Hypofractionated Radiotherapy for Ductal Carcinoma in Situ of the Breast


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Purpose/Objective(s): The main goal of treating ductal carcinoma in situ (DCIS) is to prevent the development of recurrent breast cancer with optimal cosmesis. The addition of whole breast radiotherapy (XRT) after breast-conserving surgery (BCS) has been shown to decrease the risk of local recurrence (DCIS or invasive), but the optimal dose fractionation radiotherapy regimen remains unclear. Past randomized studies administered 50 Gray/25 fractions delivered over 5 weeks (conventional dose fractionation regimen) however, treatment pattern studies on the management of DCIS report that accelerated, hypofractionated (HF) regimens are frequently used. HF radiotherapy provides equivalent rates of local recurrence after lumpectomy for invasive breast cancer, but it is unknown if the two fractionation regimens lead to similar rates of local recurrence after BCS for DCIS. We report the impact of HF radiotherapy regimen (vs. conventional regimen) on the long-term risk of local recurrence in a population of individuals with pure DCIS treated with BCS and XRT.

Materials/Methods: All women diagnosed with DCIS and treated with BCS and XRT in Ontario from 1994-2003 were identified. Treatments and outcomes were identified through administrative databases and validated by chart review. The impact of radiation fractionation scheme (conventional versus HF) on the development of local recurrence was determined using survival analyses. To account for systematic differences between women treated with HF versus conventional radiation schemes, we used a propensity score adjustment approach.

Results: We identified 1,609 women with DCIS treated BCS and radiation. Median follow-up was 10.2 years. Median age at diagnosis was 56 years (range 49-65 years). 971 women (60%) received conventional radiotherapy regimen and 638 cases (40%) received a HF regimen. The cumulative 10-year rate of local recurrence was 12% (n=190). The 10 year actuarial local recurrence-free survival rate was 86% among women treated with conventional radiotherapy and 89% for those treated with HF regimen. (p=0.03). On multivariable analyses adjusted for propensity score, year of diagnosis and administration of boost, age < 45 years at diagnosis (HR=2.4, 95% CI:1.6-3.4,p=0.0001), high (HR = 2.9, 95% CI:1.2-7.3,p=0.02) or intermediate nuclear grade (HR = 2.7, 95% CI:1.1-6.6,p=0.04) and positive resection margins (HR=1.4, 95% CI:1.0-2.1, p=0.05) were associated with an increased risk of local recurrence. Administration of HF radiotherapy was not significantly associated with an increased risk of local recurrence (or invasive recurrence) compared to individuals treated with conventional fractionation (HR= 0.8, 95% CI: 0.5-1.2, p=0.34).

Conclusion: At 10 years, the risk of local recurrence among individuals treated with HF radiotherapy after BCS for pure DCIS was similar to individuals treated with conventional radiotherapy.

Outcomes of “Unsuitable” Patients by ASTRO Guidelines Treated with Accelerated Partial Breast Irradiation via Interstitial Multicatheter Brachytherapy: A Multi-Institution Collaborative Study

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Purpose/Objective(s): To determine the clinical outcomes from 5 institutions of interstitial multicatheter multiplanar brachytherapy in the treatment of select breast cancers in the ASTRO “unsuitable unless on clinical trial” category.

Materials/Methods: Pooled data from five institutions with extensive experience delivering interstitial brachytherapy for accelerated partial breast irradiation (APBI) were collected for patients treated from 1992 to 2013. Each institution was asked to include all APBI patients, but most followed the common exclusion factors of tumors >3 cm, >3 positive nodes, extracapsular extension, or positive margins, with a small number of exceptions (included in this report). Of 938 patients who underwent APBI with interstitial brachytherapy, 849 had available follow-up information to assess for clinical outcomes. ASTRO Guidelines classified a total of 253 patients as “unsuitable”. All patients were treated with interstitial brachytherapy [I-125 LDR [50 Gy at 52 cGy/H x96 hrs] or Iridium-192 HDR[32 or 34 Gy in 8 or 10 BID fractions]] with dose prescribed at 1.5 to 2 cm beyond the lumpectomy cavity.

