Purpose/Objective(s): The current rationale for using a radiation boost after whole breast radiation (WBRT) for DCIS is largely extrapolated from phase III invasive cancer trials that have demonstrated its benefit in decreasing ipsilateral breast tumor recurrence (IBTR). Demonstrating this benefit for DCIS specifically has been a challenge due to its long natural history & limited IBTR events after WBRT. Hence, current data are limited to conflicting series restricted in size, IBTR and/or follow up. In this study, a DCIS cohort was assembled based on an a priori power analysis which estimated the sample size needed to detect the anticipated benefit from the boost. This cohort was analyzed to assess the independent effects of the boost for in-situ disease.

Materials/Methods: IRB approvals & data sharing agreements were obtained from the 10 participating academic institutions across USA, Canada & France. De-identified patient level data were uniformly re-coded at the host institution and underwent 1° and 2° review prior to inclusion for analysis. Patients with pure DCIS treated with WBRT +/- electron or photon boost and 5 years minimum follow-up were eligible. DCIS cases with micro-invasion, brachytherapy boost, or unknown boost status were excluded. Sample size calculations (ratio of 2:1, α=0.05, power=80%) estimated 2,982 patients (1,988 boost; 994 no boost) would be needed to detect a 3% or greater benefit (ie: 10 yrs IBTR: 10% no boost vs. 7% boost) Results: Of 4,376 DCIS cases collected, the cohort eligible for analysis consisted of 4,131 patients (Nboost = 2,661, Nno boost=1,470). For the entire cohort, median f/u was 9 yrs; median age was 56 yrs; median boost dose was 14 Gy. Patients with +margins, unknown ER status and +necrosis were more likely to have received a boost (all p<0.05). The IBTR-free survival was 97.1% vs 96.3% (p=0.18), 94.1% vs 92.5% (p= 0.12) & 91.6% vs 88% (p=0.03) at 5, 10, & 15 years for boost vs no boost, respectively. Of the 4,131 patients, the overall IBTR was significantly less in those receiving boost compared with no boost (p=0.013). Subset analysis failed to demonstrate any benefit of the boost when a +margin was reported (p=0.99). The multivariate analysis incorporated grade, necrosis, ER & margin status, age, size & tamoxifen-use demonstrated that the boost remained an independent predictor for decreasing IBTR (p=0.013), significant in all patients with negative margins irrespective of age group (all p<0.02).

Conclusion: In the absence of PIII data, this study represents the largest dataset with longest follow-up supporting the use of a radiation boost for DCIS. Our findings demonstrate that the boost provides a small but statistically significant benefit of similar magnitude to that seen in invasive cancers. While the use of a boost is unlikely to overcome the detrimental effects of a +margin, it should be considered for margin-negative DCIS patients undergoing WBRT who have life expectancies >10-15 years, to provide an additional incremental benefit in decreasing IBTR.
Efficacy of Mometasone Furoate in the Reduction of Moderate/Severe Radiation Dermatitis in Breast Cancer Patients Following Mastectomy

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Purpose/Objective(s): A two-arm, double-blinded randomized trial was conducted to evaluate the efficacy of 0.1% mometasone furoate (MF) versus Eucerin Original® (E) cream in the development of moderate to severe radiation dermatitis in breast cancer patients receiving postmastectomy radiation (PMRT).

Materials/Methods: Breast cancer patients undergoing chest wall +/- nodal radiation therapy (50 Gy) were eligible. Randomization (1:1) was to MF or E, applied twice daily from Day 1 of PMRT to 14 days post-PMRT. Patients were stratified by RT technique (3-D conformal or IMRT), body mass index and reconstruction status. Bolus was applied in all patients. The primary endpoint was the development of provider-assessed grade ≥2 (CTCAE v.4) radiation dermatitis with moist desquamation. Secondary endpoints were time to occurrence of maximum grade dermatitis and patient-reported skin symptoms using a skin related quality of life questionnaire, Skindex-16. Assessments were performed at baseline, weekly during PMRT and 2 weeks post-PMRT.

Results: A total of 124 patients were enrolled between August 2013 and February 2016. Eighty-nine percent were pathologic stage III, 3% were cT4d and 69% had reconstructions; 6.5% received electrons alone to the chest wall, 70.5% received electrons and photons, and 23% IMRT. Groups were well balanced for age, skin type and stage. The rate of moist desquamation was 54.8% in the entire cohort, with a significantly reduced incidence in the MF versus E arm (45% vs 64.5%, p=0.02). The MF arm had a lower incidence of maximum (grade 3) skin toxicities (18.8% vs 33.3%; P=0.036), as well as longer time to the development of grade 3 radiation dermatitis compared to E arm (46 days vs 35.5, respectively; P<0.001). There was no difference in Skindex-16 scores between arms.

Conclusion: Breast cancer patients receiving MF during PMRT experience significantly reduced rate of moist desquamation, with longer time to toxicity occurrence, compared to control cream.


Longitudinal Analysis of Patient-Reported Outcomes and Cosmesis in a Randomized Trial of Conventionally Fractionated Versus Hypofractionated Whole-Breast Irradiation

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Purpose/Objective(s): To compare longitudinal patient-reported outcomes (PROs) and physician-rated cosmesis with conventionally fractionated whole-breast irradiation (CF-WBI) versus hypofractionated WBI (HF-WBI) and to assess how these outcomes change over time.

Materials/Methods: From February 2011 to February 2014, 287 women with stage 0 to I breast cancer were enrolled on a randomized trial of CF-WBI (50Gy/25fx+10-14Gy/5-7fx) versus HF-WBI (42.56Gy/16fx+10-12.5Gy/5-7fx) following breast-conserving surgery. PROs...
were assessed using the Breast Cancer Treatment Outcome Scale (BCTOS), the Functional Assessment of Cancer Therapy for Patients with Breast Cancer (FACT-B), and the Body Image Scale (BIS), and were recorded at baseline, 0.5, 1, 2, and 3 years following radiation therapy. Physician-rated cosmesis was assessed using RTOG criteria and recorded at the same time points. Outcomes by treatment arm were compared at each time point using a two-sided t-test. Multivariable mixed-effects growth curve models assessed the effect of treatment arm on longitudinal outcomes and trends over time.

Results: Of 287 patients enrolled, 149 were randomized to CF-WBI and 138 to HF-WBI. Sixty-nine percent (n=198) of patients had at least 2 years of follow-up. Pre-radiation patient characteristics and PRO measures were well-balanced between the two groups. There were no statistically significant differences between the two arms for any PROs or physician-rated cosmesis scores at 0.5, 1, or 3 years. At 2 years, FACT-B trial outcome index (TOI) was modestly better in the HF-WBI arm (Table). In multivariable mixed-effects models, treatment arm was not associated with longitudinal outcomes after adjusting for time and baseline PRO measures (P≥0.14). The linear effect of time was significant for BCTOS pain (P=0.002, improved with time) and BCTOS functional outcomes (P=0.001, improved with time) and trended toward significance for physician-rated cosmesis (P=0.07, deteriorated with time).

Conclusion: In this randomized trial, longitudinal outcomes did not differ significantly by treatment arm. For the entire group, patient-reported pain and functional outcomes improved over time. These findings should be considered when counseling patients about what to expect following radiation therapy.

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<th>Outcome</th>
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<th>CF-WBI: Mean (N)</th>
<th>HF-WBI: Mean (N)</th>
<th>P</th>
<th>Outcome</th>
<th>Year</th>
<th>CF-WBI: Mean (N)</th>
<th>HF-WBI: Mean (N)</th>
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The Effect of Breast Irradiation on Cardiac Disease in Women Enrolled on BCIRG-001 at 10-Year Follow-up

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Purpose/Objective(s): Radiation therapy (RT) for breast cancer has been shown to increase the risk of long term cardiac morbidity. Modern techniques such as 3D-CRT and IMRT decrease cardiac dose from RT. This study investigated cardiac toxicity associated with breast RT at 10 year follow-up in BCIRG-001, a phase III trial comparing adjuvant anthracycline chemotherapy (FAC) with anthracycline-taxane chemotherapy (TAC) in women with lymph node (LN) positive early breast cancer.

Materials/Methods: prospectively collected data from all 746 patients in the control arm (FAC) of BCIRG-001 at 10 year follow up was analyzed from Project Data Sphere. Cardiac toxicities examined were grade 3 or 4 congestive heart failure (CHF), myocardial infarction (MI), and LVEF decrease of >20% from baseline. Toxicities were compared between patients who did and did not receive RT, left sided versus right sided RT, left sided versus no RT, and left internal mammary nodal (IMN) versus no RT. Statistical comparisons of categorical data were completed using the X²-test and Fisher exact test, and multivariate analysis was performed using binomial logistic regression in the R statistical package.

Results: Of the 746 patients, 538 (72%) received RT to a median dose of 50Gy (25-65Gy). Among the RT patients, 266 (49%) received left sided RT, 393 (69%) received regional nodal irradiation (RNI), and 51 (13% of RNI group) were treated to the IMNs (31% left sided). There was no significant difference in age, KPS, menopausal status, ER/PR, or HER2 status, tumor grade, history of diabetes, MI, obesity, hyperlipidemia, HTN, or arrhythmia, between patients receiving RT and those that did not. Per protocol, nearly all patients who underwent lumpectomy received RT; 241/439 (55%) of patients who underwent mastectomy received RT. There was thus fewer RT patients (versus non-RT patients) who underwent mastectomy (55% vs. 95%, p<0.001) and more RT patients with >3 positive LN (42% vs 28%, p= 0.001). MI occurred in 6 RT patients versus 8 patients non-RT patients (1% vs 4%, p = 0.8). No patient treated with left sided or left IMN RT experienced MI. Grade 3/4 CHF was seen in 14 RT patients versus 3 non-RT patients (3% vs. 1.5%, p = 0.9). Four of 14 RT patients (29%) died of complications of CHF versus no RT patients. Evaluable baseline echocardiograms were available in 270 patients. Among these, 35/198 RT patients had LVEF decrease of >20% baseline versus 6/72 who did not receive RT (18% vs. 8.3%, p = 0.09). There was no difference between LVEF decrease in right-sided versus left-sided RT. On multivariate logistic regression, MI is significantly associated with previous history of MI, obesity, and older age.

Conclusion: There is no significant increase in risk of MI at 10 years in LN positive women treated with breast RT and uniform adjuvant doxorubicin-based chemotherapy in this modern prospective study with long-term cardiac outcomes. The higher incidence of CHF morbidity and mortality warrants further study with a larger randomized cohort.

Regional Patterns of Breast Cancer Failure After Definitive Therapy: A Large, Single-Institution Analysis

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Purpose/Objective(s): Detailed patterns of failure after definitive therapy for breast cancer have not been described. We aimed to 1) demonstrate with anatomic detail the patterns of regional breast cancer recurrence, and 2) identify pathologic features predictive of recurrence in each nodal basin.
Materials/Methods: From a multidisciplinary database of 13,042 patients with Stage I-III breast cancer treated with definitive surgery +/- (neo)adjuvant therapies at our center between 2000-2010, we identified 553 who had biopsy-proven recurrent disease in regional lymph nodes. Patients with DM preceding LRR >2 months or lack of imaging of the LRR were excluded (359), leaving 183 eligible patients from whom 275 regional recurrences were transferred to a representative CT for visualization of recurrence patterns. Characteristics related to patient, disease and initial treatment were correlated with regional nodal recurrence subsite (axillary, IMN or SCV), and analyzed by multivariate analysis (MVA) and logrank for hazard ratio (HR) statistics.

Results: Of the 275 recurrences mapped from 183 patients, 93 (40%) patients recurred in the axilla, 73 (31%) in the supraclavicular (SCV), and 68 (29%) the internal mammary (IMN). 79 (43%) patients had isolated LRR (no concurrent DM). 13 (7%) patients had isolated IMN, 39 (21%) had isolated axilla, and 23 (13%) had isolated SCV recurrence. Within the IMN chain, the majority (51; 21%) of recurrences occurred in the 1st intercostal space, followed by 6% (14) in the 2nd, and 4% (10) in the 3rd intercostal space. In the SCV region, the majority (12%) of recurrences were in the medial, 9% (22) in lateral, and 3% (8) in the posterior SCV. Within the axilla, 63 (27%) had level I, 31 (13%) had level II, and 8 (3%) had level III recurrence. On multivariate analysis, ECE was not associated with axillary recurrence (p=0.9). However, LVI, ECE and ER-receptor status were each independently associated with recurrence in each nodal site. The presence of LVI increased the risk of recurrence in the SCV (HR = 4; 95% CI 3.83-4.11) more so than the IMN (HR 3.5; 95% CI 3.4-3.6) or axilla (2.6; 95% CI 2.5-2.65), as did ER negative receptor (HR = 6.7 for SCV; CI 6.42-7.05). G3 was a strong independent predictor for the risk of IMN recurrence (HR = 8.7; 95% CI 8.26-9.1) and posterior SCV recurrence (8/8 of which were high grade).

Conclusion: The presence of LVI and ER-negative receptor status highly predicted recurrence in the SCV nodes, whereas high grade was an independent predictor for IMN recurrence. These data may guide individualized contouring in which target delineation can be guided by failure patterns and clinicopathologic features of tumor at presentation.


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The 21-Gene Recurrence Score and Locoregional Recurrence Rates in Patients With Node-Positive Breast Cancer Treated on SWOG S8814

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Purpose/Objective(s): The 21-gene recurrence score (RS) assay is prognostic for locoregional failure among women with node-negative, estrogen-receptor-positive (ER+) breast cancer treated with tamoxifen. In ER+, node-positive, postmenopausal breast cancer patients treated on the phase III trial SWOG S8814, RS was prognostic for disease-free survival in women treated with tamoxifen alone and identified those who might not benefit from cyclophosphamide, doxorubicin and fluorouracil chemotherapy (CAF) prior to tamoxifen. We examine whether RS was prognostic for locoregional recurrence (LRR) in this node-positive population.

Materials/Methods: Documentation regarding locoregional recurrence (ipsilateral chest wall or regional nodal recurrence) and use of radiotherapy was extracted from the charts of 367 patients with available RS. We excluded patients treated with mastectomy and radiation (37), those treated with breast conserving surgery without documentation of radiotherapy (9) and those with unknown surgery type (S), leaving 316 for this analysis. The effect of RS on LRR was assessed using cumulative incidence with censoring at last
known contact if no LRR. If distant disease occurred first, subsequent LRR may not have been recorded. Intermediate (18-30) and high RS (>31) were grouped for the purpose of modeling. Time to LRR was tested with log-rank tests and Cox regression for multivariate models.

**Results:** Median follow up for those without LRR was 8.6 years. There were 7 LRR events among 121 patients with low RS and 27 events among 195 patients with intermediate/high RS. Estimated ten year cumulative incidence rates were 9.7% and 16.5%, respectively (log-rank p=0.018). Restricted to patients who had mastectomy the differences remained significant (low RS 7.8% for n=91 and intermediate/high RS 16.8% for n=160, p=0.027). There were only 6 events among patients who had breast conserving therapy so subset analysis was not possible. A multivariate model controlling for randomized treatment (chemotherapy or not), number of positive nodes (1-3 vs 4+) and surgery type still showed higher RS was prognostic for LRR (HR=2.35; 95% CI 1.02-5.43; p=0.045).

**Conclusion:** Higher RS was associated with increased LRR in an ER+, node-positive population treated with CAF followed by tamoxifen or tamoxifen alone after adjustment for treatment, type of surgery and number of positive nodes. This is the first validation of an association between RS and LRR in a node-positive cohort, suggesting that RS may be useful to assess risk of LRR. Low LRR among patients with low RS, node-positive disease treated by mastectomy supports a prospective trial to investigate omission of radiotherapy in these patients. Acknowledgements: NIH/NCI/NCTN grants CA 180888, CA180819, CA180821, CA180820, CA180863; and in part by Genomic Health, Inc.


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**CD47 as a Target for Immune-Radiation Therapy for HER2-Expressing Breast Cancer Cells**

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**Purpose/Objective(s):** Immune tolerance allows for tumor progression and metastasis. Despite the potential immunogenicity, cancer cells develop the capability to evade immune-surveillance. CD47 is a transmembrane cellular protein which interacts with the ligand signal regulatory protein α (SIRPα) on macrophages to initiate a signaling cascade that inhibits phagocytosis. This study reveals that CD47 is highly expressed by human breast cancer cells and radioresistant cancer stem cell-like breast cancer cells. CD47 gene expression was found to be further enhanced in response to therapeutic doses of radiation via NF-kB mediated regulation of CD47 gene promoter. In addition, CD47 and HER2 were co-expressed in breast cancer cells and HER2 acted as an upstream regulator of CD47 expression.
Materials/Methods: The cultured cells were irradiated by 5Gy, and the expression of CD47 was analyzed post-irradiation via immunohistochemistry and western blotting. The involvement of NF-kB and HER2 in CD47 expression was studied by treating the cells with their respective inhibitors and/or siRNA-mediated depletion and testing the CD47 expression as well as macrophage-mediated phagocytosis of breast cancer cells. The use of anti-CD47 antibody as a strategy to inhibit “don’t eat me” signals was also analyzed by flow cytometry to look at macrophage-based phagocytosis.

Results: Cell treated with HER2 inhibitors, Herceptin or Lapatinib significantly reduced CD47 expression and enhanced phagocytosis of breast cancer cells by macrophages. Furthermore, inhibition of CD47 resulted in reduced cell survival upon both anti-HER2 and radiation treatments. In the absence of CD47, HER2-positive breast cancer cells became less invasive but more sensitive to radiation.

Conclusion: Taken together, these data reveal that breast cancer cells with HER2-mediated intrinsic radioresistance can be additionally protected by CD47-mediated immuno-shielding against macrophage-mediated phagocytosis. Thus, CD47 expression is a potential new prognostic biomarker for radioresistant breast cancer, and radiosensitization target that can be combined to treat breast cancer by radiation.


Ten-Year Results of the Breast Intensity Modulated Radiation Therapy (IMRT) Randomized Controlled Trial

J. Pignol1, P. Truong2, E. Rakovitch3, M. G. A. Sattler4, M. Miller5, T. J. Whelan6, and I. Olivotto7; 1Erasmus MC: University Medical Centre, Rotterdam, Netherlands, 2British Columbia Cancer Agency, Victoria, BC, Canada, 3Sunnybrook Health Sciences Centre, Toronto, ON, Canada, 4Zuidwest Radiotherapeutisch Instituut, Roosendaal, Netherlands, 5Vancouver Island Cancer Centre, Victoria, BC, Canada, 6Medical University of South Carolina, Charleston, SC, 7University of Calgary, Calgary, AB, Canada

Purpose/Objective(s): We previously demonstrated in a multicenter randomized controlled trial that breast tangential breast Intensity Modulated Radiation Therapy (IMRT) resulted in improved dose homogeneity and reduced acute toxicity compared to standard wedge radiation therapy (RT). We report the 10-year outcome analysis of patients enrolled in this trial.

Materials/Methods: Participants were evaluated to compare chronic breast pain between treatment arms assessed by trained observers blinded to treatment allocation. Secondary endpoints included cosmesis, quality of life using the EORTC QLQ30 and BR23 questionnaires, and survival measures. Assuming a 2-fold reduction of chronic pain from 43% to 22%, a sample of 148 patients was sufficient to detect a 21% significant difference between the 2 arms with α = 0.05 and a power of 80%.

Results: Median follow-up time was 9.8 years. Of 358 patients accrued into the initial study, 241 were available for assessment, 125 in the breast IMRT arm and 116 in the standard RT arm. There was no significant difference in chronic pain between treatment arms (29.6% with breast IMRT and 36.2% with standard RT, OR=0.74, range 0.432 – 1.271). The study would have been able to detect, with an 80% power, a 12% reduction for patients reporting grade 1 or higher pain. There were also no statistically significant differences for the secondary endpoints. Univariate and multivariate analyses identified young age (p=0.013) and pain during RT (p<0.001) to be associated with chronic pain. Acute moist desquamation was associated with late subcutaneous fibrosis (p=0.003) and telangiectasia (p=0.039). Pain during RT was associated with a poorer self-assessed cosmetic outcome (p<0.001) and a reduced quality of life (p<0.001). No differences were observed between treatment arms at 9 years in overall survival (90.4% vs 92.6%, p=0.47), local recurrence-free survival (95.4% vs 94.1%, p=0.55), or disease free-survival (82% vs 82.4%, p=0.90).

Conclusion: Breast IMRT reduces the development of acute skin toxicity, including moist desquamation and pain, but does not reduces late side effect for all patients. Breast pain and moist desquamation during RT are associated with an increased risk of developing chronic breast pain, poorer cosmetic outcome and reduced quality of life. Radiation therapy techniques that reduce acute toxicity, including breast IMRT, should be considered for patients at higher risk of acute skin reactions.

Reinforcement Learning Strategies for Decision Making in Knowledge-Based Adaptive Radiation Therapy: Application in Liver Cancer

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Purpose/Objective(s): Treatment choices in adaptive radiotherapy are often based on subjective experiences and heuristic rules that lack an effective strategy to dynamically optimize long-term clinical outcomes. Therefore, we are investigating reinforcement learning (RL) approaches that can provide a robust framework to interactively adapt treatment regimens to individual patient’s characteristics over time. In this context, RL approaches would balance trade-offs between exploring varying dose fractionation options and exploiting knowledge synthesized from patient’s time-dependent covariates (states) history to maximize accumulative reward (TCP) and minimize long-term regret (NTCP).

Materials/Methods: We studied an institutional cohort of 145 hepatocellular carcinoma SBRT patients with 45 on non-adaptive and 100 on adaptive protocols. Adaptation was based on liver function, assessed with Indocyanine green retention, by delivering a split-course of 3 + 2 fractions with a month break in between. Median prescribed tumor dose was 40 Gy delivered in 3 or 5 fractions with doses converted into EQD2 using the LQL model. Plasma biomarkers were analyzed before and during treatment. NTCP was assessed as a 1-grade change in ALBI score. The RL radiotherapy environment was modeled as a 2-stage Markov decision process of baseline and one month into treatment states. States are represented by the patient’s clinical, dosimetric and biological covariates history. Two typical decision-making scenarios at stage-2 were considered for testing RL feasibility retrospectively: 1) choosing to adapt with a split-course or not, and 2) determining to deliver an additional 2 fractions after the initial course. The reward/regret was defined by the complication-free tumor control (P+=TCP × (1-NTCP)). Q-learning with a simple regression model of state-action mapping was used for optimizing strategy selection by solving the corresponding Bellman equation. The performance was evaluated using an adjusted R-squared (aR²) to correct for over-fitting pitfalls.

Results: Using states of clinical and dosimetric (tumor size, tumor dose, mean liver dose) covariates, Q-learning at one month (stage-2) selected split-course adaptation as an optimal action with a model fit of aR²=0.65 (p <0.001). Percentage change in TGF-β1 concentration was the only biological variable to correlate with outcomes (ALBI score, p=0.03); its addition improved the fit to aR²=0.74. In case of 3 versus 5 fractions determination, the delivery of 2 extra fractions was found to be a better action with an aR²=0.66 (p <0.001). The inclusion of TGF-β1 improved the fit to aR²=0.74. Our results demonstrate that RL approaches provide a promising framework for sequential clinical decision making in adaptive radiotherapy. Moreover, biological metrics seem to improve the goodness of fit. We are exploring advanced Q-learning with nonlinear models that may accelerate clinical adoption of RL for optimal decision-selection in adaptive radiotherapy.

Conclusion: Our results demonstrate that RL approaches provide a promising framework for sequential clinical decision making in adaptive radiotherapy. Moreover, biological metrics seem to improve the goodness of fit. We are exploring advanced Q-learning with nonlinear models that may accelerate clinical adoption of RL for optimal decision-selection in adaptive radiotherapy.

Selection of FDG Positron Emission Tomography–Based Bioparametric Matrixes for Tumor Dose Response Mapping and Adaptive Dose Painting by Number

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Purpose/Objective(s): Tumor dose response mapping between voxel values in a bio-parametric matrix and biologically equivalent dose can be used for adaptive dose painting by number (DPbN). However, it is unclear what should be the most efficient bio-parametric matrix applied for the construction of the dose response mapping and adaptive DPbN. In this study, 4 parametric matrices constructed using multiple FDG PET images obtained pre-treatment and at weekly intervals during the treatment course were evaluated to determine their predictive ability for tumor dose response.

Materials/Methods: Dual-point FDG PET/CT images of 18 HN cancer patients were used in the study. Five of the 18 patients had either local (1/5), distant (2/5), or local/distant (2/5) failure (4/5 biopsy proven) with the medium follow-up time 11.93 (0.53~38.87) months. Four spatial parametric matrices including tumor metabolism (SUV); tumor metabolic ratio (dSUV); tumor metabolic retention index (RI); and retention index ratio (dRI) were constructed following voxel by voxel deformable image registration. Each voxel value in the parametric matrices was a function of the treatment dose from 0 to 70 Gy. The voxel value distributions at each dose level were used to correlate to the patient treatment outcome. ROC analysis was used to evaluate the predictive capability of the parametric matrices at different dose levels. Correlation between dSUV and SUV or RI on those of failure voxels was also determined.

Results: Tumor metabolic ratio, dSUV(voxel, dose) = SUV(voxel, dose)/SUV(voxel, 0), shows the earliest and highest prediction of tumor dose response and treatment outcome. Volume parameters of dSUV(voxel, dose>10Gy) matrix obtained after the first week of the treatment had the excellent prediction accuracy with AUC = 95~100% (Table). The other 3 parametric matrices, (SUV, RI, and dRI) showed only poor or fair predictive capability. Depending on the baseline SUV(voxel, 0) value, the distribution of tumor voxel dSUV in the controlled group showed a clear time-trend and convergence after 40Gy indicating the feasibility to create a voxel based dose response mapping. dSUV had correlation coefficients > 0.5 with either high SUV or high RI on the failure voxels.

Conclusion: Tumor metabolic ratio observed during early treatment shows the most predictive value for tumor dose response. Tumor voxel metabolic ratio was commonly correlated to either ‘high RI’ (indicative of low perfusion/diffusion and potentially hypoxia) or ‘low RI but high SUV’ (indicative of active metabolism and potentially rapid proliferation), indicating that the dSUV might be a surrogate biomarker of tumor cell survival fraction that is directly related to both hypoxia and proliferation. This bio-image marker is ideal for adaptive DPbN.

<table>
<thead>
<tr>
<th>AUC* (%)</th>
<th>d=0Gy</th>
<th>&gt;10Gy</th>
<th>&gt;20Gy</th>
<th>&gt;30Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV(, d)</td>
<td>0.58</td>
<td>0.73</td>
<td>0.68</td>
<td>0.83</td>
</tr>
<tr>
<td>dSUV(, d)</td>
<td>NA</td>
<td>1.0</td>
<td>0.95</td>
<td>1.0</td>
</tr>
<tr>
<td>RI(, d)</td>
<td>0.48</td>
<td>0.53</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>dRI(, d)</td>
<td>NA</td>
<td>0.82</td>
<td>0.75</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Prediction accuracy was measured using the area under the ROC curve (AUC)

Apparent Diffusion Coefficients (ADCs) in Diffusion-Weighted 3.0 Tesla MR Imaging Is Useful in Predicting Therapeutic Response to Concurrent Chemoradiation Therapy in Patients With Uterine Cervical Cancer: A Prospective Study

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Purpose/Objective(s): To prospectively investigate the changes of apparent diffusion coefficients (ADCs) in diffusion weighted-MRI (DWI) of uterine cervical cancer patients receiving concurrent chemoradiotherapy (CCRT). Also, to assess the relationship between tumor ADCs in DWI prior to treatment and the tumor response to CCRT.

Materials/Methods: The institutional review board approved this study and written informed consent was obtained from all patients. Between Jun 2010 and Jan 2015, 53 consecutive women with biopsy-proven cervical squamous cell carcinomas were recruited. All patients were treated with combination of external beam radiation (EBRT) to whole pelvis with dosage of 50.4 Gy by 28 fractions for 5.5 weeks and high-dose-rate Iridium-192 intracavitary brachytherapy of 4 sessions every once a week, total dosage of 24 Gy at point A. All received concurrent chemotherapy of six cycles of weekly cisplatin (60 mg/sqm). All patients underwent MRI by 3.0 Tesla MR scanner using phased-array body coil, before initiating CCRT (pre-Tx), at EBRT dosage of 30.6 Gy (mid-Tx), and 1 month after completion of the therapy (post-Tx), respectively. At pre-, mid-, and post-Tx, each value was obtained as follows; 1) tumor size on T2 weighted image, 2) ADC values in the tumors and in the normal gluteus maximus muscles on the ADC maps, 3) ADC ratio derived from ADC in tumor divided by ADC in muscle, respectively.

