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**The influence of the boost technique on local control in breast conserving treatment in the EORTC 'Boost versus No Boost' Trial**

P.M. Poortmans, H. Bartelink, J.C. Horiot, H. Struikmans, W. Van den Bogaert, A. Fourquet, J.J. Jager, W.J. Hoogenraad, P. Rodrigus, C. Warlam-Rodenhuis, L. Collette, M. Pierart. *On behalf of the EORTC Radiotherapy and Breast Cancer Groups, The Netherlands*

**Introduction:** The EORTC Trial 22881/10882 investigating the role of a boost dose in breast conserving therapy demonstrated a significantly better local control with the higher radiotherapy dose, especially in women younger than 50 years of age. In this study, we investigated in the same patient group the potential impact of the different boost techniques on local control and on cosmetic outcome after breast conserving therapy.

**Patients and Methods:** From 1989 to 1996, 2661 patients were randomised to receive a boost dose of 16 Gy to the primary tumour bed after a microscopically complete tumorectomy and 50 Gy whole breast irradiation. The choice of boost technique was made at the institutional level. Treatment data were prospectively recorded as well as the clinical outcome in terms of local control and fibrosis. Sixty-three per cent of the patients received a boost dose with fast electrons, 28% with photon beams and 9% with interstitial brachytherapy.

**Results:** At 5 years, local recurrences were seen in 74 of the 1635 patients who received an electron boost (4.8%, C.I. 3.6–5.9%), in 28 of the 753 patients who received a photon boost (4.0%, C.I. 3.4–5.5%) and in 6 of the 225 patients after an interstitial boost (2.5%, C.I. 0.3–4.6%). The grade of fibrosis, as scored by the treating radiation-oncologist, was similar in the three groups in the whole breast as well as at the primary tumour bed. Age, together with the use of a boost dose by far the most important prognostic factor for local control, could be excluded as having a major influence on the comparison of the outcome across the 3 boost techniques. The median boosted volume was 60 cc with the interstitial technique, 144 cc with the electron boost and 288 cc with photons. The overall treatment time was 6 days longer in the interstitial boost group due to the interruption between external whole breast irradiation and the delivery of the interstitial boost.

**Conclusions:** Although the three groups are of a rather unequal size, the interstitial boost seems similar in terms of fibrosis and at least as good in terms of local control, despite the lower treatment volume and the longer overall treatment time.

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**Special focus on cardiac toxicity from a pilot study of the adjuvant sequencing chemotherapy of doxorubicin/docetaxel/CMF regimen and radiotherapy with a mid-term follow-up in patients treated for poor prognosis breast cancer**

C. Philippson[1], N. Magné[1], A. Di Léo[2], I. Veys[3], D. Larsimont[4], S. Simon[2], J.-M. Nogaret[3], M.J. Piccart[2], P. Van Houtte[1]. *[1]Jules Bordet Institute, Department of Radiotherapy, Brussels, Belgium; [2]Jules Bordet Institute, Department of Chemotherapy, Brussels, Belgium; [3]Jules Bordet Institute, Department of Surgery, Brussels, Belgium; [4]Jules Bordet Institute, Department of Anatomo pathology, Brussels, Belgium*

**Purpose:** Cardiac toxicity associated with chemotherapy and radiotherapy may be life threatening, can limit the dose and duration of the treatment and certainly adversely affect short-term and long-term quality of life. The combination of anthracyclines and taxanes is currently considered as the first choice chemotherapy in advanced breast cancer and encouraging results have taken place in adjuvant setting. The aim of the present study was to evaluate the treatment related to cardiac toxicity doxorubicin/docetaxel/CMF regimen and radiotherapy with a mid-term follow-up in patients treated for poor prognosis breast cancer.

**Materials and methods:** From March 1996 to March 1998, in the single Jules Bordet Institute, 64 patients with clinical stage II or III breast cancer were included in a pilot study exploring the efficacy/feasibility of doxorubicin/docetaxel/CMF sequential and combination regimens. Patients with significant cardiovascular history or ECG abnormalities were not eligible for the study. Radiotherapy was performed in 100% of the patients reviewed for the present study. Less than 20% of the irradiated patients were treated with 6 MV photons produced by a linear accelerator. The majority were treated with Cobalt. Two tangential photon fields were used for the chest wall or the breast, for a total ICRU dose of 50 Gy. Nodal radiation therapy was given for the 64 patients. The supraclavicular and internal mammary nodes were treated with a mixed beam (1/3 photons and 2/3 electrons) for a total ICRU dose of 45 Gy. All fields were treated 5 days per week, 2 Gy per fraction, during 5 or 6 weeks. In the case of a conservative treatment, a 12 Gy electron boost was added to the tumoral bed. Patients were regularly clinically assessed during chemotherapy and at least 4 times yearly after completion of treatment. Measurements of left ventricular ejection fraction (LVEF) were performed at baseline, during and at the end of chemotherapy. A cardiac event was defined as a myocardial infarction or clinical evidence of congestive heart failure.

