

in a Cox regression analysis, the hazard ratio for distant metastases was 0.69 (95% CI 0.52 to 0.92, $p = 0.012$). Furthermore, the CCCC haplotype formed by 5 polymorphisms upstream of the coding sequence including the -634G>C polymorphism demonstrated a significant association with distant metastases (HR 0.655, 95% CI 0.487 to 0.882; $p = 0.004$). In a multivariate analysis including tumor stage, tumor grade, initial lymph node involvement, hormone receptor status and HER2neu status as potential confounders, the CCCC haplotype remained a significant predictor of distant metastases (HR 0.614, 95% CI 0.416 to 0.906; $p = 0.014$).

Conclusion: We conclude that VEGF gene polymorphisms and haplotypes may influence the risk of developing distant metastases in postmenopausal breast cancer patients.

474

Poster

Frequency and Anatomical Characteristics of Involved Regional Lymph Nodes in Recurrent and Advanced Breast Cancer and Its Impact On Target Definition for Radiotherapy

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Background: The role of radiotherapy (RT) has been well evaluated in the multidisciplinary management of breast cancer (BC). Local-regional RT is typically delivered with traditional field borders. An analysis of the frequency of lymphatic nodal involvements with corresponding anatomical extent in recurrent and advanced BC would help to evaluate the adequacy of target definition with regard to contour guidelines.

Materials and Methods: Recurrent or advanced BC patients with CT images to cover the whole regional nodes at the time of recurrence or staging prior to systemic therapy were eligible. Additional MRI or PET-CT images were collected if presented. The regional lymph nodes were categorized into 8 anatomical substructures: medial and lateral-supraclavicular (Sc-M, Sc-L); axilla (ALN)-I, II, III; infraclavicular (Ic); Rotter's nodes (RN) and internal mammary nodes (IMN). Frequency of involvement and the anatomical characteristics were analyzed.

Result: A total of 182 regional recurrent pts and 26 advanced BC pts from July 2003 to Jan. 2010 entered study, with 352 anatomical substructures of involved nodes. The frequency of involvement includes: Sc-M: 71(20.2%), Sc-L:38(10.8%), ALN-I: 43(12.2%), ALN-II: 38(10.8%), ALN-III and Ic: 58(16.5%), RN: 44(12.5%), IMN: 60(17.0%). Apart from IMN, in pts received axillary dissection, 85.8%(200/233) had recurrent nodes cranial to the axillary vein (AV), while in advanced pts without axillary dissection, ALN-I/II remained the most frequently involved regions: 39.0% and 18.6%. 58/60 of the involved IMN occurred within the first 3 intercostal spaces. The average depth from the center of the involved nodes in ScM and Sc-L was: 35.37±10.25 mm and 47.29±18.52 mm respectively, with 62.0% and 76.3% of these measured above 3 cm. The average distance from the center of involved IMN to the midline was 29.4±6.7 mm, which was also 5.5±4.8 mm to internal mammary vessels (IMV) laterally and 5.3±4.5 mm deeply.

Conclusion: Identification of involved regional nodes in recurrent and advanced BC pts would help to better understand the natural history of lymphatic spread. The data observed in our series confirms that current target definition of is consistent with the potential risk of regional nodes. Sc and axillary nodes cranial to the AV should be considered the primary risk target in post-operative radiotherapy after axillary dissection. Individual treatment planning would be feasible with increasing knowledge of nodal involvement.

475

Poster

Perioperative Interstitial Brachytherapy as a Boost in Breast Cancer Conserving Therapy

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Background: The aim of breast-conserving treatment (BCT) in breast cancer, consisting of wide local excision (WLE) and whole breast radiation (WBR), is to obtain locoregional control of disease. Since a considerable percentage of local recurrences after BCT occurs close to the original tumor bed, WBR is supplemented with a boost on the original tumor bed. Application of perioperative brachytherapy allows more precise deposition of boost radiation energy to the lumpectomy cavity in a shorter period of time, as compared to conventional radiation schemes. This study evaluated treatment and clinical outcomes of patients with early staged breast cancer who received perioperatively placed catheters for Iridium-192 based brachytherapy.

