breaths, with their eyes closed. Fatigue was scaled in a summarized scale of 0–10. The control group did not received any treatment but their fatigue was measured daily. The results indicated that both groups experienced mild fatigue during the first week before the program with no significant difference between them. After treatment, the control group experienced sever fatigue and the experimental group experienced mild fatigue; the difference was significant. It was concluded that jogging/aerobic exercises can reduce fatigue.

326 POSTER

Intraoperative Radiotherapy (IORT) for primary breast cancer treatment

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Purpose: Presenting the technique and evaluating first results with the intraoperative application of a tumor bed boost irradiation (IORT) in breast conserving therapy.

90% of all local recurrences occur near the primary tumour location. Several authors have demonstrated the benefit of a boost irradiation to this region additional to percutaneous radiotherapy of the whole breast for local tumor control in breast conserving therapy.

This boost can be applied by several means but the "geographic miss" of the primary tumor location is considerably high. The intraoperative application of this boost offers the unique possibility to visualise and control the irradiation to this region of interest and by that completely avoiding the problem of "geographic miss". Moreover percutaneous radiotherapy can be shortened by the anticipation of this boost and results demonstrate no significant concomitant increase in postoperative morbidity. This procedure has now been applied in over 500 cases at our special dedicated unit since 10/1998. So far 200 patients have been evaluated over a 30 months follow up, with no local recurrence after IORT.

Conclusion: Experience with intraoperative radiotherapy (IORT) in breast conserving therapy (BCT) for primary breast cancer demonstrates the efficiency and safety of this high quality boost in over 500 cases during a 5 year period.

327 POSTER

Use of clipping to guide radiation boost planning for breast conservative therapy of the early breast cancer

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Purpose: Lumpectomy and quadrantentomy followed by radiation therapy are well established locoregional management of early breast cancer that has gained popularity in Japan. It is important to use boosting after whole breast irradiation for the finding of microscopic tumor in the margin, because most of mammary recurrences after breast conserving therapy develop from the tumor bed (or close to surgical margin).

Materials and Methods: One hundred and ten patients were treated with conservative surgery and irradiation for stage 0, 1, and 2 breast carcinoma between October 1996 and October 2003. Their ages ranged from 30 to 73 years old, and tumor sizes were from 0 to 35 mm. Indication of the boost is the finding of microscopic tumor in the margin, close margin, and unknown margin. We use the titanium clips, which length are 5.2 mm, because surgical clips around the resected area are helpful in planning the boost. The setting points of the surgical margins are three; close point of the nipple, bilateral half points of the distant of the nipple in the tumor bed.

Results: These distances between surgical scar and clips were 0–6.2 cm (mean 2.1 cm).It is easy to find these surgical clips at using the simulating film, ultrasoud, chest X-ray, and CT. Twenty three patients were setting this technique, and three of them were boosting after finding at the simulating film. Usually the boost dose is 1000 cGy given at the rate of 200 cGy per fraction, and the electron energy should be one that reaches the deepest part of the tumor area with the 80 to 85% isodose line. The clinically marked boost area encompassed the surgical clips adequately in 20 patients, 8 by 8 cm and 10 by 10 cm fields were placed on the breasts. The function of a boost in radiotherapy is to give a higher dose to the primary tumor bed than to the surrounding tissue. We have no severe complication of these clips.

Conclusion: To accurate the localization of the boost irradiation field, the titanium surgical clips were placed at the margin of the tumor bed of the breast cancer, in 110 patients. The conserving surgical scar is often a poor indicator for the location of the underlying tumor bed. Our presented methods is useful for easy setting the boost irradiation field and to maximize target definition.

328 POSTER

Intraoperative radiotherapy (IORT) as a boost in patients with early breast cancer

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Background: External beam radiotherapy (EBRT) of the whole-breast after breast-conserving surgery with a total dose of 45–50 Gy is the gold-standard in patients with limited stages of breast cancer. Most in-breast recurrences appear in close vicinity to the tumor-bed of the reference tumor. Therefore this area is often provided by a boost in routine practice, but no standard technique has been established. The boost dose is applicated either by different EBRT-techniques, by brachytherapy or by intraoperative radiotherapy (IORT). Since february 2002 in our department IORT is delivered in breast cancer patients by a mobile miniature X-ray source (Intrabeam™).

