patients treated at the European Institute of Oncology in Milan between June 1994 and December 2009.

Results: The main goal of surgical treatment for women with DIN is breast conservative surgery (BCS); mastectomy is still indicated in large lesions, masses or microcalcification, in about 30% of cases. RT after BCS is indicated in selective cases, mainly depending on grading of the tumour. Medical treatment is proposed in estrogen receptors-positive patients. There are significant differences in the practical applications of the theory, in particular regarding the indications of sentinel lymph node biopsy, the definition and identification of low-risk DIN subgroups patient, which can avoid RT and tamoxifen and the identification of alternative drugs for adjuvant medical therapy.

Conclusion: New large trials are necessary to define the best management of DIN patients, because nowadays it still remains complex and controversial.

457 Poster

Clinical Differences Exist Between DCIS with Low and High Ki67 Expression

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Background: molecular characteristics as Ki67 expression could define different DCIS subtypes. The aim of this study was to establish clinical differences between DCIS expressing low Ki67 levels and DCIS expressing high Ki67 levels.

Material and Methods: we reviewed all DCIS treated in our institution between January 1993 and June 2011 (N = 256). Two groups were defined upon Ki67 expression: low expression group (expression in 14% of cells or less) and high expression group (expression in 15% of cells or more). Data on patient's age, menopause, breast cancer family history, breast symptoms, breast exploration, multicentric /multifocal disease and tumour size were collected. Microsoft Access and PASW statistics 18 were used to store and analyze data. Chi2, Fisher's exact test and Student T were applied when necessary.

Results: data on Ki67 expression were obtained in 79 patients. Patients in the high expression group were significantly younger (median$\pm$SD, 55.64$\pm$10.22 vs 60.68$\pm$11.43, p = 0.05). More women in the high expression group were premenopausal (40% vs 26.7%), had a breast cancer family history (47.4% vs 24.1%) and presented a multifocal/multicentric disease (6.5% vs 2.1%), even though these differences were not significant. A similar percentage of patients in each group presented with breast symptoms (13% in the low expression group and 13.3% in the high expression group). A higher percentage of patients in the low expression group presented a positive clinical breast exploration (22.9% vs 12.9%) even though this difference was not significant. Tumour size tended to be bigger in the high expression group (median 27.70 vs 16.6 mm), but this difference was neither significant.

Conclusions: DCIS with a high Ki67 expression presents at a younger age than DCIS with low Ki67 expression. The study should include more patients for conclusive findings, but the group of high Ki67 expression showed a tendency to affect more frequently premenopausal patients and patients with a breast cancer family history. These high Ki67 expressing tumours also tended to present more frequently as a multifocal/multicentric disease and more extensive tumours.

Friday, 23 March 2012 12:45–14:00

POSTER SESSION

Radiotherapy

458 Poster discussion

Re-irradiation Plus Hyperthermia for Recurrent Breast Cancer in Previously Irradiated Area; Size Matters

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Background: Treatment options for patients with locoregional recurrent breast cancer in previously irradiated area are limited. Five hundred and eighty-three patients were treated with re-irradiation and hyperthermia (re-RT/HT) in the AMC (n = 456) and the BVI (n = 127) from January 1982 till January 2006. Response, locoregional control and toxicity were analysed as well as prognostic factors.

Materials and Methods: All patients received extensive previous treatments, including surgery, chemotherapy and irradiation to a median dose of 50 Gy with or without boost. Median interval between initial treatment and re-RT-HT was 50 months (range 3–469).

The median age was 57 years at start of re-RT/HT. The estimated tumour size was >10 cm in 60% of patients. The maximum measurable tumor size was 50 cm. Distant metastases were present in 38% and 74% had experienced 1−14 recurrence episodes, prior to the re-RT-HT. Re-RT consisted typically of 8x4 Gy, twice a week (AMC) or 12x3 Gy, four times a week, (BVI). Superficial hyperthermia was added once/twice a week using 434MHz CFMA antennas. Aim temperature: 41−43ºC for one hour. Twenty-two percent of patients received additional chemotherapy and 30% additional hormone therapy.

Results: Overall clinical response rate (50% cCR+ 32% cPR) was 82%. The infield 3-year local control (LC) rate was 20%. Tumor size, interval, previous recurrences, contralateral disease and distant metastases (DM) were important prognostic factors. For patients with isolated locoregional recurrences $\leqslant$ 5 cm the 3-year LC rate was 44%. (Table 1).

Median overall survival was 12.5 months. Acute $\geqslant$ grade 3 toxicity occurred in 26% of patients. The actuarial late $\geqslant$ grade 3 toxicity rate was 28% at 3 years.

