was associated with less risk of local relapse (HR 0.94, 95% CI; 0.91–0.98). Nodal and local relapse correlated significantly with distant metastases. After a median of 3.7 years (range 0.6−9.2) from CS 19/24 patients (79.2%) with nodal relapse and 12/27 (44.4%) with local relapse developed distant metastases (chi square test $p < 0.000$ for both). Nodal and local relapses were concomitant or followed metastases in 13 and 2 patients, respectively. Metastases were found in 8.4% patients without nodal relapse and in 9.7% without local relapse.

Conclusions: In patients with early stage breast cancer and 1−3 positive nodes the incidence of regional nodal failure is low after CS. Even though it appears to correlate with worse prognosis, we do not recommend RT of draining nodes until results are available from randomized trials.

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Significantly better cosmetic outcome after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: objective assessment of patients from a randomised controlled trial

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Background: The international randomised TARGIT Trial started accrual in 2000 to determine if there is equivalence between the novel technique of IORT [intra-operative radiotherapy with Intrabeam® (Carl Zeiss, Germany)] and conventional external beam radiotherapy (EBRT) in women with early, low risk breast cancer suitable for breast conservation as primary treatment. The main outcome measure is risk of local relapse within the treated breast. We report here the one-year data from a sub-protocol assessing cosmesis in a sub-set of 118 women over 50 years old participating in the TARGIT Trial from one centre (Perth, Australia).

Materials and Methods: Frontal digital photographs from 118 patients (60 IORT, 58 EBRT) taken at baseline and one year after completion of breast conserving surgery were assessed blinded to randomised treatment using specialist software (BCCT.core 2.0, INESC Porto, Portugal) which produces a composite score (Excellent, Good, Fair, Poor) based on symmetry, colour and scar. Statistical advice on logistic regression using Stata (StataCorp, USA) was given by the Biostatistics Group, The Joint UCL, UCLH, & Royal Free Biomedical Research Unit.

Results: Median age at randomisation was 61 (IQR 56−67) years; photographs were taken before and after surgery (median 11 months, IQR 11−12); all patients were free from recurrence. The composite scores were combined into Excellent/Good and Fair/Poor, see Table 1. 77% (46/60) of patients randomised to IORT had Excellent/Good cosmetic outcome at one year, compared with 60% (35/58) randomised to EBRT. The odds of Excellent/Good outcome at one year, adjusted for the baseline composite score, was significantly higher in the IORT group compared to EBRT, adjusted Odds Ratio = 2.38 (95% CI 1.04–5.43), $p = 0.039$.

Conclusions: These results indicate that the cosmetic effects of targeted radiotherapy using Intrabeam® are significantly improved compared to those obtained with conventional EBRT, one year after surgery.

Table 1. Cosmetic outcome by randomised treatment at baseline and one year (n = 118)

Randomised Tx →	EBRT		IORT	
After one year → Baseline	Excellent or Good	Fair or Poor	Excellent or Good	Fair or Poor
Excellent or Good	32	20	42	9
Fair or Poor	3	3	4	5

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Estimating contralateral breast exposure from breast cancer radiotherapy in clinical practice

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Background: Radiotherapy (RT) for breast cancer inevitably results in scattered radiation dose to the contralateral breast (CB). A recent paper has shown that the incidence of cancer in the CB was increased (RR 2.5) in women of less than 40 years of age who received a dose >1 Gy to the specific quadrant [1]. In this study we evaluated the CB doses of patients who received postoperative RT for breast cancer.

Material and Method: 26 patients who underwent only whole breast (WB) RT (Group 1) and 16 patients with internal mammary chain (IMC) + WBI/chest-wall + supraclavicular ± axillary lymph node RT (Group 2) were retrospectively analyzed for CB doses. All patients received RT after 3-d conformal planning using Eclipse planning system. The total RT dose for WB was 50 Gy in 25 fractions with a 60−66 Gy boost dose to primary tumor side and 50 Gy to chest wall and 46−50 Gy to regional lymphatics in 23−25 fractions. For this analyze 4 quadrants and nipple-areola complex (NAC) of CBs were contoured using treatment planning computerized tomography slices taken with 3−5 mm intervals. Maximum (D1; dose that 1% of the volume received) and mean CB and CB quadrant doses were estimated using Eclipse planning system.

Results: Results for group 1 and 2 and the statistical differences between the groups (Mann-Withney test) are shown in the table.

	Group 1 (n = 26)	Group 2 (n = 16)	p
Maximum dose, mean (min–max)	1.75 Gy (0.7−3)	5.5 Gy (1.6–14.5)	<0.001
CB dose, mean	0.5 Gy	0.9 Gy	0.012
Upper Medial (UM) dose, mean	0.8 Gy	1.5 Gy	0.002
Lower Medial (LM) dose, mean	0.6 Gy	0.8 Gy	NS
Upper Lateral (UL) dose, mean	0.3 Gy	0.4 Gy	NS
Lower Lateral (LL) dose, mean	0.2 Gy	0.2 Gy	NS
NAC dose, mean	0.4 Gy	0.5 Gy	NS

Medial wedge was used in 13 patients in group 1 and in 11 patients in group 2. It was found out that the use medial wedge for treatment planning did not significantly increased the mean CB and contralateral quadrant breast doses significantly in both groups. Fisher's exact chi-square test $p = 1.0$).