Materials/Methods: From February 2002 until October 2003 seventy patients with early stage breast cancer were treated by IORT after breast-conserving surgery. 45 of them had the IORT-treatment as a boost before consecutive EBRT. Median age was 63 years (43.1–86.5). The median tumour size was 14 mm (6–45). Definitive pathology results showed ductal-invasive histology in 18 patients, lobular-invasive histology in 13 patients, mixed histology in 10 patients, tubular-invasive histology in 2 patients, medullar histology in 1 patient and mucinous histology in 1 patient. IORT treatment time was 20 minutes (18.6–48.8). In most cases a spherical applicator with a diameter of 4.5 cm was chosen (3.0–5.0). Intrabeam™ is producing low energy X-rays, which can be applicated in an isotropic dose distribution to the tumor-bed. Therefore a single high-dose (20 Gy) can be applicated on the applicators surface reaching the wrapped breast tissue up to a tissue depth of 1.5 cm. After wound-healing all IORT-patients were treated by homogenous external-beam radiotherapy of the whole breast with a total dose of 46 Gy.

Results: Treatment was tolerated well by all patients without any skin necrosis. Three patients had wound healing problems, two showed skin erythemas °II after IORT, which disappeared without any delay. After a maximum follow-up of 20 months patients had good cosmetic outcome without any significant late effects. One patient had to be treated by secondary mastectomy because of multifocality and one patient developed cervical lymph node metastases 2 months after breast conserving surgery. In both cases additional EBRT was omitted. One other patient presented with multifocally relapsed disease with several skin metastases 10 months after IORT plus EBRT and died 4 months later.

Conclusions: IORT with the Intrabeam system is a comfortable, effective method to deliver a single high-dose to the tumour-bed as a boost. After breast-conserving surgery, the resection cavity can be ideally irradiated intraoperatively by short-distance X-rays. A miss of the target, as it happens often during external beam course, can be avoided.

Thursday, 18 March 2004 16:00–17:30

PROFFERED PAPERS

Hereditary cancer

329 ORAL

Risk of breast recurrence in relation to BRCA1/2 mutation status following breast-conserving surgery and radiotherapy

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Background: *BRCA1* and *BRCA2* germline mutations are associated with a strong risk of breast cancer, which may preclude breast-conserving treatments in carriers. We investigated whether mutation status was influencing the rate of breast recurrence following breast-conserving treatment (BCT) with surgery and radiotherapy.

Patients and Methods: *BRCA1* and *BRCA2* genes were screened for germline mutation in 131 patients (with 136 breast cancers) with a family history of breast and/or ovarian cancer, treated with BCT. Tumor features, breast recurrences (BR) and contralateral breast cancer (CBC) rates of *BRCA* mutation carriers were compared to those of non-carriers with a family history. The 131 pts. with familial history were matched to 261 pts.

without familial history, according to age at diagnosis and year of treatment. The follow-up of controls was at least equal to the time-interval between diagnosis and genetic testing in cases. The 136 tumors were matched to 271 controls. Rates of BR as first event and CBC as any event were determined using Kaplan-Meier estimates, and comparisons done with the log-rank test. A multivariate analysis using a Cox's stepwise forward regression model was done to determine the independent prognostic value of various factors on breast recurrence.

Results: *BRCA1/2* mutations were found in 20.6% pts. with a family history (21.3% tumors). Nineteen pts. (with 21 tumors) had a *BRCA1* mutation, and 8 had a *BRCA2* mutation. Breast cancers in mutation carriers were more often of grade III ($p<10^{-4}$) and estrogen receptor negative (p=0.005) than tumors in both non-carriers and controls. Medullary subtype was more frequent in *BRCA1* carriers than in other groups (11.5% vs 1.2% vs 0.9%, respectively). Median follow-up for all 392 pts. was 8.75 years (2.25–19.4 yrs.). No significant differences in BR as first event were seen between *BRCA1/2* tumors and controls (p=0.46), tumors in *BRCA1/2* carriers and non-carriers with a family history (p=0.96), or non-carriers and controls (p=0.10). On multivariate analysis, age was the only factor significantly predicting for BR, with an increased relative risk of 6% for every decreasing year of age. The rate of CBC was significantly increased in all pts. with a family history: *BRCA1/2* carriers vs. controls (p=0.0003), non-carriers vs. controls (p=0.0034), and carriers vs. non-carriers (p=0.02).

Conclusion: With a median 9-year follow-up after BCT, the rate of breast recurrence was not higher in *BRCA1/2* mutation carriers than in non-carriers, or than in patients without family history, despite more aggressive tumor features and a higher risk of CBC. Tumors in *BRCA* carriers may be more sensitive to radiation, possibly through an impaired DNA double-strand break repair capacity. Therefore, BRCA mutation carriers can be offered breast-conserving treatments of breast cancer. However, further follow-up will need to ensure that the rate of new breast cancer in the treated breast does not increase.

330 ORAL

Contralateral breast cancer and survival in non-BRCA1/2 hereditary breast cancer: a case control study

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Background: Most hereditary breast cancers (HBC) cannot be attributed to a germ-line mutation in BRCA1 or BRCA2. Specific histopathologic characteristics have been described in these non-BRCA1/2 hereditary cancers, such as more frequent low grade tumours, low mitotic count, a lower proliferation rate and more lobular carcinoma, discriminating them from both sporadic and BRCA1/2 breast cancers [1–3]. Few data exist on factors influencing survival of proven non-BRCA1–2 breast cancers, although a higher frequency of contralateral cancers as compared to sporadic cancers has been reported [4].

