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EORTC randomised phase III trial 22922/10925 investigating the role of internal mammary chain (IMC) irradiation in stage I–III breast cancer: A quality assurance report on the dummy run

Ph. Poortmans, W. van den Bogaert, J. Venselaar, G. van Tienhoven, H. Struikmans, C. Hurkmans, B. Davis, D. Huyskens, V. Vlaun, K. de Winter, B. Mijnheer, H. van Kleffens. *For the EORTC 22922/10925 Quality Assurance Committee; University Hospital, Radiotherapy, Heidelberglaan 100, The Netherlands*

Purpose: To evaluate and improve consistency between participating centres, irradiation techniques were reviewed and corrections were suggested when relevant.

Methods: Prior to participation, all centres were asked to perform treatment planning without (arm 1) and with (arm 2) irradiation of the IMC on 3 slices of a patient after mastectomy and of a patient after lumpectomy. Up to now, 19 dummy runs have been evaluated. Findings were discussed with the institutions on an individual basis. A letter with recommendations concerning the protocol prescriptions has been sent to all participants.

Results: In arm 1, the dose to the IMC region was > 25% in 30% of the treatment plans. In arm 2, the dose to the IMC region was < 75% in 12% of the plans, independent of the technique which has been used. Comments on the irradiation techniques were: dose prescription not in conformity with the protocol or with ICRU 50 (10 centres for the IMC and 12 centres for other target volumes), problems with the field set-up (positioning of the IMC field (3) and in general (3)), too low dose to the target volume (11), too large fields (3), absence of lung density correction (3), too few isodose lines (12).

Conclusion: By performing a dummy run in the early phase of a clinical trial, a number of potential systematic protocol deviations has been detected. A follow-up study is needed to check if the committee's recommendations have been incorporated correctly.

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Is hypofractionated breast radiotherapy a valid treatment option?

G. Ryan. *Peter MacCallum Cancer Institute, Radiation Oncology, Locked Bag No. 1, A'Beckett Street, AUS-3000 Melbourne, Victoria, Australia*

Hypofractionation is rarely used in the radical radiotherapy setting because of concerns about its efficacy and potential for increased long term toxicities. However, there may be patients for whom delivering a standard fraction course of radiotherapy is problematic because of age, debility etc. The experience of a group of 167 postmenopausal women treated with a hypofractionated radiotherapy schedule – 36 Gy in 8 fractions over 3 weeks – following breast cancer surgery is reviewed retrospectively. Survival, disease progression and treatment-related complications are compared with those of a group of 325 matched patients treated with a conventionally fractionated schedule – 45–66 Gy in 20–35 fractions over 4–7 weeks – over the same 10 year time period. A number of potential prognostic factors for outcome are studied – age, stage, extent of surgery, radiotherapy schedule – and additionally for complications extent of radiotherapy fields and years at risk.

For both disease-specific survival and time to disease progression, stage and prior surgery are significant ($P < 0.0001$), but age and radiotherapy schedule are not ($P = 0.23$ and 0.51). Competing risks analysis shows no difference between schedules in the sites of first progression, with patients in both groups 2–3 times more likely to have a systemic recurrence than a local recurrence. For a range of treatment-related complications (including oedema, fibrosis and telangiectasia), extent of radiotherapy fields ($P = 0.0003$) and years at risk ($P < 0.0001$) are significant, but radiotherapy schedule is not ($P = 0.80$).

Thus, in the particular group of patients studied, hypofractionation cannot be demonstrated to be associated with inferior treatment outcomes, and may be a valid treatment option. Dose comparisons using the linear quadratic equation support this conclusion, but a randomised trial is recommended to confirm these findings.

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Treatment of Paget's disease of the breast with radiotherapy only

M.R. Christiaens[1], J. Knol[1], W. Van den Bogaert[2], E. Van Limbergen[2]. *[1]Dept. of Surgery-Senology; [2]Dept. of Radiotherapy, University Hospital of Leuven, Belgium*

Paget's disease of the breast, without clinical or radiological signs of associated invasive or in situ cancer, remains a controversial treatment issue.