Results: Median age was 47. Median follow-up was 4.3 years. The most common factors for patients falling into the “unsuitable” group are age <50 yrs (78 %) or positive axillary nodes (26 %). The other factors comprise only 2 % of this group. Staging was Tis 26%, T1 63%, T2 11%, Nx 21%, N0 51%, Ni+ 1.6%, and N1 26%. With respect to disease control, 12 ipsilateral breast tumor recurrences (IBTR) were noted. The 5- and 10-year actuarial rates of local recurrence (LR) were 4.6% and 6.0%, regional recurrences [RR] 2.8% and 2.8%, distant metastases [DM] 1.8% and 4.4%, and contralateral breast failures [CBF] 2.6% and 6.5%. In the analyses of multiple clinical and pathological factors to determine the association with LR, RR, DM, and CBF, significance was only found for age less than 45 for higher local recurrence; specifically, for the unsuitable category patient less than 45 yrs of age, the 5 and 10-yr actuarial LR rates were 10.7% and 18.8%, respectively versus 3.2% actuarial at 5- and 10-years for those greater than 45 yrs (p=0.03). No association with age was found for RR, DM and CBF.

Conclusions: In this collaborative project of five institutions with expertise in delivering APBI with interstitial multicatheter brachytherapy APBI, patients in the ASTRO “unsuitable” category had few ipsilateral breast tumor recurrences. In a detailed analysis of IBRT, the one significant factor associated with an increase in LR was age younger than 45. These results underscore the importance of a reevaluation of the Guidelines in light of emerging data.

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as a surrogate marker for basal-like carcinoma. Phosphorylation of the epithelial intermediate filament protein keratin 8 at serine 73 (phospho-K8) occurs during mitosis, cellular stress and apoptosis, and inversely correlates with colorectal cancer progression. In this study, we aimed to determine the prognostic value of phospho-K8 in triple negative breast cancer (TNBC).

Materials/Methods: Tumor specimens from 369 women with breast cancer (patient age range 25-89 years) and a median follow-up of 7.02 years were constructed into a tissue microarray. The array was stained for ER, PR, HER2, and phospho-K8. Among these, 90 specimens were of the triple negative phenotype and were the focus of this study. The results were correlated with overall, local, and distant relapse-free survival. Using multivariate analysis, the relationship between phospho-K8, other co-variables, and outcome was evaluated.

Results: Positive expression of ER, PR, HER2, and phospho-K8 was detected in 61.5%, 58.3%, 12.7%, and 62.9% of all tumor specimens, respectively. In total, 35 local and 55 distant recurrences were observed. Among TNBC patients only, there were 15 local and 19 distant recurrences. In univariate analysis, among these triple negative patients, lack of phospho-K8 expression correlated with higher local recurrence and higher distant metastasis rates. At 10 years, 89.1% of women with phospho-K8 positive tumors and 70.9% of women with phospho-K8 negative tumors were local recurrence-free, respectively. At 10 years, 82.6% of women with phospho-K8 positive tumors and 60.4% of women with phospho-K8 negative tumors were distant metastasis-free, respectively. In multivariate analysis, which included T stage, nodal status, margins, and age, lack of phospho-K8 expression in triple negative phenotype patients remained a significant predictor of poor local (RR, 3.4; 95% CI, 1.11-10.1; p=0.032) and distant recurrence rates (RR, 3.7; 95% CI, 1.40-9.80; p=0.008), but not overall survival (RR, 1.4; 95% CI, 0.596-3.20; p=0.452).

Conclusions: Lack of phospho-K8 expression distinguishes a set of triple negative phenotype patients at higher risk for local and distant recurrences. This data suggests that TNBC patients with phospho-K8 negative tumors may benefit from more aggressive local and systemic therapy. Further evaluation and validation of these findings in larger data sets is warranted.


