**Material and Methods:** Between 1992 and 2005, 215 patients with advanced breast cancer received radiotherapy due to poor respond to adjuvant chemotherapy in Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland. Median age was 57 years. Sixty three (29%) patients were premenopausal, 85 were Er(+), 74 (34.5%) were Er(−), 54 (25%) had not known receptor status. Ninety eight percent of patients were in III stage disease. All had radiotherapy to the breast. Supraclavicular or axillar nodes were not irradiated in 10 (4.5%) patients. Median dose to breast, breast tumor, axillar and supraclaviular nodes were 60 Gy (44−80 Gy), 70 Gy (44−81 Gy), 60 Gy (44−81 Gy), 50 Gy (42−72 Gy) respectively. After radiotherapy 137 patients (64%) had additional hormonotherapy and 51 (24%) had ultimate mastectomy.

**Results:** In hundred and two (47%) patients distant failure was found. Among those, 49 patients (48%) had simultaneously local failure. Thirty three (15%) patients had sole local failure. The five year locoregional control (LRC) was observed in 63% of patients. The five-year disease-free survival (DFS) and metastases-free survival (MFS) were 44% and 51% respectively. Mastectomy and hormonotherapy significantly and independently influenced treatment results. Patients who ultimately underwent mastectomy had significantly higher LRC ($p < 0.001$), longer DFS ($p < 0.001$) and MFS ($p < 0.001$). Hormonotherapy significantly increased LRC ($p < 0.001$) and DFS ($p = 0.02$).

**Conclusions:** High-dose radiotherapy should be given to the patients with advanced, nonoperable breast cancer who did not respond to neoadjuvant chemotherapy, because long-term tumor control could be obtain in over half of them, mastectomy can be reconsidered then. Maintenance hormonotherapy and/or ultimate mastectomy improve treatment results.

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**10-year results of intraoperative electron radiotherapy (IOERT) in boost modality in breast cancer patients treated with breast conserving surgery**

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**Introduction:** The aim of this nonrandomized study was to compare ipsilateral breast tumor recurrence rates in patients with invasive breast cancer, who had been treated with breast conserving surgery and whole breast irradiation and conventional boost or intraoperative electron radiotherapy boost (IOERT).

**Patients and Methods:** 378 patients were included in the study, 188 patients in group 1 (conventional boost) and 190 patients in group 2 (IOERT boost). Patients were comparable with regard to age, menopausal status, tumor size, histological type, grading and axillary lymph node status. Included were patients with invasive breast cancer pT1 and pT2, N0, N1, N2, M0, and breast conserving surgery with clear margins >3 mm. Excluded were patients with DCIS only, patients with invasive breast cancers larger than pT2, patients after primary systemic therapy and patients with multicentric disease. All patients (group 1 and group 2) received postoperative whole breast irradiation of 51–56.1 Gy. Group 1 received postoperative electron boost irradiation of 12 Gy after whole breast irradiation and group 2 received one intraoperative electron boost of 9 Gy in a single fraction during surgery before whole breast irradiation.

**Results:** The 10-years actuarial rates of ipsilateral breast tumor recurrence (IBTR), true local recurrence (TLR), distant recurrence (DR) and disease free survival (DFS) were 7.1% (95% CI, 3.2–11.0%), 4.8% (95% CI, 1.5−8.0%), 14.2% (95% CI, 9.1–19.4%) and 82.4% respectively in group1 and 2.7% (95% CI, 0.0−5.9%, $P = 0.062$), 0.7% (95% CI, 0.0−2.0%, $P = 0.016$), 13.6% (95% CI, 5.0–22.2%, $P = 0.90$) and 84.0% ($P = 0.76$) respectively in group 2.

**Conclusion:** Patients treated with IOERT boost and whole breast irradiation achieve excellent local control rates at 10 years and exhibit statistically significant decreased true local recurrence rates compared to patients treated with whole breast irradiation and conventional electron boost.

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**Postmastectomy adjuvant radiotherapy in patients with less than four axillary lymph nodes: a retrospective analysis**

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**Background:** There is no consensus as yet regarding post mastectomy radiotherapy (PMRT) for patients with <5 cm tumor having less than 4 axillary lymph nodes although the same exists for patients with 4 or more positive nodes. But several recent publications (20 year result of British Columbia Study and DBCG 82 Protocol published by Overgaard et al) challenge 'this separation between 1 to 3 and 4 or more positive axillary nodes as a relevant descriptor of indication of PMRT'. This was the impetus that led us to review and analyze retrospectively from our institute data, the impact of post mastectomy radiotherapy (PMRT) in this controversial group.

