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Breast Cancer

LBA1

Randomized Trial Evaluating Radiation following Surgical Excision for "Good Risk" DCIS: 12-Year Report from NRG/RTOG 9804

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Purpose/Objective(s): NRG/RTOG 9804 is the only prospective randomized trial to assess the impact of whole breast radiation (WBRT) versus observation (OBS) in women with "good risk" DCIS, following breast conservation surgery. The primary objective is local recurrence (LR) in the treated breast. Long-term results of this trial are presented here.

Materials/Methods: "Good risk" DCIS was defined for this trial as clinically occult DCIS, found by mammogram or incidental finding at surgery, with size ≤2.5 cm, final margins ≥3 mm, with low or intermediate nuclear grade. Consented patients were randomly assigned to WBRT with standard doses or OBS; boosts were not allowed. The use of Tamoxifen (Tam) for 5 years was optional. Cumulative incidence was used to estimate LR, Gray's test to compare treatments, and Fine-Gray regression for hazard ratios (HRs). Intended accrual was 1790, to detect LR HR=0.58.

Results: 636 women were randomized from 1999 - 2006 and initial results were reported in 2013. For this long-term update, in addition to the analyses for the 585 eligible patients with follow-up, sensitivity analyses were also done including all patients with follow-up (n=629). As analyses were essentially the same, the reported results are based on all patients with follow-up. Median age was 58 years and 76% were post-menopausal. Mean pathologic tumor size was 0.60 cm, 61% ≤ 0.5 cm, and 65% had a margin width ≥1.0 cm or a completely negative re-excision specimen. Highest nuclear grade was 1 in 44% and 2 in 56%. Intention to use Tam was indicated for 69% of patients, equally between treatment arms; however actually receiving Tam was different at 58% WBRT vs. 65% OBS (p=0.05). With a median follow-up time of 12.4 years, the 12-year cumulative incidence of LR was 2.8% (95% CI: 1.1, 5.6) with WBRT and 11.4% (7.7, 15.8) with OBS (p=0.0001; HR=0.26, 95% CI: 0.13, 0.54). The 12-year cumulative incidence of invasive (INV) LR was 1.5% (0.4, 4.0) with WBRT and 5.8% (3.2, 9.5) with OBS (p=0.016; HR=0.34, 95% CI: 0.14, 0.85). On multivariable analysis, only WBRT (HR=0.25, 95% CI: 0.12, 0.53; p=0.0003) and the use of Tamoxifen (HR=0.50, 95% CI: 0.27, 0.91; p=0.024) were associated with reduced LR. Age (< 50 vs. ≥ 50) and pathologic tumor size were not significant for all LR, nor INV LR. As expected, no significant differences were observed in survival, disease-free survival or mastectomy use.

Conclusion: Whole breast radiation significantly reduced LR and INV LR in this "good risk" DCIS population. The larger than expected WBRT effect has yielded meaningful results despite not meeting targeted accrual. These results should not be presented to the patient as an absolute indication for WBRT in the defined "good risk" group, but rather should inform a meaningful patient-physician discussion that includes risks, benefits and the patient's own degree of comfort, which can vary greatly, with the differences in LR with and without radiation.

Author Disclosure: **B. McCormick**: Stock; Varian.

LBA2

FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results (CRUKE/04/015)

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Purpose/Objective(s): The UK FAST trial tested 5 fractions (Fr) of 5.7 Gy and 6.0 Gy against 25 Fr of 2.0 Gy in women prescribed whole breast radiotherapy (no boost) after local excision of early breast cancer. Analysis of primary endpoint (normal tissue effects [by photograph]) showed that the 28.5 Gy/5 Fr regimen appeared similar to control. Further follow-up now enables analysis of 10-year outcomes.

Materials/Methods: The FAST trial (ISRCTN62488883) randomised women aged ≥50 years with invasive breast carcinoma (pT1-2 pN0) to 3 whole breast radiotherapy schedules: 50 Gy in 25 Fr over 5 weeks (control), 30 Gy or 28.5 Gy in 5 Fr over 5 weeks (1:1:1). Exclusion criteria were planned lymphatic/breast boost radiotherapy or (neo)adjuvant cytotoxic therapy. Normal tissue effects (NTE) were assessed annually to 10 years by clinicians and photographs at 2 and 5 years compared with a pre-radiotherapy baseline. Breast tumour recurrence was a secondary endpoint.