Presentation Number: 299

Prevalence of Arm Symptoms and Arm Swelling in Breast Cancer Patients Treated With Hypofractionated Compared to Conventional Fractionated Nodal Radiation Therapy in the Modern Era of CT-Based RT Planning

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Purpose/Objective(s): Regional nodal radiation therapy (RT) with breast/chest wall RT can have late effects including arm symptoms and lymphedema. Hypofractionated (HF) (defined as >2 Gy / fraction) RT has advantages in terms of patient convenience and resource utilization. Our study aims to determine whether there is an increased prevalence of arm symptoms or lymphedema associated with HF courses of nodal RT compared to conventional fractionation (CF) (defined as 1.8-2Gy/fraction).

Materials/Methods: Subject patients were identified using a provincial registry including women who received nodal RT for pT1-3pN0-2M0 breast cancer from 2007-2009. Eligible patients were invited by mail to participate by completing an externally validated, Self-reported Arm Symptom Scale (SASS). SASS consists of 8 questions with responses on a 1-5 scale (5 = most severe) regarding: magnitude of arm / hand problems (numbness, pain, stiffness, immobility and swelling), and 5 questions related to activities of daily living (ADL). Comparisons between cohorts, HF vs. CF nodal RT, were performed for: Clinicopathologic and treatment characteristics, and SASS scores. Statistical analysis used both non-parametric analysis and binned chi-squared analysis (comparison of 1 vs. > 1).

Results: 508/1146 eligible patients returned a completed survey (44.3%), 308 (60.6%) patients received HF nodal RT (median total dose/fractionation 40 Gy in 16 fractions), and 200 (39.4%) received CF nodal RT.
(median 45 Gy in 25 fractions). Median interval since RT completion was 4.75 years vs 4.67 years in the HF and CF cohort respectively (p=0.58). The median age at diagnosis was 60 for the HF group, and 53 for the CF group (p<0.01). Median number of excised nodes was 11 vs 10 for HF compared with CF (p=0.33). The number of positive nodes was similar between groups while there was increased CF nodal RT use post mastectomy (p=0.01) and post chemotherapy (p<0.01). The mean sums of responses for arm problems / ADL were 12.3 / 7.5 vs. 13.0 / 7.8 for the HF and CF groups respectively (p=0.02/0.09). On analysis of individual questions, the CF group had a higher prevalence of functional limitation compared to the HF group, including shoulder stiffness (p=0.03), trouble moving the shoulder (p<0.01), ability to fasten a bra (p=0.03), and ability to reach overhead (p<0.01). There was no difference in arm swelling between the two groups (p=0.28).

**Conclusions:** Hypofractionation is not associated with more prevalent arm disability compared to CF. Our analysis identified that CF patients have more disability in certain aspects of arm/shoulder function. Factors such as differences in pre-treatment arm symptoms will be explored. Analysis of an additional set of patients with the same inclusion criteria from another province where CF predominates is in progress. This will help further power the analysis and inform natal RT prescription practices.

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**Presentation Number:** 149

**The Influence of Receptor Status on Locoregional Recurrence Risk among Breast Cancer Patients with Positive Lymph Nodes Following Neoadjuvant Chemotherapy and Mastectomy**

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**Purpose/Objective(s):** Among breast cancer patients (pts) treated with neoadjuvant chemotherapy (NAC) and mastectomy, advanced initial clinical stage and residual pathologic nodal disease (ypN) have been associated with a higher risk of loco-regional recurrence (LRR). However, initial clinical stage can be unclear despite physical exam and modern imaging techniques. Thus, ypN status is arguably one of the more robust and consistent predictors of LRR. To date, few studies have examined the impact of receptor status and additional endocrine treatment on LRR in ypN+ pts. This analysis sought to identify pts with a predetermined 5-year (yr) LRR risk of ≥10% who may benefit from post-mastectomy radiation therapy (PMRT) by examining the influence of receptor and nodal status on LRR rates among NAC pts treated with mastectomy.