**Results:** The median age was 48 years (range 29 to 65 years), the median number of positive nodes was 6 (0 to 25), stage III in 19 patients, negative estrogen receptors in 17 patients and grade III in 31 patients. The median follow-up was 6 years. The mean disease-free and overall survival were 42 and 69 months, respectively (10 to 72 and 13 to 90 months, respectively). There was a significant fall in LVEF during chemotherapy in 21 patients with a median decrease of 10% (5 to 20%). However 64 patients have kept normal cardiac function. All of them have rescued initial values of LVEF. Forty four and 19 patients received radiotherapy to the chest wall or breast, respectively, 33 of to the left side. Median radiation therapy duration was delivered in 36 days (32 to 54 days). Twenty six patients received radiotherapy concomitantly with CMF regimen. No cardiac events were observed for patients with either left- or right-sided breast cancer.

**Conclusions:** Doxorubicin/docetaxel/CMF sequential and combination regimens plus radiation therapy in particular selected non high risk cardiac patients are safe and effective with an absence of cardiac toxicity, second cancer and other complications with a mid-term follow-up.

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**The course and prognosis for loco-regional recurrences among high-risk breast cancer patients receiving adjuvant systemic treatment and randomized to +/− postmastectomy radiotherapy. Long-term results from the Danish DBCG 82b&c studies with 3083 patients**

H.M. Nielsen[1], M. Overgaard[2], C. Grau[1,2], A.R. Jensen[1,2], J. Overgaard[1]. *[1]Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus C, Denmark; [2]Aarhus University Hospital, Department of Oncology, Aarhus C, Denmark*

**Background:** Postmastectomy radiotherapy (RT) in high-risk breast cancer patients can reduce loco-regional recurrences (LR) and improve disease-free and overall survival. In the DBCG 82b&c studies (N Engl J Med 1997, 337: 949–55, Lancet 1999, 353: 1641–48), the patients were followed for 10 years or until their first recurrence, other cancer or death. This study aim to make a long-term follow-up in these patients, and to record details about LR in order to investigate the course and prognosis after LR in the RT versus no-RT group.

**Material and methods:** In the DBCG 82b&c trial 3083 patients with stage II and III breast cancer were randomized to receive +/− postmastectomy radiotherapy from 1982 to 1990. The patients who experienced a LR as their first recurrence was identified and follow-up data was selected from medical records and the National Databases (LR was defined as recurrence on the chest wall, axillary and/or supra/infraclaviculary regions without distant metastases). The risk of developing distant metastases (DM) was analysed as a function of adjuvant radiotherapy, localisation of and time interval from mastectomy to LR.

**Results:** Of the 3083 patients, 518 patients experienced a LR as their first recurrence. The 17-year probability of isolated LR was 8% (75) in the RT group and 39% (443) in the no-RT group, thus RT significantly reduced the risk of LR ($p<0.001$). For the patients with LR the 10-year probability of developing subsequent DM is 83% and 79% in the RT versus no-RT group respectively ($p=0.86$). Patients with a short LR free interval had a shorter interval to subsequent DM ($p<0.001$). Patients with supra/infraclaviculary and multiple site recurrences had a worse prognosis than patient with chest wall and axillary recurrences ($p<0.001$). The LR free interval was significantly longer in the RT group. Also the localization of the LR differed between the two groups, with a relatively higher proportion (seems to increase with longer LR free interval) of chest wall LR in the RT group (Odds Ratio = 1.3, 95% CI 1.00–1.79). Relatively the proportion of axillary LR is lower in the RT group (Odds Ratio = 0.83, 95% CI 0.74–0.93).

**Conclusion:** Adjuvant radiotherapy caused a significant reduction in the number of LR in high-risk breast cancer patients given adjuvant systemic treatment, and increased the loco-regional recurrence free interval. For patients with LR the outcome were equally severe in the two randomization groups.

Supported by the Danish Cancer Society.

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**Isolated axillary relapse in patients with breast cancer presenting axillary positive lymph nodes and extranodal tumor invasion**

H. Stranzl[1], P. Ofner[2], F. Peintinger[3], A. Hackl[1]. *[1]Univ.-Clinic of Radiotherapy, Graz, Austria; [2]Institute of Medical Informatics, Statistics and Documentation, Graz, Austria; [3]Department of Gynecology, Graz, Austria*

**Background:** To determine the incidence of isolated axillary failure rates and to evaluate the indications for axillary nodal irradiation in female breast cancer patients with positive axillary lymph node and extranodal spread.