Conclusion: Exposure to CB is found to be low and safe for patients who receive only WB irradiation after 3-d conformal treatment planning. For patients who receive IMC irradiation maximum, mean and UM CB doses found to be higher. Effort should be spend to reduce the mean UM doses for younger patients with IMC irradiation.

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The targeted intraoperative radiotherapy (TARGIT) trial for breast cancer: a review after the first 10 years of clinical application

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Background: Most early local recurrences occur in the primary tumour bed, despite the fact that multi-centric foci are found in over 60% of cases outside the index quadrant. Thus partial breast irradiation after breast conserving surgery may be an alternative to whole breast external beam radiotherapy (EBRT) for selected patients and is now recommended by many consensus guidelines. The work represents the first long term randomised safety and efficacy data of intra-operative radiotherapy (IORT) as an alternative to EBRT after breast conserving surgery for early breast cancer.

Materials and Methods: In July 1998, we pioneered the use of targeted intra-operative radiotherapy (TARGIT) with "INTRABEAM" that delivers therapeutic irradiation (~20 Gy at surface and ~5 Gy at 1 cm) delivered with a spherical applicator, inserted in the tumour bed at the time of surgery. We have established the safety and tolerability of the technique in phase II studies.

In March 2000 we launched an international trial comparing TARGIT vs. EBRT as a non-inferiority study with the primary outcome as local recurrence (LR). The recruitment goal of 2232 (powered to test non-inferiority, HR < 1.25) is expected to be complete by April 2010, by which time the maximum follow-up will be 114 months.

Results: An updated analysis of the first 300 patients in a phase II study where IORT was used as the boost, has demonstrated an actuarial 5 year local recurrence free survival of 1.5% in a group of unselected patients. Furthermore over the past 7 years, 77 patients deemed unfit for EBRT have been treated in this way, with median age of 66 years and a median follow-up of 37 months. To date there have been two local recurrences which gives an estimated annual local recurrence rate of 0.78%.

Our combined experience so far suggests that the technique is safe, well tolerated and virtually free of short-term toxicity.

Conclusions: If TARGIT is eventually shown to be non-inferior to EBRT then we could offer most women with small operable tumors complete

local therapy in one session avoiding 3−6 weeks of post-operative therapy. This may be preferable to many women including those seeking breast-conserving surgery in the developing world and for women living in remote areas of the Western world.

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Late toxicity and long term results after partial breast irradiation with high-dose-rate brachytherapy: results from a phase II prospective study

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Background: radiation therapy aims at achieving disease control with a low risk of side effects. Here late toxicity and long term results are analyzed in patients who received partial breast irradiation (PBI) with high-dose-rate (HDR) brachytherapy after conservative surgery.

Materials and Methods: 4 Gy were administered twice daily in 8 fractions over 4 consecutive days to 96 patients (median age 65 years; range 49−84). Tumors included 79 infiltrating and 13 ductal in situ carcinoma. Median tumor size was 7 mm (range 2−18). Estrogen receptors were positive in 82 cases, progesterone in 61 and HER2 in 3; Ki-67 was overexpressed (>25%) in 14 and p53 (>20%) in 7. Implantation was intra-operative in 18 cases and post-operative in 78 (median time after surgery 8 weeks; range 4−12) with implant geometry being defined with pre-implant computed tomography (CT). In the last 82 patients treatment planning was CT-based. At a median of 24 (range 1−43) days after PBI 8 patients received adjuvant chemotherapy. In 1 case PBI was performed between the first and the second CMF cycles. Adjuvant hormone therapy was given to 77 patients.

Results: median V100 was 105 cm^3 (range 22.3–271), median V150 was 27 cm^3 (range 8.04–57.10), median V200 was 11.65 cm^3 (range 4.21–27.20), median DHI was 0.751 (range 0.612–0.810). At a median follow-up of 45 months (range 14−72) late side effects were breast pain in 1 case, teleangectasis in 13 (12 G1 and 1 G2), 2 sieromas, 8 liponecrosis (1 G1 e 7 G2), 9 subcutaneous fibrosis (8 G1 and 1 G2) and 1 G3 cutaneous fibrosis. Patients and the radiation oncologist judged cosmetic results as good or excellent in all cases except 1, judged as fair. Late toxicity occured in 4/8 patient who received chemotherapy: 1 (starting CMF 43 days after PBI) developed G2 teleangiectasia and G1 subcutaneous toxicity, 1 (starting CMF 6 days after PBI) developed G1 teleangiectasia, 1 (starting EC plus paclitaxel 24 days after PBI) presented G1 subcutaneous toxicity, 1 (starting FEC 31 days after PBI) presented G1 teleangiectasia, G2 subcutaneous toxicity, G3 cutaneous toxicity and liponecrosis. The 1st, 3rd and 4th patients were implanted during surgery. Two local relapses occurred. One (48 months after PBI) was in a different quadrant to the original tumor. The second (19 months post-PBI), in a patient with a previous superior internal quadrant, was very close to the mediosternal line. One patient with negative sentinel node developed axillary metastases 7 months after PBI. All relapsed patients are alive, the first 2 in NED, the 3rd with disease.

