

≥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 not statistically significant (Chi-square test  $p=0.097$ ). Concerning DM, events rate was not 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.

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#### 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.

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#### Forward Planning Versus Inverse Planning of Multi-lumen MammoSite Brachytherapy

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**Background:** Multi-lumen MammoSite<sup>R</sup> (ML-MS) improves target coverage and reduced Organs at Risk (OAR) dose compared to single-lumen MammoSite<sup>R</sup>. 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<sub>95</sub> ≥95%, skin and rib maximum dose ≤125%, Breast V150 ≤50 cc and V200 ≤10 cc. V<sub>5</sub> 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<sub>95</sub>, maximum rib and skin dose and V<sub>5</sub> 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

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#### 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 correctly 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 0°-180° 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.

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#### 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

axillary lymph nodes although the same exists for patients with 4 or more positive nodes. But several recent publications (20 year result of British Columbia Study and DBCG 82 Protocol published by Overgaard et al) challenge this separation between '1 to 3' and '4 or more' positive axillary nodes as a relevant descriptor of indication of PMRT. This was the impetus that led us to review and analyze retrospectively from our institute data, the impact of post mastectomy radiotherapy (PMRT) in this controversial group.

**Material and Method:** Records of 785 patients with T1, T2 tumors who were registered in our department following mastectomy with axilla dissection with <4 positive axillary nodes between 2002 and 2009 were analyzed. 127/785 patients had 8 or less nodes dissected (as found in histopathology reports) and as such were excluded from the analysis. Of the remaining 658 patients, 528 received no PMRT, as per consensus. But 130 patients, as found in record, had received PMRT (possibly they appeared to be non-compliant regarding follow up). Locoregional recurrence, distant failure, disease free survival and overall survival of these 130 patients were studied and compared with 528 patients who were not offered PMRT.

As per erstwhile institutional policy, all patients had received FAC chemotherapy for 6 cycles. Receptor positive patients (164/528 of non-PMRT and 42/130 of PMRT subsets) were on Tamoxifen or an A.I.

**Results:** At a median interval of 30 months 132/528 patients not receiving PMRT suffered locoregional recurrence (chest wall recurrence alone in 36/528, supraclavicular recurrence in 81/528, chest wall + supraclavicular recurrence in 15/528, axillary and IMN recurrence in none). On the contrary only 4/130 patients receiving PMRT had locoregional failure ( $p < 0.0001$ ). Distant metastasis was recorded in 37/528 of non PMRT subset and 8/130 of PMRT subset ( $p = \text{NS}$ ). Survival data till September 2008 showed 4/130 deaths among PMRT subset against 26/528 of non PMRT ( $p = \text{NS}$ ). 121/130 of PMRT are living without disease, contrary to 432/528 of non PMRT ( $p = 0.001$ ).

**Conclusions:** This retrospective analysis revealed statistically significant reduction in locoregional recurrence as well as increased disease free survival with PMRT in T1 or T2 breast cancer patients with 1-3 positive axillary nodes. Deprivation of adjuvant radiotherapy for this subset of patients appears to be unjustified.

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#### Outcome of Breast Cancer Patients with Isolated Supraclavicular Fossa Lymph Node Recurrence Treated with Radiotherapy

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**Background:** The incidence of isolated supraclavicular fossa (SCF) nodal recurrence in breast cancer is between 4.5-7% [1, 2]. Published 2 & 5 year survival rates for patients with SCF node metastases are 52% & 34% [3]. It is unclear whether isolated SCF recurrence is a harbinger of distal disease or whether aggressive local treatment can result in cure. This is a retrospective study of the outcomes for breast cancer patients who received radiotherapy (RT) for isolated SCF recurrence.

**Materials and Methods:** Breast cancer patients who had received treatment with RT for SCF disease recurrence between 2005 & 2010 were identified from the Mount Vernon Cancer Centre (MVCC) coded 'Oracle' treatment database. RT treatment & fractionation were obtained from the database & clinical outcomes were assessed from the patient notes. Local lymph node control (LLNC), overall survival (OS) from SCF recurrence & distant disease free survival (DDFS) from radiotherapy were evaluated according to treatment received.