Material and Methods: 107 breasts in 105 patients with cT1-2 non-lobular breast cancer were treated between 1996 and 2009 with BCT, including WLE combined with perioperative brachytherapy using Iridium-192 (15 Gy applied with low dose rate or 9 Gy with high dose rate) followed by whole breast irradiation (50 Gy in 5 weeks). Outcome analysis included treatment toxicity (according to Common Terminology Criteria for Adverse Events), local recurrence rate, disease-free survival, and overall survival.

Results: Median follow-up was 6.7 years (range 0.50-14.8). Mean age was 50.2 years (±10.5). Mean tumor diameter was 15 mm (±8 mm). Three patients (2.8%) developed a true in field recurrence. Five- and ten-year local recurrence free survival was 98% and 87%, respectively. Five- and ten-year disease-specific survival was 94% and 84%, respectively. Five- and ten-year overall survival was 92% and 78%, respectively.

Acute complications consisted of wound infections of the lumpectomy site ($n = 3$, grade 1), haematoma ($n = 3$, G1), venous bleeding due to removal of catheters, necessitating surgery ($n = 1$, G3), radiation induced mastitis ($n = 2$, G1). Late complications were fibrosis ($n = 19$, G1), temporary pain ($n = 6$, G2), circumscribed teleangiectasia ($n = 6$, G1).

Conclusions: Local recurrence rate and local toxicity after perioperative interstitial brachytherapy and whole breast irradiation for breast cancer appear to be similar to that seen after external beam radiotherapy schemes in BCT. The main disadvantage is the fact that the final histological reports concerning radicality are not available during the brachytherapy treatment. The advantages are the ability to visualize the excision site at the time of implantation and reduction of outpatient treatment.

476

Poster

Palliative Radiotherapy in Patients with Metastatic Breast Cancer - Rates of Utilization, Distance Travelled and Incurred Costs

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Background: Palliative radiotherapy (PRT) is a well recognised treatment for the successful relief of symptoms associated with metastatic breast cancer (MBC). Improvements in up to 80% of MBC patients with complete resolution of pain in a third are recognised. Over half of female patients with MBC receive at least one course of palliative radiotherapy. Distance from radiotherapy centre is associated with reduced rates of PRT despite likely patient benefit. Our aim was to unveil the proportion of patients with MBC attending oncology clinics who received PRT, distance travelled and overall cost.

Materials and Methods: By reviewing the notes of 76 patients with MBC attending outpatient clinics between August 2010 and February 2011 at Wansbeck District General Northumbria, we recorded all courses of PRT received from the diagnosis of MBC for each patient. Number of attendances for delivery of treatment at the Newcastle Centre for Cancer Care (NCCC), fractionation schedule, technique used and distance travelled were recorded. IMRT costing was excluded. An estimated cost of each NCCC course of treatment was made.

Results: MBC patients comprised a median of 36% of outpatient clinic appointments, attending a median of 4 appointments each. 40 (52.6%) of these patients received at least one course of PRT since the diagnosis of MBC, totalling 463 PRT fractions with a median of 10 fractions per patient. 92.3% of patients' PRT was delivered with standardised single or parallel opposed field techniques. 3-D conformal IMRT techniques were required for 2 patients. One patient with bone metastases received stereotactic radiotherapy in a different radiotherapy centre. PRT was administered to bone in 31 (80%) of cases, 10 (27.5%) to soft tissue and 7 (17.5%) to brain. 8 (20.5%) of the patients were re-treated, 6 (15.4%) had one and 2 (5.1%) had two re-treatments. 90% of re-treatments were to bone. The total cost including transport was £37,632. The mean cost was £990 (median £800) per patient with an average price of £100 per fraction. Average distance travelled to the NCCC was 20.9 miles (range 3-63 miles).

Conclusion: Patients with MBC comprise a large proportion of outpatient consultations. Our utilization of PRT is comparable to a limited number of published reports. We show that PRT is an inexpensive and frequently used modality when treating symptomatic metastases in a majority of cases. Despite the average distance travelled to the NCCC this was not a barrier to PRT.

