam boost for breast cancer: a matched pair analysis“

J Clin Oncol 31, **2013** (suppl; abstr 1120)

http://meetinglibrary.asco.org/print/1153531

[15] J.S.Vaidya, M. Bulsara,F. Wenz, S. Massarut, D.Joseph, J.S.Tobias, N. Williams, M.Baum

“Fewer non-breast cancer deaths in the TARGIT-A trial Systematic benefit of TARGIT or lack of EBRT toxicity?

St. Gallen **2013**

http://www.oncoletter.ch/index.tpl?rubrik=738

[16] W. Malter, J. Puppe, R. Wuerstlein, R. Semrau, R. Bongartz, B. Markiefka, P. Mallmann, S. Kraemer

„Single center experience with intraoperative radiotherapy as a boost during oncoplastic breast-conserving surgery“

Abstract EBBC **2012**

Eur J Cancer 2012; **48** (suppl 1):

http://www.ecco-org.eu/Events/Past-conferences/EBCC.aspx

[17] J.S. Vaidya, D.J. Joseph, J.S. Tobias, M. Bulsara, F. Wenz, C. Saunders, M. Alvarado, H.L. Flyger, S. Massarut, W. Eiermann, M. Keshtgar, J. Dewar, U. Kraus-Tiefenbacher, M. Sütterlin, L. Esserman, H.M.R. Holtveg, M. Roncadin, S. Pigorsch, M. Metaxas, M. Falzon, A. Matthews, T. Corica, N.R. Williams

“Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial”

Lancet. **2010** Jul 10;376(9735):91-102. doi: 10.1016/S0140-6736(10)60837-9.

[18] K.G.Andersen, R.Gärtner, N.Kroman, H. Flyger, H.Kehlet

„Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial“

Breast **2012**, *Feb;21(1)*, 46-49.

[19] U. Kraus-Tiefenbacher, L. Bauer, A. Scheda, C. Schoeber, J. Schaefer, V. Steil, F. Wenz

“Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy”

BMC Cancer. **2007** *Sep 14;7*:178.

[20] E. Blank, U. Kraus-Tiefenbacher, G.Welzel, A.Keller, M.Bohrer, M- Sütterlin, F. Wenz

„Single center long-term follow-up after intraoperative radiotherapy as a boost during breast conserving surgery using low-kilovotage X-rays“

Ann Surg Oncol **2010** (17):S352-S358.

[21] U. Kraus-Tiefenbacher, G. Welzel, L. Brade, B. Hermann, K. Siebenlist, K.S. Wasser, F.S. Schneider,M. Sütterlin, F. Wenz

„Postoperative seroma formation after intraoperative radiotherapy using low kilo-voltage X-ray given during breast conserving surgery“

Int. J. Radiation Oncology Biol. Phys. **2009**, 1-6

[22] M.H. Aziz, F. Schneider, S. Clausen, E. Blank, C. Herskind, M. Afza, F. Wenz

“Can the risk of secondary cancer induction after breast conserving therapy be reduced using intraoperative radiotherapy (IORT) with low-energy x-rays?”

Radiat Oncol. **2011**, *Dec 16;6*:174

[23] B. Belletti, J.S.Vaidya, S. D’Andrea, F.Entschladen, M.Roncadin, F.Lovat, S.Berton, T. Perin, E.Candiani, S. Reccanello, A.Veronesi, V.Canzonieri, M.G.Trovò, K.S. Zaenker, A.Colombatti, G. Baldassarre, S. Massarut

“Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding”

Clin Cancer Res.**2008**:*14(5)*, 1325-1332.

[24] J.S. Vaidya, M. Bulsara, F.Wenz, S. Massarut, D. Joseph, J.S. Tobias, N. Williams, M. Baum

“Omitting whole breast radiotherapy does not increase axillary recurrence: data from TARGIT-A trial”

St. Gallen **2013**

http://www.oncoletter.ch/index.tpl?rubrik=738

[25] J.S. Vaidya, M. Baum (on behalf of the TARGIT Trialists’ group)

“TARGIT-A trial (Targeted intraoperative radiotherapy) Updated analysis of local recurrence and survival”

St. Gallen **2013**

http://www.oncoletter.ch/index.tpl?rubrik=738

[26] **G. Welzel, A. Boch, E. Sperk, F. Hofmann, U. Kraus-Tiefenbacher, A. Gerhardt, M. Suetterlin, F. Wenz**

„Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A

Radiation Oncology **2013**, *8*:9

[27] **T. Corica, A. Nowak, C.Saunders, M. Bulsara, D. Joseph**

"Patient preferences for adjuvant radiotherapy in early breast cancer – an Australian sub-study of the INTRABEAM TARGIT trial"

Abstract EBBC **2012**

Eur J Cancer 2012; **48** (suppl 1): S187.

[28] **M.R.S. Keshtgar, .D.J. Eaton, C. Reynolds, K. Pigott, T. Davidson, B. Gauter-Fleckenstein, F. Wenz**

"Pacemaker and radiotherapy in breast cancer: is targeted intraoperative radiotherapy the answer in this setting?"

Radiation Oncology **2012**, *7*, 128

[29] **S.C. Darby, M. Ewertz, P. McGale, A.M. Bennet, U. Blom-Goldman, D. Brønnum, C. Correra, D. Cutter, G. Gagliardi, B. Gigante, M.-B. Jensen, A. Nisbet, R. Peto, K. Rahimi, C. Taylor, P. Hall**

"Risk of ischemic heart disease in women after radiotherapy for breast cancer"

N Engl J Med **2013** *(386;11)* 987-998.

[30] **M.D. Alvarado, J. Conolly, C. Park, T. Sakata, A.J. Mohan, B.L. Harrison, M. Hayes, L.J. Esserman, E.M. Ozanne**

"Patients preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery"

Breast Cancer Res Treat **2013** (published online)

[31] **M.R.S. Keshtgar, S. Tobias, F. Wenz, D. Joseph, C. Stacey, M.G. Metaxas. A. Keller, T. Corica, N. R. Williams, M. Baum**

Targeted intraoperative radiotherapy for breast cancer in patients in whom external beam radiation is not possible

Int J Radiation Oncology Biol Phys. **2011**, *80(1)*, 31-38.

[32] A.B. L. Marthinsen, R. Gisetstad1, S. Danielsen, J. Frengen, T. Strickert, S. Lundgren

"Relative biological effectiveness of photon energies used in brachytherapy and intraoperative radiotherapy techniques for two breast cancer cell lines"

http://info http://informahealthcare.com/doi/abs/10.3109/0284186X.2010.504226