Results: The patient characteristics and the results of CCRT are shown in Table 1. Median follow up time was 36 months and median local recurrence free survival time was 28 months. Patients were divided into two groups: 1) local control group; achieved complete response at post-Tx with no evidence of recurrence during follow up, and progression disease during follow up period with evidence of recurrence in primary tumor proven by biopsy (relapse group). By linear regression analysis, tumor ADCs at Pre-Tx had strong correlation with the initial tumor size (R² = 0.036, P = 0.036), while ADCs at mid- Tx or post-Tx had no correlation to that. Tumor size (mm) at each therapeutic time (pre-, mid-, and post-Tx) was 44.9 +/-19.0, 23.8 +/-11.8, 5.3 +/-8.7 (mean +/- S.D.), respectively. And ADC value (x10 ⁴ mm²/s) at each therapeutic time was, tumor: 0.85 +/-0.25, 0.93 +/-0.17, 1.47 +/-0.28, gluteus muscle : 1.47 +/-0.10, 1.49 +/-0.09, 1.48 +/-0.11, respectively. ADC ratio at Pre-Tx showed significant difference between local control group (0.64 +/-0.58) and relapse group (0.43 +/-0.25) (P=0.03), while that at mid- and post-Tx showed no significant difference by paired t-test.

Conclusion: ADCs obtained by pre-Tx DWI may have potentials in predicting the therapeutic response to CCRT in patients with cervical cancer.


Detection of Local Cancer Recurrence After Stereotactic Ablative Radiation Therapy (SABR) for Lung Cancer: Physician Performance Versus Radiomic Assessment

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Purpose/Objective(s): Stereotactic ablative radiotherapy (SABR) is a guideline-specified treatment option for early-stage lung cancer. However, significant post-treatment fibrosis can occur and confound the detection of local recurrence. The goal of this study was to assess physician ability to detect timely local recurrence on computed tomography (CT) imaging, and compare physician performance
with that of a radiomics tool. We hypothesize that radiomic image features can predict recurrence using images acquired <6 months post-SABR with lower error than physician assessors.

**Materials/Methods:** CT scans of 45 patients (15 with proven local recurrence matched to 30 with no local recurrence) were used to measure physician and radiomic performance in assessing response. Scans were individually scored by three thoracic radiation oncologists and three thoracic radiologists, all of whom were blinded to clinical outcomes. Radiomic features (first-order, second-order grey-level co-occurrence matrix, and size- and shape-based) were extracted from the same images. Performance of the physician assessors and the radiomics signatures were compared.

**Results:** A total of 182 follow-up CT scans were analyzed with a median imaging follow-up of 20 months. When taking into account all CT scans during the entire follow-up period, median sensitivity for physician assessment of local recurrence was 83% (range 67–100%) and specificity was 75% (range 67–87%), with only moderate inter-observer agreement (kappa=0.54). The median time to detection of recurrence across all observers was 15.5 months. When predicting recurrence using images acquired <6 months post-SABR, physicians assessed the majority of images as benign injury/no recurrence, with a mean error of 35%, false positive rate (FPR) of 1%, and false negative rate (FNR) of 99%. At the same time point, a radiomic signature consisting of five post-SABR image appearance features in the consolidative and surrounding peri-consolidative regions demonstrated excellent discrimination, with an area under the receiver operating characteristic curve of 0.85, leave-one-out cross-validation classification error of 24%, FPR of 24%, and FNR of 23%.

**Conclusion:** These results suggest that radiomics can detect early changes associated with local recurrence that are not typically considered by physicians. Patients with recurrence tend to have increased presence of ground-glass opacity surrounding consolidative changes compared to patients with benign injury at this early follow-up time point. These appearances detected by radiomics may be early indicators of the promotion and progression to local recurrence; our ongoing studies include using correlative histology to determine their composition. This has the potential to lead to a clinically useful computer aided decision support tool based on routinely acquired CT imaging, which could lead to earlier life-saving salvage opportunities for patients with local recurrence following SABR.


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**Lung**

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**Efficacy and Toxicity Analysis of NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Non-Small Cell Lung Cancer (NSCLC)**

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Purpose/Objective(s): The phase I results of NRG/RTOG 0813 trial were reported at ASTRO 2015. We hereby report the phase II results - efficacy and toxicity beyond year 1.

Materials/Methods: Medically inoperable patients (pts) with biopsy proven, PET staged T1-2 (<5cm)N0M0 centrally located NSCLC (within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura) were successively accrued onto a dose-escalating 5 fraction SBRT schedule ranging from 10-12 Gy/fraction (fr) delivered over 1.5-2 weeks. Phase I data analysis revealed that maximum tolerated dose was the highest dose level allowed on the study, 12 Gy/fr x 5 fractions. Thirty-three eligible pts were treated with 12 Gy/fx, and another 38 pts were treated on the preceding dose level of 11.5 Gy/fr ; this is the report of efficacy based on patients in those two cohorts.

Results: Patients were elderly, majority had performance status 0-1. T1 cancers were treated in 58% of pts in the 11.5 Gy/fr cohort and 70% in 12 Gy/fr cohort. Median PTV volumes were 43cc (range 14.85 - 155.05cc) and 32 cc (7.48 - 117.25) respectively. Organs closest to PTV/most at risk were main bronchus (45% and 39% respectively) and large vessels (53% and 21%). Median follow-up was 33 months (mo) for the 11.5 Gy/fr cohort and 29.8 mo for the 12Gy/fr cohort (49 and 31.8 mo for the surviving pts respectively). Late toxicities grade 3 or greater (G3+) attributed to SBRT were 2 G5 toxicities in the 11.5 Gy/fr cohort, and in the 12Gy/fr cohort 3 G3 (2 respiratory, 1 cardiac), 1 G4 (esophageal perforation) and 1 G5 (pulmonary hemorrhage) toxicities. The table details the incidence of attributed G3+ toxicity, observed failure patterns and outcomes.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>11.5 Gy x 5fr</th>
<th>12 Gy x 5fr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n) of eligible patients</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Pts w Toxicity G3+ (at any time)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Pts w Early Toxicity G3+ (within 1st yr)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pts with Late Toxicity G3+ (beyond 1st yr)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pts with primary tumor failure</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Pts with involved lobe failure</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pts with regional (lymph node) failure</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pts with distant failure</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>2-year local control</td>
<td>89.4% (81.6-97.4%)*</td>
<td>87.7% (78.3-97%)*</td>
</tr>
<tr>
<td>2 yr progression free survival</td>
<td>52.2% (35.3-66.6%)*</td>
<td>54.5% (36.3-69.6%)*</td>
</tr>
<tr>
<td>2-year overall survival (OS)</td>
<td>70.2% (52.6-82.3%)*</td>
<td>72.7% (54.1-84.8%)*</td>
</tr>
</tbody>
</table>

*90% confidence interval

Conclusion: Observed local control at 2 yrs in 71 pts treated with the two highest doses levels (11.5-12Gy/fr x 5 fr) in this multicenter trial was high, and G3+ toxicity rates were acceptable. Two-year OS rates of 70% in this medically inoperable group of elderly pts with comorbidities were comparable to pts with peripheral early stage tumors. This project was supported by grants U10CA21661 (RTOG-Ops-Stat ), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U10CA37422 (CCOP), CA81647 (ATC) from the National Cancer Institute (NCI).

A Phase 2 Randomized Study of 2 Stereotactic Body Radiation Therapy (SBRT) Regimens for Medically Inoperable Patients With Node-Negative, Peripheral Non-Small Cell Lung Cancer

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Purpose/Objective(s): This phase II, multi-institutional randomized study was conducted to compare incidence of RTOG grade 3 or higher adverse events (AEs) associated with 2 different, established SBRT regimens for non-small cell lung cancer (NSCLC).

Materials/Methods: Patients with documented baseline medical conditions precluding lobectomy and biopsy-proven peripheral (greater than 2 cm from the central bronchial tree) T1/T2, N0 (clinically node negative by PET), M0 tumors were eligible. Patients were randomized to receive either 30 Gy in one fraction (arm 1) or 60 Gy in 3 fractions (arm 2) over at least 8 days. Heterogeneity corrections were not used. Randomization was stratified by treatment center and Karnofsky performance status (100, 90, 80 and below.) The study was designed to detect whether AE rate > 17% at a 5% significance level (1-sided) and 81% power. Secondary endpoints included: local control, greater than 1-year toxicity, overall survival (OS) and progression-free survival (PFS).

Results: The study opened in September 2008, was suspended between April 2010 to June 2010 as well as October 2010 to April 2011 while RTOG 0915 was open, and closed on April 15, 2015 after accruing a total of 98 patients. All patients received planned treatment. Median follow-up was 24 months. Following SBRT, 10 patients were lost to follow-up: 1 in arm 1 and 9 in arm 2. Baseline patient and tumor characteristics were balanced between both arms. On arm 1 13 (27%) patients and 16 (33%) patients on arm 2 experienced RTOG grade 3 AEs: Pulmonary-related grade 3 AEs were experienced by 8 (16%) patients on arm 1, and 6 (12%) patients on arm 2. There were no grade 4 AEs. One grade 5 event was seen per treatment arm: arm 1 [death of unknown cause] and arm 2 [disease progression]. There were no differences in OS or PFS survival, log rank p= 0.44 and 0.98 respectively. Overall survival at 2 years was 70% (95% CI, 53-82%) for arm 1 and 64% (95% CI, 44-78%) for arm 2. Progression-free survival at 1 year was 63% (95% CI, 45-77%) for arm 1 and 50% (95% CI, 32-65%) for arm 2.

Conclusion: This randomized phase II study demonstrated that 30 Gy in one fraction was equivalent to 60 Gy in 3 fractions in terms of OS, PFS, and toxicity.


Impact of Incidental Cardiac Radiation on Cardiopulmonary Toxicity and Survival for Locally Advanced Non-Small Cell Lung Cancer: Reanalysis of NRG Oncology/RTOG 0617 With Centrally Contoured Cardiac Structures

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Purpose/Objective(s): RTOG 0617 showed high dose RT had a greater risk of death than standard dose. Higher heart dose was associated with worse overall survival (OS) on multivariate analysis. However, the variability in submitted heart contours and no contouring of substructures limited the ability to accurately quantify the role of heart dose and ultimately set meaningful dose constraints.

Materials/Methods: Five thoracic radiation oncologists collectively contoured the cardiac structures for each available case, guided by a common atlas. Anatomic structures defined were pericardium (P), ventricles (V), atria (A) and coronary space (CS). Volumes of each structure and overlap with PTV, distribution of V5, V10, V20, V30, V40, V45, V60, maximum dose (Dmax) and mean dose (MD) were analyzed. Volumes and doses were compared between centrally contoured P and submitted heart contours. Impact of volume and dose to each structure and combined structures on OS, local failure (LF), distant failure (DF), progression free survival (PFS) and treatment related pulmonary, esophageal, cardiovascular and esophageal toxicity were evaluated using Cox PH model and logistic regression model with multiplicity adjustments.

Results: Among 495 analyzable cases, 57 (11.5%) were not available for re-contouring and excluded. Re-contoured P volumes, PTV overlap with P, and dose volumes were larger than submitted heart contours. On univariate analysis all analyzed dose volumes and MD to P were associated with increased risk of death, p<0.001. Similar relationships were found with V5-60 and MD to A and V and Dmax to the V, p<0.01. On multivariate analysis, larger PTV volume and Gr3+ esophagitis remained associated with worse OS (p<0.05); in addition, MD to P (HR=1.019, p=.007) and V45 for A (HR=1.007, p=0.022), V (HR 1.015, p=0.0043), and CS (HR=1.005, p=0.0022) each had a detrimental impact on OS. On Univariate analysis MD to P and V5-45 were associated with all Gr3+ pulmonary toxicity (p<0.05) and MD and V30-60 with Gr3+ pneumonitis (<0.05). On multivariate analysis MD to P (OR 1.044, p=0.0372) and stage IIIIB disease (OR 2.51, P=0.0342) were associated with Grd3+ pneumonitis.

Conclusion: Excessive RT doses to cardiac structures including pericardium MD, V45 to Atria, ventricles, and CS have a detrimental effect on overall survival. Pericardium MD was associated with severe treatment related pneumonitis. Acknowledgments: This project was supported by grants U10CA21661 (RTOG-Ops-Stat), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U10CA37422 (CCOP), CA81647 (ATC), U24CA180803 (IROC), UG1CA189867 (NCORP)from the National Cancer Institute (NCI) and Bristol Myers Squibb and Eli Lilly.


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Safety of Dose Escalation by Simultaneous Integrated Boosting Radiation Dose in Unresectable Stage III Non-Small Cell Lung Cancer
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Purpose/Objective(s): The aim of this study is to determine the maximum-tolerable dose of hypofractionated radiotherapy (RT) with concurrent chemotherapy (CT), and evaluate the safety of dose escalation by simultaneous integrated boosting (SIB) radiation dose in unresectable stage III non-small-cell lung cancer (NSCLC).

Materials/Methods: Patients with unresectable stage III NSCLC were treated with escalating radiation dose of 4 levels (table1), with SIB to GTV. The GTV was defined as the primary tumor and all involved nodes. The clinical target volume (CTV) was defined as the GTV plus a 0.6 cm margin. The two planning target volumes (PTVs) were defined: the PTV-G (the GTV plus a 0.8cm margin) and the PTV-C (the CTV plus a 0.8cm margin), while meeting the normal tissue constraints:≤ 45 Gy to the spinal cord; lung V20 ≤ 25%; mean lung dose ≤ 15
Gy; and (4) mean heart doses 30 Gy. Patients concurrently received 6 cycles of cisplatin (20 mg/m$^2$ d1) and paclitaxel (20 mg/m$^2$d1). The CT cycles were repeated every week. Dose-limiting toxicity (DLT) was defined as any Grade 3 or higher acute toxicities causing continuous interruption of radiation for over 1 week. A minimum of 5 patients were treated at each dose level. Five patients must then have been followed for a minimum of 3 months from the initiation of radiotherapy before dose escalation was permitted.

**Results:** From April 2012 to October 2013 dose has been escalated up to LEVEL 4 (PTV-G 60.5Gy/20Fx, PTV-C 50Gy/20Fx). All of the 25 patients finished the prescribed radiation dose. The most common grade 1 and 2 radiation-related toxicity was radiation esophagitis and pneumonitis, occurring in 35 % and 55% respectively of all patients. Two patients at LEVEL 1-2 developed Grade 3 acute esophagitis. All patients completed the planned RT and CT without interruption at LEVEL1-3. One patient at LEVEL 4 failed to complete 6 CT cycles because of grade 3 nausea, and died of upper gastrointestinal hemorrhage within 6 month after completion of RT, which was not definitely correlated with treatment yet. Upper gastrointestinal hemorrhage was Grade 5 acute toxicity but difficult to be distinguished between radiation toxicity and upper gastrointestinal underlying disease, so 5 additional patients were enrolled at this level to ensure safety of this trial. Unfortunately, one of the second 5 patients at LEVEL 4 experienced grade 5 radiation pneumonitis and died within 2month after RT. Interruption of RT occurred on one patient because of fever (3 days) in the second 5 patients.

**Conclusion:** Dose escalation in unresectable stage III NSCLC has been safely achieved up to LEVEL 3 (PTV-G 60.Gy/22Fx, 2.75Gy/Fx; PTV-C 49.5Gy/22Fx, 2.25Gy/Fx). Acute toxicities were well tolerable, further investigations should focus on late toxicities and long-term outcomes.

**Table 1**

<table>
<thead>
<tr>
<th>Dose LEVEL</th>
<th>PTV-G</th>
<th>PTV-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60Gy/30Fx (2Gy/Fx)</td>
<td>54Gy/30Fx (1.8Gy/Fx)</td>
</tr>
<tr>
<td>2</td>
<td>60Gy/24Fx (2.5Gy/Fx)</td>
<td>50.4Gy/24Fx (2.1Gy/Fx)</td>
</tr>
<tr>
<td>3</td>
<td>60.5Gy/22Fx (2.75Gy/Fx)</td>
<td>49.5Gy/22Fx (2.25Gy/Fx)</td>
</tr>
<tr>
<td>4</td>
<td>60Gy/20Fx (3Gy/Fx)</td>
<td>50Gy/20Fx (2.5Gy/Fx)</td>
</tr>
</tbody>
</table>

**Author Disclosure:** Q. Zhang: None. X. Fu: None.

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**Radiation Dose to the Thoracic Vertebral Bodies Is Associated With Acute Hematologic Toxicity in Patients Receiving Concurrent Chemoradiation for Lung Cancer**

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**Purpose/Objective(s):** Concurrent chemotherapy and radiation (CRT) for the treatment of non-small cell (NSCLC) and small cell (SCLC) lung cancers is often associated with severe acute hematologic toxicity (HT). Few studies have evaluated the relationship between radiation (RT) dose to the thoracic vertebral bodies (TVB) and the development of HT. We hypothesized that increasing RT dose to the TVB contributes to the development of HT in lung cancer patients receiving CRT.
Materials/Methods: We identified cases of non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) treated with curative intent CRT at our institution from 4/2007 to 2/2015. The TVBs from T1-T10 were retrospectively contoured for all patients. The mean TVB dose and the volume of TVB receiving at least 5-60 Gy (V5-V60) were calculated from the dose volume histogram. HT was graded according to the Common Terminology Criteria for Adverse Events, v4 based on the leukocyte, neutrophil, and platelet nadirs during treatment. The endpoint analyzed was grade≥3 HT (HT3+). Logistic regression was used to test associations between HT3+ and dosimetric/clinical parameters. Receiver operating characteristics (ROC) analysis was used to determine the optimal cutpoint for dosimetric parameters.

Results: We included 138 cases: 73 men (53.0%); median age 63 years (range, 42-83); predominantly NSCLC (N=114, 82.6%). Most patients received either platinum/etoposide (N=83, 60.1%) or carboplatin/taxol (N=48, 34.8%). Median RT dose was 61.2 Gy (range, 45-70 Gy). The rate of HT3+ was 41.3% (n=57). Increasing mean TVB dose (per Gy) was associated with a higher odds of developing HT3+ (OR=1.06, 95% CI 1.01-1.10, p=0.012). Increasing TVB V5-V40 were all significantly correlated with increased odds of developing HT3+. ROC analysis found that the optimal cutpoint for mean TVB dose was 23 Gy. The OR for developing HT3+ was 2.80-fold higher in patients with mean TVB dose>23 Gy compared to ≤23 Gy (95% CI 2.80-5.63, p=0.001). On multivariate analysis, increasing mean TVB dose, increasing age and decreasing BMI were all statistically significantly associated with increased odds of developing HT3+. When excluding patients with SCLC, mean TVB dose and V5-V20 remained significantly associated with HT3+.

Conclusion: We found that increasing TVB dose was associated with clinically significant HT in patients with lung cancer treated with CRT. This suggests that efforts to spare dose to the TVB may reduce rates of HT and potentially improve patient outcomes. Further prospective validation of these results is needed.


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Identifying Patients With Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Most Likely to Benefit From Intensive Radiation Therapy

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Purpose/Objective(s): In responding patients with ES-SCLC who have residual intrathoracic disease after induction chemotherapy, the addition of thoracic radiotherapy reduces the risk of intrathoracic recurrence and improves overall survival. In order to identify patients most likely to benefit from inclusion in studies evaluating high-dose thoracic or extra-thoracic radiotherapy, we studied the prognostic importance of metastatic load (numbers, sites) in patients included in the CREST trial.

Materials/Methods: Additional patient data was collected from the top 9 recruiting centers in the randomized CREST trial comparing thoracic radiotherapy (TRT) with no TRT in ES-SCLC patients after any response to chemotherapy. All patients received prophylactic cranial irradiation. Individual records of 260 patients (53% of 495 study patients) were analyzed for details on sites and numbers of metastases.

Results: Median age was 63 years, 52% male, 24% WHO Performance Status (PS)=0, 61% WHO PS=1 and 15% WHO PS=2. At randomization, 4% of patients had a CR after chemotherapy, 69% a PR and 27% a ‘good response’. Post-chemotherapy residual intrathoracic disease was present in 89% of patients. The characteristics and clinical outcome of the 260 patients analyzed were not significantly different from the 235 non-selected patients included in the CREST trial, with the exception of fewer WHO 0 scores (24% vs
45%) and a higher portion of WHO=2 patients (15% vs 5%; overall: p<0.0001). Patients in the analysis had a similar PFS (3.5 months), but a trend for inferior OS compared to the non-selected patients (median 7.4 vs 8.1 months; p=0.06). No distant metastases were recorded in 5%, 39% had metastases confined to one organ, 34% to two, and 22% to three or more organ sites. Metastases were present in liver (47%), bone (40%), lung (28%), distant lymph nodes (19%), supraclavicular nodes (18%), adrenal glands (17%) and other sites (12%). The OS (p=0.02) and PFS (p=0.04) were significantly better in patients with up to 2 metastases, and OS was significantly worse if liver (p=0.03) and/or bone metastases (p=0.04) were present. In 121 patients with liver metastases, TRT did not significantly influence OS or PFS. However, in 119 patients without liver metastases, TRT was associated with significantly longer PFS (p=0.001) and a trend for improved OS (p=0.08).

**Conclusion:** This analysis of patients recruited from the top 9 accruing CREST centers suggests that future studies evaluating more intensive thoracic and extrathoracic radiotherapy in ES-SCLC should focus on patients with less than 3 metastases and without liver or bone metastases.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=</th>
<th>Overall survival</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 metastases</td>
<td>72</td>
<td>HR =1.43 (95%CI = 1.07-1.92) p=0.02</td>
<td>HR=1.35 (95%CI = 1.02-1.78) p=0.04</td>
</tr>
<tr>
<td>&gt; 2 metastases</td>
<td>188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No liver metastases</td>
<td>139</td>
<td>HR=1.34 (95%CI = 1.03-1.73) p=0.03</td>
<td>HR=1.27 (95%CI = 0.99-1.53) p=0.06</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>121</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bone metastases</td>
<td>157</td>
<td>HR=1.33 (95%CI = 1.02-1.73) p=0.04</td>
<td>HR=1.39 (95%CI = 1.08-1.79) p=0.01</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>103</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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The Differential Impact of Postoperative Radiation Therapy for Completely Resected Stage IIIA(N2) Non-Small Cell Lung Cancer: Based on the Risk Prediction Model for Locoregional Recurrence

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**Purpose/Objective(s):** The value of postoperative radiotherapy (PORT) for completely resected non-small cell lung cancer (NSCLC) remains controversial because the effect on survival has been inconclusive. Growing evidence suggests that PORT using the modern 3D-CRT technique has a favorable effect on survival of patients with pN2 disease. After complete resection and adjuvant chemotherapy (CT), 20%-40% of cases have a risk of locoregional recurrence (LRR). Identification of factors that predict for LRR after surgery may help in precise PORT strategies. In this study, we aimed to establish a clinical risk prediction model for LRR and evaluate the efficacy of PORT based on the risk stratification.

**Materials/Methods:** Data were analyzed for all consecutive patients between 2005 and 2012 with pathologic T1-3N2M0 NSCLC treated with complete resection with negative surgical margins and no neoadjuvant RT and/or CT. The Prognostic Index (PI) was built first in the
Role of Surveillance Imaging Versus Symptoms and Signs in Detection of Recurrence of Non-Small Cell Lung Cancer After Curative Intent Therapy

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Purpose/Objective(s): Lung cancer is the most common cause of cancer-related mortality in the United States. While studies suggest that symptoms and physical exam signs detect recurrence as well as imaging for Non-Hodgkin’s Lymphoma, few studies have examined this issue in Non-Small Cell Lung Cancer (NSCLC). We compared surveillance imaging with symptoms and signs as modalities of recurrence detection in NSCLC. The goal of this study was to determine what proportion of recurrences was found by surveillance imaging versus by symptoms/signs and to compare survival outcomes between imaging- and symptom/sign-detected recurrences.

Materials/Methods: We retrospectively reviewed records of patients who underwent curative intent therapy and surveillance imaging at our institution for Stage I-III NSCLC diagnosed between 2004 and 2013. Exclusion criteria included NSCLC metastasis during treatment, synchronous primaries, second primary after treatment, other metastatic malignancies, and discontinuation of follow-up after treatment. Locoregional recurrence (LR) comprised failure within ipsilateral lung and/or new hilar or mediastinal lymphadenopathies. Distant recurrence (DR) comprised metastases to contralateral lung and/or extrathoracic sites with or without LR. Chi square test and Cox regression were used to compare the association of imaging or symptoms/signs with type of recurrence and survival outcomes.

Results: Out of 1197 patients treated for NSCLC between 2004 and 2013 at our institution, 508 met the inclusion criteria for analysis. Of that cohort, we identified 203 patients who developed recurrence a median of 11.5 months after completion of treatment, 42.4% with initial stage I disease; 13.8% with Stage II; and 43.8% with stage III. LR was found in 88 (43.3%) patients and DR in 115 (56.7%). Patients with LR and DR had a median survival (95% CI) from the time of recurrence of 2.01 (1.48-2.54) and 0.88 years (0.71-1.06), respectively (log-rank: p=0.0003). Surveillance imaging detected 71.9% of all recurrences, symptoms detected 26.6%, and physical exam signs detected 1.5%. Compared with symptoms/signs, surveillance imaging detected 96.6% of LR and 53.0% of DR (Chi square test: p<0.0001). In univariate Cox regression, symptom/sign-detected recurrences were associated with decreased overall survival (OS)
compared with imaging-detected recurrences (Hazard Ratio [HR] 1.79, 95% CI 1.25–2.58, \(p=0.002\)). In patients with LR, initial stage was not associated with differences in OS on univariate and multivariate Cox regression.

**Conclusion:** The ability of imaging to detect most LR, which are candidates for potentially curative salvage therapy, suggests a potential benefit of post-treatment surveillance imaging in patients with Stage I-II NSCLC.

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**Palliative Care**

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**Palliative Care Education in Radiation Oncology Training Programs Across the United States: A Program Directors’ Survey**

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**Purpose/Objective(s):** To assess the state of palliative care training in radiation oncology residency programs across the United States.

**Materials/Methods:** An electronic survey was sent to program directors of all 90 ACGME accredited radiation oncology residency programs in the US from September to November 2015. The survey consisted of questions on perceived relevance of palliative care training during radiation oncology residency, availability and nature of formal didactic sessions on domains of palliative care, preferred/ideal teaching formats for palliative care education, and perceived barriers for integrating palliative care into the residency curriculum.

**Results:** Sixty-three percent (57/90) of residency program directors completed the survey. The vast majority (93%) of program directors agree or strongly agree that palliative care is an important competency for radiation oncologists. Most (90%) programs have inpatient and outpatient palliative medicine services at the institutional level. However, only 57% of programs offer the residents an opportunity to spend elective time on a palliative care service, of which only 30% reported residents electing to rotate on a palliative care service in the past two years. Notably, 67% of residency programs have formal educational activities in principles and practice of palliative care. These palliative care curricula included faculty-led lectures (73%), resident-led lectures (42%), and seminars (22%). Programs offered one or more hours of formal didactic teaching on management of pain (66%), neuropathic pain (64%), nausea and vomiting (64%), fatigue (35%), anorexia (46%), and anxiety/depression (48%). On the other hand, a majority of programs had no formal didactic teaching in communication skills with regard to selection of health care proxy with patient/family (67%), and managing conflict within or among families and health care teams (70%). A majority of residency directors (77%) see a need to incorporate additional education on palliative care during residency.

**Conclusion:** A majority of radiation oncology residency program directors believe that palliative care is an important competency for their trainees and see a need for integration of additional education on its principles and practice. Our findings reveal that many programs have structured curriculum on palliative care education, but that clinical services dedicated specifically to palliative RT are relatively uncommon.

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The TEACHH Model: Clinical Utility of Identifying Patients Living Fewer Than 2 Months
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Purpose/Objective(s): Predicting prognosis is one of the most difficult tasks faced by oncologists, but also one of the most important. Specifically, knowing that a patient has a very limited life expectancy (i.e. less than 2 months) can significantly alter a physician’s treatment recommendations. The TEACHH prognostic model was developed to identify patients with metastatic cancer who are at the extremes of the prognostic spectrum. The purpose of this study was to assess the utility of the TEACHH model in identifying patients likely to live < 2 months.

Materials/Methods: The TEACHH model divides patients with metastatic cancer into three survival groups based on their number of risk factors: Type of Cancer (non-breast, non-prostate), ECOG PS 2-4, Age > 60, receipt of prior palliative chemotherapy, any prior hospitalizations in the last 3 months, and the presence of hepatic metastases. Survival groups are as follows: 1) Group A, 0-1 risk factors (median survival 19.9 months) 2) Group B, 2-4 risk factors (median survival 5 months), 3) Group C, 5-6 risk factors, (median survival 1.7 months). The goal of the model is to identify patients living > 1 year (Group A) and patients living < 2 months (Group C), as these are important decision-making endpoints in radiation oncology. We retrospectively analyzed the records of 72 consecutive patients with metastatic cancer seen in consultation from 8/1/2014 – 12/1/2015 for palliative radiation therapy and used the TEACHH model to divide these patients into the three respective survival groups. We then assessed sensitivity, specificity, positive predictive value and negative predictive value of the model in identifying patients living < 2 months.

