463 Poster

Concurrent Radiotherapy and Trastuzumab in Early-stage Breast Cancer − A Prospective Single Institutional Experience

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Background: To evaluate the early and late heart and skin toxicities, as well as the efficacy of concurrent adjuvant trastuzumab-radiotherapy for breast cancer (BC), particularly in the case of internal mammary chain (IMC) irradiation.

Materials and Methods: Prospective study of 173 patients treated between 06/2003 and 03/2009 by concurrent trastuzumab-radiotherapy for non-metastatic BC. Left ventricular ejection fraction (LVEF) was assessed at baseline, before and after radiotherapy and then every 4−6 months. All toxicities were evaluated using CTCAE v3.0. Survival data were defined as the time from the histological diagnosis of BC until occurrence of the event. Loco-regional recurrence free- and alive patients were censored at the date of their last known contact. Survival and interval rates as well as their confidence interval (CI) were calculated by the Kaplan–Meier method.

Results: Median age was 52 years [25−83]. Previous adjuvant anthracycline-containing chemotherapy was administered in 157 patients (90.8%). All patients received trastuzumab every three weeks (8 mg/kg in the first infusion followed by 6 mg/kg) at the median dose of 6020 mg [1285–29180] for a median duration of 12 months [2−62]. 88 patients (50.9%) presented with left-sided BC. The IMC was irradiated in 134 patients (77.5%).

Acute skin toxicity was acceptable with 132 (76.3%) grade 1, 32 (18.8%) grade 2 and 6 (3.5%) grade 3 skin reactions. Esophagitis occurred in 18 patients (10.4%): 14 (8.0%) grade 1; 3 (1.7%) grade 2, and 1 (0.5%) grade 3. Out of 172 patients with assessments after 12 months, late telangiectasia grade 1−2 occurred in 14 patients (8.5%), local pain grade 1 in 23 patients (14.0%) and grade 2 in 4 patients (2.4%), fibrosis grade 1 in 31 patients (18.0%) and grade 2 in 8 patients (4.6%).

Out of 156 patients with LVEF assessments after completion of the radiotherapy, 5 patients (3.2%) experienced a reversible grade 2 left ventricular systolic dysfunction.

Median follow-up was 52 months [17−88]. Loco-regional control at 48 months was 95% CI95% [91;98]. Overall survival at 48 months was 98% CI95% [95;100].

Conclusions: In this prospective study of BC patients treated with trastuzumab and radiotherapy with, in most cases, anthracycline-based chemotherapy and IMC irradiation, both the rates of abnormal LVEF and skin toxicity were deemed acceptable with excellent local control.

464 Poster

Preliminary Results Following Hypofractionated Irradiation in Breast-conserving Therapy

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Background: Over the last several years there has been renewed interest in hypofractionated adjuvant radiotherapy (RT) in breast cancer patients treated by conservative surgery in the light of radiobiological and clinical evidence. We present our experience regarding preliminary outcomes of a hypofractionated RT schedule.

Materials and Method: Between October 2007 and October 2009 80 women with early breast cancer were treated by 42.75 Gy/15 fractions over 5 weeks. This treatment involved three fractions per week (Monday-Wednesday-Friday). All patients received an additional boost dose to the tumor bed of 8.55 Gy in 3 fractions using 6 MV photons. Acute radiation toxicity was the principal endpoint. Cosmetic appearance including changes in breast appearance together with breast shrinkage/hardness/swelling was assessed. Methods of evaluation were photos (before and after the end of RT treatment at one/three/six month intervals), ultrasound examinations (before and after the end of RT treatment) and mammograms (three/six months and one year after RT).