**Material and methods:** From 1994 to 2002, the medical records of 1078 female patients with breast cancer were examined in order to identify those with histopathologically positive axillary lymph nodes and extranodal tumor spread (n=301, 28%). Ninety-one (30%) out of 301 patients were identified as having ⩽3 lymph nodes involved and 70% of patients 4 or more lymph nodes. Patients were postoperatively treated with adjuvant irradiation. Irradiation was given to the breast (n=160) or thoracic wall (n=141) up to a total dose of 50 Gy (range, 46–54 Gy). Regional irradiation was given to patients with ⩾4 positive axillary lymph nodes. Chemotherapy was administered to 70% (n=210) patients, hormonal therapy to 53% (n=160) and combined systemic treatment to 26% (n=78) patients.

**Results:** The median observation time was 34 months (range, 2–99). The median age of the patient population was 58 years (28–84 years). In 91% of patients more than 10 axillary lymph nodes were removed. Of the 28 (9.3%) patients with a recurrence, 6.6% had an isolated local relapse, 1% experienced a regional failure (isolated axillary, 0.7%; isolated supraclavicular 0.3%) and 1.7% had a simultaneous local and regional failure (local+supraclavicular, 0.7%; local+axillary, 1%). Subsequently 27% of patients experienced distant failure.

**Conclusion:** Isolated axillary failure is uncommon among patients with positive axillary lymph nodes and extranodal spread. Balancing the risks and benefits of adjuvant radiotherapy, we conclude that axillary irradiation should not routinely be given following an adequate axillary dissection.

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**Long-term radiation sequelae after breast conserving therapy in women with early-stage breast cancer treated with 2.5 Gy per fraction**

S. Tribius, F. Fehlauer, A. Bajrovic, U. Hoeller, D. Rades, W. Alberti. *University of Hamburg, Department of Radiooncology, Hamburg, Germany*

**Background:** Breast irradiation after lumpectomy is an integral component of breast-conserving therapy (BCT). An optimal fractionation schedule for breast irradiation has not been uniformly accepted world wide and altered fractionations are discussed. We examined retrospectively late toxicity of a 22-day fractionation schedule (2.5 Gy per fraction to 55 Gy, 4×/wk, without additional boost).

**Patients and Methods:** Between 1988 and 1993 1662 patients with early-stage breast cancer (pT1-2, pN0-1, cM0) were treated with adjuvant radiation therapy (85% with 6 MV photons) using 2.5 Gy single fraction size to a total dose of 55 Gy, 4×/week. During their last follow-up visit late toxicity was assessed in 345 relapse free women using the LENT-SOMA criteria (mean follow-up 9 years, range 6.5–13 years).

**Results:** Moderate and severe toxicity (grade 2; grade 3 and 4) were observed as follows: pain (14%; 2%), breast edema (2%; 0%), breast fibrosis (41%; 10%), telangiectasia (7%; 10%), arm edema (1%, <1%), atrophy/ retraction (22%; 8%), skin ulceration (<1%; 0%). Six percent of women were using pain medication at the time of follow-up and 4% were regularly undergoing lymph drainage treatments.

Conclusion: The LENT-SOMA criteria are a useful tool for assessing radiation induced late toxicity after BCT using 2.5 Gy fraction sizes to a dose of 55 Gy. In this study population, late radiation effects do occur not infrequently. However, in the majority of patients they are asymptomatic when scored using the LENT-SOMA criteria.

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**Post-mastectomy adjuvant internal mammary lymph node irradiation – benefit and cardiac toxicity: an Indian experience**

S. Saha[1], P. Maity[2], S. Ganguly[2]. [1]*Medical College Hospital Calcutta, Department of Radiotherapy, Kolkata, India;* [2]*Medical College Hospital, Department of Radiotherapy, Kolkata, India*

**Background:** Worldwide there is no consensus as to whether post-mastectomy internal mammary node (IMN) irradiation should or should not be used in medial or central quadrant **(m/c)** breast cancer patient.

**Aim of study:** The present study was aimed to evaluate the benefit of inclusion of ipsilateral IMN field during post-mastectomy adjuvant radiotherapy in axilla positive m/c tumor and to analyze the cardiac effect amounting from radiation of this additional anatomical area.

**Material and method:** After simple mastectomy with level I/II axilla dissection, IMN radiation was considered only in m/c disease with axilla involvement. Out of total 1068 patients receiving post-mastectomy radiation in Cobalt-60, 203 cases had axilla positive m/c disease and were studied between June 1995 and November 2002. Of these 203 cases, 94 Pt.s (Left breast cancer in 43) received IMN radiation. Remaining 109 Pt.s (Lt breast = 55) did not receive IMN. Total dose was 45 Gy/20 fractions/4 wks. All patients received 6 cycles of adj. chemotherapy (FAC or AC). All patients had CT-based treatment planning in 3D TPS to optimize the IMN coverage. Volume of heart irradiated and dose received were quantified individually from integral DVH. Cardiac effects were studied by ECG, CXR, Doppler Echocardiogram at the start of radiation, on completion and then 6 monthly. TMT and 24 hr. Halter monitor were done in selected cases.