Results: Of the 72 patients with metastatic cancer seen for palliative radiation therapy, 17 (24%) died in < 2 months from consult, 21 (29%) died > 2 months and < 1 year from the time of consult, and 34 (47%) were still alive at the time of analysis. Of those patients still alive at the time of analysis, 3 (8%) were alive > 1 year from the time of consult. All patient consults occurred at least 2 months prior to the time of analysis. Using the TEACHH model as detailed above, 5 (7%) patients were categorized as Group A, 59 (82%) patients were categorized as Group B and 8 (11%) patients were categorized as Group C. Categorization into Group C had 100% specificity and positive predictive value in determining patients living less than 2 months, and had 47% sensitivity and a 14% negative predictive value.

Conclusion: Patients falling into the lowest survival group of the TEACHH model (Group C) have a high likelihood of dying in less than 2 months. However, the sensitivity and negative predictive value of the model are limited and revision of the model is necessary to improve model performance. Further study must also be done to determine the ability of the model to predict patients living longer than 1 year.

Author Disclosure: M.S. Krishnan: None. R. Shiloh: None. P. Dougherty: None. C.M. Whitehouse: None. A. Buckman: None. T.A. Balboni: None.

Diagnostic Computed Tomography (CT)-Based Preplanning Coupled With Posttreatment Cone Beam CT Dosimetry Allows for Rapid, Safe, Image Guided Delivery of Emergent Radiation Therapy
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Purpose/Objective(s): For emergent patients, CT simulation-based planning adds unnecessary and potentially dangerous time to clinical workflows. “Mark and Start” (M&S) hand calculations are a commonly employed alternative to limit time medically unstable patients are outside of a critical care setting. However, M&S uses simple beam arrangements without heterogeneity corrections or modern image-guidance. We evaluated the feasibility of “Diagnostic and Start” (D&S), an adaptive clinical workflow which combines
pre-treatment planning on diagnostic CT (dCT) with on-board cone beam CT (CBCT) image guided radiation therapy (IGRT) to rapidly deliver safe, accurate, and high quality emergent radiation.

**Materials/Methods:** Hounsfield unit calibrations of our institutional CT scanners were determined. In the D&S workflow, the pre-treatment dCT is used for contouring, treatment planning and DRR construction. PTV is standardized as a 2.0 cm expansion of the clinical target volume. The patient is clinically set up to approximate dCT position. Initial orthogonal kV imaging is acquired, with adjustments made until deemed within tolerance. CBCT images are acquired and final positioning changes applied. Port films are taken and patient marks applied while CBCT images are exported to the treatment planning system for post-treatment dosimetric validation.

To dosimetrically evaluate the D&S and M&S workflows, we simulated a 12 Gy in 3 fraction treatment for 4 patients, 2 with lung cancer on a ventilator and 2 gynecologic cancer patients with bleeding. Patients were required to have pre-treatment dCT and CBCT-IGRT images. M&S plans were defined as AP-PA with primary collimators. D&S plans were defined as 4-field box with 2 MLC-defined control points per beam (1 cm PTV expansion, 1 cm PTV contraction). D&S beam weights and control points were optimized. Dosimetric comparisons, including dose validation on CBCT, were performed for PTV, total body dose, and relevant OARs.

**Results:** Patient time in the department for the D&S workflow is approximately 30-45 minutes, a dramatic time savings compared to a conventional several-hour treatment workflow beginning with CT-simulation. Contrary to M&S, CBCT IGRT provides 3D anatomic information for improved accuracy. Dosimetric comparison between M&S and D&S show both techniques can deliver safe and robust treatment plans despite large variations in patient position between dCT and CBCT. Maximum doses computed on dCT and CBCT were 123%-126% of prescription for M&S, and 118%-121% for D&S.

**Conclusion:** M&S and D&S plans were dosimetrically similar. D&S has practical advantages of IGRT, short patient time in the department, and potential OAR-sparing with 3+ beam arrangements. Our D&S workflow represents a rapid, safe, and effective means of delivering emergent linac-based radiation therapy using commonly available CBCT technology without the additional burden of CT simulation.

**Author Disclosure:** B.W. Maidment: None. W. Watkins: None. C. Hodge: None. N.A. Faria: None. A.D. Harrell: None. P.W. Read: None.

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Consideration of Patient and Disease Characteristics in Selecting Radiation Regimens for Treatment of Bone Metastases

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**Purpose/Objective(s):** Bones are a common site of metastasis and radiation therapy is one of the most effective interventions for pain control. However, the optimal fractionation and dosing of radiation for given patient and disease characteristics is still a subject of debate.

**Materials/Methods:** We retrospectively examined 537 patients who received radiation for bone metastases at our institution from 2009-2014 and evaluated survival outcomes based on parameters of their first treatment course and patient demographics. Cox proportional hazards analysis was used to analyze factors associated with overall survival (OS).

**Results:** In our patient cohort, median age at consult was 62 years and median KPS was 70. Median OS from time of treatment was 6 months. We found that survival time formed 3 strata by primary tumor type: breast (median: 14.3 months), melanoma/prostate/other tumors (median: 6.5 months), and GI/lung (median: 4 months) (p<0.0001). Patient disease and treatment characteristics are shown in Table 1. Patients less than age 60 at consult had significantly longer survival (median: 7.1 months vs. 5.6 months) (p=0.01). Patients with KPS under 80 had significantly shorter survival (4.4 months vs. 8.6 months) (p=0.019). Patients treated for bone metastasis sites of skull or pelvis had a trend toward higher median survival than patients treated for bone metastases at other sites (8.7 months vs. 5.6 months) (p=0.067). Patients treated emergently had lower median survival (3.3 months vs. 7.0 months) (p=0.045). We also found a trend toward improved survival with higher BED, although patients treated with 30Gy/10fx had very similar survival to patients treated with 20Gy/5fx (median: 5.0 months vs. 5.3 months). **Table 1. Patient, Disease and Treatment Characteristics**
<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Breast</th>
<th>GI/Lung</th>
<th>Melanoma/Prostate/Other</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td><strong>KPS &lt;80 ≥80</strong></td>
<td>17.6%</td>
<td>9.2%</td>
<td>27.5% 5.6%</td>
<td>28.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>73.9%</td>
<td>26.1%</td>
<td>75.3% 24.7%</td>
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<tr>
<td>Treated Site Chest/ex/spine/other Skull/pelvis</td>
<td>15.3% 6.3%</td>
<td>28.3% 8.0%</td>
<td>31.7% 10.5%</td>
<td>73.9% 26.1%</td>
</tr>
<tr>
<td>Age&lt;60 ≥60</td>
<td>11.8% 7.3%</td>
<td>13.6% 26.2%</td>
<td>18.1% 22.8%</td>
<td>43.6% 56.4%</td>
</tr>
<tr>
<td>Fractionation by BED&gt;1010-3030-4545-50&gt;50</td>
<td>4.9% 8.9% 61% 22.8% 2.4%</td>
<td>14.0% 17.7% 52.7% 10.8% 4.8%</td>
<td>7.9% 11.4% 53.1% 18.9% 8.8%</td>
<td>9.3% 13.0% 54.7% 16.9% 6.0%</td>
</tr>
<tr>
<td>Total Patients</td>
<td>22.9% 34.6%</td>
<td>42.5%</td>
<td>43.6% 56.4%</td>
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</tr>
</tbody>
</table>

**Conclusion:** These data demonstrate that radiation fractionation schedules should take into account primary tumor diagnosis, KPS, bone metastasis site, age, and whether the treatment is emergent. In patients with shorter expected survival times, a shorter fractionation schedule may be more beneficial for the patient’s quality of life. Also, we found no difference in survival for patients treated with 30Gy/10fx vs. 20Gy/5fx, suggesting that the substitution of the shorter fractionation schedule should be considered in certain situations.

**Author Disclosure:** Y. Liu: None. R. von Eyben: None. E.A. Kidd: None.

### Recursive Partitioning Analysis Is Predictive of Overall Survival for Patients Undergoing Spine Radiosurgery for Spine Metastasis

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**Purpose/Objective(s):** Spine radiosurgery (SRS) offers excellent radiographic and pain control for patients with spine metastases. We aimed to create a prognostic index using recursive partitioning analysis (RPA) to enable clinicians to better select patients for spine SRS.

**Materials/Methods:** All patients (2006-2015) who underwent single-fraction spine SRS for spine metastases were included. Primary histologies were divided into favorable (breast and prostate), radioresistant (renal cell, sarcoma, melanoma) and other. Cox proportional hazards regression was done to identify if any of the following factors were associated with overall survival (OS): age, gender, KPS, time from primary diagnosis (TPD), histology, control of primary disease, systemic disease status, spine disease extent (single level, multilevel [2-5 levels], diffuse [>5 levels]), oligometastatic disease (1-5 metastatic foci) and presence of epidural disease. RPA was done to identify if any of the above factors could be used to classify patients into distinct risk groups with respect to OS.

**Results:** A total of 444 patients were included in this analysis. Median dose was 16 Gy (range, 8-18) in 1 fraction and median follow-up was 11.7 months. At time of analysis, 103 (23.1%) patients were alive. Median survival was 12.9 months. Multivariable analysis showed that KPS >70 (HR 0.50, p<0.01), controlled systemic disease (HR 0.66, p<0.01), single level spinal disease (HR 0.65, P<0.01), absence of visceral metastases (HR 0.62, p<0.01) and TPD (HR 0.99, p=0.02) were predictive of better overall survival. RPA identified three distinct classes. Class 1 was defined as KPS >70 and controlled systemic disease (n=142); Class 2 was defined as KPS>70 with uncontrolled
systemic disease or KPS ≤70, age ≥54 and absence of visceral metastases (n=207); Class 3 was defined as KPS ≤70 and age <54 years or KPS ≤70 age ≥54 years and presence of visceral metastases (n=95). Median overall survival was 26.7 months for Class 1, 13.4 months for Class 2, and 4.5 months for Class 3 (p<0.01).

**Conclusion:** Our analysis demonstrates that there is considerably variability in survival among patients undergoing spine SRS. We created an objective risk stratification via RPA for spine SRS. Given the safety and efficacy of spine SRS, this RPA can help clinicians identify patients who may benefit the most from this treatment.


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**Hemostatic Radiation Therapy for Malignant Tumors—A Retrospective Analysis of Bleeding Resolution Rate**

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**Purpose/Objective(s):** To evaluate if hemostatic radiation therapy was effective in resolving the bleeding and to analyze the factors associated with treatment success.

**Materials/Methods:** Records from patients treated with hemostatic radiation therapy between May 2012 and May 2014 in a single institution were reviewed. The endpoints analyzed were: initial bleeding control rate, re-bleeding incidence and final bleeding control (after salvage treatment of initial treatment failures or re-bleeding). Biological equivalent dose (BED) was categorized (<30 Gy10 vs >/ =30 Gy10). The statistics were done using Kaplan Meier representation of re-bleeding events in time and Fisher Exact test as hypothesis test for categorical variables using SPSS V2.0 software. The study was previously approved by IRB.

**Results:** In total, eighty patients were treated during the period studied. Information concerning symptom response was available for 72 of 80 patients. The overall initial bleeding control rate was 81.9% (59/72). It was 85.7% (12/14), 100% (4/4), 76.5% (13/17), 78.3% (18/23), 77.8% (7/9) and 100% (5/5) in H&N, Urinary, GI, Airway and extremities, respectively. Re-bleeding incidence was 25.4% (15/59) of the patients with initial bleeding control, and when it occurred the median time was 8 weeks after the irradiation (range: 1–96 weeks). With salvage treatment, the final bleeding control was 64.3%, 100%, 76.5%, 78.3%, 75% and 100% in H&N, Urinary, GI, Airway and extremities, respectively. BED less than 30 Gy10 was not associated with a significant lower control (75.6% vs 92.3%, p=0.113). Treatment interruptions due to death or worsening of clinical condition (8 cases) were more common in schedules with more than 5 fractions (20% vs 4%, p=0.047).

**Conclusion:** Independently of the fractionation used, radiation therapy was effective in resolving the bleeding from malignant tumors in the urgency scenario, with more than 80% of resolution. However the probability of treatment discontinuation was greater with the use of more protracted schedules (more than five fractions).

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**Clinical Outcomes of Palliative Radiation Therapy for Pediatric Oncology Patients**

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**Purpose/Objective(s):** Limited data exist detailing palliative radiotherapy (RT) experiences pediatric oncology patients. We aim to characterize the practice, efficacy of symptom control, and toxicity of palliative radiation therapy delivered at a single institution.
**Materials/Methods:** We performed a retrospective review of all pediatric patients age < 25 years treated with RT with palliative intent, defined as with the goal of symptom control or prevention of impending, life-threatening progression, in a single institution over a 6.5-year span from July 2009-January 2016. In several instances, single patients received palliative RT to more than one site; hence, more cases are reported than total patients. Response for each case was determined by patient report at post-RT clinical encounters, dated at time of encounter.

**Results:** Of 385 total pediatric patients treated with RT, 43 patients (11%) were treated with palliative intent to a total of 76 separate sites. Most common malignant histologies included leukemia/lymphoma (33%), rhabdomyosarcoma (18%), neuroblastoma (12%), retinoblastoma (9%), Ewing's sarcoma (8%), osteosarcoma (5%), and other (15%). Seventy-one sites were treated at a median of 27.9 months (range 0.7-158.4 months) after diagnosis. Median survival after completion of palliative RT was 3.5 months (95% CI 1.2 to 5.9 months). Indications for palliative RT were as follows: 63% pain, 8% cord compression, 8% intracranial symptoms, 8% respiratory compromise, 7% asymptomatic lesions risking impending symptoms, 4% post-laminectomy, 1% bowel obstruction, and 1% cosmesis due to a facial lesion. Of the 76 sites treated, response data were available after 59 (78%) of the treatments. Of these 59 treatments, 74% resulted symptomatic relief (44% complete and 30% partial response), of which 36% responded prior to completion of the palliative RT course. Overall median time to response was 22 days (range, 2-96 days). Most commonly prescribed palliative RT regimens were 3 Gy x 10 (20%), 2 Gy x 10 (16%), and 4 Gy x 5 (11%). Symptom stabilization was achieved in 17%, and continued clinical progression occurred in 8% of RT cases. An exception was leukemia and lymphoma—the most common malignant histologies in this cohort—for which 100% of treatment courses led to clinical responses. Overall, RT was terminated early in 11% of treatment courses due to clinical deterioration. One patient experienced RTOG grade 3 acute anorexia with 50 Gy in 25 fractions to a 15 cm pelvic sarcoma invading the bilateral ureters and rectum; otherwise, the palliative regimens were well-tolerated.

**Conclusion:** Palliative RT is a useful, safe, and effective tool for pediatric oncology patients. These data may be used for education of other health care professionals to illustrate its merits. Future research on minimizing dose and number of fractions necessary for symptomatic relief in pediatric patients is warranted.

**Author Disclosure:** A.D. Rao: None. S.R. Alcorn: None. J. Moore: None. S.A. Terezakis: None.

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**Quality of Life Outcomes Following Spine Stereotactic Radiosurgery**

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**Purpose/Objective(s):** Stereotactic radiosurgery (SRS) offers excellent pain relief and local control of spine metastases. However, quality of life (QOL) outcomes have not been previously reported, and it is unknown whether SRS alleviates the QOL decline associated with progressive metastatic disease. We hypothesized that pain relief following SRS is associated with a significant overall QOL benefit.

**Materials/Methods:** Patients undergoing spine SRS with at least one month follow-up were included. The EuroQol 5-Dimensions (EQ-5D) and Patient Health Questionnaire 9 (PHQ-9) were prospectively collected before and after SRS as measures of overall QOL and depression, respectively. Patients without pre- and post-SRS measures were excluded. A QOL increase or decrease from baseline exceeding the minimum clinically important difference (MCID) was defined as QOL improvement or failure. Time to EQ-5D failure was the primary outcome. Kaplan-Meier analysis was used to determine actuarial QOL outcomes. Cox proportional hazards modeling was used to determine the QOL benefit of pain relief.

**Results:** 177 treatments (128 patients) were eligible for inclusion. The median prescription dose was 16 Gy in 1 fraction. Before SRS, the mean EQ-5D and PHQ-9 were 0.692 and 6, respectively. At a median follow-up of 13 months, these measures had worsened to 0.644 and 7 (p<0.01); however, this difference did not exceed the MCID. Among EQ-5D subscores, mobility (p=0.01), self-care (p=0.04), and
completion of usual activities ($p=0.01$) worsened. However, pain/discomfort ($p=0.22$) and anxiety/depression ($p=0.16$) remained stable. Among all patients, 49% experienced EQ-5D index failure during the course of their disease, while 30% experienced improvement. PHQ-9 failure and improvement were observed among 25% and 20% of patients, respectively. 12-month actuarial QOL preservation was 59% (EQ-5D) and 81% (PHQ-9). The median time to EQ-5D index failure was 16 months. Multivariate analysis demonstrated that patients achieving pain relief (HR 0.49, $p=0.02$) experienced superior QOL preservation, while patients experiencing pain progression (HR 2.50, $p=0.01$) experienced poorer preservation. Post-SRS fracture and pain flare were not associated with decreased long-term QOL.

**Conclusion:** QOL preservation must remain a critical therapeutic endpoint for patients with metastatic disease. At a median follow-up of 13 months, QOL decline did not exceed the MCID. Pain and discomfort did not significantly worsen, and 28% of patients experienced a clinically significant QOL improvement. Patients achieving pain relief experienced superior overall QOL preservation, highlighting the benefit of SRS in the management of spine metastases.

<table>
<thead>
<tr>
<th>Health Status Measure</th>
<th>Pre-SRS</th>
<th>Last Follow-Up</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D Index</td>
<td>0.692 ± 0.231</td>
<td>0.644 ± 0.221</td>
<td>0.02</td>
</tr>
<tr>
<td>MCID (Failure)</td>
<td>87 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCID (Improvement)</td>
<td>52 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9</td>
<td>6 ± 6</td>
<td>7 ± 6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MCID (Failure)</td>
<td>20 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCID (Improvement)</td>
<td>10 (20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Patient Safety**

**Indicators of Safety-Critical Events in Radiation Oncology Derived From the Oncology Information System**

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**Purpose/Objective(s):** When safety-critical events occur in the course of treatment there is often a trace left in the patient’s electronic medical record. Such “trigger indicators” have been used to identify safety-critical incidents and adverse events in other areas of medicine. The goal of this study is to develop a panel of indicators specific to the oncology information system (OIS) to objectively identify safety-critical events in radiation oncology treatments. An objective indicator would have many applications including as an outcomes predictor, a way to benchmark practices, and as a tool to objectively measure culture of safety.

**Materials/Methods:** We derived a panel of indicators based on a review of data in an incident learning system (ILS) database. We identified 16 potential indicators which could be queried in an OIS, including: a change in prescription, a voided treatment plan document and a delay in treatment start. We selected 10 indicators and queried our OIS over a four year period. The results were then cross-correlated with our ILS database to find patient charts with a reported high grade near-miss safety event. Univariate analysis was used with Pearson’s chi-squared test with Yate’s continuity correction.

**Results:** Over the four years there were 3313 treatment courses of which 12% had high-grade near-miss safety events. The following indicators were found to be significantly correlated with safety events: missed fractions ($p = 0.02$), new fields after course start ($p <
0.001), new radiation prescription (p < 0.001), two or more physics documents (p < 0.001), physics document after start of treatment (p < 0.001). The following indicators were found to be not statistically significant: hidden fields (p = 0.07), delayed first fraction (p = 0.47), rejected port films (p = 0.16), a voided plan (p = 0.16), no physics document (p = 0.60).

Conclusion: To our knowledge this is the first study in radiation oncology to examine post-incident indicators and the presence of safety-critical events, and represents a way to identify high grade safety events free from the biases of voluntary incident reporting. Though the indicator panel can only be queried after a treatment course completion, initial results suggest statistically significant correlation between our panel of indicators and safety-critical events. Further efforts will focus on refining indicator selection using machine learning algorithms to find the most sensitive and specific combination and exploring applications.


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Improving Efficiency and Safety in External Beam Radiation Therapy Treatment Delivery Using a Kaizen Approach


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Purpose/Objective(s): Modern external-beam radiotherapy treatment delivery processes potentially increase the number of tasks to be performed by therapists, and thus additional opportunities for errors. Yet the need to treat a large number of patients daily requires a balanced allocation of time per treatment slot. The goal of this work was to create a value-stream map of the underlying workflow in such time-interval constrained processes to enhance both execution efficiency and active safety surveillance. The underlying hypothesis was that the use of a Kaizen approach would enhance the opportunity for safety surveillance by minimizing non-value adding workflow steps.

Materials/Methods: A Kaizen project was initiated by mapping the workflow for a Varian TrueBeam (TB) linear accelerator. Over 90 steps by 2 treating therapists were identified and average execution times for each measured. Next, the time-consuming steps were stratified into a 2x2 matrix arranged by potential workflow improvement versus the level of effort required for their correction. Finally a work plan was created to launch 4 initiatives with high potential for workflow improvement but modest effort to implement on the busiest of 3 TB machines in our department. Average treatment times were extracted for 17035 treatment slots from the oncology information system over a 13 month period for all machines. Time spent on safety surveillance and average treatment times per slot were used to metric workflow improvement.

Results: The 1st initiative was to deploy an additional monitor for setup acknowledgment within the treatment vault, to avoid unnecessary motion to the console area (estimated at 64 hours annually per machine). The 2nd was to turn off a collision-detection feature that required multiple spurious overrides due to suboptimal cross-vendor systems integration. The 3rd was to realign the time-consuming export of setup verification images to non-treating staff. The 4th was to make the division of labor by treating therapists as well as peer-review more explicit. The average treatment time per slot reduced by 9.1 % within the 1st month of implementation of the initiatives (p-value <0.001) and was sustained thereafter. The time spent on safety reviews remained the same (20% of the allocated interval), but the peer review component increased. Subsequently introducing 2 of these initiatives on a 2nd TB machine resulted in a corresponding 6% reduction of treatment time (p-value <0.003).

Conclusion: The Kaizen approach has the potential to improve operational efficiency and safety with statistical rigor and quick turnaround in modern radiotherapy practice by addressing non-value adding steps characteristic of individual department workflows in a multidisciplinary, structured manner. Higher-effort opportunities are identified to guide continual downstream quality improvements.

Purpose/Objective(s): Radiotherapy (RT) treatment planning is vulnerable to human error and technical failures that can compromise patient safety and clinical efficiency. It is standard practice in radiotherapy for treatment plans to receive a quality control review (QCR) by a qualified medical physicist (QMP) prior to final approval for treatment. This process is prone to human error and also time consuming. While RT plan discrepancies with severe consequences are rare, even small deviations that escape early detection result in late-stage plan revisions which can be made under time constraints and thus carry additional risks. We report the results of an analysis to assess the effectiveness of in-house automatic physics check software, Verifier, developed to improve efficacy and efficiency of the treatment plan QCR.

Materials/Methods: A retrospective review of patient RT plan data for the time period from Verifier’s inception in 2009 through 2015 was performed to assess the impact of our software on patient safety and clinical efficiency. Verifier is designed to aid the QMP with the detailed parametric aspects of the QCR. It retrieves RT plan parameters directly from our integrated treatment planning database and uses these data to perform a wide range of tests. The user is alerted to potential errors which are color coded by severity. Plan properties reviewed include treatment prescription, isocenter, dose rate, dose limits, MLCs, and 70 others. The software code is continuously updated to address new concerns and is tailored to address issues related to specific techniques, treatment sites, and specific locations within our department. Verifier was assessed by determining the decrease of the incidence where treatment plans were revised after final approval to correct errors that could have been detected in advance. We also evaluated the effectiveness of the software at reducing the amount of time for the QMP to perform an effective QCR.

Results: Plan revisions due to several issues were reduced by Verifier checks implemented specifically to detect these issues. Four examples are included in the table below. The number of Verifier checks increased from 15 in 2012 to 75 by the end of 2015. Over this time, the total number of plan revisions dropped from 18% in 2012 to 11% in 2015. Although Verifier is responsible for some of this drop, some is due to other software and QI improvements, and plans can also be revised for clinical reasons outside of Verifier’s scope. Results also suggest that the Verifier checks decrease average time for treatment plan QCR checking by ~15%.

Conclusion: Verifier software developed at our institution to support the QCR process is an integral part of our clinical practice and has demonstrated direct clinical impact on the accuracy of RT plans, efficiency of QCRs and patient safety.

<table>
<thead>
<tr>
<th>Verifier Check Implemented</th>
<th>Ave Revisions/Yr Before Check</th>
<th>Ave Revisions/Yr After Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaws Wider Than Dynamic MLC</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>Delivery Time Issue</td>
<td>11.6</td>
<td>2</td>
</tr>
<tr>
<td>Field Bolus Not Consistent</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Gantry at 180E versus 180</td>
<td>79.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Improvements in Clinical Workflow Measures and Clinician Group Performance Following Implementation of a Physician Dashboard Monitoring and Feedback Process

D. Song¹, T. R. McNutt¹, K. S. Smith², and T. L. DeWeese³; ¹Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, ²Johns Hopkins Hospital, Baltimore, MD, ³Johns Hopkins University School of Medicine, Department of Radiation Oncology and Molecular Radiation Sciences, Baltimore, MD

Purpose/Objective(s): A significant proportion of critical steps in simulation and treatment planning are dependent upon physician input. Inaccuracies or unplanned delays in these steps can lead to patient treatment postponement, and/or potential treatment error due to subsequent steps being performed in less than originally allotted time. Our hypothesis is that implementing a program of regular monitoring and feedback of physician performance in the treatment planning process ('Physician Dashboard') is associated with measurable improvements in such performance.

Materials/Methods: The setting was a large (>10 physician) practice. A leadership team with representation from physicians, physicists, therapists, dosimetrists, and nurses selected 5 clinically relevant measures for monitoring and feedback. Over a 2-year period, data were collected from the electronic patient information management system, as well as a departmental variance reporting system. Measures were reported quarterly to each physician on their individualized performance. A graduated intervention model as described by Hickson et al (Acad Med 2007, 82:1040) was utilized on an individual basis for physicians not meeting predetermined minimums (<20%) on a metric over two consecutive quarterly periods. To assess for changes in clinic-wide metrics after implementation of the program, comparisons were made with the year prior to Dashboard implementation, with the exception of variance report-based data for which we utilized the previous quarter as baseline, prior to which focused staff encouragement and training to improve rates of variance reporting had been carried out.

Results: Data comprised >5500 simulation procedures. Specific metrics and their pre-Dashboard and post-Dashboard values are shown in Table 1, measured in terms of percentage of undesirable workflow events or variances. All metrics exhibited statistically significant reductions in the post-Dashboard era compared with the pre-Dashboard comparison periods. Measures in the most recent 3-month period continue to exhibit rates which are statistically lower than pre-Dashboard era.

Conclusion: Implementation of a Physician Dashboard program was associated with measurable, durable improvements in performance on metrics of physician-related clinical workflow and accuracy.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Pre-Dashboard (1 year*)</th>
<th>Post-Dashboard (2 years)</th>
<th>Most recent 3 month period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim order late or inaccurate/incomplete</td>
<td>14.3%*</td>
<td>10.6%†</td>
<td>7.3%†</td>
</tr>
<tr>
<td>Sim orders completed by covering/non-treating physician</td>
<td>16.1%</td>
<td>8%†</td>
<td>11.2%†</td>
</tr>
<tr>
<td>Submitted plan contours incomplete or inaccurate</td>
<td>27.9%*</td>
<td>4%†</td>
<td>7.7%†</td>
</tr>
<tr>
<td>Plan Contours submitted late (one day or more)</td>
<td>43.1%</td>
<td>25.8%†</td>
<td>17.0%†</td>
</tr>
<tr>
<td>Plan contours submitted late (two days or more)</td>
<td>30.8%</td>
<td>20.9%†</td>
<td>13.8%†</td>
</tr>
</tbody>
</table>

*3 months for variance reporting-based metrics

†p ≤ 0.02 for all comparisons (two-sample t statistic, two-sided)

Author Disclosure: D. Song: Stock; Merck, Roche. T.R. McNutt: None. K.S. Smith: None. T.L. DeWeese: Chair of Radiation Oncology; Johns Hopkins University.
Clinical Pathways—A Step to Further Improve Implementation of Quality Radiation Delivery for Breast Cancer
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Purpose/Objective(s): Whole-breast irradiation (WBI) is the standard of care for many women after breast-conserving surgery. We have previously shown significantly improved adoption of hypofractionation in our network using clinical pathways. Pathways also outline criteria for dose homogeneity and critical organ dosimetry. Based upon an internal audit showing suboptimal compliance with breast dosimetry parameters, we conducted a mandatory web-based teaching conference for the network. This study reports the impact of this initiative on subsequent treatment plans.

Materials/Methods: Radiation plans were collected for the preceding ten patients receiving WBI at 16 network sites. Plans were evaluated and information shared at a network-wide meeting. A web-based conference was given to staff physicians, physicists, and dosimetrist with recommendations for contouring and goals for dose homogeneity and critical organ dosimetry. The preferred technique was 3D field-in-field (FiF) with conformal heart block. Six months post-conference, ten plans were collected for patients subsequently treated at each site. Pre- and post-conference plans (n=320) were compared using univariate and multivariate analysis of factors predictive for dosimetric compliance.