**Results:** 33 patients were identified with a median age of 57 (range 34-89). The ER/PR status was: 20 (61%) positive & 13 (39%) negative. The HER2 status was: 12 (35%) positive, 15 (45%) negative & 6 (20%) unknown. The RT regimens (Gy/#) used were: 40 Gy/15# in 3 weeks ( $n = 13$ ), 20 Gy/5# in 1 week ( $n = 5$ ), 50 Gy/25# in 5 weeks ( $n = 9$ ), 30 Gy/10# in 2 weeks ( $n = 2$ ), 18 Gy/4# in 1 week ( $n = 1$ ), 8 Gy/1# in 1 day ( $n = 1$ ), 45 Gy/15# in 3 weeks ( $n = 1$ ) & 27 Gy/6# in 3 weeks ( $n = 1$ ). 18 (55%) patients received chemotherapy & 21 (64%) received endocrine therapy prior to RT. Median LLNC was 45 (range 1-133) months with a median DDFS of 12 (range 3-60) months. Median OS was 25 (range 2-85) months from recurrence with 4 (12%) patients surviving >5 years from SCF recurrence. A significant difference was seen for DDFS & OS in favour of ER +ve status ( $p < 0.05$  &  $P < 0.001$ ) & in OS for longer RT regimens ( $P < 0.05$ ).

**Conclusions:** Outcomes at MVCC are akin to those published as only 12% of patients survived for >5 years following RT. Our data also demonstrates that ER status influences DDFS and OS is better with longer hyperfractionated regimens & +ve ER status. This however, may have been biased by confounding factors, such as co-morbidity, and furthermore the sample size was small. A prospective analysis is suggested to establish a stronger evidence base for best practice in this patient group, including evaluation of outcomes for those patients not treated with RT.

## References

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#### Preclinical Assessment of Multidirectional Firing Laser Ablation in Porcine Liver and Human Breast Tissue

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**Background:** Minimally-invasive thermal ablation is a promising new tool for local destruction of small carcinomas of the breast. Currently, cryosurgery, radiofrequency ablation, laser-induced thermal therapy, microwave ablation, and high-intensity focused ultrasound ablation are clinically available local ablation modalities. Laser-induced thermal therapy requires a laser fiber to guide the light energy directly into the tissue to be treated. Most laser fibers are designed for forward firing i.e. the light is emitted at the distal end along the optical axis of the fiber. But laser ablation using a forward firing fiber cannot transmit the energy evenly to the lesion, so the exact size of the thermal lesion cannot be predicted.

We developed multidirectional firing laser fiber using the femtosecond laser and an arc discharging process. The aim of this study was to compare the ablation properties of forward firing laser fiber and multidirectional firing laser fiber in relation to the application time and power.

**Materials and Methods:** Laser ablations with each fiber were performed in porcine liver and human breast tissue ex vivo. Laser energy was applied at powers of 5, 7.5 W and 10 W, with exposure times between 5 and 15 minutes. Directly after ablation, the tissues were cut open along the applicator axis. The lesions were macroscopically inspected. We regarded clearly demarcated portions of the visibly damaged area as necroses and measured each axial and transversal diameter.

**Results:** Gross pathologic examination showed a bullet-shaped thermal lesion applied with forward firing fiber and more circular-shaped thermal lesion with multidirectional firing fiber. We got the same results in porcine liver and human breast tissues. When a forward firing fiber was used, the greatest ablation diameters ranged from 15 mm at the lowest dose (5 W, 5 minutes) to 30 mm at the highest dose (10 W, 15 minutes). Multidirectional firing fiber created ablation zones as large as 40 mm in greatest diameter with the lasers operating at 10 W for 15 mins.

**Conclusions:** The results of this study demonstrated a dose response relationship for laser-induced thermal therapy. The application of higher energy volumes leads to the induction of larger lesions up to complete coagulation of the available organs. And we found the thermal lesions with multidirectional firing fiber were more spherical shape and easily predictable the size.

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#### The Role of VEGF Gene Polymorphisms in the Development of Distant Metastases in Postmenopausal Breast Cancer Patients

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**Background:** Vascular endothelial growth factor (VEGF) is a key regulator of tumor-induced angiogenesis and is required for tumor growth and distant tumor spread. Aim of the present study was to evaluate the role of VEGF polymorphisms and haplotypes for metastatic progression of breast cancer in postmenopausal women.

**Methods:** We carried out a prospective study including 584 postmenopausal breast cancer patients from the Austrian TIGER ("tumor of breast tissue: incidence, genetics, and environmental risk factors") study. Development of metastases was examined in regular follow-up investigations. Seven VEGF polymorphisms were selected and determined by a 5'-nuclease assay (TaqMan). Haplotypes and linkage disequilibrium were determined using the Haploview program.

**Results:** Within a median follow-up time of 77 months (range 0-121 months), 122 (21%) patients developed distant metastases.

In a Kaplan-Meier analysis, carriers of the -634G>C polymorphism were at decreased risk of developing distant metastasis ( $p = 0.027$ ) and