Results: The median follow-up time was 24 months. In order to score radiation toxicity, patients were evaluated according the RTOG scoring system for radiation reactions at the end of treatment and 3, 6 and 12 months after treatment). At the end of RT RTOG grades 0, 1, 2 for acute skin toxicity were: 56/80 (70.0%), 19/80 (23.8%) and 5/80 (6.3%) respectively. After 3 months RTOG grades 0, 1, 2 were 64/80 (80%), 14/80 (17.5%) and 2/80 (2.5%). After 6 months RTOG grades 0, 1 were 72/80 (90.0%) and 8/80 (10.0%) respectively whereas after 1 year they were 78/80 (97.5%) and 2/80 (2.5%). Breast shrinkage and breast hardness were the most common changes especially in patient with large breast volumes. An excellent to good cosmetic outcome (i.e. no change in breast appearance) was observed in 90% of patients. There wasn't local or distant recurrence in any patient during this limited two years follow up.

Conclusions: Preliminary results (skin reactions and cosmetic appearance) from this study are consistent with published data that support the use of shorter fractionation schedules in early breast cancer patients after breast conserving surgery, in terms of cosmesis and effectiveness in local control. However a median follow-up of 2 years is too short to allow assessment of all the potential late normal tissue effects. This study is still on going to estimate late radiation morbidity for final evaluation.

465 Poster

Role of Simultaneous Integrated Boost IMRT in Carcinoma Breast

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Background: Breast conservation has been widely accepted in treatment of women with early stage breast cancer. The most common adjuvant radiation strategy after BCS, consists of irradiation of the whole breast using two tangential photon beams in 5−6 week period, with doses of 1.8−2.0 Gy/fraction to a total dose of 50 Gy followed by boost irradiation by electrons and/or photons up to a total dose of 60 Gy, resulting in total duration of 7−8 weeks. With this technique there may be appreciable dose inhomogenity within the irradiated volume and dose to lung heart and contralateral (C/L) breast can be high. IMRT can shorten the overall treatment time by integration of the additional tumor bed boost significantly. In patients with node-negative invasive breast cancer or carcinoma in situ treated by BCS, postop whole breast RT with SIB-IMRT is a good option with the aim to minimize the target dose inhomogeneities and to provide differential dosing to the whole breast and the resection cavity. The sequential boost is eliminated as the overall treatment course is shortened by giving greater dose per fraction to the resection cavity. This retrospective study reports our experience of SIB IMRT in terms of radiation toxicity, cosmetic outcome and local control in cancer breast.

Material and Methods: 12 patients of cancer breast stage I-III treated with SIB IMRT after BCS between March to December 2010 were analyzed for normal tissue dose and corresponding toxicities with a follow up of 6 months. Virtual simulation done and CTVs for breast, cavity and normal structures were contoured on Eclipse planning system. Dose prescribed was 50 Gy/25# to PTV breast and 60 Gy/25# to PTV cavity and inverse planning IMRT done.

Results: Mean 95% PTV_{breast} and PTV_{cavity} 49.8 and 59.2 Gy respectively. No hot spots found inside PTVs. $V_{40\,Gy}$ of heart in left breast patients ranged from 1−7% and mean dose 12.8 Gy for the whole group. The mean dose to the ipsilateral lung, total lung, C/L lung and C/L breast were 18.1 Gy, 13.0 Gy, 2.5 Gy and 3.2 Gy respectively. The treatment was completed in scheduled 5 weeks without any interruption. Acute skin toxicity of RTOG grade I in 6, grade II in 4 and grade III in 2 patients were observed. At a follow up of 6 months 3 patients had induration and tenderness at lumpectomy site. The breast cosmoses were excellent in 90% of case. No pulmonary toxicitiy was seen.

Conclusion: The overall treatment time was reduced by SIB IMRT about a week with favorable acute toxicity profile. Longer follow up is necessary and larger number of patient to be taken for the study to assess the ultimate cosmoses, late toxicity and locoregional recurrence.

466 Poster

Benefit of Different Radiation Boost Dose Based on Surgical Margins − Single-institution Experience on 2 173 Patients Treated with Radiotherapy After Breast-conserving Surgery

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Background: Local recurrence (LR) of breast carcinoma (BC) is reduced by whole-breast radiotherapy (RT) after breast-conserving surgery (BCS). There is no a worldwide consensus about the effective dose of radiations to prescribe, especially for what concerns the boost after the irradiation of the whole breast. The aim of this study is to validate the use of different doses of RT boost based on surgical margins.