Results: Baseline characteristics including breast laterality and volume, prescribed dose, and use of hypofractionation were similar between cohorts. Dose homogeneity significantly improved after the conference with decrease in breast volume receiving 105% of the prescribed dose (V105%) from 15.6% to 11.2% (p=0.004) and breast V110% from 1.3% to 0.04% (p=0.008). Breast V105% >20% decreased from 22.5% to 7.5% (p=0.0002) and breast V110% >0% from 13.8% to 4.4% (p=0.003). Factors predictive of breast V105% or V110% above recommended dose on multivariate analysis were pre-conference (odds ratio [OR]=3.33, p=0.0002) and increased breast size (OR=1.06 per 100 cc, p=0.016). Rates of dosimetric deviations by facility were pre-conference: <30%: 10, 40-60%: 2, and >70%: 4; post-conference: <30%: 14, 40-60%: 1, and >70%: 1. There was a trend towards reduction in cases with heart mean dose >3 Gy and ipsilateral lung volume receiving 20 Gy after the conference. Use of tangential beam IMRT (20% pre- vs. 36.9% post-, OR=2.34, p=0.001) and high-energy photons (51.9% pre- vs. 65.6% post-, p=0.012) increased after the conference. IMRT was used over 3D FiF as breast size increased (OR=1.15 per 100 cc, p<0.0005).

Conclusion: This study demonstrates that a web-based teaching conference was an effective method to improve adherence to recommended dosimetric guidelines for whole breast irradiation in a large radiation oncology network. This may be an effective model to ensure outcomes seen in clinical trials translate to everyday practice.


Lymphoma/Leukemia/Hematologic

Combined Modality Therapy for Early-Stage Grade 3 Follicular Lymphoma Improves Overall Survival
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Purpose/Objective(s): The management of early-stage grade 3 follicular lymphoma is an area of controversy with no clear consensus regarding the role of consolidation radiotherapy in the era of modern systemic therapy. Early-stage grade 3 FL may be treated as low-grade follicular lymphoma or diffuse B-cell lymphoma according to national guidelines. We examined this question using the National Cancer Database (NCDB) to evaluate practice patterns and outcomes for patients with early-stage grade 3 follicular lymphoma.
Materials/Methods: Patients with early-stage grade 3 follicular lymphoma diagnosed from 2004-2013 who received multiagent systemic therapy were identified from the NCDB. Multivariable proportional hazards modelling was used to examine the association of treatment and mortality adjusting for demographic, socioeconomic and clinicopathologic factors.

Results: There were 2,031 patients who met inclusion criteria with a median follow-up time of 54 months with an overall survival of 82.4%. Among these patients, 52% had stage I disease, 57% were aged ≥ 60 years of age, 84% had a Charlson-Deyo comorbidity index of zero, 74% had no B symptoms, and 36% of patients received consolidative radiotherapy. Multivariate analysis showed OS was associated with age, insurance status, Charlson-Deyo comorbidity index, clinical stage, B symptoms, and consolidative radiotherapy. Consolidative radiotherapy was associated with improved OS with a 5-year OS of 93.3% compared to 77.9% (adjusted hazard ratio 0.44; 95% CI, 0.32-0.60, P < .0001). Factors associated with receipt of consolidative radiotherapy included facility location, age, clinical stage and B symptoms.

Conclusion: Consolidative radiotherapy was associated with improved 5-year OS in patients with early-stage grade 3 follicular lymphoma who received multiagent chemotherapy. Further studies are warranted to better delineate which groups benefit from consolidative radiotherapy.

Author Disclosure: J.M. Mann: None. X. Wu: None. P. Christos: None. D. Nori: None. S. Formenti: Research Grant; Regeneron, Janssen Biotech, Eli Lilly. Speaker's Bureau; Varian. Advisory Board; BMS, Smith Kline, Astra Zeneca, Eisai. H. Nagar: None.

Consolidation Radiation Therapy Improves Outcome of Diffuse Large B-cell Lymphoma Independent of Pretreatment Prognosis or Response to Chemotherapy

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Purpose/Objective(s): Consolidation radiotherapy (RT) is frequently used in diffuse large b-cell lymphoma (DLBCL) but its exact impact on outcome is still being debated. Our purpose was to assess the impact of consolidation RT in an unselected population treated homogenously and examine whether the impact is related to initial prognosis or response to chemotherapy.

Materials/Methods: The study included 180 patients with DLBCL treated in our institution between April 2005 & March 2015. Eligibility criteria were histologically confirmed DLBCL, treatment with RCHOP, response assessment with PET/CT. Exclusion criteria included concomitant active low-grade lymphoma. The median number of cycles was 6. 26 patients (14.4%) had stage I disease. 71 patients (39%) received consolidation RT as part of their initial treatment. Median dose was 30.6Gy in 17 fractions. IPI score was calculated for all patients at time of diagnosis. Response was assessed during & after chemotherapy using PET/CT scans and patients were designated as “complete metabolic responders” (CMR) if they had Deauville score 1-3 after 2, 4 or all cycles of chemotherapy. The end point of the study was progression-free survival (PFS), defined as the time from diagnosis to the point of progression or death from any cause. Patients who were still alive at the date of last contact were censored.

Results: The median follow up was 51.2 months. The 2 year PFS for the whole group was 73.8% and overall survival was 84%. 162 patients completed all planned treatment and 18 progressed during first line treatment and switched to salvage. In total 149 patients (82.8%) achieved CMR during or at the end of chemotherapy. Of those there was only 1 patient who achieved CMR during chemotherapy and progressed by the end. The 2 year PFS of patients who were treated with chemotherapy alone is 58.5% compared to 98.6% for those treated with combined modality treatment (p<0.001). On univariate analysis IPI, CMR & RT were statistically significant (HR 2.39, 0.32, 0.25 respectively & p<0.001 for all). Multivariate analysis showed that CMR (HR 0.22 p<0.001) & RT (HR 0.31 p<0.001) were independently predictive of PFS. To avoid bias introduced by early progression during chemotherapy, we repeated the analysis after excluding patients who progressed early (<6 months). The 2 year PFS for chemotherapy alone is 69.3% compared to 100% for combined modality (p<0.001). Both IPI (HR 2.52 p=0.005) and RT (HR 0.22 p<0.001) were predictive of PFS on univariate analysis but only RT (HR 0.24 p=0.001) was independently predictive of PFS on multivariate analysis.
**Conclusion:** In this cohort of patients, the addition of radiotherapy improved PFS significantly independent of IPI and metabolic response to chemotherapy.

**Author Disclosure:** F. Rahman: None. J.L. Brady: None. J.T. Dunn: None. D. Smith: None. S.F. Barrington: None. G. Mikhaeel: None.

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**Prognostic Significance of the Postchemotherapy Positron Emission Tomography (PET)/Computed Tomography in Early-Stage Hodgkin Lymphoma: Can PET-Positive Patients Be Cured With Radiation Alone?**

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**Purpose/Objective(s):** Early stage classical Hodgkin lymphoma (HL) patients are evaluated by PET-CT after completion of chemotherapy and before initiation of consolidative radiation therapy (RT). These scans are assessed using the Deauville 5-point scale, which reflects disease response to chemotherapy. We aimed to report the outcomes of patients treated with chemotherapy and RT, as a function of Deauville score. Secondarily, we assessed if patients with post-chemotherapy PET-CT scans scored as a Deauville 4-5 can be cured with RT alone and spared intensive salvage chemotherapy.

**Materials/Methods:** All patients treated at a single institution for stage I-II HL with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy and RT from 2002-2015, ≥18 years of age, with analyzable post-chemotherapy PET-CT scans were eligible. The primary endpoint was event-free survival (EFS), with events defined as disease progression or death from HL.

**Results:** The cohort consisted of 173 patients. Median age at diagnosis was 31 years (range 18-83), and 56% of patients were female. Disease was stage I in 18% and stage II in 82%. B symptoms were present in 31%, extranodal disease in 5%, and bulk (>10 cm in any dimension) in 34%. Patients received ABVD or ABVD-like chemotherapy for a median of 4 cycles (range 2-6), followed by RT to a median dose of 30.6 Gy (range 20-42.2). Median follow-up was 53 months from diagnosis (range 7 – 146). A PET-CT, performed after chemotherapy and prior to RT, was categorized as Deauville 1-2 in 97 patients (56%), Deauville 3 in 56 (32%), Deauville 4 in 17 (10%), and Deauville 5 in 3 (2%). Three of the 20 patients with a Deauville score of 4-5 underwent a biopsy to exclude residual active disease; all 3 biopsies were negative for HL. In total, there were 3 disease relapses after completion of ABVD and RT: 1 in the Deauville 3 subgroup, 1 in Deauville 4, and 1 in Deauville 5. There was 1 death from disease, which was in the Deauville 5 group. 5-year EFS was 98% for the entire cohort. 5-year EFS was 100% for the Deauville 1-2 subgroup (0 relapses/97 patients), 98% for Deauville 3 (1/56), 94% for Deauville 4 (1/17), and 67% for Deauville 5 (1/3). Compared to the Deauville 1-2 subgroup, there was no significant difference in EFS for Deauville 3 (P = 0.19), while there was a significant difference in EFS for Deauville 4 (P = 0.03) and Deauville 5 (P<0.001).

**Conclusion:** In early stage HL patients treated with combined modality therapy, a post-chemotherapy Deauville score of 4-5 is associated with worse EFS; however, select patients with residual FDG-avid disease are cured with RT alone and may be spared intensive salvage chemotherapy. The small number of events limited our analysis. Studies of larger cohorts are warranted to confirm our findings and to identify characteristics of patients with residual PET-positivity after chemotherapy, who can be salvaged effectively with RT alone.

Utilization of Positron Emission Tomography/Computed Tomography Parameters to Identify Patients at Risk for Progression After Treatment With Dose-Adjusted R-EPOCH for Primary Mediastinal B-Cell Lymphoma (PMBCL)

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Purpose/Objective(s): Immunochemotherapy followed by radiation therapy (RT) was the standard of care for PMBCL until a recent study reported high cure rates omitting RT and using DA-R-EPOCH, (dose adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin). With PET-CT emerging as an essential tool to guide clinical decisions, we sought to investigate if PET-CT parameters can predict the subset of patients that would fail DA-R-EPOCH treatment. Materials/Methods: Patients with stage I/II PMBCL treated with DA-R-EPOCH (2009-2015) with available baseline and post chemotherapy PET-CT were included. We examined PET-CT parameters as continuous and dichotomized variables including CT tumor volume (CTTV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff points. Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier. Differences between PFS curves were evaluated using the log-rank test. Results: We identified 46 patients that met eligibility criteria with a median follow up of 27 months (5-72). Median age was 34 years (19-65). Fifty percent were women (n=23), 58.7% (n=27) had stage II disease; 54% (n=25) had mediastinal masses > 10 cm in maximum axial dimension; and 96% (n=44) received 6 cycles of DA-R-EPOCH (range, 4-7 cycles). The 2 yr PFS and OS were 76% and 100%, respectively. Disease progression was evident in 11 patients (23.9%) at completion of DA-R-EPOCH; 26% received RT (n=12), including 10 patients with salvage intent and 2 with consolidative RT. On Cox proportional hazards model, elevated baseline CTTV (p=0.01), TLG (p=0.01) and MTV (p<0.01) were significantly associated with PFS. Post-treatment parameters were significantly associated with PFS including: residual CTTV (p<0.01), SUVmax (p<0.01), TLG (<0.01), MTV (<0.01) and Deauville score (<0.01). ROC curve analysis identified optimal cut point for each parameter to identify two groups designated high (> cutoff value) and low (< cutoff value) (Table 1). Of the PET-CT parameters identified at baseline, a significantly worse 2 yr PFS was associated with high MTV (22%) vs low MTV (89%, p<0.0001). Several post-chemotherapy PET-CT parameters were also predictive of inferior 2 yr PFS, including high SUVmax (31%) compared to low SUVmax (100%, p<0.0001). Conclusion: RT still has a role in patients with PMBCL treated with DA-R-EPOCH. Volume based and metabolic parameters on baseline and post-chemotherapy PET-CT imaging seem to identify, beyond Deauville score, patients who will not be cured with DA R-EPOCH alone.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff Value</th>
<th>2 Year PFS</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(Low vs High)</td>
<td></td>
</tr>
<tr>
<td>Initial CTTV</td>
<td>497.67 cc</td>
<td>92% vs 52%</td>
<td>0.001</td>
</tr>
<tr>
<td>Initial MTV</td>
<td>429.42 cc</td>
<td>89% vs 22%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Initial TLG</td>
<td>2792.65 cc</td>
<td>93% vs 49%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Residual CTTV</td>
<td>23.62 cc</td>
<td>100% vs 47%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post SUVmax</td>
<td>3.93</td>
<td>100% vs 31%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post MTV</td>
<td>25.4 cc</td>
<td>87% vs 55%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Post TLG</td>
<td>30.81</td>
<td>100% vs 57%</td>
<td>0.001</td>
</tr>
<tr>
<td>Deauville</td>
<td>0-3 vs 4-5</td>
<td>100% vs 52%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Spatial Patterns of Local Failure Following Chemotherapy in Hodgkin Lymphoma: Volume Reduction From Involved Site/Nodal Radiation Therapy

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Purpose/Objective(s): Involved site/nodal radiation therapy (ISRT/INRT) is the current standard of care for Hodgkin lymphoma (HL) following chemotherapy. ISRT/INRT is accomplished by superimposing prechemotherapy (pre-C) imaging onto postchemotherapy (post-C) images. Here we examine site-specific spatial patterns of relapse following a complete response (CR) with chemotherapy and evaluate if coverage of only the post-C residual soft tissue adequately covers subsequent relapse sites.

Materials/Methods: The records of 700 HL patients treated from 2000 to 2015 were retrospectively reviewed. Patients with available PET/CT (pre-C, post-C and relapse) images who achieved site-specific CR after chemotherapy and then relapsed at the same site were evaluated. PET/CTs from pre-C, post-C and relapse were imported into commercial imaging software and deformable image registration was performed on the image sets. PET avidity was contoured with automated thresholding above background liver uptake. Background avidity was determined by placing a 3 cm sphere in the liver followed by calculation of the mean standard uptake value of the sphere plus twice the standard deviation. A radiation oncologist contoured post-C residual soft tissue volumes. Contours from each image set were used to compute the % overlap of each volume relative to the smaller volume. A treatment plan with pre-C and post-C volumes was compared. A 1 cm GTV to CTV expansion respecting anatomic boundary and a 0.5 cm PTV expansion was used. Dose-volume histograms were used to assess target coverage and normal tissue dose.

Results: 26 HL patients were identified with site-specific CR after chemotherapy with same site relapse in soft tissue. Most patients did not receive consolidation radiotherapy. Only six patients had PET/CTs appropriately digitized for image fusion and these were further analyzed. Median time for site specific relapse was 9.4 months (range 3.9 - 24.8 months). Median time from pre-C to post-C and post-C to relapse imaging was 4.5 and 5.1 months, respectively. The mean % overlap of volumes was: pre-C vs. post-C (78%), pre-C vs. relapse (87.5%) and post-C vs. relapse (60%). Mean pre-C, post-C and relapse volumes were 289, 64.8 and 187.6, respectively. Treatment planning was performed on one patient to investigate dosimetric parameters. Dosimetric advantages favoring the post-C vs. pre-C volumes for V20 (9% vs. 22%), max spinal cord dose (9.5 Gy vs. 31.5 Gy) and mean esophageal dose (8.4 Gy vs. 13.5 Gy) were notable.

Conclusion: Further site-specific volume reduction from ISRT/INRT may adequately cover subsequent relapse sites while providing reduced normal tissue dose. Our analysis revealed that some relapses occur in residual soft tissue following CR, which raises the possibility of radio-resistant clonogens confined within metabolically inactive tissue.


Brentuximab Vedotin and AVD Chemotherapy Followed by ISRT: A Safe Primary Treatment Regimen for Early-Stage, Unfavorable Hodgkin Lymphoma

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Purpose/Objective(s): This is a pilot multicenter trial designed to assess the safety and efficacy of brentuximab vedotin (Bv), a novel CD30-targeting antibody-drug conjugate, and doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy followed by involved-site radiation therapy (ISRT) for patients with early stage, unfavorable risk classical Hodgkin lymphoma (HL).

Materials/Methods: Thirty patients between the ages of 18 and 60 with untreated early stage HL with unfavorable risk factors were enrolled on study. All patients had stage II disease and 77% of patients had bulky disease as defined by >7cm in maximal transverse or
coronal diameter. All patients had a baseline hemoglobin-adjusted diffusing capacity for carbon monoxide (DLCO) ≥ 60% on pulmonary function testing (PFT). Patients received four cycles of Bv and AVD followed by ISRT to 30.6 Gy in 17 daily fractions if they were PET negative (Deauville 1-3) at the end of chemotherapy. Twenty-five patients completed all planned treatment.

**Results:** Ninety-six percent of patients received RT to the neck and mediastinum: 46% of these patients received intensity-modulated RT for extensive local disease involving bilateral neck and chest and 63% were treated using deep inspiration breath hold (DIBH) to maximally spare normal lung and heart tissue. Median planning target volume was 892 cc (range: 120 to 2871 cc). The percent of total lung volume receiving 20 Gy (V20) and 10 Gy (V10) was 7-36% (median: 18%) and 9-56% (median: 33%), respectively. Median mean dose (Dm) to the right lung was 9 Gy, to the left lung 10 Gy and to the total lung volume 9 Gy. The median volume of heart receiving 30 Gy was 3% and the median Dm to the heart was 10 Gy. In women under the age of 30, median Dm to the right breast was 2.7 Gy and to the left breast 0.8 Gy. All patients tolerated ISRT well with only grade 1-2 toxicity. The most common acute toxicities were fatigue (88%), dermatitis (80%), dysphagia (80%), and esophagitis (52%). During RT, 9 patients developed grade 1 cough and 1 patient developed grade 1 dyspnea, but ISRT was not associated with worsening pulmonary function as measured by DLCO immediately after completion of ISRT and at 12 months post completion of ISRT. Thus far, 15 patients who received ISRT to mediastinum have undergone repeat PFT at 12 months post-treatment: 12 (80%) of these patients were found to have an improved DLCO from baseline. All patients who completed 4 cycles of Bv and AVD followed by ISRT (n=25) achieved a complete metabolic response with no relapses to date at 19-month median follow up.

**Conclusion:** Bv and AVD followed by ISRT is a safe treatment paradigm for patients with early stage, unfavorable HL. Acute toxicity during ISRT is mild and there is no evidence of increased pulmonary toxicity after treatment, even in patients with large mediastinal RT fields. DIBH in carefully selected patients can be used to further spare normal tissues. Finally, initial clinical data show excellent rates of complete response and disease control.


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**Intensity Modulated Radiation Therapy by Tomotherapy (IMRT) Concurrent With a Short Systemic Treatment for Solitary Plasmacytoma of the Bone (SPB) With Improvement of Progression-Free Survival**

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**Purpose/Objective(s):** To determine the impact and tolerance of a short treatment with Immunomodulatory Drugs (ImIDs) or proteasome inhibitors (PI) in association with 40 Gy IMRT on the progression-free survival of SPB patients.

**Materials/Methods:** We retrospectively reviewed the medical and dosimetric records of all patients treated for solitary plasmacytoma of the bone at a single institution between 2004 and 2013. All patients had histologically proven plasmacytoma of the bone, without bone marrow involvement. Initial evaluation included clinical examination, biological tests and radiological exams. The absence of additional lesions was assessed by standard radiographies associated with a more sensitive technique such as total body MRI, CT-scan and/or PET-CT. Radiotherapy modalities were reviewed. Additional treatment was assessed. Toxicity was evaluated weekly during radiotherapy, then at 6 weeks, 4 months and 1 year using CTCAE v3.0. Local control of the lesion was defined as negativation of PET-CT. Progression was defined as the incidence of a new plasmacytoma or a multiple myeloma. Statistical analysis: Progression-Free Survival (PFS) was defined as the period from the beginning of radiotherapy to the first documentation of progression or death. Patients alive without progression were censored at the date of last known contact. PFS was estimated using the Kaplan Meier method and compared with the log-rank test.

**Results:** 28 patients were analyzed. Median age was 53.5 y. Median follow-up was 52.2 months (7-99). 15 patients received the standard treatment, a local 40 Gy radiotherapy (group 1); 13 patients (46%) received treatment with ImIDs or PIs, in addition to the 40 Gy local radiotherapy delivered by IMRT (group 2). In group 2, 9 patients (69%) received 4 cycles of lenalidomide+dexamethasone,
A Prospective Pilot Study Evaluating Feasibility and Utility of ECG-gated CT Angiography for Coronary-Sparing Radiation Therapy Planning in Mediastinal Lymphoma

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Purpose/Objective(s): Cardiovascular morbidity and mortality is common among survivors of mediastinal lymphomas treated with radiation therapy (RT). Toxicity data suggests that mean heart doses of 15 Gy and 25 Gy are sufficient to cause accelerated atherosclerosis and valvular disease, respectively. Dose to cardiac substructures likely influences toxicity but most RT plans evaluate heart as a single structure. We hypothesized that RT planning with contrast enhanced coronary CT angiography (E-CTA) would allow for accurate cardiac substructure dose calculation and dose reduction to critical heart structures.

Materials/Methods: After providing informed consent, patients receiving RT for mediastinal lymphoma underwent E-CTA in breathhold in addition to conventional noncontrast imaging with breathhold. Cardiac substructures visualized on E-CTA were contoured in systolic and diastolic positions and combined to create organ-at-risk (OAR) structures. Target and other OAR structures (including heart) were contoured on conventional imaging. Two volumetric intensity-modulated arc RT plans were generated for each patient. A conventional RT (CRT) plan was generated by optimizing target and OAR dosimetry without heart substructure constraints. A coronary-sparing RT (CSRT) plan was optimized with the same target coverage normalization but with coronary and valve structure constraints included. Mean heart and lung, and cardiac OAR D0.03cc and V15Gy were calculated.

Results: Patients with Hodgkin’s Lymphoma (HL) (n=6), or Non-Hodgkin’s Lymphoma (NHL) (n=4) underwent planning as above. Patient characteristics include median age of 21 (range 14-58). Stage in HL patients was IIA (n=3), IIB (n=1), or IV (n=2) and Stage II (n=4) in NHL patients. Response to chemotherapy was complete (n=8) or partial (n=2) prior to radiotherapy. Median prescription dose and fractionation was 30 Gy (range 21-40) in 15 fractions (range 14-20). Heart and lung mean for CSRT and CRT plans were 9.3 vs 9.6 (p=.68) and 9.0 vs 9.3 (p=.04), respectively. CSRT resulted in significant reductions in average D0.03cc compared to CRT plans for most cardiac substructures (Left main 15.6 vs 18.6 Gy, p<.01, left anterior descending 17.3 vs 19.1 Gy, p=.02, right coronary 20.8 vs 22.7, p=.04 and aortic valve 21.5 vs 23.3 Gy, p=.13). Average percent reduction in V15Gy also favored CSRT (Left main 50.8%, p=.14; left anterior descending 34.3%, p=.2; right coronary 11.4%, p=.05; and aortic valve 31.7%, p=.08).

Conclusion: RT planning using E-CTA is feasible and significantly reduces dose to critical cardiac structures without increasing overall heart and lung mean dose compared to conventional planning.

Concurrent Chemoradiation Therapy Versus Acceleration of Radiation Therapy With or Without Concurrent Chemotherapy in Locally Advanced Head and Neck Carcinoma (GORTEC 99-02): 7-Year Survival Data From a Phase 3 Randomized Trial and Prognostic Factors

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Purpose/Objective(s): Previous results from our phase III randomised trial (Bourhis, et al. Lancet Oncol. 2012) showed that acceleration of radiation therapy (RT) is probably not beneficial in concurrent chemoradiation therapy (CRT) schedules in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) at 3 years. Here we report the 7-year survival data, and investigate the relation between prognostic factors and survival.

Materials/Methods: Patients with locally advanced, stage III and IV (non-metastatic) HNSCC were enrolled in our open-label phase III randomized trial. Patients were randomly assigned in a 1:1:1 ratio to receive conventional CRT (70 Gy in 7 weeks plus three cycles of 4 days’ concurrent carboplatin-fluorouracil, 279 patients), accelerated CRT (70 Gy in 6 weeks plus two cycles of 5 days’ concurrent carboplatin-fluorouracil, 280 patients), or very accelerated radiation therapy alone (VART: 64.8 Gy, 1.8 Gy twice daily, in 3.7 weeks’ concurrent carboplatin-fluorouracil, 281 patients). The progression-free survival (PFS) was the primary endpoint and assessed in all enrolled patients.

Results: Median follow-up was 7.7 years (IQR 4.9-6.2); chemotherapy and radiation therapy compliance were good in all groups. Accelerated CRT offered no PFS benefit compared with conventional CRT (HR 1.02, 95% CI 0.85-1.2; p=0.82) but marginally significant benefit compared with VART (0.83, 0.69-0.998; p=0.048); conventional CRT improved PFS compared with VART (0.81, 0.67-0.98; p=0.03). 7-year PFS was 22.7% after conventional CRT, 24.8% after accelerated CRT, and 20.3% after VART. With adjustment for the type of treatment (VART vs CRT), prognostic factors analysis showed that oropharynx, T1-3, N0-1, Karnofsky ≥90, female, Hb>13 were associated with better PFS. Male, Karnofsky 70-80, Non oropharynx, T4, NO-1 benefited from CRT as compared to VART, while no difference between the treatment modalities was observed for female, Karnofsky ≥90, oropharynx, T1-3, N2-3; however no significant interaction was observed between treatment type and these factors. Long-term late toxicities will be presented during the meeting.

Conclusion: Long term follow-up confirmed the benefit of concurrent chemoradiation therapy compared with very accelerated RT and acceleration of radiation therapy cannot compensate for the absence of chemotherapy. We could not find beneficial effect of acceleration of radiation therapy when concurrent chemotherapy was administrated.

Intensity Modulated Radiation Therapy Versus 3-Dimensional Conformal Radiation Therapy in Head and Neck Squamous Cell Carcinoma: A Pooled Analysis of NRG Oncology/RTOG 0129 and 0522


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Purpose/Objective(s): To compare intensity-modulated radiotherapy (IMRT) with three-dimensional conformal radiotherapy (3D-CRT) for locally advanced head and neck squamous cell carcinoma (HNSCC) treated on Radiation Therapy Oncology Group (RTOG) 0129 and 0522.

Materials/Methods: RTOG 0129 is a phase III trial comparing standard fractionation radiation with concurrent cisplatin to accelerated fractionation by concomitant boost (AFX-C) with concurrent cisplatin. All patients were treated with 3D-CRT. RTOG 0522 is a phase III trial comparing AFX-C with concurrent cisplatin to AFX-C with concurrent cisplatin and cetuximab, in which both IMRT and 3D-CRT were allowed. Patients treated with IMRT were compared to patients treated with 3D-CRT in 0522 and 0129 regarding toxicity including: acute mucositis, acute dysphagia, xerostomia, and feeding tube dependency and efficacy endpoints including: local-regional failure (LRF), progression free survival (PFS), and overall survival (OS). This analysis is limited to eligible patients for their trials, with oropharynx, hypopharynx, or larynx cancers who received at least 50 Gy.

Results: From RTOG 0129, 664 of 743 (89%) patients met this study’s eligibility criteria, all of whom received 3D-CRT. From RTOG 0522, 859 of 940 (91%) patients were eligible for analysis; 103 received 3D-CRT (12%) and 756 (88%) IMRT. Distribution of patients by primary site were: oropharynx 68%, larynx 25% and hypopharynx 8%. There were significantly more oropharynx in the IMRT arm than the 3DRT arm (72.6% vs 62.6%, p = 0.0003). Patients treated with IMRT had higher grades of acute mucositis (grade 3-4 42% vs. 34%, p=0.0054) and acute dysphagia (grade 3-4 59% vs. 30%, p<0.0001) but lower grades of xerostomia at 1 (grade 2-3 20% vs. 33%, p=0.0022) and 2 years (grade 2-3 15% vs. 28%, p=0.0019). Patients treated with IMRT were less likely to have a feeding tube at 1 year (16% vs. 21%, p=0.0424) but not at 2 years (10% vs. 10%, p=0.9103). IMRT may be associated with decreased risk of death and this trend is similar in the same multivariable models for LRF and PFS, but none of these is statistically significant. In subsite analysis, the benefit of IMRT in reducing xerostomia and PEG tube dependence remained for patients with oropharyngeal cancer, but not for laryngeal or hypopharyngeal cancer.

Conclusion: IMRT is associated with reduced xerostomia at 1- and 2-years, and less PEG tube dependence at 1-year. In subgroup analysis the lower incidence of xerostomia and PEG tube dependence was only observed in oropharyngeal cancer patients. IMRT is associated with higher incidence of acute mucositis and acute dysphagia possibly due to only IMRT patients were treated with cisplatin and cetuximab arm. IMRT should be considered as a standard radiotherapy technique in locally advanced oropharyngeal cancer. However, further studies are needed in patients with laryngeal and hypopharyngeal cancer.