Conclusions: Our results demonstrate that PBI, administered with HDR brachytherapy, is associated with very low relapse and late toxicity rates. Late toxicity was higher in patients implanted during surgery, in whom the dose to the skin was >70% of the prescribed dose, which may account for the teleangectasis development. PBI-chemotherapy timing does not seem to affect toxicity.

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Can total lung volume increase predict the benefit in respiratory gated patients with left-sided breast cancer?

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Background: To investigate the proportion of left-sided breast cancer patients that may have an advantage of respiratory gated radiotherapy. To investigate whether the increase in lung volume can predict which patients have the highest benefit.

Materials and Methods: Twenty-one left sided-breast cancer patients, treated with radiotherapy on the breast alone were sequentially enrolled in this study. 18 patients underwent a non-gated CT-scan on the virtual simulator (Siemens Sensation Open™), followed by a CT scan using prospective gating (PG). To perform the PG CT-scan, the RPM system (Varian™) was used to record the patients breathing pattern and patients were audio-coached to breath deeply. A gated window was chosen in deep inspiration and by an automatic interface between the RPM system and the CT scanner, CT acquisition was triggered in this window. For 3 patients, only a non-gated (NG) CT scan was performed because coached breathing was too difficult or they were belly-breathers, these patients were excluded from the study. The clinical target volume (breast) and normal tissues (heart and lung) were delineated on both the NG and PG CT-scans. For each patient, a treatment plan was designed on both CT-scans, using an isocentric photon technique. Dose volume histograms were used to evaluate the normal tissue doses.

Results: For all patients (N = 18), a significant reduction in mean heart dose [3.1 Gy (NG) to 2 Gy (PG), $p < 0.0005$] and heart V30 [3.9% (NG) to 3.2% (PG), $p < 0.0006$] was achieved with respiratory gating. The total lung volume increased by 66% [2800 cm^3 (NG) to 4652 cm^3 (PG)]. Mean lung dose was comparable in both CT scans [3.1 Gy (NG) and 3 Gy (PG)] and V20 was the same (3%). Mean reduction in heart dose in all patients was 35%. 9 patients (50%) had an advantage in mean heart dose of >35% and were considered for treatment with respiratory gating. Patients that were selected for gated treatment based on an advantage for the heart, had a significant higher increase in total lung volume (87%) [2388 cm^3 (NG) to 4464 cm^3 (PG)] compared to patients not treated with gating (53%) [3130 cm^3 (NG) to 4802 cm^3 (PG)].

Conclusions: In this study, respiratory gating leads to a significant heart (>35%) sparing effect in 50% of left-sided breast cancer patients, irradiated on the breast alone. The patients with the highest increases in total long volume correlate with the patients which benefit most from the gated treatment.

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Is exclusive radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy?

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Background: Neoadjuvant chemotherapy (NCT) emerged in the 1990s as a treatment option that challenged primary surgery for non-metastatic operable breast adenocarcinomas, especially when they were deemed too large to be treated by breast-conserving surgery. The study was designed to determine whether exclusive radiotherapy (ERT) could be an option after complete clinical response (cCR) to NCT for early breast cancers (EBC).

Material and Methods: Between 1985 and 1999, 1477 patients received NCT for EBC considered to be too large for primary conservative surgery. Of 165 patients with cCR, 65 were treated by breast surgery (with radiotherapy) and 100 by ERT.

Results: Median follow-up was 12 years. The two groups were comparable in terms of baseline characteristics, except for larger initial tumor sizes in the ERT group. There were no significant differences in overall, disease-free and metastasis-free survivals. Five-year and 10-year overall survivals were 91% and 77% in the no surgery group and 82% and 79% in the surgery group, respectively ($p = 0.9$). However, a non-significant trend towards higher locoregional recurrence rates (LRR) was observed in the no surgery group (31% vs. 17% at 10 years; $p = 0.06$). In patients with complete responses on mammography and/or ultrasound, LRR were not significantly different ($p = 0.45$, 10-year LRR: 21% in surgery vs. 26% in ERT). No significant differences were observed in terms of the rate of cutaneous, cardiac or pulmonary toxicities.

Conclusion: Surgery is a key component of locoregional treatment for breast cancers that achieved cCR to NCT.

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Single dose intra-operative radiotherapy for breast cancer patients where external beam radiation was not feasible − results after 3 years of follow-up

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Background: Intra-operative radiotherapy (IORT) with Intrabeam® (Carl Zeiss, Germany) has been used since 2000 in the international randomised TARGIT Trial to determine if there is equivalence between IORT and conventional external beam radiotherapy (EBRT) in women with early breast cancer. The primary endpoint is local recurrence. Some patients were unsuitable for inclusion in our trial for a number of reasons and were given IORT as a single treatment off-trial.

Materials and Methods: Patients with invasive breast cancer underwent wide local excision followed by IORT (n = 74). Low energy x-rays are