**Summary of result:** In a median duration of F.U. of 39 months, 4 patients had chest wall recurrence – 2 received IMN and 2 did not. **IMN recurrence was observed in none whether received IMN radiation or not.** Regarding **cardiac effects**, 2 out of 43 **left** breast patients receiving IMN developed constrictive percarditis, 3/43 had LV dysfunction (EF<50%), 3/43 had congestive failure and no toxicity in 55 Lt breast cases not receiving IMN ($p<0.001$). So significant late cardiac toxicity was observed in 8/43 Lt breast IMN-treated and in 0/55 Lt breast IMN not treated cases ($p<0.001$). It was also absent in Rt breast radiation **even if received IMN**. Analysis of compiled integral DVH data revealed 50% heart volume was exposed to 22–25 Gy in IMN treated vs. 8–10 Gy in IMN not treated Lt breast patients.

**Conclusion:** In centers equipped with only Cobalt 60 and with no facility of IMRT or electron, addition of IMN portal is not justifiable at least in left breast cancer even in axilla positive medial quadrant disease as it may invite fatal late cardiac toxicity *without any additional gain* in loco regional control.

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**Pulsed dose rate peri-operative brachytherapy (PDR BT) as an interstitial boost in conservative treatment (BCT) of breast cancer. Preliminary results**

K. Serkies[1], J. Jaskiewicz[2], J. Jassem[1]. [1]*Medical University of Gdansk, Department of Oncology and Radiotherapy, Gdansk, Poland;* [2]*Medical University of Gdansk, Department of Plastic Surgery, Gdansk, Poland*

**Background:** Reduced risk of local recurrence in patients treated with BCT including a boost dose to the tumor bed in addition to whole breast irradiation (EBRT) was confirmed in a large randomized trial. In practice, the extent of boost tumor volume may be incorrect if the tumor bed is determined using clinical parameters. The intra-operative implantation of BT catheters allows for decreasing the risk of "geographical miss" in determining the target volume. Despite its favourable radiobiological features, PDR BT has rarely been used in breast cancer. We present here our early experience with this method employed as an interstitial boost.

**Material and Methods:** A total of 40 consecutive T1–3N0–1M0 breast cancer pts (4 pts with T2–3 tumor after prior chemotherapy) who underwent BCT between 05/2002 and 08/2003 were analyzed. Breast sparing surgery consisted of primary segmenetectomy (27 pts) or reexcision after excisional biopsy (13 pts), full-axillary sampling in all but 2 pts with negative sentinel node, immediate tumor cavity reconstruction, and intra-operative BT tube placement. Peri-operative PDR BT of 15 Gy (1 Gy/pulse/h) was administered with Paris system rules and volume optimization technique using BT planning system PLATO. BT was followed by whole breast EBRT after the final histology had been obtained.

**Results:** Tube implantation (mean 9, range 5–13) prolonged time of surgery by no more than 20 minutes. Two-plane implant was used in 38 pts (95%) and one-plane in the remaining 2. BT started the day after implant placement in 38 pts and was delayed by 1–3 days in 2 pts. Temporary peri-operative breast infection in one reexcised case and fat necrosis in another one were the only side effects observed. The median period between BT and whole breast EBRT was 12 days (range, 10 to 31). Subsequent breast EBRT was abandoned in 3 pts (7.5%) including one pt with multiple pathological factors implying the superiority of mastectomy, one with final histology of LCIS and one with no malignant tumor; all these pts were diagnosed by fine needle aspiration cytology.

**Conclusions:** Peri-operative PDR BT with tube implantation at the time of surgery is a safe and convenient boost method. In some pts therapeutic strategy has to be verified after the final histology is obtained. Therefore, this approach necessitates careful pt selection and preoperative histological diagnosis.

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**The effect of exercise program on the fatigue of cancer under external radiotherapy**

S. Lakdizajee, A.M. Agdam. *Nursing&Midwifery School of Tabriz, Medical Surgical Nursing, Tabriz, Iran*

Cancer fatigue is the commonest complication during and after cancer treatment, especially radiotherapy. It is possible that exercise with its physical and emotional effects might be useful in reducing cancer fatigue. This study was intended to convey the effects of the scheduled exercise program on the fatigue of cancer patients under radiotherapy and to compare it with a control group. The experimental group was trained for four weeks; the first week before the program; the second and third weeks were the exercise week when the subjects were required to have exercises for 20 minutes each day followed by a 10 minute bed rest and deep slow