**Materials/Methods:** The records of 86 consecutive breast cancer pts (87 breast tumors) treated with modern anthracycline and/or taxane-based chemotherapy, mastectomy, and lymph node evaluation between 1997 and 2011 at our institution were reviewed. No patient received PMRT. All estrogen receptor (ER)+ pts received adjuvant endocrine therapy. Pts were classified based on ypN status (ypN0 versus ypN+), and then stratified by receptor subtype. Actuarial rates of LRR were calculated using the Kaplan-Meier method. The log-rank test was performed to evaluate the impact of receptor class on LRR, with statistical significance defined as a p value of ≤0.05.

**Results:** Following NAC and mastectomy, 35 pts (40%) and 52 pts (60%) had positive and negative nodes, respectively. Median follow-up period was 52.6 months (range, 5.4 - 201.0 months). Among ypN+ pts, the 5-yr LRR risk in pts with ER+, Her2+, and triple negative disease was 5%, 33%, and 37%, respectively (p=0.02). The majority (92%) of pts with ER+/ypN+ disease had fewer than 4 lymph nodes positive (ypN1). Among the ypN+/ER+ pts, the presence of lymphovascular space invasion (LVI) and grade 3 disease increased a patient’s 5-yr risk of LRR to 13% and 11%, respectively. Among ypN0 pts, the 5-yr LRR risk in pts with ER+, Her2+, and triple negative disease was 0%, 22% and 10%, respectively (p=0.53). In pts with ypN0/triple negative breast cancer, the presence of grade 3 disease increased the 5-yr LRR risk to 13%.

**Conclusions:** Among breast cancer pts treated with NAC and mastectomy, receptor and ypN status may guide PMRT decisions, particularly when a pt’s initial clinical stage is uncertain. PMRT appears warranted in pts with ypN+/Her2+ or triple negative tumors, as these pts are at high-risk of LRR regardless of other
clinicopathologic factors. However, in pts with ypN+/ER+ disease, the risk of LRR is low and endocrine therapy appears sufficient adjuvant treatment, except in those women with LVI or grade 3 disease where PMRT may still be warranted.


Presentation Number: 1030

Outcome Following Local-regional Recurrence (LRR) in Women with Early Stage Breast Cancer: Impact of Biologic Subtype

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Purpose/Objective(s): LRR after breast-conserving surgery (BCS) and radiation (RT) can result in distant metastasis and decreased disease-free survival (DFS). This study examines factors associated with outcome following LRR.

Materials/Methods: The initial study population included 2,233 consecutive women who underwent BCS and RT from 1998 to 2007. Patient characteristics, treatment and disease factors were assessed for disease-free interval after LRR. Biologic subtype was approximated by receptor status: estrogen receptor (ER) positive or progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER-2) negative and moderately or well differentiated = luminal A; ER+ or PR+, HER-2- and poorly differentiated = luminal B; ER+ or PR+ and HER-2+ = luminal-HER2; ER-, PR- and HER2+ = HER-2; ER-, PR- and HER-2- = triple negative breast cancer (TNBC). Cumulative incidence of subsequent recurrence following initial LRR and DFS were calculated. The association of clinical and pathologic parameters with these endpoints was evaluated using a Cox proportional hazards regression model.

Results: At a median follow-up of 105 months, 82 patients (3.7%) had a LRR. Of these LRRs, 66 (80%) were in-breast and 16 (20%) involved the ipsilateral lymph nodes. Twenty patients subsequently developed distant metastases a median of 56 months after LRR. Five-year DFS after initial recurrence was 69.6% for the overall cohort. On univariate Cox analysis, TNBC was associated with reduced DFS after LRR compared to other subtypes (HR = 3.8; 95% CI 1.8-8.1; p<0.001). Other factors associated with reduced DFS were larger tumor size (HR=1.3; 95%CI 1.03-1.6; p=0.02), shorter time interval from initial diagnosis to LRR (HR=0.98 per month; 95%CI 0.97-0.99; p=0.02), and no salvage surgery (HR=0.2; 95%CI 0.09-0.5; p=0.001). On multivariate Cox analysis, TNBC remained the most significant factor associated with reduced DFS (HR = 4.8; 95% CI 2.25-10.4; p<0.001). Shorter time interval between initial diagnosis and LRR (HR=0.2, p=0.02) and no salvage surgery (HR=0.23, p=0.001) were significantly associated with reduced DFS. Compared to women with luminal A disease, those with TNBC had significantly worse DFS (p<0.001 on log-rank test); 5-year DFS after an initial LRR was 37.5% with TNBC and 88.3% with luminal A.