Radiation Therapy Variation in the Randomized Phase 3 Positron Emission Tomography Neck Study


Purpose/Objective(s): 564 patients with squamous cell carcinoma of the head and neck receiving definitive chemoradiation in the PET Neck phase 3 trial were randomised to either planned neck dissection or PETCT scan guided surveillance. The primary endpoint for this study has been previously reported. As the trial spanned the period of IMRT introduction in the UK, a pragmatic approach to radiotherapy fractionation and technique was adopted and thus three dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) were permitted as were 4, 6 or 7 week radiotherapy schedules. It was the purpose of this analysis to investigate whether the use of different radiotherapy techniques or fractionation had an effect on either overall survival or global quality of life.

Materials/Methods: In the 532 (94%) patients where data on technique was available 200 (38%) received 3D-CRT and 332 (62%) received IMRT. In the 525 patients where fractionation data was available, 181 (34%), 288 (55%) and 56 (11%) patients received 68-70 Gy in 34-35 fractions (#), 60-66 Gy in 30## and 55 Gy in 20## fractions respectively. Baseline characteristics including treatment arm, timing of neck dissection, chemotherapy regime, tumour site, age, sex, T stage, N stage, performance status, smoking status, alcohol status and p16 status were compared in the two technique and three fractionation cohorts. Overall survival was compared in these cohorts as was global quality of life measured using EORTC QLQ C30 at baseline, immediately post treatment and at 2 years.

Results: There were no significant difference in baseline characteristics between the 2 technique cohorts, with the exception that 157 (79%) patients in the 3D-CRT cohort had oropharyngeal cancer compared with 293 (88%) in the IMRT cohort (p=0.014). At a minimum follow up of two years since treatment, there was no significant difference between 3D-CRT and IMRT in overall survival or global quality of life. There were significantly more patients in the 4 week cohort who were p16-ve: 23 (48%) compared with 37 (16%) and 41 (30%) in the 6 and 7 week cohorts respectively (p=0.0001). When patients receiving IMRT were considered, there were no significant differences in overall survival or global quality of life between the three fractionation cohorts. Lower overall survival was seen in the 20# cohort receiving 3D-CRT reflecting the higher rate of p16 negativity in this cohort (p=0.04).

Conclusion: Despite randomised data illustrating a clear reduction in xerostomia with IMRT, evidence for a significant benefit on global QOL of life remains elusive. The absence of a detriment in global QOL or survival in patients receiving IMRT with resource sparing 4 or 6 week schedules supports the continued examination of hypofractionated accelerated schedules in international randomised studies.

Multi-Institution Analysis of Intensity Modulated Radiation Therapy–Based Reirradiation for Head and Neck Cancer: Prognostic Factors and Recursive Partitioning Analysis for Overall Survival

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Purpose/Objective(s): Selection of patients with recurrent or second primary (RSP) head and neck cancer who are candidates for a protracted course of re-irradiation is challenging given the potentially narrow risk-benefit ratio. There are many other less time and/or treatment intensive options for patients unlikely to benefit from protracted radiotherapy including stereotactic radiotherapy and palliative care with chemotherapy or radiotherapy. Here we performed a multi-institution analysis to identify prognostic subgroups when treated with modern IMRT based re-irradiation (re-IMRT).

Materials/Methods: Patients with RSP squamous cell carcinomas originating in a field previously irradiated to at least 40 Gy and treated with re-IMRT to at least 40 Gy were collected. Univariate and multivariate (MVA) Cox proportional hazards regression was used to identify factors associated with overall survival (OS). To identify patients who may be amenable to alternative treatments, factors associated with OS on MVA were entered into a recursive partitioning analysis (RPA) for OS.

Results: From 8 institutions 412 patients with recurrent (n=305, 74%) or second primaries (n=107, 26%) were included. The median dose of initial RT was 66 Gy (range 40-80 Gy) and of re-IMRT 60 Gy (range 39.6-79.2 Gy). The median time between RT courses was 2.4 years (3 months-34 years). Chemotherapy was used in 77% (n=315); 84% of these received concurrent chemotherapy and 10% received induction followed by concurrent chemotherapy. The 2-year OS for the entire cohort was 43.5% (95% CI 38.5-48.6%); The most common cause of death was uncontrolled locoregional disease (n=122 42%). Patients treated with surgery followed by re-IMRT (n=195) had an improved OS compared to those treated with definitive re-IMRT (HR 0.683, p=0.0015). Factors associated with inferior OS on multivariate analysis included organ dysfunction (tracheostomy or feeding tube before re-IMRT), >2 years between RT courses, patients unable to undergo surgery and tumor site (inferior OS among oral cavity, oropharynx, larynx, hypopharynx and isolated neck recurrences). RPA identified three distinct prognostic subgroups (see table): those >2 years from their initial course of RT with resectable tumors (Class I); those >2 years with unresectable tumors or those ≤2 years and without organ dysfunction (Class II) and those ≤2 years with organ dysfunction (Class III).

Conclusion: Through the RPA presented, patients with recurrent head and neck cancer can be divided into three distinct prognostic subgroups based on pre-treatment factors. These subgroups should be used to guide the selection of patients for protracted re-IMRT.

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>Patients</th>
<th>Median Survival (95% CI)</th>
<th>2-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>&gt;2 Years from previous RT &amp; Resectable</td>
<td>46 months (32-73)</td>
<td>69.5%</td>
</tr>
<tr>
<td>Class II</td>
<td>&gt;2 Years from previous RT &amp; Unresectable OR ≤2 Years from previous RT without Organ Dysfunction</td>
<td>20 months (16-22)</td>
<td>40.8%</td>
</tr>
<tr>
<td>Class III</td>
<td>≤2 Years from previous RT with Organ Dysfunction</td>
<td>11 months (9-15)</td>
<td>22.6%</td>
</tr>
</tbody>
</table>
Optimal Treatment Selection of Stereotactic Body Radiation Therapy and Intensity Modulated Radiation Therapy for Reirradiation of Head and Neck Cancer: A Multi-Institution Comparison


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Purpose/Objective(s): SBRT has emerged as a reasonable re-irradiation option for patients with recurrent or second primary (RSP) head and neck cancer. There is little data available to guide appropriate treatment selection between SBRT and a more protracted course of IMRT. Here a multi-institution analysis was performed to compare SBRT and IMRT-based re-irradiation techniques.

Materials/Methods: Patients with RSP squamous cell carcinoma originating in a field previously irradiated to ≥40 Gy and re-irradiated definitively with SBRT (1-5 fractions, ≥5 Gy per fraction) or IMRT (≥40 Gy) were collected from 8 US institutions. Using the Cox proportional hazards technique for overall survival (OS), our concurrently reported recursive partitioning analysis (RPA) was examined on multivariate analysis in the SBRT patients. Subsequently, patient subgroups were compared in terms of acute toxicity, late toxicity (CTCAE v4.0) and overall survival (OS) when treated with SBRT or IMRT.

Results: 414 patients were included: 217 treated with definitive IMRT and 197 treated with definitive SBRT. Grade ≥3 acute toxicity occurred in 16.6% of IMRT and 11.7% of SBRT patients (p=0.153). Grade ≥4 toxicity occurred in 5% of IMRT and 0.5% of SBRT patients (p=0.006). Grade ≥3 late toxicity (>90 days after treatment) occurred in 25.0% of IMRT patients and 22.6% of SBRT patients (p=0.695). On multivariate analysis, the RPA previously defined in the IMRT cohort remained prognostic for OS following SBRT (HR 1.97, 95% CI 1.19-3.20, p=0.01), thus we used the RPA to help define the comparative effectiveness in terms of OS between IMRT versus SBRT. Among RPA class III patients (those <2 years from the previous course of RT and tracheostomy or feeding tube dependent), no difference in OS was detected between IMRT and SBRT (HR 1.53, p=0.354). Among RPA class II patients with “small” tumors (≤25 cc or rT0-r2), no difference in OS was detected between IMRT and SBRT (HR 1.31, p=0.152). Among RPA class II patients with “large” tumors (>25 cc or rT3-4), IMRT to doses ≥66 Gy was associated with improved OS compared to those treated with IMRT to <66 Gy (HR 1.90, p=0.025) or SBRT regardless of doses ≥44 Gy (HR 2.932, p<0.0001), or <44 Gy (HR 2.804, p=0.0006). This difference persisted on multivariate Cox regression when controlling for age, second primary, tumor site, time between courses of radiotherapy and previous treatment.

Conclusion: The concurrently reported RPA for IMRT patients is externally validated within a multi-institution SBRT cohort. Given the reduced rate of severe acute toxicity coupled with comparable survival and late toxicity, SBRT may be the preferred modern re-irradiation strategy for patients with RPA class III and RPA class II tumors ≤25 cc. A protracted course of IMRT may be preferable for the RPA class II patient with rT3-4 tumors >25 cc. Novel systemic agents may continue to improve outcomes with SBRT.
Multi-Institution Analysis of Intensity Modulated Radiation Therapy–Based Reirradiation for Head and Neck Cancer: Improved Risk-Benefit Profile in the Modern Era

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Purpose/Objective(s): Conventional re-irradiation for recurrent or second primary (RSP) head and neck cancer is associated with high treatment related morbidity with modest disease and survival outcomes. We performed a pooled analysis of patients receiving re-irradiation with IMRT (re-IMRT) with the hypothesis that disease and toxicity related outcomes would be more favorable than previous techniques. We also investigated the impact of dose, volume and fractionation on these outcomes.

Materials/Methods: Patients with RSP squamous cell carcinomas originating in a field previously irradiated to ≥40 Gy and treated with re-IMRT to ≥40 Gy were collected. Both patients managed with salvage surgery and re-IMRT and non-operatively with definitive re-IMRT were included. Outcomes in the latter group were compared to the RTOG 99–11 trial. For definitive patients, the influence of dose on overall survival (OS), elective neck RT (ENRT) on regional nodal failure and hyperfractionation on acute and late (>90 days) toxicity was investigated using Cox proportional hazards, logistic and Fine-Gray competing risks regressions accounting for recurrence or death. Results: From 8 institutions, 412 patients were included. The median dose of initial RT was 66 Gy (range 40-80 Gy) and of re-IMRT 60 Gy (39.6-79.2 Gy). The median time between RT courses was 2.4 years (3-34 years). Surgery before re-IMRT was performed in 47%. Chemotherapy was given to 76%. For the entire cohort, 19% developed acute grade ≥3 and 2% grade 5 toxicity. Only chemotherapy use (OR 2.5, p=0.01) was associated with acute grade ≥3 toxicity. At 2 years, the cumulative incidence of late grade ≥3 toxicity was 13% (95% CI 9.6-16.6%). On multivariate analysis, only the presence of a PEG or tracheostomy pre-treatment was associated with grade ≥3 late toxicity (HR 2.2, p=0.01). OS for all patients at 2 years was 43% (95% CI 39-49). Comparing the subgroup of definitive re-IMRT patients (n=204) to the RTOG 99–11 trial, 2yr OS (37% vs. 26%) was significantly improved (HR 1.4, p=0.02). Toxicity was also less, both for acute grade ≥3 (19% vs. 78%), and grade 5 toxicity (2% vs. 8%). Similarly, late grade 3-5 toxicity was 11% in our cohort, compared to 31% grade 4-5 toxicity in RTOG 99–11. For patients who completed definitive re-IMRT (n=204), a dose ≥66 Gy was associated with improved OS compared to doses below 60 Gy (HR 1.5, p=0.051) or 60-65.9 Gy (HR 1.5, p=0.03). Among N0 pts (n=108), ENRT was not associated with a decreased risk of nodal failure at 2 years (18% without ENRT vs. 27% with ENRT, HR 1.5, p=0.37). Hyperfractionation was not associated with OS or late toxicity.

Conclusion: Re-IMRT for RSP head and neck cancer has a substantially more favorable risk-benefit ratio than reported in previous studies. Doses of ≥ 66 Gy are associated with improved OS. These results can provide for more accurate informed consent to patients considering re-IMRT.

Phase 2 Trial of Induction Chemotherapy Followed by Attenuated Chemoradiation Therapy for Human Papillomavirus–Positive Locally Advanced Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): Due to the exquisite radiosensitivity of HPV-positive squamous cell carcinoma of oropharynx, it has been suggested that patients with this disease might be currently “over-treated” using traditional chemoradiotherapy regimens and can effectively be treated with de-intensified strategies which result in improved tolerability and enhanced quality of life without compromising disease control or overall survival. We conducted a phase II multi-center trial of induction chemotherapy followed by response-adapted dose-reduced chemoradiotherapy for these patients.

Materials/Methods: Eligibility required patients to present with newly diagnosed, biopsy-proven stage III or IV squamous cell carcinoma of the oropharynx, age at least 18 years, Zubrod performance status 0 to 1, and no prior chemotherapy or radiation. Treatment was induction paclitaxel 175 mg/m2 and carboplatin area under the concentration-time curve (AUC) 6 for two cycles every 21 days followed by concurrent paclitaxel 30 mg/m2 every 7 days with dose-reduced radiation of 54 Gy or 60 Gy for responders and non-responders, respectively. The primary endpoint was progression-free survival. Acute and late reactions were scored using the Common Terminology Criteria for Adverse Events scale (version 3).

Results: From October 2012 to March 2015, a total of 45 patients (26 tonsil; 19 base of tongue) were registered, of which 44 were analyzable. The median age was 60 years old (range, 43 to 83). Sixty-nine percent were lifelong never smokers. For former smokers, the intensity of tobacco use ranged from 2 to 60 pack-years (median, 20 pack-years). T-classification was: T1 (36%); T2 (42%); T3 (7%); T4 (6%). After induction chemotherapy, 5 patients (11%) had a complete response at all disease sites and 19 patients (43%) had a partial response. The remaining 20 patients (45%) had minor response or stable disease. No patient experienced progression during induction chemotherapy. With a median follow up of 22 months, three patients developed local-regional recurrence and another distant metastasis, yielding a 2-year progression-free survival of 91%. The 2-year rates of overall survival, distant metastasis-free survival, and local-regional control were 98%, 97%, and 94%, respectively. The incidence of any grade 3+ and non-hematologic acute toxicity observed during protocol therapy was 50% and 24%, respectively. The proportion of patients with a gastrostomy-tube at the completion of therapy and at 3-months post-therapy was 5% and 0%, respectively.

Conclusion: By decreasing toxicity while maintaining cure rates, de-intensification of radiation dose has the potential to improve the therapeutic ratio and optimize long-term function for patients with a disease that is rapidly increasing in incidence in the general population. If the currently observed results are confirmed with longer follow-up, de-intensified radiation should become the new standard of care for patients with HPV-positive squamous cell carcinoma of the oropharynx.

Cetuximab-Based Bioradiation Therapy Versus Cisplatin-Based Chemoradiation Therapy in the Definitive Treatment of Locally Advanced Oropharyngeal Squamous Cell Carcinoma

O. Bhattasali, and S. Iganej; Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Purpose/Objective(s): Although several retrospective reports have questioned the efficacy equivalence of cetuximab versus high-dose cisplatin when administered concurrently with radiotherapy in the definitive management of locally advanced head and neck cancer, very few have reported outcomes exclusive to oropharyngeal cancer. Here we report our control and toxicity outcomes in patients treated with cisplatin or cetuximab concurrent with intensity-modulated radiotherapy for locally advanced oropharyngeal squamous cell carcinoma.

Materials/Methods: From 2006 to 2014, 186 patients with stage III-IVB oropharyngeal squamous cell carcinoma were treated definitively with triweekly high-dose cisplatin (81%) or weekly cetuximab (19%) and concurrent intensity-modulated radiotherapy. Induction chemotherapy was not administered, and definitive oncologic surgery was not performed prior to concurrent therapy. Median age was significantly higher in cetuximab patients (70 vs. 56; p<0.0001). Although the cisplatin group had significantly more T4a patients (17% vs. 3%; p=0.03), the cetuximab group had significantly more T4b patients (14% vs. 3%; p=0.03). Nodal stage, smoking status, and p16 status were well-balanced between the groups. Among 118 patients with known p16 status, 88% were p16-positive.

Results: Median follow-up for surviving patients was 43.4 (8.1-113.9) months. Cisplatin was associated with significantly increased 3-year overall survival (OS) (86% vs. 64%; p=0.006) cancer-specific survival (CSS) (88% vs. 76%; p=0.01), and progression-free survival (PFS) (83% vs. 52%; p=0.0002). Cisplatin was also associated with significantly lower rates of locoregional recurrence (9% vs. 23%; p=0.0075) and distant metastasis (7% vs. 21%; p=0.04) when compared to cetuximab. T4 disease was associated with significantly worse 3-year OS (84% vs. 70%; p=0.02), and PFS (80% vs. 62%; p=0.03). Current smokers had significantly decreased 3-year OS (70% vs. 85%; p=0.01), CSS (74% vs. 91%; p=0.01), and PFS (63% vs. 80%; p=0.01). Among patients with known p16 status, p16-negative disease was associated with significantly worse 3-year OS (57% vs. 85%; p=0.006), CSS (57% vs. 88%; p=0.0004), and PFS (46% vs. 84%; p<0.0001). Compared to cetuximab, cisplatin was associated with increased rates of dose reduction (51% vs. 25%; p=0.005) and feeding tube placement (63% vs. 39%; p=0.01).

Conclusion: This retrospective analysis suggests that despite a more favorable toxicity profile, cetuximab use should be discouraged in patients with locally advanced oropharyngeal cancer who are eligible for cisplatin-based therapy. T4 disease, current smoker status, and p16-negative disease were poor prognostic factors in this population. We await the results of a head-to-head comparison of these agents in randomized controlled trials.

Author Disclosure: O. Bhattasali: None. S. Iganej: None.

Genitourinary

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Purpose/Objective(s): To determine if combined external beam therapy (EBT) and transperineal interstitial permanent brachytherapy (B) results in better progression-free survival (PFS) at 5 years compared to B alone, among selected intermediate-risk prostatic carcinoma patients (pts). This is the initial primary endpoint report.

Materials/Methods: Men with prostate cancer, clinical stage T1c-T2b and either Gleason Score (GS) 2-6/PSA 10-20 or GS 7/PSA <10 were eligible and randomized to receive either 45 Gy partial pelvis EBT and brachytherapy (EBT+B) or B alone. External beam therapy could be delivered by 3D or IMRT. Transperineal interstitial permanent brachytherapy allowed the use of 1-125 or Pd-103, prescribed to 110 Gy or 100 Gy boost dose respectively, in the EBT+B arm and 145 Gy or 125 Gy respectively, in the B arm. The study was designed to test for a 10% increase in 5-year PFS for the EBT+B arm, with a 1-sided α of 0.025, 90% statistical power, and 5 interim analyses requiring 586 pts. Progression-free survival (failure: ASTRO PSA, clinical, or death from any cause) was estimated by the Kaplan-Meier method, and arms were compared using a 2-sample binomial test. Protocol-specified interim efficacy and futility analyses were conducted and presented to an external Data Monitoring Committee (DMC). Efficacy testing used Haybittle-Peto at an α of 0.001 and futility was tested by reversing the null and alternative hypotheses at an α of 0.0001.

Results: Between June 2003 and February 2012, 588 men were randomized; 287 EBT+B and 292 B eligible, with median follow-up of 6.7 years. There were no significant differences in baseline characteristics between arms; median age 67, 89% had GS 7/PSA <10, and 67% were T1. At the fifth interim analysis, of the required 443 pts with 5 years of follow-up, 5-year PFS (95% CI) was 85% (80, 89) for the EBT+B arm and 86% (81, 90) for the B arm (HR=1.02, futility p=0.0006). Based on these futility results, the DMC recommended early release for the initial reporting of the primary endpoint. Acute overall ≥ grade 3 toxicity was similar, with 8% for EBT+B and 8% for B. Overall ≥ grade 3 late toxicity was 12% for EBT+B compared to 7% for B. Grade 3 or higher GU toxicity was 7% and 3%, while GI was 3% and 2% in the EBT+B and B arms, respectively. Analyses of secondary efficacy and other objectives are forthcoming.

Conclusion: Among men with intermediate-risk prostate cancer in this study, the addition of external beam therapy to brachytherapy did not result in superior PFS compared to brachytherapy alone in this initial report. Toxicity in both groups was limited, but there were fewer late effects, mostly GU, noted in the brachytherapy alone arm. Supported by NCI grants U10CA21661, U24CA81647, U10CA37422, U10CA180868, U10CA180822, U10CA10953, & U24CA180803

Purpose/Objective(s): To assess differences in health related quality of life (HRQoL) between hypofractionated (H) and conventional (C) schedule radiation therapy (RT) in men with low-risk prostate cancer.

Materials/Methods: Eligibility included: stage T1-2a, Gleason ≤6, PSA <10, randomized to a C schedule (3D/IMRT 73.8 Gy in 41 fractions [fx] over 8.2 wks) or a H schedule (3D/IMRT 70 Gy in 28 fx over 5.6 wks). HRQoL was assessed with the Expanded Prostate Index Composite (EPIC) at baseline, 6 and 12 mos. EPIC assesses prostate cancer-specific HRQoL on a Likert scale with responses transformed to 0-100 (higher scores indicating better HRQoL; 0.5 SD change indicating clinical significance). EPIC has 4 domains: bowel, urinary, sexual, and hormonal. Each domain requires at least 80% of items to be completed. Change scores, calculated as follow-up – baseline, at 6 and 12 mos were compared between arms. Wilcoxon test was used to assess differences. A significance level of 0.0125 to adjust for multiple comparisons with respect to the 4 domain scores was used for an overall two-sided type I error of 0.05.

Results: Of 1092 pts analyzable for the primary endpoint, 962 consented to HRQoL (478 on 73.8 Gy arm; 448 on 70 Gy arm). Baseline characteristics were similar between treatment arms. Median age = 67 yrs; HRQoL compliance was 89.4% at baseline, 72.7% at 6 mos, and 65.9% at 1 yr. Compared to men without cancer, most pts reported poor baseline EPIC sexual domain scores in both H and C arms, median 44.2 and 47.5, and only slightly lower than average bowel and urinary scores. No statistically significant differences with regard to any of the HRQoL baseline domains were measured between treatment arms. There were no differences in change score between arms of any domain scores at 6 mos. At 12 mos, those on the 70 Gy arm experienced a larger decline as compared to those on the 73.8 Gy arm in the bowel domain (median 12 mo. scores 91.1 vs 94.6; median change scores from baseline -3.6 vs. -1.8, respectively, p=0.0037), but not clinically significant.

Conclusion: Compared to a study of EPIC norms in men without cancer, baseline scores for bowel and urinary domains were about 5-6 points lower and sexual function was 15 points lower than norms. Men receiving either H or C fractionation schedules demonstrated 12 mo. bowel, urinary, and better sexual HRQoL comparable to the recent large European H study. EPIC scores exhibited only a small magnitude of decline at 1 yr follow-up from baseline. As compared with C fx, pts treated with H demonstrated a small statistically, but not clinically significant, larger decline in bowel HRQoL at 1 yr, thus late toxicity is comparable between arms, supporting value based care with H. Acknowledgements: This project was supported by grants U10CA21661 (RTOG-Ops-Stat), U10CA37422 (RTOG-CCOP), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC) from the National Cancer Institute (NCI).


Randomized Trial of Hypofractionated Dose-Escalated Intensity Modulated Radiation Therapy Versus Conventionally Fractionated Intensity Modulated Radiation Therapy for Localized Prostate Cancer

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Purpose/Objective(s): Hypofractionated prostate radiotherapy shortens prostate cancer treatment duration and may increase biologically effective dose delivered to the prostate. We report cancer control and toxicity outcomes from a randomized trial testing the hypothesis that dose-escalated moderately hypofractionated radiation therapy improves prostate cancer control.

Materials/Methods: 206 men with localized prostate cancer were randomized to conventionally fractionated intensity-modulated radiation therapy (CIMRT, 75.6 Gy in 1.8 Gy fractions) delivered over 8.4 weeks or to dose-escalated hypofractionated IMRT (HIMRT, 72
Gy in 2.4 Gy fractions) delivered over 6 weeks. Recurrence was defined as either PSA recurrence using the Phoenix definition of nadir plus 2 ng/ml, or initiation of salvage therapy. Late (> 90 days after completion of radiotherapy) genitourinary (GU) and gastrointestinal (GI) toxicity were graded using modified Radiation Therapy Oncology Group criteria.

Results: Most men had cT1 disease (72%), Gleason 6 (34%) or 7 (65%) disease, PSA < 10 ng/ml (90%), and did not receive androgen deprivation therapy (76%). With a median follow up of 8.4 years, there were 31 recurrences. Men treated with HIMRT had fewer recurrences than men treated with CIMRT (p=0.034). Eight-year recurrence was 10.7% (95%CI 5.8-19.1%) with HIMRT and 15.4% (95%CI 9.1-25.4%) with CIMRT. No one died from prostate cancer. There was no difference in overall survival between treatment groups (p=0.37). Late grade 2 or 3 GU toxicity was similar between treatment groups (p=0.83). There was a non-significant numeric increase in late grade 2 or 3 GI toxicity in men treated with HIMRT (8-year 5.0% vs. 12.6%; p=0.08). There were no grade 4 toxicity events.

Conclusion: This moderate hypofractionation radiation treatment regimen of 72 Gy delivered in 2.4 Gy fractions shortens prostate cancer treatment duration and provides better prostate cancer control than 75.6 Gy delivered in 1.8 Gy fractions with acceptable toxicity.


Five-Year Outcomes From a Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

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Purpose/Objective(s): Single-institution studies suggest stereotactic body radiotherapy (SBRT) is a cost-effective alternative to IMRT as primary therapy for prostate cancer. We hypothesized that dose-escalated SBRT could be safely administered across multiple institutions, with grade 3+ toxicities not exceeding 10%. With median follow up greater than five years, we report toxicity, survival and relapse-free survival (RFS) outcomes.

Materials/Methods: After completing rigorous credentialing requirements, 21 community, regional, and academic hospitals enrolled 309 evaluable patients with biopsy-proven adenocarcinoma of the prostate, confirmed by central pathologic review: 172 low-risk (CS T1-T2a, Gleason 6, PSA < 10 ng/mL) and 137 intermediate-risk (CS T1c-T2b with either Gleason=7 and PSA < 10 ng/mL, or Gleason 6 and PSA between 10 and 20 ng/mL). All patients were treated with a non-isocentric robotic SBRT platform using real-time tracking of implanted fiducials. The prostate was prescribed 40 Gy in 5 fractions of 8 Gy and seminal vesicles received 36.25 Gy. Normal tissues were rigidly constrained (rectal V36 Gy <1 cc; bladder V37 Gy <5-10 cc). No patient had concomitant or adjuvant androgen ablation therapy. Toxicities were assessed using CTCAE v3 criteria. Patient-reported quality of life outcomes were recorded and reported elsewhere. Biochemical failure was assessed using the ASTRO consensus and the nadir+2 definitions. Actuarial survival outcomes were calculated using Kaplan Meier methods. The study populations yielded a 90% power of identifying excessive (>10%) rates of grade 3+ GU or GI toxicities at the one-sided 5% significance level.

Results: Median follow-up was 61 months. Five grade 3+ toxicities (1.6%) were reported, far below the 10% rate deemed excessive. There were no grade 4 or 5 toxicities. All reported grade 3 toxicities were GU; these occurred between 11 and 51 months after treatment. Toxicities rates are summarized below. Five patients (1.6%) developed urinary retention which required a temporary catheter placement. Seven patients were diagnosed with bladder cancers between 21 and 50 months after treatment. For the entire
population, actuarial 5-year overall survival was 95.6%. Actuarial 5-year nadir+2 RFS was 97.1% for all patients, and was 97.3% and 97.1% for the low- and intermediate-risk groups, respectively. Actuarial 5-year ASTRO RFS was 92.3% and 91.3% for these respective risk groups.

**Conclusion:** With appropriate treatment delivery and constraints, dose-escalated prostate SBRT can be safely administered across multiple institutions. Toxicity rates and RFS rates compare favorably to other radiotherapies. SBRT appears to be a suitable option for low- and intermediate-risk prostate cancer. ClinicalTrials.gov identifier NCT00643994

<table>
<thead>
<tr>
<th>GU Toxicity</th>
<th>GI Toxicity</th>
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<tbody>
<tr>
<td>Gr1</td>
<td>Gr2</td>
</tr>
<tr>
<td>Any time</td>
<td>165 (53%)</td>
</tr>
<tr>
<td>&lt; 3 mos</td>
<td>182 (59%)</td>
</tr>
<tr>
<td>&gt; 3 mos</td>
<td>87 (28%)</td>
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**Author Disclosure:** R. Meier: Research Grant; Accuray. A. Beckman: None. G. Henning: None. N. Mohideen: None. S.A. Woodhouse: None. C. Cotrutz: None. I.D. Kaplan: None.

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**Purpose/Objective(s):** Data comparing androgen-deprivation therapy (ADT) combined with external beam radiation therapy (EBRT) versus EBRT-alone have clearly demonstrated a survival benefit for the combined strategy in localized prostate cancer. Data comparing ADT-alone with ADT + EBRT combinations are scarcer and have more limited follow-up. This study aims to investigate progression-free survival (PFS) with long-term follow-up.