Therefore we assessed the incidence of second breast cancers and disease free and overall survival in patients with hereditary breast cancer but no BRCA1/2 gene mutation. We'll try to assess the impact of prognostic and treatment factors.

Methods: We selected all 236 women registered in the Erasmus University Medical Centre with primary breast cancer diagnosed between 1–1-1980 and 31–12–2002 and a family history of at least 3 confirmed breast or breast and ovarian cancers, but a negative test for a BRCA1 or BRCA2 mutation. Patients with unknown tumour stage or <6 months follow-up were excluded. To each case a control patient without a family history was matched for age at onset and year of diagnosis. Tumour and treatment characteristics were extracted from medical files. Kaplan-Meier curves were used to estimate the occurrence of ipsilateral and contralateral breast cancer, local and distant disease free survival (DFS) and overall survival (OS).

Results: In the 236 cases;mean age at diagnosis was 45 years (range 23–77); the median follow-up 6.1 years (0.56–21.8). Tumours were preinvasive in 5% and <2 cm in 63%; 52% was node-negative. The histologic grade of the tumours was I in 7%, II in 20%, III in 41%, unknown in 32%. Breast conserving therapy (BCT) was performed in 49%, mastectomy in 47%. 37% received adjuvant chemotherapy. Contralateral preventive mastectomy was performed in 10%, risk reducing oophorectomy in 6.7%. On average, the yearly incidence of metachronous second breast cancer was 1.8%. The 5, 10 and 15-year contralateral breast cancer incidence for women with their first BC detected <50 year was 12%, 16% and 25% respectively and 6%, 8% and 8% for women over this age. Distant DFS at 5, 10 and 15-year was 75%, 62% and 56% respectively; OS 86%, 71% and 61%.

Conclusion: Especially in patients diagnosed under age 50 years, contralateral breast cancer incidence appeared to be much higher than expected for sporadic patients, but lower than the rate that was found in our BRCA1 patients. Contralateral BC incidence had no impact on survival. Analyses including the matched controls and the impact of different therapies on survival will be presented. These results are important for the counselling of hereditary breast cancer patients without a BRCA 1/2 germline mutation.

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331 ORAL

High prevalence of BRCA1 mutations in breast + ovarian cancer patients at the region of Gdansk, Poland

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Background: Coexistence of breast and ovarian cancer constitutes a significant predictive factor for *BRCA1* positivity.

Material and methods: Prevalence of BRCA1 mutations was analyzed in breast–ovarian cancer syndrome patients registered at the Regional Cancer Registry of Gdansk region, Poland. The screening covered the most common founder mutations. Methods included ASA PCR (exon 2 and 20) and RFLP PCR (exon 5). Prescreening for 3819del5 in exon 11 was performed with nondenaturating polyacrylamide electrophoresis.

Results: Sixty-three cases of coexisting breast and ovarian cancers were found among 9436 breast cancer cases and 2388 ovarian cancer cases registered. The age at diagnosis of breast cancer was 30 to 81 years (median 50 years) and at the diagnosis of ovarian cancer – 30 to 79 years (median 52 years). Seven patients had their first cancer (breast – 4 cases, ovarian – 2 cases, both – 1 case) diagnosed before the age of 40. There were 5 cases of synchronous cancers. The time span between metachronous malignancies varied between 4 and 287 months (median 49 months). Breast cancer preceded ovarian cancer in 46 patients and followed in 12.

Five patients had bilateral breast cancer, the second tumor occurred after a median of 63 months (range 37–134 months). Family history of breast and/or ovarian cancer was positive in 19 of 42 patients with available data. In 10 patients multiple family members were affected. In 42 patients no readily identifiable risk factors for the breast-ovarian cancer syndrome were present. In 2 patients third primary cancer was diagnosed (vulva, thyroid). One patient developed 2 subsequent primary malignancies (endometrium, skin).

BRCA1 typing was performed in 22 patients and mutations were found in 10. Three types of mutations included well known global and European founder mutations were found: 5382insC (6 cases), 185delAC (2 cases) and 300T>G (1 case). The less frequent 3819del5 mutation (1 patient) was recently found in the Polish population.

All patients with germline mutations had a strong family history of breast and/or ovarian cancer (at least 2 cases in all but one patient). In two patients breast cancer occurred before the age of 40, whereas all ovarian cancers occurred after that age. One patient had bilateral breast cancer.

Conclusion: High prevalence of founder BRCA1 mutations was found among breast-ovarian cancer syndrome patients from the region of Gdansk, Poland. Strong family history was the best predictor of BRCA1 positivity in this population.