Conclusions: Women with TNBC who developed LRR were at higher risk of subsequent recurrence compared to those with other subtypes. Efforts should be targeted towards both preventing initial recurrence and decreasing the risk of subsequent metastasis in this high-risk population.

Does Size Matter: Examining the Association of BMI with Breast Cancer Recurrence and Survival in an Early Stage Breast Cancer Cohort with a High Median BMI

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Purpose/Objective(s): High body mass index (BMI) or obesity and dysregulated glucose metabolism have been identified as risk factors for distant recurrence and decreased survival in breast cancer. Our institution aimed to determine whether BMI and/or diabetic status correlated with local recurrence and reduced survival in a cohort of predominantly obese women, as measured by BMI, treated with breast conservation therapy (BCT).

Materials/Methods: From 1998-2006, 119 women with early stage invasive breast cancer were treated with prone whole breast irradiation (WBI) using 3D conformal radiation. A retrospective review was performed examining BMI and diabetic status at diagnosis. The association of BMI and crude recurrence rates was examined using Fisher’s Exact test. The association of BMI and diabetes with local recurrence-free survival (LRFS), recurrence-free survival (RFS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) was examined using Cox proportional hazards regression.

Results: The median age was 60. Median follow-up was 90 months. Seventy-five percent of patients were post-menopausal. Mean tumor size was 1.5 cm. Nodal disease (N1) was present in 16%, and 78% of patients with invasive disease were ER/PR+. Appropriate systemic therapy was recommended to all patients. Median BMI was 33.5 (mean 34.6); 90% were overweight (BMI≥25), 71% of patients were clinically obese (BMI≥30), and 37% had ≥WHO class II obesity (BMI≥35). Twelve patients had diabetes (10%). For the cohort, 5-year LRFS, DMFS, and OS were 93%, 94%, and 91%, respectively. Diabetes was not associated with cancer progression or recurrence. The crude recurrence rate for those with greater than the median BMI (33.5) was 9.4%, versus 0% for those with BMI less than the median value (p=0.013). BMI was significantly associated with decreased DMFS (HR 1.14, p=0.011), RFS (HR 1.13, p=0.008), DFS (HR 1.16, p<0.0001), and OS (HR 1.10, p=0.004), and there was a trend for increased local regional recurrence with higher BMI (p=0.08). Diabetic status did not correlate with breast cancer related outcomes. On multivariate analysis, adjusting for tumor size, subtype, grade, age, nodal involvement, chemotherapy, and diabetes, BMI remained a significant predictor of poorer RFS (p=0.01), DFS (p=0.001), DMFS (p=0.01), and OS (p=0.0009).

Conclusions: In this cohort of early stage breast cancer patients with high BMI, increasing BMI predicted for worse RFS, DFS, DMFS, and OS. In addition, this data suggests that BMI may impact the rate of local recurrence, warranting investigation in larger cohorts of patients. This investigation adds to growing evidence that BMI is an important prognostic factor in early stage breast cancer treated with BCT.

approved trial (institutional trial #10-01969) to test the feasibility and efficacy of this combination in terms of rates of local control, distant recurrence, and overall survival.