**Materials/Methods:** This multicenter phase III trial included 273 biopsy-proven T3-4 or pT3NOMO patients with prostate cancer randomly assigned to ADT alone or ADT+EBRT. Luteinizing hormone-releasing hormone (LHRH) agonist (leuprorelin 11.25 mg, subcutaneous) was started within seven days of randomization and continued every three months for three years in both arms. Oral flutamide (750mg/day) was administered during the first month. EBRT volumes encompassed pelvic lymph-nodes and the prostate. An EBRT quality assessment was performed by 4 independent physicians.

**Results:** 263 patients were included in the Intention-to-treat analyses with a median follow-up of 88 months (0-128). PFS was significantly higher in the ADT+EBRT arm than in the ADT-only arm (50.4% versus 4.6%; p<0.0001). The specific survival rate was 78.3% in the ADT-only arm and 89.4% in the ADT+EBRT arm (p=0.0305). The overall survival rate was 56.2% in the ADT-only arm and 63.9% in the ADT+EBRT arm, p=ns. Patients in the ADT-only arm were more likely to experience local progression (HR = 3.4, 95%CI 1.9 - 6.1; p <0.0001), and they had a higher risk of developing metastases (p=0.0363). Analysis of toxicities revealed acute lower tolerance (diarrhea, pollakiuria and dysuria) in the ADT+EBRT arm with a gradual decrease in intensity during follow-up from 6 months after the end of EBRT.

**Conclusion:** These long-term results of the TAP32 study confirm the oncological benefit of combining EBRT with ADT in the treatment of locally advanced prostate cancer.

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Androgen Deprivation and High-Dose Radiation Therapy in Prostate Cancer: Report on Late Toxicity from DART 01/05 Randomized Phase III Trial

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Purpose/Objective(s): We present secondary endpoints of late toxicity from a randomized trial (DART 01/05) conducted to determine whether long-term androgen deprivation (LTAD) was superior to short-term androgen deprivation (STAD) when combined with high-dose radiotherapy (HDRT) in prostate cancer (PCa). The hypothesis is that LTAD does not increase radiation-induced toxicity compared to STAD.

Materials/Methods: 355 eligible men with cT1c-T3aN0M0 PCa with intermediate and high-risk factors according to 2005 NCCN criteria were randomized to 4 months of androgen deprivation (AD) combined with HDRT median dose 78 Gy (STAD), or the same treatment followed by 24 months of AD (LTAD). Treatment related complications were assessed using EORTC-RTOG and CTCAEs v3.0 scoring schemes. Cumulative incidence of toxicity was calculated according to the product-limit (Kaplan-Meier) method. A logistic regression analysis was performed to identify prognostic factors affecting the risk of late rectal, urinary and cardiovascular (CV) side effects. Median follow-up was 63 months.

Results: The 5-year incidence of grade ≥2 rectal and urinary toxicity was 10.7% and 8.4% for LTAD and 7.8% and 7.8% for STAD respectively. Compared to STAD, LTAD was not significantly associated with a higher risk of late grade ≥2 rectal (OR: 0.721, 95%CI: 0.337-1.542, p=0.399) and urinary (OR: 1.015, 95%CI: 0.469-2.195, p=0.970) toxicity. On multivariate analysis, a baseline history of intestinal comorbidity (OR: 4.103, 95%CI: 1.722-9.772, p=0.001) and the VR60 (OR: 1.039, 95%CI: 1.002-1.077, p=0.039) were the only factors significantly correlated with the risk of late grade ≥2 rectal complications. A history of previous bladder and prostate manipulations was significantly associated with a higher risk of grade ≥2 urinary complications (OR: 2.912, 95% CI: 1.145-7.409, p=0.025). The 5-year cumulative incidence of a CV event was 17.9% and 7.4% for LTAD and STAD, respectively (p=0.025). LTAD (OR: 2.032; 95% CI: 1.086-3.802, p=0.027) and the antecedent of myocardial infarction (OR: 2.476; 95% CI: 1.245-4.924, p=0.010) were independent factors associated with a higher risk of CV events.

Conclusion: The results of this trial showed that LTAD did not significantly impact urinary or rectal radiation-induced toxicity in PCa patients treated with HDRT, although it was associated with a higher risk of non-fatal CV events. Longer follow-up is needed to ascertain the magnitude of the influence of AD on late morbidity and non-PCa mortality.

Staging of Biochemically Relapsing Prostate Cancer Using the Positron Emission Tomography Tracer Fluciclovine F18

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Purpose/Objective(s): Staging the extent and location of prostate cancer in biochemical relapse (BR) is critical to informing further management of both post-surgical and post-radiation patients with focal or systemic therapies. This retrospective, observational study hypothesised that the investigational amino acid PET tracer fluciclovine F18 could effectively detect disease recurrence in this patient group and would be well tolerated. Diagnostic performance of fluciclovine F18, as compared to histopathology and clinical follow-up, was determined in a patient cohort with sufficient data for truth determination. The safety profile and imaging positivity rate relative to PSA level were evaluated in the larger cohort.

Materials/Methods: Overall, 714 cancer patients underwent fluciclovine F18 PET-CT scanning at 4 sites in Norway, Italy and USA, including 596 patients who presented with BR of prostate cancer. Imaging positivity or detection rate (DR) was determined according to PSA quartile. To determine diagnostic performance in prostate cancer BR, fluciclovine F18 PET-CT results were compared to available histopathological findings (n=143) and to histopathology plus clinical follow-up (n=125). Determination of DR, sensitivity and specificity, positive and negative predictive value (PPV, NPV) were made, as applicable, at lesion, regional and subject level (prostate/prostate bed (P/B) or extra-prostatic (E/P)).

Results: Fluciclovine F18 was very well tolerated: adverse events possibly related to fluciclovine were reported by 0.6% of patients; no significant treatment-related effects on laboratory values or ECG variables were noted. Risk factors for the prostate cancer BR cohort included: Gleason score ≥7 (80%); intermediate/high risk by D’Amico criteria at initial treatment (65%); median PSA before imaging: 2.03 ng/mL. For diagnostic performance vs. histopathology (n=143) the sensitivity for detection of P/B disease was 88.1%, with specificity of 32.6% and PPV of 71.8%. The PPV for E/P disease was higher at 92.3%. For diagnostic performance vs pathology plus clinical follow up (n=125), sensitivity, specificity, PPV and NPV for the regions P/B and E/P were: P/B: 95.1%, 48.8%, 78%, 84%, and E/P: 84.2%, 89.7%, 78.0%, 92.9%. Analysis of patient level DR (%) by PSA quartile (ng/mL) in the full BR cohort (n=596) was: ≤0.79: 41%; >0.79 to ≤2.03: 59%; >2.03 to ≤6.0: 75%; >6.0: 86%.

Conclusion: Fluciclovine (18F) PET-CT scanning is well tolerated and able to sensitively detect recurrent prostate cancer, even at PSA levels below 1ng/mL, potentially facilitating the optimization of subsequent patient management, including the scope and dose of radiotherapy.

Purpose/Objective(s): Early salvage radiation therapy (SRT) following radical prostatectomy (RP) has been shown to reduce biochemical recurrence and distant metastases. Using a consortium database including data from 10 academic institutions, we assessed the impact of SRT initiation at lower prostate specific antigen (PSA) levels on prostate cancer-specific mortality (PCSM) and all-cause mortality (ACM).

Materials/Methods: In this IRB-approved retrospective study, 2,454 node-negative patients (pts) with detectable post-prostatectomy PSA (≥0.01 ng/mL) treated with SRT ± neoadjuvant/concurrent androgen deprivation therapy (n/c ADT) were included. Exclusion criteria included previous ADT or incomplete treatment, staging, or follow up details. Cumulative incidence method of Fine-Gray and Kaplan-Meier methods were used to estimate rates of PCSM and ACM, respectively. Univariate and multivariable analyses (MVA) were performed by competing risks regression (CRR) and Cox proportional hazards (CPH) methods for PCSM and ACM, respectively. Results: Median follow-up was 5.1 years following SRT end-date; 597 pts (24%) had pathologic Gleason score (GS) of ≤6, 1383 (56%) GS 7, and 474 (19%) GS ≥8. There were 1365 (56%) with extraprostatic extension, 451 (18%) seminal vesicle invasion, 1430 (58%) positive surgical margins, and 390 (16%) received n/c ADT for a median of 6 months. Median age at RP and SRT were 61 years (IQR 56-66) and 64 years (59-69), respectively. Median SRT dose to the prostate bed was 66 Gy (IQR 64.8-68) and median pre-SRT PSA was 0.5 ng/mL (IQR 0.3-1.1). The 5 and 10-year PCSM rates were 3% and 6%, respectively. The 10 year PCSM rate was 5% for pre-SRT PSA ≤0.2 ng/mL, 6% for 0.21-0.50 ng/mL, 8% for 0.51-1.0 ng/mL, 18% for 1.01-2.0 ng/mL, and 22% for >2.0 ng/mL, P <.0001. The 5 and 10-year ACM rates were 7% and 23%, respectively and at 10 years was 14% for pre-SRT PSA ≤0.2, 16% for 0.21-0.50, 23% for 0.51-1.0, 30% for 1.01-2.0, and 38% for >2.0, P <.0001. On MVA, higher pre-SRT PSA (HR = 2.13, p<.0001), higher GS (GS 7 vs. ≤6: HR 2.01 p=.0012; GS ≥8 vs. 6: HR 3.34 p<.0001), seminal vesicle invasion (HR 2.48 p<.0001), and year of SRT (2000-2004, 1995-1999, 1985-1994 vs. 2005-2012; HR 2.87 p=.021, HR 2.50 p=.0097, HR 3.58 p=.0016, respectively) were significantly associated with higher PCSM, while extraprostatic extension, surgical margins, ADT use, SRT dose, age at SRT, and age at RP were not. These same variables were significantly associated with higher ACM on MVA, in addition to advanced age at RP (HR 1.06 p<.0001). Conclusion: Initiation of early SRT at low PSA levels compared to higher PSA levels following RP is associated with reduced risk of PCSM and ACM. Other factors significantly associated with PCSM include higher GS, seminal vesicle invasion, and earlier year of SRT.

Circulating Cell-Free Human Papillomavirus DNA as a Marker of Treatment Outcome in Patients With HPV-Positive Squamous Cell Head and Neck Cancer After Radio(chemo)Therapy

Purpose/Objective(s): Recent studies confirmed that circulating cell-free HPV DNA (cfHPV DNA) could be found in blood of most patients with HPV-related HNSCC that its level changes as the treatment progresses and may be related to the treatment outcome. As the response to treatment is reflected in cfHPV DNA detection, it may become a feasible tool in monitoring of treatment results. The study presents original results on cfHPV DNA estimation before, during radiotherapy (RT) or chemoradiotherapy (CHRT) and after their completion in patients with HNSCC.

Materials/Methods: Between February 2012 and December 2015 collection of blood samples from 477 consecutive patients with HNSCC before definitive RT or CHRT was performed. If HPV-positive sample was identified, serial blood collections were taken during treatment, after its completion and during follow-up. The cfHPV DNA status was assessed in plasma blood samples by TaqMan/PCR and confirmed in formalin-fixed paraffin-embedded tumor samples. The results of cfHPV DNA assessment were correlated with the treatment outcome. The cfHPV DNA complete remission (cfHPVrem) was defined as a not detectable level of cfHPV DNA in blood serum. The cfHPV DNA recurrence (cfHPVrec) was defined as a detection of cfHPV DNA in serum of previously cfHPVrem patients during follow-up.

Results: In 67 patients (14%) cfHPV DNA was found. Two patients were excluded due to palliative approach (1) or loss in follow-up. Thus the cfHPV DNA was subsequently assessed in 65 (13.5%) patients after treatment. Three patients (0.5%) presented uncured disease after the treatment and their cfHPV DNA remained detectable over the observations. The rest of 62 patients had cfHPVrem after treatment completion and all of them were followed with cfHPV DNA estimation during follow-up. Subsequently cfHPVrec was found in 6 patients (9%) during follow-up. Despite of no evidence of locoregional recurrence of disease neither in physical examination nor on imaging diagnostic (TK or MRI) PET scanning was additionally performed in these patients and revealed locoregional recurrence and metastatic HNSCC in 3 (4.5%) and 3 (4.5%) patients respectively.

Conclusion: In patients with HPV-related HNSCC the presence of cfHPV DNA in blood reflects active cancer progression. The estimation of cfHPV DNA in patients controlled by RT or CHRT suggests sub symptomatic HNSCC relapse and/or dissemination what opens a chance for successful salvage.


Identification and Validation of Intrinsic Subtypes of Prostate Cancer


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**Purpose/Objective(s):** To identify the first ever intrinsic molecular subtypes of primary prostate cancer through unbiased high-throughput analyses.

**Materials/Methods:** RNA expression patterns captured from high-density microarrays and transcriptome sequencing were analyzed in 4,236 primary prostate cancer samples from nine independent cohorts. K-medoids clustering was used in training and validation sets to identify intrinsic subtypes. The subtypes were correlated with distant metastasis-free survival (DMFS). The Database for Annotation, Visualization and Integrated Discovery (DAVID) was used to identify biological functions enriched in the subtype genes. Mutation analysis was performed using the cBioPortal for Cancer Genomics.

**Results:** Clustering in the training dataset initially was strongly influenced by stromal genes, likely indicative of tumor content, as well as genes strongly associated with warm ischemia, likely indicative of elapsed time between specimen harvest and fixation. After these tumor extrinsic factors were removed, we identified three distinct groups based on 100 genes (PC100). These findings were validated in the remaining seven frozen or FFPE retrospective cohorts as well as in a prospective validation cohort of 2,113 patients. The intrinsic subtypes were associated with known drivers of prostate cancer, including AR and ERG, but do not appear to be driven by mutations or rearrangements. The 10-year rates of DMFS across the three subtypes were 73.6% (A), 64.4% (B), and 57.1% (C) (B vs. A: Cox HR=1.31 [95%CI 1.04-1.66], p=0.02, C vs. A: HR=1.65 [1.29-2.10], p=0.0001). The subtypes were independently associated with DMFS after adjusting for clinicopathologic variables (B vs. A: Cox HR=1.31 [1.03-1.65], p=0.026, C vs. A: HR=1.33 [1.04-1.71], p=0.024). Furthermore, on multivariate interaction analysis, subtype C was significantly associated with response to post-operative radiotherapy (Wald p=0.0016). Within the 100 genes, enriched biological functions relate to clusters of genes governing protein degradation, RNA processing, apoptosis, the cell cycle, ATP synthesis, and a large cluster of genes relating to protein localization.

**Conclusion:** We have identified three novel intrinsic subtypes of prostate cancer in the largest study of its kind, and validated our findings across sequencing platforms, storage methods, and within both retrospective and prospective cohorts. In defining unique biological clusters of disease, the PC100 represents a step towards personalization of prostate cancer care. Future work will focus on validating the predictive capacity of these subtypes to therapy such as radiation therapy.


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**CAPP-Seq Circulating Tumor DNA Analysis for Early Detection of Tumor Progression After Definitive Radiation Therapy for Lung Cancer**

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Purpose/Objective(s): Response Evaluation Criteria in Solid Tumors (RECIST) is the primary method used to evaluate response to cancer therapeutics in clinical trials but can be challenging to perform after radiotherapy. Cancer Personalized Profiling by deep Sequencing (CAPP-Seq) is a novel blood-based assay that uses next-generating sequencing to quantitate circulating tumor DNA (ctDNA). We performed a prospective study to compare response evaluation by CAPP-Seq and RECIST after definitive radiotherapy for lung cancer.

Materials/Methods: We prospectively enrolled 30 patients treated with definitive radiotherapy for non-metastatic primary lung cancer at our institution between June 2010 and December 2014. Our cohort included 21 (70%) patients with stage III, 5 (16.7%) patients with stage II and 4 (13.3%) patients with stage IB disease. All patients received pre-treatment evaluation by thoracic CT and PET/CT scans and ctDNA quantitation by CAPP-Seq. Twenty-one (70%) patients were treated with chemo-radiation and 9 (30%) were treated with hypofractionated radiotherapy. Following treatment, patients underwent disease surveillance by CT scans and CAPP-Seq every 3-6 months. CT scans were evaluated using RECIST criteria by an experienced radiologist and radiation oncologist. CAPP-Seq was performed at each time point as previously described (Newman et al, Nature Medicine, 2014).

Results: Median follow-up time was 20.8 months. Median overall survival was 23.1 months. Sixteen (53.3%) patients progressed based on RECIST criteria, while the remaining 14 (46.7%) patients demonstrated complete response, partial response or stable disease. CAPP-Seq detected ctDNA at or before the time of RECIST progression in all patients who progressed with a lead-time of 113.6 +/- 27.8 days (mean +/- SEM) and did not detect ctDNA at last follow-up in non-progressing patients. In the majority of patients who progressed (11 of 16; 68.8%), ctDNA was detected prior to RECIST progression with a lead-time of 165.2 +/- 28.9 days (mean +/- SEM). The ctDNA concentration at time of progression was 76.6 +/- 50.7 haploid genome equivalents/mL (mean +/- SEM). Two-year overall survival for patients with ctDNA progression was 21.1% versus 90.9% for non-progressors (p=0.0003, HR=6.7, 95% CI=2.4-18.7).

Conclusion: Our data suggest that CAPP-Seq-based ctDNA assessment is an accurate and sensitive method for evaluating response to thoracic radiotherapy. On average, detection of ctDNA anticipated imaging-detected disease progression by over 3.5 months, potentially facilitating clinical studies of early therapeutic interventions when disease burden is minimal.


Suppression of Major Histocompatibility Complex (MHC) Class I and II Mediates Resistance to Anti-PD-1 in Lung Adenocarcinoma Tumors That Can Be Overcome by Radiation Therapy

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Purpose/Objective(s): PD-1/PD-L1 blockage therapy, given as single agent have produced objective response rates ranging from 15% to 25% in patients with chemotherapy refractory non-small-cell-lung-carcinoma (NSCLC). Nevertheless, large proportions of patients do
not respond to anti-PD-1/PD-L1 immunotherapies. Therefore, we sought to investigate the mechanisms of nonresponses and potential strategies to overcome resistance. Here we generated an anti-PD-1-resistant preclinical tumor model with which to identify mechanisms of resistance, which should provide novel insights to expand the benefit of immunotherapies.

**Materials/Methods:** This model was generated by inoculating the murine lung cancer cell line 344SQ (containing p53R172H;g/εK;rasLA1+/− mutations) into syngeneic 129Sv/ev mice, which were then given 4-5 doses of anti-mouse PD-1 antibody (10 mg/kg). The anti-PD-1 resistant tumor model was successfully generated after sequential in vivo passage of a nonresponsive tumor with ongoing anti-PD-1 treatment. For the combined radiation plus anti-PD-1 therapy studies, the first dose of anti-PD-1 (10 mg/kg) was given on the same day of first fraction of radiation (12G in 3 fractions) and continued for additional 3-4 doses. For experiments involving blockade of type I IFN signaling, anti-mouse IFNAR-1 antibody was injected daily for 14 days, starting on the day of first dose of anti-PD-1. For studying the growth rate of the tumor mass, the length (L) and width (W) of tumors were measured with calipers. Tumor volume (V) was calculated as: V=W² x L/2. The unpaired Student t test was used for analysis of most data except that the tumor growth curve was analyzed by multiple t tests for each time points. All reported P values are two-sided and were declared as significant at the level of 5%.

**Results:** PD-L1 expression was not different in the resistant vs. parental tumor cells. Microarray and flow cytometry studies demonstrated that genes in the antigen presentation pathway, including major histocompatibility complex (MHC) class I and II, were significantly downregulated in the anti-PD-1-resistant tumors compared with parental tumors. Resistant tumors also showed fewer CD8+ and CD4+ tumor-infiltrating lymphocytes and reduced production of interferon (IFN)γ. Local tumor radiotherapy induced IFNγ production, which in turn induced MHC class I expression on both parental and resistant tumor cells and restored the resistant tumor to anti-PD1 response. Blockade of type I IFN signaling abolished the effect of radiation on sensitization of anti-PD-1 response.

**Conclusion:** We discovered a novel mechanism of PD-1 resistance and demonstrated radiation can be used to overcome such resistance. Our findings suggest that the poor efficacy of anti-PD1 as an immune checkpoint therapy in most patients might be accentuated greatly by adjuvant radiotherapy, thereby broadening its useful application against melanoma and lung cancers where robust but relatively infrequent responses have been documented.

blockade. Imaging of the respective knockout mice, blocking experiments with an excess amount of unlabeled antibodies, and the analysis of animals bearing both wild-type B16 melanomas and PD-L1-CRISPR knockout melanomas demonstrated the high specificity of the two newly developed PET tracers. The in vivo imaging data were confirmed by ex vivo biodistribution analyses. The targets of the PET tracer antibodies were verified by ex vivo flow cytometric analyses. Visualization of immune-related adverse events was also possible.

**Conclusion:** We developed two innovative PET tracers that allow imaging the expression of the receptor/ligand pair of the important PD-1/PD-L1 checkpoint and the biodistribution of surrogate checkpoint-blocking antibodies in fully immunocompetent mice. This technology also enables whole-body pictures of combination radio/immunotherapies.

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## Gynecologic

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**A Phase III Randomized Trial Comparing Patient-Reported Toxicity and Quality of Life (QOL) During Pelvic Intensity Modulated Radiation Therapy as Compared to Conventional Radiation Therapy**


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**Purpose/Objective(s):** To determine if pelvic intensity modulated radiation therapy (IMRT) results in a significant reduction in patient reported acute toxicity, and better QOL as compared to standard radiation.

**Materials/Methods:** Patients with cervical and endometrial cancer who received pelvic radiation postoperatively were stratified by dose (45 or 50.4 Gy), use of chemotherapy (none or 5 cycles of weekly cisplatin at 40 mg/m2), and disease site, and then randomly assigned to standard 4-field radiation or IMRT. The primary endpoint was change in acute gastrointestinal (GI) toxicity from baseline to 5 weeks measured by the bowel domain of Expanded Prostate Cancer Index Composite (EPIC). Change in EPIC score was calculated such that a negative change scores indicated a decline in function. With an effect size of 0.4, a t-test with 1 interim look and a 2-sided alpha=0.05, 225 patients were needed for 85% power. Secondary endpoints included a comparison of adverse events, urinary toxicity using EPIC and QOL using the FACT-G with cervix subscale. A Wilcoxon signed rank test was used for non-normal data.

**Results:** There were 289 patients enrolled between November 2012 and August 2015; 11 patients were found to be ineligible, leaving 278 eligible patients. The conventional RT arm had a significantly larger mean decline in EPIC bowel summary score at 5 weeks as compared to the IMRT arm (-23.6 vs. -18.6, p=0.048). The median change in bowel function subscale was -17.9 for the conventional RT arm, as compared to -14.3 for the IMRT arm (p=0.03). For the bother subscale, the median change in score was -21.4 as compared to -21.4 (p=0.18). The conventional arm experienced a significantly larger mean decline in EPIC urinary summary score at 5 weeks as compared to the IMRT arm (-10.4 vs. -5.6, p<0.03). At 5 weeks from the start of RT, the conventional arm experienced more high-level adverse events measured by the Patient-Reported Outcomes version of the Common Terminology for Adverse Events (PRO-CTCAE) for diarrhea (frequency, p<0.01), and fecal incontinence (frequency, p<0.01; interference, p<0.04). In addition, 20.4% of women on the
standard RT arm took 4 or more antidiarrheal medications daily, as compared to 7.8% of women on the IMRT arm \((p=0.04)\). Quality of life measured with the FACT-Cx demonstrated a greater decline in the trial outcome index score in patients treated with conventional radiation as compared to patients receiving IMRT \((-12.8\ vs. \ -8.8, \ p=0.03)\).

**Conclusion:** Intensity modulated radiation therapy reduces acute patient reported GI and GU toxicity as compared to standard RT. Furthermore, patients treated with IMRT experienced better QOL during treatment. Longer follow-up will be needed to determine if differences in acute toxicity result in lower rates of chronic toxicity.


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**Phase 3 Randomized Trial of Comparing Chemoradiation Therapy Versus Radiation Therapy Alone in Lymph Node–Negative Patients With Early-Stage Cervical Cancer Following Radical Hysterectomy**

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**Purpose/Objective(s):** Chemotherapy concurrent with radiation therapy has become the standard treatment for cervical cancer patients with high risk factors. However, the treatment modality in patients with low-risk is still disputable. The purpose of this study is to determine whether concurrent paclitaxel/cisplatin chemoradiation therapy are more effective than radiation therapy alone in treating early-stage cervical cancer patients with negative lymph nodes after radical hysterectomy.

**Materials/Methods:** Between January 2011 and November 2014, 165 eligible cervical cancer patients with stage IA2 to IIB and negative lymph nodes were enrolled, randomized to chemoradiation therapy (CRT) (80 patients) and radiation therapy (RT) (85 patients), respectively. An RT dose of 46-50 Gy was administered in 23-25 fractions with two or four-field box technique. Chemotherapy consisted of paclitaxel 135 mg/m\(^2\) d1 and cisplatin 25mg/m\(^2\) d1-3 intravenously every 4 weeks with radiation.

**Results:** The hazard ratios \((HR)\) for disease-free survival \((DFS)\) and overall survival \((OS)\) in the CRT arm versus the RT alone arm were 0.84 (95% CI = 0.36–1.93, \(p = 0.67\)) and 0.61 (95% CI = 0.20–1.86, \(p = 0.38\)), respectively. The 5-year DFS and OS for CRT and RT alone groups were 85.9% versus 83.5%, and 92.6% versus 88.4%, respectively. For subgroup analysis, CRT significantly increased the 5-year DFS and OS for patients tumor sizes ≥3 cc \((HR 0.23; 95\% CI 0.05–1.0 and HR 0.21; 95\% CI 0.04–0.99, for DFS and OS, respectively). For patients with negative lymphovascular invasion, CRT increased 5-year DFS \((HR 0.21; 95\% CI 0.04–0.99). Multivariate analysis indicated that tumor size was a significant prognostic factor associated with both DFS and OS, and age was significantly associated with OS. Grade 2 to 4 gastrointestinal disorders, radiation enteritis, radiation cystitis and myelosuppression were more frequent side effects observed in the CRT arm. Grade 3 and 4 toxicities were rare and manageable overall.

**Conclusion:** Chemoradiation therapy with cisplatin and paclitaxel achieved better DFS and OS in early-stage cervical cancer patients after radical hysterectomy with negative lymph nodes compared with RT alone, along with a higher rates of acute grade 2-4 complications. Concurrent chemotherapy might enhance radiosensitizing effect to improve survival outcome for patients with large tumor size. Grade 3 and 4 toxicities were infrequent and tolerable overall.

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Nodal Failure After Chemoradiation and Magnetic Resonance Imaging Guided Adaptive BT in Cervical Cancer: A Subanalysis Within Embrace

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Purpose/Objective(s): Advanced cervical cancer patients treated with chemoradiation and MRI guided adaptive brachytherapy (MR-IGABT) have high local control rates with acceptable treatment related morbidity. However, nodal failure (NF) is still a matter of concern. The aim of this study was to describe the pattern of NF in patients enrolled in the EMBRACE study and to explore potential prognostic factors.

Materials/Methods: Within this sub-study NF was analyzed in 1077 patients treated with pelvic ± PAO chemoradiation and MR-IGABT at least 12 months prior. Five hundred sixteen patients (48%) had nodal disease at time of diagnosis detected on CT, MRI, US, PET-CT or by histopathology. We performed frequency analyses of anamnestische, gynaecological and histological items, MRI findings and treatment related factors for all patients as well as for patient groups with/without NF. Crude numbers and actuarial analyses are provided. Univariate analyses were used to explore potential prognostic factors for nodal pelvic and PAO failure.

Results: Nodal failure occurred in 80 of the 1077 patients (7%) with a median FU of 24 months (range 2-72); NF was detected within the first year after treatment in 84%. Persistent nodal disease was observed in 6%, whereas 90% were true nodal recurrences (4% not defined). Nodal disease at diagnosis was predominantly located in the pelvic nodes whereas nodal recurrences predominantly occurred in the PAO (table). The 3-year nodal failure free (NFF) actuarial rates were 89% for all patients. Kaplan-Meier analyses for overall NF showed 94% for patients without and 84% for patients with nodal disease at diagnosis (p < 0.001). Besides nodal disease, FIGO stage (I+II vs III+IV) or (I,II NO vs any N+ and any III+IV), tumor width (below vs above median), uterine corpus involvement (no vs yes), lymphovascular space invasion (no vs yes), haemoglobin level (< vs ≥ 6 mmol/L), white blood cell count (< vs ≥10 x10^9/L), smoking (no vs yes), overall treatment time (< vs ≥ 49 days) and Hb level during treatment (Hb nadir dropping < vs ≥ 6 mmol/L) were significant prognostic factors. For all these variables 3-year NFF rates were significantly different ranging between 95-91% vs 86-77% with a respective difference of 6-13%.