477

Poster

Feasibility Study On Pre-operative MRI-guided Irradiation in Breast-conserving Therapy

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Background: Today's radiotherapy (RT) after breast-conserving surgery is prone to uncertainties due to high interobserver delineation variation

and postoperative seroma. In a recent study, no association between the irradiated target volume and the original tumor size was found in patients with DCIS and early stage breast cancer [den Hartogh et al., Breast cancer res treat, October 2011]. Therefore, two hypotheses were developed:

1. Tumor delineation on pre-operative imaging could lead to smaller target volumes, which are associated with superior cosmetic results and lower radiotherapy toxicity outcomes.
2. Supine breast MRI acquisition for RT delineation would result in superior soft-tissue contrast compared to the standard CT imaging in RT.

We have performed a feasibility study to test these hypotheses in order to perform a larger prospective cohort study.

Material and Methods: To test the first hypothesis, 9 patients with early stage breast cancer (pT1N0) who were treated with breast-conserving therapy (BCT), were retrospectively analyzed. Breast tumors were delineated on pre-operative prone contrast-enhanced MRIs. Clinical target volumes (CTVs) were created by adding a 1.5 cm surrounding margin. These MRI-CTVs were compared to the CT-CTVs acquired from post-operative delineations on RT planning CT scans. CT-CTVs were created by adding a 1.5 cm margin minus the minimal microscopic margin. Consequently, a 1.5 cm margin around the tumor was minimally treated.

To test our second hypothesis, we developed a protocol for MRI of the breast in RT position, since diagnostic MRI acquisition in prone position is not suited for supine RT delineation. Patients were positioned supine on a MRI compatible wedge board.

Results: The median tumor size was 12 mm (range 11–20 mm). The median excised specimen volume was 63 ml (range 26–174 ml). The median pre- and post-operative CTV values were 49.3 ml (range 28.6–96.8 ml) and 66.9 ml (range 20.0–218.6 ml), respectively. The median relative volume reduction was 31% (range –146–87%).

Furthermore, it was technically feasible to acquire high quality MRIs in supine RT position when using a 1.5T Philips Ingenia wide bore magnet. Within 25 minutes, the following 3D MRIs with fat suppression were acquired: T1 weighted FFE (DIXON), T2 weighted TSE (VISTA) and a dynamic series of contrast enhanced T1 (THRIVE) MRIs after Gadovist® administration. The Flexcoverage anterior receive coil was positioned on a PMMA support to prevent deformation of the outer contour of the patient.

Conclusions: In early breast cancer patients, treated with BCT, preoperative irradiation can result in a substantial reduction of irradiated target volumes in BCT. The developed MRI sequences are applied in a prospective cohort study which is currently running at our department. Pre- and post-operative target volume delineation and interobserver variability will be compared on both CT and MR imaging.

478

Poster

Radiation-induced Pulmonary Injury After Radiotherapy for Early Breast Conserving Therapy

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Purpose: We observed a rare and unique occurrence of radiation-induced pulmonary injury after radiotherapy for early breast conserving therapy. We separated the pulmonary injury into inside and outside the tangential field. The goal of this study was to report and determine the incidence, analyze the characteristics of the pulmonary lesions on the images.

Materials and Methods: A retrospective analysis was conducted of 750 consecutive patients that underwent breast-conserving therapy (BCT) from January 1992 to December 2010. The patients were observed at least one year after radiotherapy for BCT. Radiotherapy was administered by 4 MV photons in all patients. The patients underwent chest X-rays and/or computed tomography (CT) periodically. We divided the appearance time of radiation pneumonitis into the super-early stage (during radiation therapy to 3 months after radiotherapy), the early stage (3 to 12 months after radiotherapy), and late stage (over 12 months after radiotherapy). If the pneumonitis was found on chest X-P, chest CT was conducted to identify the characteristics of the pulmonary lesion inside and/or outside the radiation field.

Results: The findings outside radiation field appeared to be idiopathic and were called radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome. The incidence of the radiation-induced BOOP syndrome was about 1.8%. We did not find a relationship between the characteristics of patients and the occurrence of radiation-induced BOOP syndrome. The pulmonary findings were classified into four patterns on chest CT. Progression of the pulmonary lesions observed on chest X-ray was classified into three patterns. Pneumonitis appeared within 6 months after radiotherapy was completed and disappeared within 6–12 months after its onset. The incidence of rate of the interstitial pneumonitis outside radiation field appeared in the super-early stage is 0.1%. On the other hand, the occurrence of the pulmonary findings inside field appeared in

the early and late stage is approximately 85%. But these patients have no respiratory symptoms.