**Materials/Methods:** Women with Stage I - II (pT1-T2, pN0) TNBC are eligible after segmental mastectomy and axillary lymph node assessment. Weekly carboplatin (AUC=2.0) is delivered x6 weeks with RT to the whole breast, delivered during weeks 2-4 via a 3D-CRT or an IMRT technique in the prone position. The whole breast receives 40.5 Gy in 15 fractions (Monday-Friday). The tumor bed receives an additional 3 Gy boost, delivered on 2 consecutive Sundays (beginning on the 2nd and 3rd weeks of RT). Consequently, a total of 46.5 Gy is delivered to the tumor bed in 17 fractions over 19 days. Adverse effects of treatment are assessed weekly during treatment, and once at 45-60 days, thereafter, using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

**Results:** A total of 27 patients have accrued so far. The median age was 56 years (range: 27-82). Reported acute skin toxicities are displayed (see Table). With a median follow-up of 26 months all of the women remain alive and without recurrent disease.

**Conclusions:** Adjuvant concurrent carboplatin and prone accelerated radiotherapy appears to be a safe and effective treatment for women diagnosed with early stage TNBC. Since approximately 50% of TNBC carriers recur within 2 years from treatment, it is encouraging that none of the patients in the trial have experience a recurrence. The trial remains open for patient accrual.

### Reported Acute Skin Toxicities

<table>
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<th>Radiation Toxicity</th>
<th>Number of Patients</th>
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**Presentation Number:** LBA3

**Hypofractionated Whole Breast Irradiation Results In Less Acute Toxicity And Improved Quality Of Life At 6 Months Compared To Conventionally Fractionated Whole Breast Irradiation: Results Of A Randomized Trial.**


**Purpose/Objective(s):** To report acute and short-term toxicity and patient-reported quality of life (QOL) data for a randomized trial comparing conventionally fractionated whole breast irradiation (CF-WBI) to hypofractionated whole breast irradiation (HF-WBI), both delivered with a sequential tumor bed boost.

**Material/Methods:** Patients with stage 0, I or II breast cancer treated with breast conserving surgery eligible for treatment with WBI only were randomized to receive CF-WBI (50 Gy in 25 fractions WBI followed by a tumor bed boost of 10-14 Gy in 5-7 fractions) or HF-WBI (42.56Gy in 16 fractions WBI followed by a tumor bed boost of 10-12.5 Gy in 4-5 fractions). Acute toxicities were scored using structured templates by the treating physician on a weekly basis during treatment and on an as-needed basis within 45 days of
completing radiation. Toxicities six months after completing radiation were also scored using structured templates by the treating physician. Patient-reported physical well-being and fatigue were assessed using the FACT-B at baseline and at 6 months. All analyses were based on intention-to-treat, with differences in outcomes by treatment assessed using chi-square, Cochran-Armitage test for trend, and student’s t-test as appropriate.

**Results:** Between March 2011 and February 2014, 287 patients underwent treatment, 149 randomized to CF-WBI and 138 to HF-WBI. Only one patient (0.3%) did not receive the radiation schedule allocated by randomization. Groups were well-matched for all measured baseline clinical-pathologic covariates, including age, stage, and receipt of chemotherapy. Overall rates of acute grade ≥ 2 toxicity were significantly lower among patients randomized to receive HF-WBI vs. CF-WBI (46.4% vs. 77.9%, p<.001). In particular, patients randomized to HF-WBI had significantly lower grade ≥ 2 dermatitis (36.2% vs. 69.1%, p<.001), pruritis (2.1% vs. 7.0%, p<.001), breast pain (5.1% vs. 8.7%, p=.001), hyperpigmentation (8.7% vs. 20.1%, p=.002), and fatigue (8.7% vs. 16.8%, p=.02). At baseline, patients in both arms had comparable physical well-being (p=.63) and self-reported fatigue (p=.94) as assessed using the FACT-B. Six months after completion of radiation, patients randomized to HF-WBI had significantly better physical well-being on the FACT-B than those treated with CF-WBI (25.5 vs. 24.6, p=.0497) and less patient- and physician-reported fatigue (p<.001 and 0.01, respectively).

**Conclusion:** During radiation, HF-WBI results in less acute toxicity than CF-WBI. Six months after completing radiation, HF-WBI results in improved physical well-being and lower rates of patient- and physician-reported fatigue.