Conclusion: The actuarial rate of NF in patients treated with pelvic ± PAO chemoradiation and MR-IGABT within EMBRACE is overall 11% at 3 years. Whereas at diagnosis int/ext iliac involvement is predominant, the PAO region becomes predominant at the time of failure. Nodal disease at diagnosis is the strongest prognostic factor for the development of nodal failure. Location of nodes at diagnosis and nodal failure; multiple sites per patient possible

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Phase 2 Multicenter Clinical Trial of Bone Marrow–Sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin for Stage IB-IVA Cervical Cancer

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Purpose/Objective(s): To test the hypothesis that intensity modulated radiation therapy (IMRT) reduces acute hematologic and gastrointestinal (GI) toxicity for patients with stage IB-IVA cervical cancer undergoing chemoradiation therapy.

Materials/Methods: We enrolled patients age > 18 with stage IB-IVA cervical carcinoma on a single-arm phase II trial at 6 centers. All patients received 5-6 weekly cycles of cisplatin (40 mg/m²) concurrently with once daily IMRT (45.0-50.4 Gy in 25-28 fractions to the pelvis; gross nodes received up to 59.4 Gy simultaneously), followed by intracavitary brachytherapy as indicated. All centers underwent IMRT credentialing and centralized quality assurance review. Intensity modulated RT plans were designed to minimize radiation dose to the pelvic bone marrow, bowel, bladder, and rectum, while maintaining target coverage. The primary endpoint was the occurrence of either acute grade ≥ 3 neutropenia or clinically significant GI toxicity (grade ≥ 2 diarrhea requiring intravenous fluids and/or combination opiate/anticholinergic antidiarrheal medication) within 30 days of completing chemoradiation therapy. A pre-planned subgroup analysis was designed to test the hypothesis that PET image-guided bone marrow-sparing IMRT (IG-BMS-IMRT) lowers the risk of acute neutropenia. Toxicity grading was according to NCI CTCAE v4. The trial is registered (NCT01554397).

Results: From October 2011 to April 2015, we consented 91 patients, with 8 screen failures and 83 eligible for analysis (86% were FIGO stage IIB-IVA). Median follow-up was 16 months. The incidence of any primary event was 26.5% (95% CI, 18.2-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data (2-sided t-test p=0.007). The incidences of grade ≥ 3 neutropenia and clinically significant GI toxicity were 19.3% (95% CI, 12.2-29.1%) and 12.1% (95% CI, 6.7-20.8%), respectively. The incidences of any grade ≥ 3 hematologic and grade ≥ 2 GI toxicity were 38.6% (95% CI, 28.8-49.3%) and 42.2% (95% CI, 32.1-52.9%), respectively. Compared to patients treated without IG-BMS-IMRT (N=48), patients treated...
with IG-BMS-IMRT (N=35) had significantly lower grade ≥ 3 neutropenia (8.6% vs. 27.1%, 2-sided chi-square p=0.035), and non-significantly lower grade ≥ 3 leukopenia (25.7% vs. 41.7%, p=0.13) and any grade ≥ 3 hematologic toxicity (31.4% vs. 43.8%, p=0.26). The 18-month disease-free survival and overall survival were 86.6% (95% CI, 78.1-95.9%) and 98.5% (95% CI, 95.5-100%), respectively. The 18-month cumulative incidences of locoregional failure, distant metastasis, and grade ≥ 3 late toxicity were 7.2% (95% CI, 3.6-10.8%), 5.0% (95% CI, 2.1-7.8%), and 8.9% (95% CI, 5.0-12.9%), respectively.

**Conclusion:** Intensity modulated RT reduces acute toxicity compared to standard treatment, with promising outcomes in the international population; IG-BMS-IMRT reduces the risk of acute neutropenia. A phase III trial of IG-BMS-IMRT versus standard of care is warranted.


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**Computed Tomography Consensus Clinical Target Volume Contouring for Intensity Modulated Radiation Therapy in Intact Cervical Carcinoma**

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**Purpose/Objective(s):** Target definition is crucial for the definitive treatment of cervix cancer with intensity modulated radiation therapy (IMRT). Consensus guidelines for the clinical target volume (CTV) have been established using magnetic resonance imaging (MRI). However, treatment planning MRI is not as readily available as computed tomography (CT) and image fusion carries inherent uncertainties. Therefore, the aim of this study was to evaluate the variability in CTV definition amongst physicians experienced in IMRT for the definitive treatment of cervical cancer in preparation for a collaborative NRG clinical trial.

**Materials/Methods:** A consensus working group that had participated in prior CTV definition was convened to contour on two treatment planning CT scans. Observers were blinded to the corresponding MRI scans. One case was an early cervical cancer and the other a locally-regionally advanced case. Clinical vignettes for the two cases were distributed and each participant was asked to draw CTV contours which included a CTV1 contour for the uterus/cervix and a CTV 2 contour for the vagina/parametria. Participants contoured on CT images of the pelvis using their own treatment planning software. Nodal CTV contours have been well described and were not included in this study. The CTV contours were then analyzed for consistency and clarity of target delineation using an expectation-maximization algorithm for simultaneous truth and performance level estimation (STAPLE, CERR), with kappa statistics as a measure of agreement between observers.

**Results:** Contoured datasets were merged and analyzed for agreement. CTV1 contours showed almost perfect agreement (Kappa > 0.8), while CTV2 showed moderate agreement (0.4 < Kappa < 0.6) among observers (see table).

**Conclusion:** Agreement among the experienced gynecologic radiation oncologists was excellent for CTV delineation in two representative intact cervical cancer cases. Consensus demonstrated near perfect agreement for the uterus and cervix and moderate agreement for the vagina and parametria. The variability seen in vaginal contours was primarily due to the vaginal length included in the CTV. The value of this data, building on previously published guidelines for IMRT in the post-operative setting and MRI guidance in
the intact setting, provides clinically valuable information to promote safety and quality among radiation oncologists treating cervical carcinoma. Furthermore, this atlas will be used for future trials utilizing IMRT for the definitive management of intact cervical cancer.

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National Cancer Data Base Analysis of Uterine Carcinosarcoma (UC): Improvement in Survival With the Use of Radiation Therapy

E. M. Nichols, S. M. Bentzen, D. Scartoni, I. Giacomelli, D. M. Roque, G. Rao, N. Hanna, and P. Mohindra; 1University of Maryland School of Medicine, Baltimore, MD, 2University of Florence, Florence, Italy, 3University of Maryland Medical Center, Baltimore, MD

Purpose/Objective(s): The value of radiotherapy in the management of UC is controversial. Several multi-institutional studies have suggested a benefit from radiation therapy (RT), although sample sizes are small due to rarity of disease. The purpose of this analysis was to estimate the association between RT and overall survival of UC using the NCDB which provides the largest report of this patient population to date.

Materials/Methods: The NCDB was queried to identify women diagnosed with UC between 1998-2012. A total of 9317 cases were identified. After excluding patients with stage IV disease or missing stage, survival, or RT data, there were 4255 evaluable cases. The primary endpoint was overall survival (OS). Chi-square tests and Kaplan-Meier estimates and Cox proportional hazards model were used in the analysis. Results: Median age at diagnosis was 68 years; 52% had stage I (n=2169), 13% stage II (n=541), and 36% stage III (n=1545) disease. Nearly 25% were African-American. Among all patients, 35% did not receive either chemotherapy (CT) or RT, 24% received RT alone, 18% received CT alone, and 20% received CT and RT. Data was missing data for 3%. Among the 1912 patients who received RT, 1387 received external beam with or without brachytherapy, 440 brachytherapy only and treatment was not otherwise specified in 85 patients. RT use did not change over time when divided into quartiles. With a median follow up of 23 m (maximum 191 m), estimated median and 5-year OS with RT was 48 months and 45% and without RT 29 months and 35% (p<0.001). When stratified by stage, receipt of RT was associated with improved OS in all stages, with the largest magnitude of benefit seen for stage I patients with a median OS of 97 versus 56 m (p<0.001) followed by 38 versus 26 m for stage II (p<0.014) and 23 versus 17 m for stage III.
(p<0.001). Improved OS with the use of RT persisted independent of receipt of CT. In patients who did not receive CT, median OS with and without RT was 38 m versus 27 m (p<0.001); in patients who received CT, median OS with and without RT was 70 m versus 33 m without (p<0.001). Five-year OS was 51.3% for patients receiving CT and RT; 39.1% for patients receiving CT alone; 40.1% for patients receiving RT alone and 33% with no CT or RT. On multivariate analyses, receipt of RT (HR 0.75: 95% CI: 0.68-0.83, p<0.001) and receipt of CT (HR 0.59; 95% CI: 0.53-0.66, p<0.001) were favorable while African American race (HR 1.34; 95% CI: 1.2-1.5), higher stage (HR 1.7; 95% CI: 1.6-1.8), older age (HR 1.03; 95% CI: 1.02-1.03), and higher Charlson/Deyo comorbidity score (HR 1.12; 95% CI 1.03-1.2) were associated with worse survival.

Conclusion: This large population based analysis provides strong evidence for an association between survival and the use of RT in the treatment of stage I-II UC. When combined with existing data, RT should be considered in patients with stage I, II, or III disease until randomized data can be obtained.


Updated 4-Year Results for NRG Oncology/RTOG 0921: A Phase 2 Study of Postoperative Intensity Modulated Radiation Therapy With Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients With Endometrial Cancer

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Purpose/Objective(s): To report 4-year outcome results including late adverse events (AEs) >1 year from treatment start, overall survival (OS), para-aortic failure (PaF), distant failure (DF), and disease-free survival (DFS) in a prospective Phase II clinical trial of bevacizumab (Bev) and pelvic intensity modulated radiation therapy (IMRT) with chemotherapy in high-risk endometrial-cancer patients.

Materials/Methods: Patients had a hysterectomy, lymph node removal, and ≥1 of the following high-risk factors: grade 3 carcinoma with >50% myometrial invasion (n=15); grade 2 or 3 disease with any cervical stromal invasion (n=10); or known extrauterine extension confined to the pelvis (n=13). Treatment included pelvic IMRT and concurrent cisplatin on days 1 and 29 of radiation and Bev (5 mg/kg on days 1, 15, 15 and 29 of radiation) followed by adjuvant carboplatin and paclitaxel for 4 cycles. Univariate OS and DFS estimates were obtained using the Kaplan-Meier method and PF and DF rates were determined by the cumulative incidence method.

Results: Thirty-four patients were accrued from November 2009 through December 2011, 30 of whom were eligible and received study treatment. The median follow up is 3.92 years (min-max: 1.13-4.96). There were 5 patients with reported grade 3 or 4 AEs > 1 year from treatment start as follows: grade 3 diarrhea/ vomiting/ low lymphocyte count/ dyspnea/ acute kidney injury; grade 3 hematura; grade 3 vaginismus; grade 3 skin/pelvic infection; and grade 4 low lymphocyte/neutrophil count. Four-year OS was 86.7% (95% CI: 68.3, 94.8), DFS was 73.2% (95% CI: 53.4, 85.6), para-aortic failure (2 patients) was 6.7% (95% CI: 1.1, 19.5) and DF (7 patients) was 23.5% (95% CI: 10.2, 39.9). No patient had recurrent disease in the pelvis throughout the duration of follow-up.
Conclusion: Postoperative Bevacizumab added to chemotherapy and pelvic IMRT was well tolerated and resulted in high overall survival rates with no pelvic recurrences at 4 years for patients with high-risk endometrial carcinoma. This combination of RT, cisplatin and bevacizumab may be considered for future clinical trials. Supported by NCI grants U10CA21661, U10CA180868, U10CA180822, U10CA37422, U24CA81647, and U24CA180803.


Implication of Adjuvant Radiation Therapy and Dose-Response Relationship for Margin-Positive Vulvar Squamous Cell Carcinoma

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Purpose/Objective(s): Patients undergoing radical vulvectomy with positive margins remain at high risk for locoregional relapse, which may be challenging to salvage. Using a national hospital-based registry, we assessed the impact of adjuvant radiotherapy (aRT) and dose on outcomes.

Materials/Methods: Patients diagnosed with vulvar squamous cell carcinoma from 1998-2012, undergoing upfront extirpative surgery with positive surgical margins were extracted from the National Cancer Data Base. Patients without known stage were excluded. Factors associated with aRT and use of specific radiotherapy dose levels were analyzed using logistic regression. Log rank test and multivariable Cox regression were utilized for overall survival (OS) analysis.

Results: In total, 3075 patients were identified with a median age of 66 years. A majority had FIGO stage IA/B disease (41.2%) with median tumor size of 3 cm (interquartile range [IQR] 1.5-4.7). Of those undergoing lymph node (LN) assessment (80.8%), 68.1% had positive LNs. With a median dose of 54.0 Gy (IQR 48.6-60.0), 35.3% (n=1085) received aRT. Among these patients, 38.8% received chemotherapy, mostly with aRT (91.7%). Intensity-modulated radiotherapy was used in 17.2% of patients, increasing over time (OR 1.51, p<0.001). With 36.4-month median follow-up, 3-year OS was 64.2% in all patients, which was improved with aRT (67.4 vs. 58.5%, p<0.001). On multivariable analysis, older age, higher comorbidity score, higher stage, tumor size >4 cm, and adverse nodal characteristics (no dissection, low dissection yield, greater number of involved LNs) were significant predictors of inferior OS. Receipt of aRT reduced the risk of overall death (HR 0.70, p<0.001). Radiotherapy dose was associated with OS on univariate analysis as a continuous variable (p<0.001). Patients were stratified by dose: <48.6 Gy (24.8%), 48.6-53.9 Gy (15.6%), 54-59.9 Gy (28.7%) and ≥60 Gy (30.9%). Unadjusted 3-year OS suggested a dose-response relationship: 49.8, 57.3, 70.1 and 65.3%, respectively (p<0.001). On multivariable analysis using a 4-month conditional landmark, patients receiving ≥54 Gy derived the greatest mortality reduction: 48.6-53.9 Gy (HR 0.80, p=0.673), 54-59.9 Gy (HR 0.67, p=0.027), ≥60 Gy (HR 0.65, p=0.019). No survival benefit was seen when receiving ≥60 Gy (HR 0.94, p=0.738) compared to 54-59.9 Gy. Patients with FIGO stage IVA disease and nodal involvement were less likely to receive doses ≥54 Gy. For node-positive patients, aRT dose ≥54 Gy retained a similar mortality reduction on multivariable analysis (HR 0.55, p<0.001).

Conclusion: Patients with vulvar squamous cell carcinoma and positive surgical margins derive an overall survival benefit from adjuvant radiotherapy with an optimal dose range of 54-59.9 Gy.

Impact of Cumulative Radiation Doses to Vagina on Late Toxicity and Sexual Quality of Life in Patients Treated With Postoperative Adjuvant Radiation Therapy for Cervical Cancer

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Purpose/Objective(s): Post-operative pelvic radiation leads to vaginal atrophy, telangiectasia and vaginal shortening which may impact sexual quality of life (QOL). With an aim to investigate dose response relationship with clinically significant vaginal morbidity and QOL, we undertook this study.

Materials/Methods: Patients receiving postoperative pelvic radiation in ongoing clinical trials treated between January 2011 to December 2014 were studied. All patients received external beam radiation therapy (EBRT) (50 Gy/25#/5 wks) +/- concurrent cisplatin chemotherapy followed by high dose rate endo-vaginal brachytherapy (BT) (6 Gy at 0.5 cm from surface x 2 # once weekly). Patients with disease free and atleast 9 months follow-up period were included in this study. Baseline vaginal length was determined from CT imaging done with vaginal cylinders for brachytherapy planning. Vaginal dose points were defined circumferentially along vaginal cylinder and at 5 mm depth at 12, 3, 6 and 9 ‘o’ clock positions at every 2 cm from vaginal apex to introitus. The average treated length of vagina was 3-4 cm. Equivalent doses in 2Gy (EQD2) for EBRT and BT were calculated for vagina with α/β=3. Vaginal stenosis was reported as percentage shortening in reference to baseline length and mucosal changes were recorded according to CTCAE version 3.0. Receiver Operator Characteristics curve was used to identify dose thresholds that predicted vaginal shortening with highest specificity. All dosimetric data was dichotomized across these thresholds. Sexual QOL was reported using 6 QOL domains in EORTC Cx24. Univariate and multivariate analysis was performed using SPSS version 20.0.

Results: Ninety-two patients with a median age of 49 (32-71) years were included. The mean dose at vaginal apex at mucosa and 5 mm depth was 122 (78-198) Gy3 and 87.6 (70-149) Gy3 respectively. At median follow up of 25 (9-48) months vaginal shortening ≥ 25% and grade ≥II telangiectasia was observed in 33.7% and 40% patients respectively. On univariate analysis vaginal apex mucosal and 5 mm depth dose >142 Gy3 and > 88 Gy3 predicted for vaginal shortening (p=0.004 and 0.04). No correlation was observed with volume of vaginal mucosa receiving >142 Gy3. Age, type of surgery, BT technique, chemotherapy, sexual activity or follow up duration were not significant. On multivariate analysis only vaginal mucosal doses >142 Gy3 predicted for stenosis (p=0.004). None of aforementioned factors predicted for telangiectasia. Overall there was improvement in vaginal function QOL scores at 1 year (p =0.04). No correlation was observed between vaginal shortening ≥ 25% and sexual QOL.

Conclusion: Vaginal apex mucosal dose >142 Gy3 independently predicts for clinically significant vaginal stenosis but not for telangiectasia. No correlation could however be established between vaginal shortening and sexual QOL.

Deferring Radiation Therapy for Brain Metastases in Patients With EGFR-Mutant Non-Small Cell Lung Cancer: A Multi-Institutional Analysis

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Purpose/Objective(s): Stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT) remains the standard of care treatment for brain metastases from non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are being considered as treatment options for asymptomatic brain metastases in patients with EGFR-mutant NSCLC. This multi-institutional study looks to determine if the deferral of radiotherapy (RT) in favor of EGFR-TKI impacts patient outcomes.

Materials/Methods: Between 1/1/2008 and 12/31/2014, 162 patients from 4 institutions with EGFR-mutant NSCLC developed brain metastases and met inclusion criteria for the study. Exclusion criteria were the following: prior EGFR-TKI use, EGFR-TKI resistance mutation, failure to receive EGFR-TKI after WBRT/SRS or less than 6 months follow-up. Patients were treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI or EGFR-TKI followed by SRS or WBRT within two to four weeks of intra-cranial progression. Overall survival (OS) and intra-cranial progression free survival (IC-PFS) was measured from the date of brain metastases and determined using the Kaplan Meier method.

Results: The median OS was longer in the upfront RT group compared to the upfront EGFR-TKI group (29.4 vs 20.5 months; p=0.0015). On subgroup analysis, the SRS group had longer median OS than the upfront EGFR-TKI group (40.8 vs 20.5 months; p=0.0001), but the WBRT group did not (25.3 vs. 20.5 months; p=0.07). Median intra-cranial PFS was improved in patients receiving upfront RT compared to those receiving upfront EGFR-TKI (21.1 vs. 13.4 months; p = 0.003). A disease specific-graded prognostic assessment was calculated for each patient and was similar between all three groups (p=0.28).

Conclusion: The current study suggests that the use of upfront EGFR-TKI, and the deferral of upfront RT, may result in inferior OS and IC-PFS in patients with EGFR-mutant NSCLC who develop brain metastases. A prospective, multi-institutional randomized trial of upfront EGFR-TKI with RT at intra-cranial progression versus upfront RT followed by EGFR-TKI is urgently needed.


Treatment of Cerebral Radiation Necrosis With Nerve Growth Factor—A Prospective, Randomized, Controlled Phase 2 Study

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Purpose/Objective(s): A prospective, placebo controlled phase II trial was conducted to test the efficacy of Nerve Growth Factor (NGF) for the treatment of symptomatic temporal lobe necrosis (TLN).
Materials/Methods: Patients with symptomatic TLN were randomly assigned to either the control or the study group in a 1:1 ratio. The control group received corticosteroids with gradually reduced dosage. The study group received NGF with corticosteroids. NGF was dissolved in 2 mL normal saline and injected intramuscularly at 18μg/time, once a day for 2 months. The efficacy was evaluated by both the objective and subjective methods every 3-4 months after treatment. The objective method compared volumes of the necrotic masses on MRI before and after treatment. The subjective method compared the neurocognitive score as evaluated by the mini–mental status examination (MMSE).

Results: Twenty-eight cases were enrolled into this study. The objective evaluation showed that the response rate (RR) in the study group was higher than the control group. The ratio was 10 versus 2 (p=0.006), and 12 versus 3 (p=0.002) at 3-4 months and 6-8 months after intervention, respectively. The subjective evaluation demonstrated both groups were effective in controlling the necrosis related symptoms in the first 6 months after treatment. But NGF was more effective than corticosteroids at 9 months (13 versus 4, p=0.001). The only observed side effect was mild pain at the injection site in 3 patients in the study group.

Conclusion: Our results demonstrated that the process of TLN is not irreversible. NGF is more effective in recovering TLN than corticosteroids with little side effect. NGF has a longer duration in controlling the necrosis related symptoms than corticosteroids.

Author Disclosure: X. WANG: None. H. Ying: None. X. He: None. C. Hu: None.

Omission of Radiation Therapy for Low-Grade Gliomas: Molecular and Radiographic Correlates of Treatment Response and Disease Progression on a Phase 2 Clinical Trial of Adjuvant Temozolomide

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Purpose/Objective(s): Optimal adjuvant management of adult low grade gliomas (LGG) remains controversial, with adjuvant radiotherapy conferring improved survival outcomes at the cost of potential late toxicity. Previously presented results from a phase II clinical trial investigating the use of adjuvant temozolomide (TMZ) as an alternative to radiation in patients with LGG demonstrated progression-free survival (PFS) and overall survival (OS) comparable to historical controls receiving radiation alone. However, optimal candidates for omission of adjuvant radiation have not been established, and newly defined molecular subgroups may be crucial to appropriately risk stratify patients.

Materials/Methods: 120 patients with newly diagnosed WHO grade II LGGs with gross residual disease after surgical resection were enrolled in a phase II clinical trial. Patients received monthly cycles of TMZ for up to 1 year or until disease progression, and were monitored with serial MRI prior to treatment and every 2 months during treatment. 97 patients with available tissue were grouped into molecular subtype based on 1p19q codeletion and IDH1 status (1p19q codel: 1p19q codeleted/IDH1-R132H mutated; IDH1mut: 1p19q intact/ IDH1-R132H mutated); IDH1wt: 1p19q intact/IDH1-R132H wild type). For 71 patients with available serial imaging, volumetric analysis was performed with tumor volume defined as the region of hyperintensity on fluid-attenuated inversion-recovery (FLAIR) imaging.

Results: Tumor volume decreased significantly during the first 6 months of treatment for the entire cohort (28% median decrease, p<0.001); volume was significantly decreased in 1p19q codel patients (32% decrease, p<0.001), but not in IDH1mut (22% decrease, p=0.11) or IDH1wt (15% decrease, p=0.13). Molecular subtype was associated with the rate of disease progression during treatment (p<0.001), PFS (p=0.007) and OS (p<0.001). Pretreatment tumor volume was strongly associated with PFS and OS (p<0.001). We identify a low-risk group of patients with 1p19q codeletion and pretreatment tumor volume ≤ 68 cm³ with a 0% risk of progression during treatment, median PFS of 4.9 years, and median OS not reached (95% lower CI, 10.8 years).

Conclusion: We observe a significant decrease in tumor volume during treatment with TMZ specific to patients with 1p19q codeletion. Molecular subtype and pretreatment tumor volume are important predictive factors for PFS and OS in patients with newly diagnosed
LGG receiving adjuvant TMZ. Patients with 1p19q codeletion and limited residual disease after surgery may thus be optimal candidates for omission of upfront adjuvant radiotherapy.


Hippocampal Dosimetry Predicts for Cancer-Related Cognitive Impairment in Patients Treated With Cranial Radiation Therapy: Dosimetric Results of a Prospective Clinical Trial

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Purpose/Objective(s): Cancer-related cognitive impairment (CRCI) is relatively common after treatment of primary and metastatic brain tumors, however the temporality of cognitive decline after radiation therapy (RT) is not well defined, with reports of both early (<4 months) and late onset (>12 months) symptoms. Identifying dosimetric parameters predictive of CRCI is difficult due to the heterogeneity of patient characteristics, as well as inadequate documentation of confounding factors. Memory function is especially susceptible to radiation effect after treatment. The objective of this study is to correlate volumetric radiation doses received by critical neuroanatomic structures to post-RT memory impairment.

Materials/Methods: Between 2008 and 2011, 53 patients with primary brain malignancies were treated with conventionally fractionated RT on a prospectively accrued clinical trial performed at our institution (WFU97100/91105). Tumor types included glioblastoma (13%), primitive neuroectodermal tumors (21%), and low grade/benign tumors (66%). Ten patients received whole brain RT with region boost, all other patients received partial brain RT. The median radiation dose was 54.0Gy (range 40.0-60.6Gy) delivered in 1.8Gy/fraction (range 1.5-2.5 Gy/fraction). Dose-volume histogram analysis was performed for the hippocampus, parahippocampus, amygdala, and fusiform gyrus. Hopkins Verbal Learning Test-Revised (HVLT-R) scores were obtained at least 6 months after RT. Impairment was defined as a HVLT-R immediate recall score ≤15, based upon studies reporting optimal sensitivity and specificity for detecting impairment using HVLT-R cut-off scores of 14.5-15.5. For each anatomic region, serial regression was performed to correlate volume receiving a given dose (V_D(Gy)) with memory impairment.

Results: Hippocampal V_{53.4Gy} - V_{60.9Gy} significantly predicted post-RT memory impairment (p<0.05). Within this range, the hippocampal V_{55Gy} was the most significant predictor (p=0.004). Hippocampal V_{55Gy} of 0%, 25%, and 50% were associated with post-RT impairment rates of 14.9% (95% CI: 7.2% - 28.7%), 45.9% (95% CI: 24.7% - 68.6%) and 80.6% (95% CI: 39.2% - 96.4%), respectively. Dose received by the fusiform gyrus was a significant predictor of impairment, with the most significant relationship at V_{46.5Gy} (p=0.003). No statistically significant relationship was observed for the amygdala or parahippocampus.

Conclusion: Injury to the hippocampus plays a fundamental role in CRCI. This analysis provides dosimetric guidelines to limit cognitive decline after cranial RT. The hippocampal V_{55Gy} is a significant predictor for impairment, and limiting dose below 55Gy may minimize treatment related neuro-cognitive toxicity.

Postoperative Stereotactic Radiosurgery Versus Observation for Completely Resected Brain Metastases: Results of a Prospective Randomized Study

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Purpose/Objective(s): Stereotactic radiosurgery to a surgical cavity (SRS-cav) to improve local control (LC) after resection of brain metastases (BM) is an alternative to adjuvant whole brain radiotherapy (WBRT), which is associated with toxicity, particularly cognitive decline. However, limited prospective data regarding the efficacy or complications of SRS-cav for LC is available. In addition, LC after SRS-cav has not been compared to observation (OBS) alone after BM resection with modern surgical techniques.

Materials/Methods: Patients with one to three BMs with complete resection of at least one metastasis were enrolled. Patients were randomized to either SRS-cav or observation (OBS) of the surgical cavity (or cavities if >1 lesion was resected). Stratification variables were: 1) 1 vs 2-3 BM, 2) melanoma vs other histology and 3) pre-operative tumor size <3 cm vs >3 cm. The remaining 1-2 unresected BMs in both groups were treated with SRS. Maximum eligible diameters of the cavity and an unresected BM were 4 cm and 3 cm, respectively. SRS dose (12-14-16 Gy) was assigned by cavity volume at time of SRS. The primary endpoint was failure of LC in the resection cavity as determined by the study neuro-radiologist on follow up MRIs. Major secondary endpoints included overall survival (OS), development of distant BM (DBM), complications and use of WBRT. The study was designed with an 80% power to detect a HR of 0.6 assuming a two-sided 5% alpha and 50% LC at 6 mo in the OBS arm.

Results: From 10/2009 to 10/2015, 131 eligible patients (61 female, 70 male, median age 58 y) with a total 140 resected BMs were randomized to SRS-cav (n=64) vs OBS (n=67). 34 and 28 additional BMs were present and received SRS in the SRS-cav and OBS arms, respectively. There were no differences between the groups based on relevant demographic factors. Median follow-up for all patients was 12.6 mo, (range 0.3-70.6 mo). LC rates were superior in the SRS-cav vs OBS group with a HR of 0.46: 95% (CI 0.25, 0.85, p=0.011. LC rates for SRS-cav and OBS were 83% vs 57% at 6 mo and 72% vs 45% at 12 mo, respectively. No significant SRS-cav complications were noted. DBM rate at 12 mo was 43% vs 33% in the SRS-cav vs OBS groups, respectively, (HR 0.79, 95% CI 0.50, 1.24, p=0.29). WBRT was given in 24 SRS-cav and 30 OBS patients with a median time to WBRT of 16.1 and 15.2 mo, respectively (HR 0.8, 95%CI 0.5,1.4, p=0.42). Median OS was 17 mo in both arms (HR 1.22, 95% CI 0.79,1.87, p=0.37). On multivariate Cox regression analysis, histology, lesion number, systemic disease status or GPA did not affect LC. Use of SRS-cav (HR 0.4, 95% CI 0.2,0.8) was associated with better LC and pre-operative tumor > 3 cm (HR 2.4, 95% CI 1.2,4.9) was associated with worse LC.