Between 1971 and 1997, 28 (27 female, 1 male) patients have been treated for Paget's disease with radiotherapy only. One patient was excluded because no follow-up data were available. Mammogram and ultrasound showed no underlying malignancy. In all patients a biopsy confirmed the presence of typical Paget's cells. None of those patients had an excision of the nipple-areola complex. Total breast irradiation varied between 45 and 65 Gy. An electron boost was delivered, resulting in a total dose between 60 and 70 Gy. With a follow-up varying between 12 and 213 months (median 79 m), 4 local recurrences (3 Paget's disease; 1 invasive carcinoma) were treated by mastectomy in one, and modified radical mastectomy in 3 cases. All are disease-free until now.

Although similar series are scarce, in our experience breast conservation with radiotherapy only, promises to be a safe procedure for pure Paget's disease, providing recurrences are detected and treated at an early stage. Further study is warranted.

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Radiosurgery of T1 breast cancer: A dosimetry study

C. Formenti[1], S. Jozsef[2], G. Parisky[3], V. Skinner[4], K. Luxton[2]. *[1]Southern California School of Medicine, University Los Angeles; Departments of [2]Radiation Oncology; [4]Surgery; [3]Radiology, USA*

Purpose: To develop a radiosurgery-like technique for T1 breast tumors.

Methods: Post-menopausal women with less than 1.5 cm. invasive breast cancer were elegible to pilot-test the role of radiosurgery in early breast cancer. At diagnostic core biopsy, a tantalum surgical clip was placed in the lesion. Transverse CT scans with the patient prone on a special table were aquired, covering the full superior-inferior extent of the breast with the clip used as reference points to define the isocenter. RS was delivered with the patient exactly in the same position on the same table that allows for beams to enter from a solid angle of about 220° × 90°. With a 4MV beam the clip is visible on port films to verify the isocenter. A 20 Gy/single fraction dose is given.

Results: By utilizing the arbitrary plane reconstruction and beams, eye view features of our treatment planning software, one can rule out beam directions which would deliver dose to normal structures. In the first test case the limits of the arc lengths were about 30° from the contralateral side, 15–20° from the ipsilateral side and less than 10° from the superior direction. The resulted dose distribution for one fraction of 20 GY is similar to that which would be produced by a single arc in the coronal plane through the isocenter. In the case of a deep seated tumor, seven, unequally weighted, horizontal, 32 mm diameter fixed beams results in virtually zero lung dose, with 90% of the maximum dose over the 30 mm diameter target, and 20–25% to the surface of the breast.

Conclusion: From dosimetric point of view the described technique is feasible.

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Variation in normal tissue complication probability with radiation technique in early breast cancer

P.A. Canney, R. Sanderson, C. Deehan, T. Wheldon. *Dept. of Radiation Oncology and Dept. of Clinical Physics, Beatson Oncology Centre, Glasgow, Scotland, UK*

Purpose: To investigate the effect of varying the treatment position to try and minimise the heart dose during post-operative radiotherapy fields for the treatment of breast cancer.

Methods: Using the same arrangement of glancing fields for each patient the effect of positioning was studied in 11 patients with left sided tumours. Cardiac doses were calculated from dose-volume histograms using a 'Helax' planning system. With the data available, using pericarditis as the end-point for radiation induced heart damage [Emami et al. 1991], the DVH reduction algorithm of Lyman and Wolbarst [1989] was applied to each DVH to produce a value for the normal tissue complication probability (NTCP).

Results: Comparing the optimal treatment position to our standard treatment position, the reduction in mean cardiac dose was 60% ($p < 0.001$), and in maximum dose was 32% ($p < 0.001$). The volume of cardiac tissue irradiated was also reduced for all patients. The mean NTCP with the standard technique was 7.4 ± 5.6% (range 0.6–17%) and for the new technique the mean NTCP was 0.3 ± 0.6% (range 0–2%), $p < 0.003$ for the difference between the 2 techniques.

Conclusion: The comparison between the two techniques has shown how simple variation in radiotherapy planning can result in substantial variations in NTCP, with a predicted reduction in late cardiac complications of 23 fold, not clearly evident from cardiac DVH raw data.