**Material and Method:** Records of 785 patients with T1, T2 tumors who were registered in our department following mastectomy with axilla dissection with <4 positive axillary nodes between 2002 and 2007 were analyzed. 127/785 patients had 8 or less nodes dissected (as found in histopathology reports) and as such were excluded from the analysis. Of the remaining 658 patients, **528** received no PMRT, as per consensus. But **130** patients, as found in record, had received PMRT (possibly they appeared to be non-compliant regarding follow up). Locoregional recurrence, distant failure, disease free survival and overall survival of these 130 patients were studied and compared with 528 patients who were not offered PMRT.

As per erstwhile institutional policy, all patients had received FAC chemotherapy for 6 cycles. Receptor positive patients (164/528 of non-PMRT and 42/130 of PMRT subsets) were on Tamoxifen or an A.I.

**Results:** At a median interval of 30 months 132/528 patients not receiving PMRT suffered locoregional recurrence (chest wall recurrence alone in 36/528, supraclavicular recurrence in 81/528, chest wall + supraclavicular recurrence in 15/528, axillary and IMN recurrence in none). On the contrary only 4/130 patients receiving PMRT had locoregional failure ($p < 0.0001$). Distant metastasis was recorded in 37/528 of non PMRT subset and 8/130 of PMRT subset (p=NS). Survival data till September 2008 showed 4/130 deaths among PMRT subset against 26/528 of non PMRT (p=NS). 121/130 of PMRT are living without disease, contrary to 432/528 of non PMRT ($p = 0.001$).

**Conclusions:** This retrospective analysis revealed statistically significant reduction in locoregional recurrence as well as increased disease free survival with PMRT in T1 or T2 breast cancer patients with 1−3 positive axillary nodes. Deprivation of adjuvant radiotherapy for this subset of patients appears to be unjustified.

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**Loco-regional recurrence after breast conservative surgery and radiotherapy to the breast in patients with T1−2 disease and 1−3 positive axillary nodes**

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**Aim:** To assess relapse of invasive breast cancer after conservative surgery (CS), radiotherapy (RT) to the breast, adjuvant chemo (CT)- and/or hormone-therapy.

**Patients and Methods:** 575 patients (median age 53.6 years; range 25−82) with T1-T2 breast cancer and 1−3 (median 1) positive axillary nodes underwent CS. A median of 19 nodes (range 8−63) were examined (<10 nodes in 12 patients; unknown number in 1). Estrogen and progesterone receptors were respectively positive in 442 and 345 cases, negative in 107 and 200, unknown in 26 and 30. Lymphovascular invasion was present in 152 cases, absent in 417, not determined in 6. All patients received whole breast RT with standard fractionation (1.8−2 Gy/fraction up to 50.4−50 Gy) with boost (dose range: 10−16 Gy) to tumor bed in 561 (97.6%). Draining nodes were never irradiated. Adjuvant CT was given to 459 (80.2%) patients, tamoxifen to 432 (75.1%) and no adjuvant systemic therapy to 3. Kaplan Meter curves and log-rank test were used for survival analyses and Cox model for multivariate analyses.

**Results:** Median follow-up was 7.3 years (range 1.8−10). After a median of 4.4 years (range 1.7−9.1) from CS 24 patients (4.17%) had nodal relapses in the supraclavicular region (13), axilla (2), internal mammary nodes (2), more than 1 site (3). The 10 year nodal relapse-free survival was 94% (CI 95% 90.6–96.2). After a median of 4.2 years (range 1.0−9.3) from CS 27 patients (4.7%) had local relapse. The 10 year local relapse-free survival was 92.8% (CI 95% 89.0–95.3). In univariate analysis risk factors were higher grading and negative/unknown receptor status for nodal relapse; positive, close/unknown margin status and positive/excised node ratio for local relapse. In multivariate analysis, G3 tumors significantly increased the risk of nodal relapse (HR 5.1, 95% CI: 1.6–13.8 vs G1-G2 cases). ER and/or PgR positivity afforded significant protection (HR 0.33, CI: 0.14–0.78). Increased risk of local relapse was associated with close and positive margins (HR 3.2, 95% CI: 1.3−7.5) and positive to examined axillary node ratio (HR 1.006, 95% CI: 1.001–1.01). Older age

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.

**References**

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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