Conclusion: This study confirms the benefit of SRS to a surgical cavity in improving LC compared to observation alone. Larger lesions may have a worse LC than smaller ones. OS and DBM were not affected by the use of SRS. Further study on failure patterns and cause of death is ongoing.

Mibefradil Dihydrochloride With Hypofractionated Radiation for Recurrent Glioblastoma: Preliminary Results of a Phase 1 Dose Expansion Trial

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Purpose/Objective(s): Recurrent Glioblastoma Multiforme (GBM) has limited treatment options and the prognosis is poor. Our group recently performed a high-throughput screen for novel DNA repair inhibitors which identified mibefradil dihydrochloride, a T-type calcium channel blocker. We and others subsequently revealed that mibefradil is active as a glioma radiosensitizer. More recent studies in our laboratory indicate that mibefradil blocks non-homologous end joining (NHEJ). Based on these findings, we sought to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of mibefradil and radiation therapy (RT), in a Phase I recurrent GBM study.

Materials/Methods: The Primary objective was to determine mibefradil MTD when administered with concurrent hypofractionated RT. Secondary objectives included safety, pharmacokinetics (PK), progression-free survival (PFS) and overall survival (OS). A tertiary objective included assessing intra-tumoral drug concentrations in patients enrolled in the translational sub-study within this trial. In this highly novel part of the study, patients were given mibefradil for 5 days prior to surgery, which was immediately followed by a re-resection. Resected tissues were then analyzed for the presence of drug in situ using LC/MS, in both T1-post contrast and FLAIR enhancing areas of disease; as identified by intraoperative MRI. Inclusion criteria included histologically proven GBM progressive or recurrent following RT and temozolomide. Patients received mibefradil, which was dose escalated from 150mg/day until the maximum tolerated dose (MTD) is determined, or until a dose of 350 mg/day was reached using a standard 3 + 3 design. RT consisted of 5 fractions of 600 cGy each, delivered over two weeks for a total of 3,000 cGy using stereotactic, intensity-modulated RT.

Results: To date, 12 patients have enrolled including two translational patients, and 11 have been successfully treated. There were three DLTs, and a final dose level of 200 mg/day was reached. One patient experienced a complete radiographic response on MRI. The median PFS was 5.25 months and the median OS was 12.75 months. Intriguingly, Mibefradil was detected at micromolar levels in GBM tumor tissue in two patients enrolled in the translational sub-study. Of note, we detected drug levels in biopsies specifically from T1-post contrast and FLAIR regions of disease. These levels in the tumor correlate with that required for tumor cell radiosensitization in vitro.

Conclusion: Our preliminary data suggest mibefradil can be safely co-administered with RT over a 17 day period at 200 mg/day. Promising local control signals apparent in a selection of patients, and we have demonstrated adequate levels of the drug directly in resected brain tumor tissue. Based on the positive results of this study, we are now designing a Phase I trial testing the efficacy of this drug in front-line GBM.

Purpose/Objective(s): In this study we attempt to better discern the factors predictive of distant brain failure (DBF) and determine for which patients initial whole brain radiotherapy (WBRT) may reasonably be deferred.

Materials/Methods: A total of 2,941 patients from eight academic centers were initially treated with upfront SRS alone for brain metastasis. Competing risks analysis was performed to estimate the cumulative incidence of DBF versus death prior to DBF, as well as the cumulative incidence of first salvage with SRS versus WBRT versus death prior to salvage. Univariate and multivariate analysis were performed to estimate subdistribution hazard ratios (HR) for predictor variables of interest.

Results: Of the 2,941 patients treated with upfront SRS alone, 2441 (83.0%) patients were deceased at the time of analysis, with DBF occurring in 1358 (46.5%) of all patients. Median overall survival (OS) was 9.8 months (95% CI: 9.2-10.3 mo.). The estimated cumulative incidences of DBF at 6, 12, and 24 months were 27.2%, 35.7%, and 45.1%, respectively. Predictors of DBF identified on univariate analysis included age (p<0.001), KPS (p<0.001), systemic disease status (p<0.001), number of brain metastases (p<0.001), SRS dose (p<0.001), and melanoma histology (p<0.001). Multivariate analysis (MVA) identified an increased hazard of DBF associated with increasing number of brain metastases (HR = 1.08, p<0.001) and melanoma histology (HR = 1.31, p < 0.001), while there was a decreased hazard of DBF (and an increased hazard of death prior to DBF) associated with age > 60 (HR = 0.82, p < 0.001), KPS < 70 (HR = 0.54, p < 0.001), progressive systemic disease (HR = 0.86, p<0.003), and SRS dose < 20 Gy (HR = 0.79, p<0.001). MVA for SRS vs. WBRT vs. death prior to salvage revealed an increased hazard of first salvage WBRT seen with increasing number of brain metastases (p<0.001), which was most significant when using a cut-point of >8 vs ≤8 brain metastases (HR = 3.09, p<0.001). For patients with >8 brain metastases, the 9 month cumulative incidence of first salvage WBRT was 25.7% (SRS: 10.0%) versus 9.1% (SRS: 14.3%) for ≤8 brain metastases.

Conclusion: Predictors of DBF included an increased number of brain metastases and melanoma histology, while age > 60, KPS < 70, progressive systemic disease, and initial SRS dose < 20 Gy were predictive of increased risk of death prior to DBF/WBRT. Patients with ≤8 brain metastases were less likely to need WBRT salvage following initial DBF, while those with > 8 brain metastases had a higher incidence of initial salvage with WBRT than with SRS. Initial deferral of WBRT therefore appears reasonable for patients with ≤8 brain metastases, while it may be worthwhile to consider WBRT for patients with >8 brain metastases provided the aforementioned features predictive of death prior to DBF (particularly KPS < 70) are not present.

Does Whole-Brain Radiation Therapy for Oligometastatic Brain Metastases Translate Into a Survival Benefit for Patients With a Limited Competing Risk From Extracranial Disease? A Secondary Analysis of EORTC 22952-26001

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Purpose/Objective(s): The failure of randomized trials to find a survival benefit for whole brain radiation (WBRT) has been attributed to a competing risk of death from extra-cranial disease. We assessed the survival benefit of WBRT for patients with controlled extra-cranial disease and those with favorable disease-specific graded prognostic assessment (GPA) scores within EORTC 22952.

Materials/Methods: In the EORTC 22952 trial, patients with 1-3 brain metastases with stable systemic disease or asymptomatic primary tumors were randomized to WBRT versus observation prior to stereotactic radiosurgery (SRS) or after surgical resection. We performed an exploratory analysis using cox regression and Kaplan-Meier analysis to evaluate overall survival according to receipt of WBRT, accounting for 1) extracranial progression (evidence of progressive disease outside the brain) and 2) calculated GPA score (unfavorable = [0.5-2.0] or favorable = [2.5-4.0]). We adjusted for performance status, primary site, number of metastases, and initial presence of extracranial disease in multivariable analysis including time to extracranial progression as a time-dependent covariate.

Results: A total of 358 patients were included for analysis with a median follow up of 6.5 months. The most common primary site was lung (53 %) followed by breast (12 %), colorectal (8 %), and kidney (8 %). 93 of 196 patients undergoing SRS and 79 of 162 patients undergoing surgery were randomized to WBRT. A total of 140 (39 %) patients had no extracranial progression, while 81 (23 %) patients had extracranial progression < 90 days, 57 (16 %) patients between 90 and 180 days, and 80 (22 %) patients > 180 days. Overall, there was no significant interaction between the effect of WBRT and time to extracranial progression (p = 0.25) on overall survival. Although model-based risk of death was lower for the WBRT group before extracranial progression (HR [95 % CI] = 0.81 [0.54-1.22]), this was not statistically significant (p = 0.32). There was no significant difference between WBRT groups after extracranial progression (HR [95 % CI] = 1.10 [0.81-1.49]). 266 patients had data for GPA calculation with the majority (72 %) representing lung cancer. There was no overall survival benefit to WBRT among patients with favorable GPA scores (p = 1.00) or unfavorable GPA scores (p = 0.87).

Conclusion: After careful patient selection, we were unable to find a subset of patients with controlled extracranial disease or favorable GPA scores that benefited from the addition of WBRT. This secondary analysis of phase III data further supports the omission of WBRT for patients with 1-3 brain metastases undergoing SRS or surgery and close surveillance.

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Gastrointestinal

The Initial Results for a Phase 3 Study of Short-Term Versus Long-Term Chemoradiation Therapy in Locally Advanced Rectal Cancer (STELLAR Trial)

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Purpose/Objective(s): To present initial results of an interim analysis of a phase III trial of Short Term chemoradiotherapy (SCRT) (experimental group) versus Long-term chemoradiotherapy (LCRT) (control group) in Locally Advanced Rectal cancer (LARC) [STELLAR trial].

Materials/Methods: Patients with distal or middle third, T3-T4 and/or N+ rectal adenocarcinomas diagnosed by magnetic resonance imaging, were randomly assigned to experimental group or control group. In experimental group, patients received SCRT (25 Gy/5 fractions/5 days), followed by 4 courses of CAPOX. In control group, patients received LCRT (50 Gy/25 fractions/35 days with concurrent capecitabine). TME surgery was performed 4 and 6 or 8 weeks in experimental group and control group, respectively, and 2 or 6 courses of CAPOX was prescribed as the postoperative adjuvant chemotherapy in experimental group and control group, respectively. An interim analysis of the first 100 patients was planned as little is known about toxicity of short-term radiation combined with sequential chemotherapy except Polish study, the primary endpoint of this interim analysis were pCR and acute toxicities. The primary endpoint for the phase III study was 3-year disease-free survival (DFS) and the hypothesis is 3-year DFS in experimental group was non-inferior to that in control group. The estimated enrolled number of patients is 552.

Results: Until February 14, 2016, 97 eligible patients from 7 Chinese hospitals were enrolled: 52 in experimental group and 45 in control group, with median distances from tumor edge to anal verge were 3 cm and 5 cm respectively. Sixty-four patients, who had finished neoadjuvant treatment, were eligible for toxicity analysis. Grade 3+ acute toxicity was observed 26.6% of patients in experimental group and 5.9% in control group. As to 35 patients who had received TME surgery (15 in experimental group and 20 in control group), R0 resection rates and pathological complete response (pCR) rates were 93.3%, 46.7% (7/15) and 90.0%, 10.0% (2/20), respectively. An interim analysis of the first 100 patients was planned as little is known about toxicity of short-term radiation combined with sequential chemotherapy except Polish study, the primary endpoint of this interim analysis were pCR and acute toxicities. The primary endpoint for the phase III study was 3-year disease-free survival (DFS) and the hypothesis is 3-year DFS in experimental group was non-inferior to that in control group. The estimated enrolled number of patients is 552.

Conclusion: The initial analysis revealed the acute toxicity was tolerable in both groups, and the experimental group showed a surprising pCR rate (ClinicalTrials No.: NCT02533271)
Results: Thirty-seven patients have been screened and 12 patients (10 male, 2 female) enrolled. Nine patients are evaluable for toxicities thus far. Patients have been enrolled to all 3 dose levels without dose-limiting toxicities. There are no grade 4 toxicities, and the most common toxicities observed are shown (Table). Skin rash due to trametinib (2mg) led to dose-reduction in 1 patient and holding trametinib in another, both for the last 3 days of CRT. There were no interruptions in radiation therapy. 5FU was held for 3 days in 1 patient due to mucositis. One third (1/3) of the patients treated on trametinib 2mg cohort had pathologic complete response.

Conclusion: Trametinib in combination with CRT has been well-tolerated. Additional patient enrollment and longer follow-up time are needed to further evaluate toxicity and the activity of the MTD on rates of pathologic response, local control, distant relapse, and survival.

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<tr>
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<tr>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Rectal pain</td>
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Impact of Radiation Dose Escalation for Cervical Esophageal Cancer: A National Cancer Data Base (NCDB) Analysis
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Purpose/Objective(s): For cervical esophageal cancer (CEC), current NCCN guidelines support radiation therapy to 50-50.4 Gy with chemotherapy but acknowledge that higher doses may be appropriate. We sought to use the National Cancer Database (NCDB) to characterize current RT practices and identify if a dose-response relationship exists for overall survival (OS) for definitive treatment of CEC. Materials/Methods: We queried the NCDB for patients diagnosed with Stage I-III CEC from 2004-2013, and selected patients receiving definitive chemoradiation with RT doses in the range of 50-74 Gy. Using multivariate logistic regression, the database was analyzed to determine factors associated with the use of high-dose (>50.4 Gy) radiation for the treatment of CEC. Patients were then stratified into three dose levels within the 50-74 Gy range. Predictors of OS were analyzed with univariate and multivariate methods using Kaplan-Meier and Cox proportional hazards analysis. Results: 876 patients with CEC were treated with radiation to 50-74 Gy with or without concurrent chemotherapy with 826 of these patients not receiving surgery. Three dose strata were created: 50-50.4 Gy...
301 (36%) patients received control doses, 316 (38%) received medium doses, and 209 (25%) patients received high doses. Patients treated at facilities in Middle Atlantic states, female patients, and those with stage II disease were less likely (p<0.05) to receive total radiation exceeding 50.4 Gy, whereas patients with squamous cell histology were more likely (p<0.001). There was no significant association between academic/research vs. community programs and the use of greater than 50.4 Gy. Follow-up survival data was available for 743 (90%) of the remaining patients, with a median follow-up of 20 months (range 2-129). On univariate analysis, no significant associations were found between dose strata and OS for the medium (hazard ratio [HR], 1.16, p = 0.15) or high (HR, 0.86, p=0.21) groups. On multivariate analysis adjusted for factors including age, sex, race, insurance payer, academic/community facility type, geographical region, Charlson/Deyo comorbidity score, use of concurrent chemotherapy, and squamous vs. adenocarcinoma histology, there continued to be no significant associations between dose strata and OS for the medium (HR, 1.12, p=0.35) or high (HR, 0.95, p=0.75) groups. Stage III disease (HR, 1.74, p=0.003) was associated with higher mortality, while female sex (HR, 0.74, p=0.01) and use of chemotherapy (HR, 0.44, p<0.001) were associated with lower mortality. 

**Conclusion:** Nearly two-thirds of CEC patients in the United States are treated with radiation doses exceeding 50.4 Gy. Higher radiation doses were not associated with increased OS in CEC patients in the NCDB, both before and after controlling for demographics and risk factors.

**Author Disclosure:** B. De: None. R. Rhome: None. M. Buckstein: None.

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**A Randomized Phase II Trial of Neoadjuvant Chemotherapy Compared With ChemoradiationTherapy in Locally Advanced Gastroesophageal and Gastric Adenocarcinoma: Preliminary Results**

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**Purpose/Objective(s):** Whether the addition of neoadjuvant chemoradiotherapy (NACRT) to surgery can improve outcomes better than neoadjuvant chemotherapy (NACT) followed by surgery is not clear. This phase II study was designed to evaluate whether NACRT was superior to NACT with both followed by surgery and postoperative chemotherapy for locally advanced gastroesophageal and gastric adenocarcinoma.

**Materials/Methods:** Patients with resectable or unresectable gastric cancer (cT3-4NxM0 or cTxN1-3M0) were randomized to either NACT arm or NACRT arm in a 1:1 ratio with stratification by clinical T stage (cT1-3 vs cT4). NACT arm consisted of three cycles of SOX (S1: 40~60mg, orally twice daily on days 1 to 14, oxaliplatin 130mg/m² intravenously on day 1, 21 days per cycle followed by radical surgery and another postoperative three cycles of SOX. NACRT arm received intensity-modulated radiotherapy with a simultaneous integrated boost (SIB-IMRT) to primary tumor (45.1Gy and 40.04Gy in 22 fractions) concurrently with S1 (40mg/m², orally twice daily, 5 days/week) followed by surgery and four to six cycles of SOX at the same dosage with NACT arm. Surgery was scheduled to begin within 4-10 weeks of NACRT or NACT. The primary endpoint was surgical resection rate, second points were pathological response rate, postoperative complications, 3-year local control rate, disease free survival and overall survival. According to the plan design, 30 patients have to be enrolled for each arm. As for preliminary results, we investigated the effect of these two preoperative treatment on the pathologic parameters. (ClinicalTrials.gov identifier, NCT02301481)

**Results:** From November 2013 to August 2015, 43 patients were randomly assigned to this trial: 22 in NACRT arm (3 with stage II, 19 with stage III, AJCC 7th) and 21 in NACT arm (4 with stage II, 17 with stage III). Three patients did not undergo surgery because of tumor progression in each arm. R0 resection rate was 88.4% in NACRT arm (19/22). Of 18 patients who underwent surgery after the first evaluation in NACT arm, 15 had R0 resection (71.4%, 15/21), with 1 receiving R1 and 1 receiving R2 resection. The other patient who was not a surgical candidate received additional chemoradiotherapy following NACT and finally received R0 resection. Pathologic response and complete pathologic response were achieved in 100% (19/19) and 21% (4/19) of patients in NACRT arm, while 66.7% (12/18) and 11.1% (2/18) in NACT arm, respectively. More preoperative grade 1 to 3 thrombocytopenia occurred in NACT arm (38% vs
4.5%) and NACRT arm developed more dysphagia (45% vs 0%). There were no toxic death or postoperative death in both arms. Postoperative complications were similar in the two treatment groups (NACRT vs NACT, 4.5% vs 4.8%).

**Conclusion:** The design of preoperative concurrent SIB-IMRT with oral S-1 showed promising pathologic results with an acceptable toxicity profile, which encouraged future randomized phase III trials comparing NACRT with NACT for resectable or unresectable gastric cancer.


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### Patient-Reported Outcomes (PROs) in NRG Oncology/RTOG 0436: A Phase 3 Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for Esophageal Cancer Treated Without Surgery

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**Purpose/Objective(s):** RTOG 0436 evaluated the benefit of cetuximab added to chemoradiation (CRT) for the non-operative management of esophageal cancer. The primary PRO objective was an improvement in the FACT-Esophageal cancer subscale (ECS) score with cetuximab. An important secondary objective was to assess if an improvement in ECS score is associated with a clinical complete response (cCR).

**Materials/Methods:** Patients (pts) with esophageal squamous cell or adenocarcinoma (T1N1M0; T2-4AnyNM0; AnyT/NM1a) were stratified by histology, tumor size & celiac node status & randomized to weekly cisplatin (50 mg/m²), paclitaxel (25 mg/m²) & RT 50.4Gy/1.8Gy ± weekly cetuximab (400 mg/m² day 1 then weekly 250 mg/m²). Overall survival (OS) was the primary endpoint, with a target accrual of 420 pts, providing at least 82% power to detect a 15-20% ECS improvement on the cetuximab arm; α=0.05. The ECS, version 4, was given at baseline, 6-8 weeks (wks) post-treatment (tx), & at 1 & 2 years (yrs). An improvement in ECS, & its Swallowing Index (SI) & Eating Index (EI), was defined as increases of 5, 4 & 2 points, respectively, from baseline to 6-8 wks post-tx. Categorical data comparisons were performed using the chi-square test, & univariate logistic regression models were used to determine if cCR is associated with an improvement in ECS, SI, & EI scores.

**Results:** From 2008-2013 344 pts were accrued, closing early after a protocol-specified analysis of OS did not meet continuing criteria. The ECS was completed by 261 pts (93%) at baseline, 173 (62%) 6-8 wks post-tx, 117 (42%) at 1 yr & 68 (25%) at 2 yrs. Pts completing the ECS were significantly associated with higher Zubrod (p=0.01) & adenocarcinoma histology (p=0.01). At 6-8 wks, pts on the CRT+cetuximab arm did not experience improved ECS scores (36.8 vs. 52.8 CRT; p=0.96). Interestingly, pts with improved ECS were only 0.64 times as likely to be a cCR (95% CI: 0.34, 1.20); conversely, stable/declined ECS were 1.56 times (95% CI: 0.83, 2.94). The proportion of CRT pts with an improvement in SI at 6-8 wks was 9% higher than with cetuximab, but not significant (39.3% vs. 30.3%, p=0.22). There was no association between tx arm & EI at 6-8 wks, or with ECS, SI or EI at 1 or 2 yrs. Pts with a cCR did have higher ECS,
SI, & EI baseline scores, which may have partly contributed to these results. As previously reported, cCR, local control & OS were not significantly different among treatment arms.

**Conclusion:** The addition of cetuximab to chemoradiation for the nonoperative management of esophageal cancer did not improve PROs, and unexpectedly, stable or declining ECS scores following therapy were associated with a cCR.


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**Prospective Randomized Phase 2 Study of Concurrent Chemoradiation Therapy (CCRT) Versus Chemotherapy Alone in Stage IV Esophageal Squamous Cell Carcinoma (ESCC)**

T. Li, J. Lv, F. Li, P. Diao, J. Wang, C. Li, L. Liang, and L. Sun; Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Chengdu, China

**Purpose/Objective(s):** Stage IV ESCC carries a poor prognosis with a median survivals of 6-9 months. The standard treatment has traditionally been chemotherapy. Palliative radiation therapy was used for symptom relief. The optimal treatment for stage IV ESCC has not yet been established. The aim of this study was to compare the efficacy and safety of CCRT versus chemotherapy alone in patients with stage IV ESCC.

**Materials/Methods:** Patients with stage IV ESCC were randomly assigned to the CCRT group and the chemotherapy group. Both groups of patients received at least 2 cycles of chemotherapy with cisplatin and docetaxel every 3 weeks. Patients in CCRT group received 50-60 Gy/ 25-30 fractions/ 5-6 weeks of concurrent radiation therapy to the esophageal primary tumor. The primary end point was overall survival (OS). The secondary end points were progression-free survival (PFS), object response rate (ORR) of primary tumor and toxicity.

**Results:** Between August 2013 and October 2015, 60 patients were enrolled and divided into the CCRT group (n=30) and the chemotherapy group (n=30). The 60 patients were comprised of 48 male and 12 female patients, with a median age of 56 years (range 36 - 70 years). The baseline clinical characteristics of the 2 groups were similar. Patients in the CCRT group received a mean 54.7 Gy of radiation therapy and a mean 3.6 cycles of chemotherapy, whereas patients in the chemotherapy group received a mean 3.8 cycles. The ORR of the primary tumor was higher in the CCRT group than in the chemotherapy group (83.3% vs. 46.7%, p = 0.001). At a median follow-up of 18 months, median PFS (9.3 vs. 4.7 months, p = 0.021) and median OS (18.3 vs. 10.2 months, p = 0.001) were significantly longer in the CCRT than that in the chemotherapy group. Overall survival rates at 1 and 2 years were 73.3% and 43.3% respectively, in the CCRT group, and 46.6%and 26.7% respectively in chemotherapy group (p= 0.030) Although ≥ grade 3 neutropenia was significantly more frequent in the CCRT group than that in the chemotherapy group (33.3% vs. 20.0 %, p < 0.05), the rates of other toxicities did not differ.

**Conclusion:** Concurrent chemoradiation therapy was well tolerated and associated with longer PFS and OS than chemotherapy alone in patients with stage IV ESCC. Controlled randomized, multi-center trials are required to determine whether CCRT is a primary treatment option for patients with stage IV ESCC.

**Author Disclosure:** T. Li: None. J. Lv: None. F. Li: None. P. Diao: None. J. Wang: None. C. Li: None. L. Liang: None. L. Sun: None.
Combined Analysis of 2 Prospective Trials of Individualized Adaptive Stereotactic Body Radiation Therapy for the Treatment of Hepatocellular Carcinoma (HCC) or Liver Metastases

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Purpose/Objective(s): Patients with unresectable hepatocellular carcinoma or liver metastases are often at high risk for worsening liver dysfunction following radiation therapy secondary to the presence of underlying liver disease. We performed two prospective trials of individualized adaptive stereotactic body radiotherapy (SBRT) for the treatment of HCC or liver metastases and herein report the combined results.

Materials/Methods: We analyzed all patients accrued and treated with SBRT on two consecutive institutional review board approved prospective trials for individualized adaptive radiation therapy for HCC or liver metastases from 2009-14. Initial plans limited NTCP <15% for radiation-induced liver disease (RILD). Adaptive SBRT dosing was based on pre- and mid-treatment indocyanine green (ICG) clearance. Patients typically received 3 fractions, followed by a one month treatment break, and then received up to 2 additional fractions based on ICG clearance. We performed univariate and multivariable analysis using the Cox proportional hazards model to identify predictive factors for local control and overall survival.

Results: 117 patients (median age 63, range 33-86) were treated to a total of 169 tumors. 69% of tumors were treated on the first trial. Median pre-SBRT Child-Pugh score was 6 (range 5-10). Median follow-up post-SBRT was 34 months (95% CI: 25-37). Median tumor size was 2.7 cm (IQR: 1.7-42.3). 73% of patients had cirrhosis, and 73% had received prior liver directed therapy. 80% of tumors were HCC. Median dose delivered was 46 Gy (IQR 34-50) in 5 fractions with a median biologically equivalent dose (BED) of 92 Gy (IQR 69-107). 56 tumors were treated with only three fractions due to projected ICG of >44% one month post-initial treatment. Local control was not associated with dose, tumor size, or pre-treatment liver-directed therapy. The actuarial 1 and 2-year rates of local control were 98% and 91%. Median OS was 17 months (95% CI: 15-22), and in a multivariable analysis decreased survival was associated with increasing number of prior liver directed therapies (HR: 1.13, p=0.02), increasing tumor size (cm) (HR: 1.15, p<0.01), and lower prescription dose (Gy) (HR: 0.97, p<0.01). There was no difference in LC or OS between patients enrolled on the two trials. Treatment was well tolerated with no cases of RILD. There were 4 treatment-related gastrointestinal bleeds and 4 cases of asymptomatic biliary stenosis.

Conclusion: Individualized adaptive liver SBRT base on ICG clearance is safe and provides overall excellent local control. Overall survival is significantly associated with the total radiation dose delivered. Our adaptive protocols allow for aggressive treatment that will maximize the probability of durable local control while limiting the likelihood of treatment related toxicity.

Protocol RAD 0902: A Pilot Study of Transarterial Chemoembolization Followed by Stereotactic Radiation Therapy for Locally Advanced Hepatocellular Carcinoma

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Purpose/Objective(s): Transarterial chemoembolization (TACE) is currently the standard of care for unresectable hepatocellular carcinoma (HCC) with a median survival of 20 months recently reported at our institution. This pilot study evaluates the addition of stereotactic radiation therapy (SRT) following TACE in unresectable HCC patients with primary endpoints of tolerability and local tumor control.

Materials/Methods: Patients with a single HCC lesion 3-8 cm, ≤ 3 lesions none over 5 cm, or lesions <3cm in unfavorable locations were eligible following at least one TACE procedure. Multidisciplinary review of post-TACE imaging deemed all patients ineligible for transplantation or surgical resection at time of enrollment. SRT was delivered within 45 days of enrollment to a dose of 45 Gy in 3 fractions utilizing image-guidance on a linear accelerator. Between 2009 and 2014, 17 patients were treated on protocol (PC, protocol cohort) and 24 patients were treated per protocol though failed to meet inclusion criteria (OPC, off protocol cohort). All OPC exclusions were due to large tumor size and/or location, medical comorbidity or history of previous malignancy. Characteristics between cohorts were compared with T-test, Wilcoxon test, or Fisher’s exact test when appropriate. Median time to intrahepatic tumor progression (TTP), median survival (MS) and overall survival (OS) were evaluated using the Kaplan-Meier method and log-rank test.

Results: There were no significant differences in age, race, time to initial TACE, or total TACE procedures between the PC and OPC. Mean tumor size in the PC was 4.6 cm and in the OPC was 5.1 cm (p=0.652). Median intervals between TACE and SRT completions were 69.5 days and 89 days for the PC and the OPC (p=0.063). No patient experienced > grade 2 acute toxicity. Intrahepatic recurrences occurred in 7/17 (41.2%) PC patients and 6/24 (25%) OPC patients (p=0.273) with 2 and 4 in-field recurrences, respectively. TTP was 30 months among the PC and was not reached among the OPC (p=0.391). No patient had isolated distant metastasis at time of first recurrence. OS for the PC and the OPC was 82.3% and 29.2%, respectively, with a median follow-up of 27.7 and 20.1 months. MS was 28.9 months for the OPC and was not reached for the PC (p=0.046). A total of 7 patients—3 in the PC (17.7%) and 4 in the OPC (16.7%)—were successfully down-staged for curative liver transplantation with no evidence of active tumor at the SRT site on explant pathology.

Conclusion: Combination of TACE followed by SRT is well-tolerated and demonstrates excellent local tumor control and MS as compared to our institution’s historical outcomes with TACE alone. This held true among both highly-selected patients as well as those with suboptimal performance statuses and tumor sizes, with a substantial number of patients treated both on and off protocol successfully down-staged for curative transplantation. TACE followed by SRT as definitive therapy for unresectable HCC merits further investigation in larger clinical trials.

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