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Non-invasive follow-up of the viscoelasticity of the breast skin following radiation therapy

R. Gorodetsky[1], C. Lotan[1], I. Polyansky[1], A. Vexler[1], M. Saunders[2], K. Piggot[2], S. Dische[2], L. Pierce[3], A. Lichter[3]. *[1]Dept. of Oncology, Hadassah University Hospital, Jerusalem 91120, Israel; [2]Mount Vernon Hospital, Northwood, UK; [3]Dept. of Radiation, Oncology, University of Michigan, Ann Harbor, MI, USA*

Post-lumpectomy external-beam irradiation may be associated with early and Late radiation effects to the skin of the preserved breast. We have introduced a new method for the measurement of skin viscoelasticity following different protocols of radiotherapy. For the objective assay of skin condition we used our novel non-invasive viscoelasticity skin analyzer (VESA) which records accurately the speed of propagation of elastic mechanical surface waves on the skin. The VESA readings are inversely proportional to the viscoelasticity. A high correlation between the VESA measurements in contralateral areas of the breasts of healthy women was recorded with similar anisotropy. For the evaluation of late effects of radiotherapy, skin viscoelasticity of the breasts in 110 breast cancer patients from 3 medical centers was measured. In patients irradiated with 45–50 Gy in 1.8 Gy per fraction no significant late changes in the skin viscoelasticity were recorded in the treated relative to the untreated breast. Skin viscoelasticity seemed to be reduced with the increase in the dose of radiation per fraction rather then by the increase in the total accumulated dose given.

We have initiated a follow-up of early radiation effects in the skin with VESA and other dedicated devices that can evaluate other skin physiological parameters. The attenuation of radiation effects induced by high dose radiotherapy by daily application of Zn-based dermal regeneration cream is now being tested. Non-invasive analysis of metals in the skin with our unique Diagnostic-x-ray spectrometry (DXS) device have shown that the Zn in the cream tested (Triple Care, Smith & Nephew) is absorbed in the skin and its elevated concentration stay relatively constant along the continuous treatment. The radio-protective effect of this treatment is being now evaluated in breast cancer patients treated by radiotherapy following lumpectomy.

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Effect of radiotherapy in addition to 6 cycles CMF in node positive breast cancer patients

C. Schmoor[1], G. Bastert[2], H. Bojar[3], W. Sauerbrei[1], M. Schumacher[1]. *For the German Breast Cancer Study Group (GBSG); [1]Institute of Medical Biometry and Medical Informatics, University of Freiburg; [2]Department of Gynecology, University of Heidelberg; [3]Department of Chemical Oncology, University of Düsseldorf, Germany*

Purpose: In 1984 the GBSG started a multicenter randomized trial to compare 6 cycles CMF with 6 cycles CMF plus radiotherapy as adjuvant treatment in node positive breast cancer patients treated with mastectomy.

Methods: During 5 years, 199 patients were randomized from 17 institutions. After a median follow up time of 8 years, the treatment groups (6 × CMF: 101 patients, 6 × CMF + Rad.: 98 patients) are compared with respect to time to recurrence and death.

Results: As first event of failure we observed in 22 patients a locoregional recurrence (LR) and in 80 patients distant metastases and/or death (DIST). With respect to disease free survival (DFS) no significant difference was observed (relative risk radiotherapy vs. control RR = 0.82 with 95% CI [0.55, 1.21]). An event specific analysis showed a significant benefit of radiotherapy with respect to LR (RR = 0.35, 95% CI [0.14, 0.91]) and no benefit with respect to DIST (RR = 1.01, 95% CI [0.65, 1.57]). With respect to overall survival (94 deaths) no treatment effect can be demonstrated (RR = 0.93, 95% CI [0.62, 1.40]).

Conclusion: There is a beneficial effect of radiotherapy on LR. Concerning DFS a tendency in favor of radiotherapy is observed, but this is not significant.