Table 1

Tumor size	Isolated			With DM		
	n	cCR (%)	3-y LC (%)	n	cCR (%)	3-y LC (%)
$\leqslant$ 5 cm	63	81	44	29	52	21
5−10 cm	88	60	24	53	36	20
>10 cm	204	51	15	141	30	10

*Data unknown for 5 patients.

Conclusion: The combination of re-irradiation and hyperthermia results in high response rates despite extensive disease and resistance to previous treatments. Early referral is needed to achieve long term locoregional control. Currently a randomized phase 2 study of RT-HT versus RT-HT and CisDiamineDichloroPlatinum is performed to further improve results.

459 Poster discussion

Pre-operative CT Scan in Breast Conserving Therapy for Determination of the Boost Volume for Radiotherapy

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Background: There is a large interobserver variation of the boost volume delineation on the post-operative (post-op) radiotherapy planning CT scan. The aim of this study was to investigate whether a pre-operative (pre-op) contrast enhanced CT scan (CE-CT) can improve the accuracy of the boost volume delineation.

Material and Methods: Twenty patients with early breast cancer, planned for breast conserving surgery (BCS), underwent a pre-op CE-CT. After BCS a post-op radiotherapy CT scan was made in the same position.

A radiation oncologist and two physician assistants delineated the boost volume on the post-op CT scan (BVpost) without knowledge of the pre-op CE-CT. Minimally one month later the delineation was repeated (BVpre) after matching the pre-op CE-CT with the post-op CT on bony anatomy.

A radiologist delineated the tumour on the pre-op CE-CT, to assess tumour visibility.

Breast contour changes were analyzed.

All delineated boost volumes were measured, the average of BVpre and of BVpost was calculated.

The conformity index (CI = overlapping volume/encompassing volume) was calculated for both BVpre and BVpost, for each patient and for each observer pair (interobserver).

The center of mass distance (COMD) between BVpre and BVpost was calculated for each patient, and each observer pair.

Results: There was agreement on tumour visibility and location between all 4 observers in 19 of 20 patients on the pre-op CE-CT. These 19 patients were analyzed.

In 3 patients the projection of the tumour on the post-op CT scan was partly outside the body contour, due to contour change after surgery.

The mean BVpre (34.7 cc) and BVpost (37.6 cc) were not significantly different.

The interobserver CI showed a significant (p = 0.03) increase from 0.59 to 0.68 when the pre-op CE-CT was used. A significant (p = 0.01) decrease

in the COMD was found, from 5.5 mm to 2.9 mm, in favour of the use of a pre-op CE-CT.

Conclusions: With agreement of tumour location in 19 of 20 patients, the tumour visibility on pre-op CE-CT was good.

Using a pre-op CE-CT, an increased CI and a decreased COMD was found, resulting in an improved accuracy of the boost volume delineation.

460 Poster discussion

A Seven-gene Signature Predicting Benefit of Postmastectomy Radiotherapy in High Risk Breast Cancer

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Background: Recommendations for postmastectomy radiotherapy (PMRT) are well established in patients estimated to have a high risk of loco-regional recurrence (LR) (e.g. tumor size >5 cm or $\geqslant$ 4 positive lymph nodes). Large randomized trials, including the DBCG82 trial (Danish Breast Cancer Cooperative Group), have also shown a substantial overall survival benefit after PMRT in patients with low risk of LR (e.g. 1−3 positive nodes), and shown that the largest translation of LR reduction into breast cancer mortality reduction occurs within the most favorable prognosis group. Our hypothesis is that a more refined partitioning of patients likely to benefit from PMRT can be established through identification of genes whose transcription interacts with PMRT to modify the hazard of LR.

Material and Methods: The DBCG82bc cohort constitutes high risk patients (tumor size >5 cm and/or positive lymph nodes and/or invasion in skin or pectoral fascia) diagnosed between1983−89, treated with mastectomy and partial axillary lymph nodes dissection and randomized to +/− PMRT. From 267 DBCG82bc patients, fresh frozen samples histologically verified to contain invasive tumor were available. Whole genome arrays (Applied Biosystem Human Genome Survey Microarray v2.0®, Applied Biosystem, Foster City, USA) were successful in 195 samples. Genes, whose expression levels interacted with PMRT on the association with LR, were identified through a two step Cox Proportional Hazard model with lasso penalty.

Results: Seven genes were identified whose expression interact with the effect of PMRT, and a specialized index was generated based on the expression levels of these genes. Among patients not receiving PMRT, a low index was associated with a significantly higher risk of LR compared to patients with a high index. PMRT significantly reduced the risk of LR in patients with a low index; equalizing the risk to patients with a high index, who showed no LR reduction by PMRT. Among the seven genes, only two were associated with risk of distant metastasis (DM) in patients with 1−3 positive nodes, and yet another gene in the group of patients with $\geqslant$4 positive nodes.