Conclusions: We have to understand the occurrence of the radiation induced or related pneumonitis, and its associated prognosis are not significant, the patients' clinical condition must be carefully followed.

479

Poster

Does the Effect of Clip Displacement On Target Volume Potentially Hamper the Concept of Partial Breast Irradiation in Prone Position?

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Background: To analyse and compare the displacement of surgical clips in prone (Pr) and supine (Su) positions and assess the consequences on target volumes in case of partial breast irradiation (PBI).

Material and Methods: 30 post-lumpectomy breast cancer patients underwent CT imaging in Su and Pr. Displacements of the surgical clips were measured by the distances from the chest-wall (CW) and from a common fix bony reference point (3D vector analysis). On each dataset, the tumour bed (TB = clips ± seroma), clinical target volume (CTV = TB+1.5 cm) and planning target volumes (PTV = CTV+1 cm) for PBI were determined and the volume pairs were compared. Volumes were studied by multiple regression analysis with respect to a set of covariates: age, body weight, left/right side, cup size, localization within the breast, number of clips, presence of seroma and 'deep' clips (defined as located <1 cm from CW).

Results: Clip displacements varied considerably with respect to their position to the CW. The largest displacement was observed for clips situated close to the skin ($p < 0.0001$). The mean volumes of seroma (8.61 ± 8.61 (Pr) vs. 7.67 ± 7.51 cm³ (Su), $p = 0.037$), CTV (88.5 ± 37.0 vs. 75.0 ± 32.3 cm³, $p = 0.0001$) and PTV (233 ± 76.4 vs. 211 ± 70.1 cm³, $p = 0.0008$) were significantly higher in Pr than in Su. The PTV volume difference (Pr-Su) was significantly higher in patients with presence of seroma (48.1 ± 33.2 vs. 10.8 ± 24.8 cm³, $p = 0.002$), TB locations in the superior-internal-quadrant (SIQ) and at the border of superior quadrants (bSQ) (46.4 ± 31.2 vs. 5.72 ± 20.6 cm³, $p = 0.0002$) and in case of 'deep' clips (31.2 ± 32.8 vs. 0.47 ± 17.2 cm³, $p = 0.013$). When combining these factors in a multivariate analysis, two variables remained significant: seroma ($p = 0.0037$) and localization in SIQ-bSQ ($p = 0.0006$).

Conclusions: Pr position in selected patients potentially leads to a significant increase in target volumes in the frame of PBI. Factors independently predicting this volume increase are the presence of seroma and location of TB in the SIQ-bSQ.

480

Poster

Improved Cosmetic Outcome After TARGIT Compared with External Beam Radiotherapy for Early Breast Cancer

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Background: Early results from the randomised controlled TARGIT Trial have demonstrated non-inferiority between the novel technique of TARGIT [intra-operative radiotherapy with Intrabeam® (Carl Zeiss, Germany)] and conventional external beam radiotherapy (EBRT) in women with early breast cancer, in terms of local relapse within the treated breast and clinically significant toxicity. We report here data from a sub-protocol assessing cosmesis in 114 women over 50 years of age participating in the TARGIT Trial from one centre (Perth, Australia).

Material and Methods: Frontal digital photographs from were assessed, blind to treatment, using specialist software (BCCT.core 2.0, INESC Porto, Portugal) which produces a composite score based on symmetry, colour and scar. Statistical analysis was by generalised estimating equations (GEE) on all of the data, and logistic regression analysis at year 1.

Results: 55 and 59 patients were randomised to receive EBRT or TARGIT, respectively. The median age at randomisation was 62 years (IQR 56 to 68). Photographs were taken at baseline (before surgery) and one, two, three and four years after initial breast conserving surgery; none had subsequent breast surgery. The scores were dichotomised into Excellent and Good (EG), and Fair and Poor (FP). There was a non-significant 45% increase in the odds of having an outcome of EG for patients in the TARGIT group relative to the EBRT group (OR = 1.45, 95% CI 0.78–2.69, $p = 0.245$)