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Neo-adjuvant chemo-radiotherapy for operable breast cancer. Preliminary results of an ongoing phase II study

P. Pacini, G.P. Ausili-Cefaro, L. Nardone, M. Rinaldini, L. Irtelli, C. Menichelli, R. Bagnoli, A. Rubagotti, F. Boccardo. *For the GROCTA (Gruppo Ormono Chemioterapia Adiuvante) Group; Policlinico Careggi, Radiotherapy, Viale Morgagni 85, 50134 Florence, Italy*

Purpose: Primary chemotherapy (CT) is a widely adopted method to reduce the tumor diameter in operable breast cancer (BC) patients (pts) not suitable of conservative surgery (CS). Preoperative radiotherapy (RT) has shown, mainly in the treatment of locally advanced BC, to be at least as effective as CT in determining a significant tumor shrinkage. The aim of this study was to evaluate if the concurrent administration of preoperative CT and RT was a safe and effective method as primary treatment of operable BC.

Methods: From December 1994 to September 1997 52 pts entered the study. 31 are evaluable for results and toxicity. Age ranged from 32 to 70 years (median: 50 years). All patients had been considered not eligible for CS by the surgeon. Clinical tumor diameter ranged from 3 cm. to 6 cm. 26 pts were classified as T2 and 5 as T3. Treatment consisted of CMF (CTX 600 mg/sqm, MTX 40 mg/sqm, 5Fu 600 mg/sqm iv) on day 1 and 8. RT started on day 11 and 36 Gy were delivered to the whole breast in 2 weeks (5 days/week: 1.8 Gy b.i.d.). A second cycle of CMF started on day 28. Re-evaluation and surgery occurred about 3 weeks after the completion of the second course of CT. Postoperative chemotherapy consisted of 4 courses of CMF or EC according to the nodal status (negative or positive). Tamoxifen was given to all the ER+ pts.

Results: 28 (90.3%) pts were submitted to CS. In 3 cases a pathological complete response was achieved. 4 pts submitted to CS had focal involvement of the specimen margins. After the completion of postoperative CT 1 was submitted to mastectomy and 3 to re-excision of the tumor bed. Pathological examination revealed no residual tumor in the case submitted to mastectomy and in 2 out of the 3 submitted to re-excision. A total of 4 (12.9%) pts were, at the end, submitted to mastectomy. Local control was obtained and maintained up to date. Toxicity was mild and only a transient redness of the skin was observed after RT.

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Breast cancer in premenopausal women / should mastectomy be recommended?

A. de la Rochefordière, E. Mouret-Fourme, F. Campana, R. Dendale, P. Pouillart, A. Fourquet. *For the Members of the Breast Cancer Study Group; Institut Curie, Radiotherapy, rue d'Ulm, F-75231 Paris Cedex 5, France*

Purpose: To evaluate the role of age at diagnosis, as well as of local treatment on breast cancer outcome.

Methods: We retrospectively reviewed 3476 premenopausal women treated between 1981 and 1990 for stage I–III breast cancer. Median follow-up was 10 years. 1853 were treated by limited surgery and RT, 876 by RT, and 747 by mastectomy. We analyzed 3 groups of patients according age at diagnosis: Age 18–35 (335 patients), Age 36–40 (560 patients), Age 41–55 (2581 patients).

Results: 10-year rates of local and distant relapses according to age were 39%, 33% versus 19% ($p < 0.0001$) and 46%, 44% versus 30% ($p < 0.0001$), respectively. Multivariate analyses showed that: 1. The risk of local as well as of distant relapses was independently increased by young age; 2. The risk of distant relapse was strongly correlated to the time to local failure: the earlier the local failure, the stronger the risk or distant failure. The model was no more significant for a local failure which occurred >5 years following treatment; 3. The risk of distant failure was not influenced by the type of local treatment.

Conclusion: This study confirms, with a 10-year median follow-up time, that age at diagnosis (£40) is a strong independent predictor both for local and distant relapses, whatever the local treatment. In this study, local treatment was performed on the basis of clinical presentation. The higher risk of distant relapses associated with early local failure may reflect tumor aggressiveness rather than inadequate local procedure. So far, mastectomy does not seem to be able to improve the poor outcome of this particular age group.