Conclusion: A seven gene-signature attaining prognostic and predictive impact was identified. The gene-signature may provide a method to identify patients expected to benefit from PMRT in terms of LR. The gene-signature is only weakly associated with risk of DM after PMRT in patients who may already have disseminated disease at time of diagnosis.

461 Poster

Clinical Outcomes of Proton Beam Therapy for Accelerated Partial Breast Irradiation

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Background: Previously we reported dosimetric advantage of proton beam therapy for accelerated partial breast irradiation (PB-APBI). Clinical use of PB-APBI for patients with early-stage breast cancer was prospectively evaluated.

Materials and Methods: Thirty-one patients with breast cancer were treated with PB-APBI in a Phase II clinical trial. A total dose of 30 Cobalt Gray Equivalent (CGE) was delivered to the lumpectomy bed in 5 fractions, daily 6 CGE over 5 working days consecutively.

Results: At the median follow-up of 40 months (range, 23−48 months), one ipsilateral axillary lymph node recurrence has been detected. PB-APBI produced acute skin toxicity with moderate erythema in 9 (29%) at 2 months and 4 (13%) patients at 6 months, and among these, 2 patients persistently exhibited moderate hyper-pigmentation at 3 years. Cosmetic outcome judged by physician was good or excellent in 84% of patients before PB-APBI, which gradually changed during follow-up to be 75% and 70% of patients at 2 and 3 years, respectively. The mean the percentage breast retraction assessment index (pBRA) in all patients before PB-APBI (10.5%) and at 3 years (15.5%) significantly differed ($p = 0.02$). Although single field PB-APBI group ($n = 15$) showed significantly worse pBRA at 3 years than at baseline ($p = 0.005$), pBRAs of two field PB-APBI group ($n = 16$) did not change by time ($p = 0.3$).

Conclusions: In addition to dosimetric advantage, PB-APBI with five consecutive fractions achieved in excellent local control in this clinical study of patients with early stage breast cancer. However, relatively high incidence of skin toxicity and worse cosmetic outcome by time are the main factors limiting use of this treatment modality. Modifications of technique such as 3-dimensional proton technique as well as schedule of fractionation and overall treatment time should be explored to avoid skin toxicity and to improve better cosmetic outcome.

462 Poster

Pre Radiotherapy Calcium Scores of Coronary Arteries in Women with Breast Cancer: a Comparative Study

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Background: Breast cancer radiotherapy has been associated with an increased risk of cardiac toxicity. However, no data are available on the probability of developing coronary artery disease (CAD), specifically in the group of breast cancer patients when compared to that of healthy women. Therefore, baseline Coronary Artery Calcium (CAC) scores were determined in a cohort of breast cancer patients (R-cohort) and compared to the CAC scores of a healthy, asymptomatic cohort, the M-cohort. This M-cohort was designed from 2000–2002, to study the prevalence, risk factors and progression of subclinical cardiovascular disease in a population-based sample of 6814 men and women aged 45−84 years [1].

Material and Methods: Eighty consecutive patients with ductal carcinoma in situ or infiltrative breast cancer referred for radiotherapy after breast conserving surgery were included in our study. Their cardiovascular risk-profile was registered and a 64multi-slice CT-scan was performed.

The CAC scores of an unselected (Caucasian only) R-cohort, as well as of those of a selected (co morbidity and race adjusted) R-cohort, were determined. The scores of both R-cohorts were compared to those of the female (Caucasian only) M-cohort.

Results: For the unselected R-cohort ($n = 62$) we found significant ($p < 0.01$) higher scores for women in the age category '55−64' when compared to those of the M-cohort. This becomes apparent in the percentiles of the CAC scores, see table.

Table: Calcium values

Cohort	45−54		55−64		65−74	
	R	M	R	M	R	M
Caucasian, n	11	379	33	356	18	379
25th	0	0	0	0	12	0
50th	0	0	1	0	46	13
75th	0	0	100	16	131	119
90th	7	8	474	102	323	391
95th	8	31	666	209	415	674

In the selected R-cohort ($n = 55$) the CAC scores of the women in the age category '55−64' were significantly ($p = 0.02$) higher when compared to the M-cohort. No significant differences were noted in the other age categories.

Conclusions: The unselected as well as the selected R-cohort revealed, that CAC scores in the age category '55−64' were significantly higher than the CAC scores in the asymptomatic (female) M-population. These data suggest that breast cancer patients bear a higher risk of developing coronary heart disease before the start of radiotherapy. Therefore, measures to (further) decrease cardiac dose in breast cancer radiotherapy are even more important.

References

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