Materials and Methods: A total of 2 173 infiltrating BC treated with BCS and adjuvant RT in our institution between 1987 and 2007 were retrospectively reviewed. A median dose of 50 Gy was prescribed to the whole breast. A 10 Gy boost was prescribed in case of surgical margins

⩾5 mm (n = 1690); 16 Gy if 1−5 mm margins (n = 391); 20 Gy in case of close (⩽1 mm) or positive margins (n = 92).

Results: Median age of the series was 57 years (range 22−86). 1 763 patients were pT1 and 410 pT2; nodal status was positive in 26%. Hormonal receptor status was positive in 75% of patients.

At a mean follow up of 8.5 years (range 3−20), 43 patients (2.0%) experienced LR and 126 distant metastases (DM = 5.8%) were diagnosed. Mean time to LR was 4.1 years (range 0.6−16; SD = 2.98); mean time to DM was 3.4 years (range 0.6−14; SD = 2.46).

Concerning LR, 10 Gy boost group relapsed in 1.8%; 16 Gy boost group in 2.3% and 20 Gy boost group in 2.2%. Differences were no statistically significant (Chi-square test p = 0.097). Concerning DM, events rate was no significantly influenced by different RT boost dose (p = 0.26).

Conclusions: Although the appropriate boost dose still remains a debated issue, our analysis validated the local guidelines of the institution, showing that different boost doses based on surgical margins do not influence LR rate of BC patients.

467 Poster

Accelerated Partial Breast Irradiation with Intensity-modulated Radiotherapy (IMRT): the Florence Phase III Randomized Clinical Trial at 3 Years Median Follow-up

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Background: Long-term evidence from prospective randomized trials demonstrated that breast-conserving surgery (BCS) followed by whole breast radiotherapy (RT) is comparable to mastectomy in treatment of early breast carcinoma (BC). The majority of BC recurrence seems to occur near the surgical bed; this finding led to an interest in adjuvant accelerated partial breast irradiation (APBI), that is hypothesized to be safe to deliver larger RT doses in smaller high-risk breast volume. In particular intensity-modulated radiotherapy (IMRT) is able to improve on three-dimensional conformal planning technique by using inverse planning algorithms for optimal dose delivery to small target volumes, sparing surrounding normal tissues.

We evaluate with a Phase III randomized clinical trial the efficacy and safety of treating the index quadrant with external IMRT, in a highly selected group of patients affected by early-stage BC.

Material and Methods: For IMRT, the clinical target volume was drawn with a uniform 1 cm margin around the surgical clips in three dimensions. The ipsilateral and contralateral breast, ipsilateral and contralateral lung, heart, and spinal cord were contoured as organs at risk. All the regions of interest were contoured according to the International Commission on Radiation Units and Measurements reports 50 and 62 recommendations.

The Florence trial has been conducted from September 2005, to compare conventional fractionated whole-breast treatment (Arm A; n = 209), with APBI using IMRT technique (Arm B; n = 199). Arm A patients received a total dose of 50 Gy in 2 Gy consecutive fractions (5 weeks treatment), plus 10 Gy boost to surgical bed; Arm B patients received a total dose of 30 Gy in 6 Gy non-consecutive fractions (10 days treatment).

Results: In June 2011, 408 patients were randomized and treated. At a median follow-up of 3 years (range 0.3−6.4), the rate of Grade 1 and Grade 2 acute skin toxicity in Arm A (using Radiation Therapy Oncology Group scale) was 25% and 20%, respectively. The tolerance in Arm B was excellent with only 6% Grade 1 and 2% Grade 2 acute skin toxicity. The local recurrence rate was 0.5% in Arm A (1/209) and 1.5% in Arm B (3/199). The distant metastases rate was 2% in Arm A (4/209) and 0.5% in Arm B (1/199).

Conclusions: The interim analysis of the Florence trial at 3 years median follow-up seems to confirm that APBI represents a safe and effective treatment in early BC patients.

468 Poster

Forward Planning Versus Inverse Planning of Multi-lumen MammoSite Brachytherapy

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Background: Multi-lumen MammoSite^R (ML-MS) improves target coverage and reduced Organs at Risk (OAR) dose compared to single-lumen MammoSite^R. Inverse planning can be used to optimise ML-MS but resulting source positioning and dwell times may be unintuitive and sometimes result in unexpected regions of high and low dose. ML-MS optimisation using a Forward Planned Individualised Plan (FPIP) was compared with Inverse planning simulated annealing (IPSA) for target coverage, OAR dose and planning time.

Materials and Methods: CT datasets of twelve consecutive patients who participated in the FORUM (Feasibility Of breast Radiotherapy Using MammoSite) trial were used. All planning was carried out using Oncentra Masterplan treatment planning software. IPSA was completed using the optimisation package with constraints set to achieve required PTV coverage as priority. FPIP was completed using a standard line source plan as a starting point. The standard line source plan was devised locally using the symmetrical average of 7 patients planned using a single lumen catheter. All patients were planned with the dose constraints of PTV D_{95} ⩾95%, skin and rib maximum dose ⩽125%, Breast V150 ⩽50 cc and V200 ⩽10 cc. V_5 heart, Dose Homogeneity index (DHI), Full Width Half Maximum (FWHM) of the PTV differential DVH and planning time were recorded for all patients.

Results: The mean PTV D_{95}, maximum rib and skin dose and V_5 heart were comparable for IPSA and FPIP (table1). IPSA fulfilled all dosimetric constraints in 6/12 patients as compared to 7/12 patients with FPIP. 5/12 patients who failed the maximum skin dose constraint had balloon-skin distance of ⩽9 mm. The DHI and FWHM were similar with the two techniques. The average planning time was 5 minutes with IPSA compared to 12 minutes with FPIP.

Conclusions: FPIP optimisation of ML-MS is comparable to IPSA for target coverage and OAR dose. ML-MS can be used in centres without commercially available inverse planning software with an acceptable average planning time.

Table 1. Comparison between Inverse Planning (IPSA) and Forward planned Individualised Plan (FPIP)

	IPSA (mean)	FPIP (mean)
PTV D95	96.6	96.3
Maximum Rib dose	119%	121%
Maximum Skin dose	118%	114%
Heart V5	13.6%	12.9%
HI	0.62	0.62
FWHM	218	216

469 Poster

3D-conformal Partial Breast Irradiation (3D-CRT PBI): How to Optimize Its Reproducibility

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Background: To report how 2D or 3D Image Guided RT (IGRT) and surgical clips located in the tumoral bed can avoid target missing in 3D-CRT PBI.

Materials and Methods: Seventeen patients (pts) treated with tumorectomy plus sentinel node biopsy for stage I-II breast cancer were randomized in a phase III trial to receive PBI with 3D-CRT (IRMA trial). Five radiopaque clips (1 in the center of the surgical cavity and the others at 4 cardinal points) were placed immediately after surgery to correcly delineate the surgical bed and were used as reference markers for IGRT, either 2D or 3D modality. RT was given twice per day, 10 fractions in 5 days (total ICRU dose 38.5 Gy). Checks were obtained before every treatment with CBCT in 10 pts and KV 0º-180º in the 7 pts treated with respiration gated RT. The surgical clips matching was performed with the planning CT ones.

Results: We registered the isocenter shifts along the longitudinal, vertical and lateral axes before each RT session. The mean and median vertical shifts were 0.27 and 0.3 cm, the longitudinal ones 0.23 and 0 cm, the lateral ones 0.32 and 0.15 cm respectively.

Conclusions: The use of optimal IGRT reduces the uncertainties due to breathing and patient motion in 3D-CRT PBI and allows us to prescribe this treatment as a valid and daily reproducible alternative to brachytherapy or intraoperative PBI.

470 Poster

Retrospective Analysis of Postmastectomy Adjuvant Radiotherapy in Patients with Less Than Four Axillary Lymph Nodes

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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