Results: 915 women were recruited from 18 UK centres (2004-2007). Composite endpoint of any clinician-assessed breast NTE showed significantly higher levels at 5 and 10 years for 30 Gy compared with 50 Gy (Table). Prevalence of marked NTEs at 5 and 10 years were very low. Compared with 50Gy excess of moderate/marked effects for 30Gy were: 5 years +10.5%, 95%CI 4.9 to 16.1%; 10 years +9.4%, 95%CI 1.1 to 17.6% and for 28.5 Gy, were +2.4%, 95%CI -2.5 to 7.3% at 5 years and +5.5%, 95%CI -2.3 to 13.3% at 10 years. At 9.9 years median follow up, 10 local recurrences (50 Gy: 3, 30 Gy: 3, 28.5 Gy: 4) and 96 deaths (50 Gy: 33, 30 Gy: 33, 28.5 Gy: 30) have been reported.

Conclusion: Marked NTEs were rare for all schedules. Late moderate/marked NTE after 28.5Gy/5 Fr/5 weeks were similar to 50Gy/25 Fr/5 weeks, but higher after 30Gy/5 Fr/5 weeks. Local recurrence rates were very low at 10 years for all schedules. Further research of a 5-Fr regimen is warranted; the UK FAST-Forward trial is testing 5 Fr delivered in 1 week. 15 or 16-Fr schedules of adjuvant radiotherapy for early breast cancer have now been shown to be effective and safe but a once-weekly 5-Fr schedule may be considered for patients in whom a daily visit for 3 or 5 weeks is not acceptable however careful consideration of the dose per Fr is required. Table: Clinician assessments of NTE at 5 and 10 years

Worst grade of any NTE in the breast[1]	**50Gy/25Fr (5 weeks) n (%)**	**30Gy/5Fr (5 weeks) n (%)**	**28.5Gy/5Fr (5 weeks) n (%)**
At 5 years: None Mild Moderate Marked *P-value[2]*	**N=254** 160 (63.0) 75 (29.5) 15 (5.9) 4 (1.6) -	**N=267** 152 (56.9) 67 (25.1) 40 (15.0) 8 (3.0) *0.008*	**N=253** 155 (61.3) 73 (28.8) 24 (9.5) 1 (0.4) *0.475*

At 10 years: None Mild Moderate Marked *P-value*[2]	**N=132** 90 (68.2) 30 (22.7) 11 (8.3) 1 (0.8) -	**N=130** 66 (50.8) 40 (30.8) 18 (13.8) 6 (4.6) *0.003*	**N=130** 72 (55.4) 39 (30.0) 17 (13.1) 2 (1.5) *0.034*

[1] Shrinkage, induration, telangiectasia, oedema; [2] χ^2 trend test (none, mild, moderate/marked); comparison with 50Gy/25Fr

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Reconstruction Failure Rates in Breast Cancer Patients with Two-Stage Expander/Implant Reconstruction Receiving Regional Nodal Irradiation with VMAT: Early Results of a Phase II Trial

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Purpose/Objective(s): Reconstruction failure (RF) is a well-known complication of radiation therapy (RT) in breast cancer patients with reconstruction. Results may vary based on RT timing and technique. We conducted a phase II trial of volumetric modulated arc therapy (VMAT) in breast cancer patients with immediate, implant-based reconstruction, hypothesizing that homogenous dose distribution to the chest wall achieved with VMAT may enhance reconstructive outcomes.

Materials/Methods: RF rates were prospectively assessed in breast cancer patients with two- stage tissue expander(TE)/permanent implant (PI) reconstruction enrolled onto an IRB-approved trial. VMAT was delivered to the chest wall and regional lymph nodes (50 Gy/25 fractions, 3mm daily bolus, no chest wall boost). The primary endpoint was RF, defined as removal of the prosthesis with or without subsequent replacement. Secondary endpoints were quality of life, cosmesis and capsular contracture rates (CC) assessed by BREAST-Q and MRI. Clinical follow-up and MRIs were performed at pre-RT, 12-18 mo and 24-30 mo post-RT. Two cohorts were identified based on RT timing: RT_PI and RT_TE. Kaplan Meier methods estimated time to RF, calculated from start of RT. Fisher's exact and chi-squared tests compared group characteristics.

Results: 121 patients were enrolled between 5/2014 – 8/2016; 107 patients completed all study assessments and were evaluable. 48 (45%) were stage II and 59 (55%) stage III. 44 (41%) received RT_PI, 63 (59%) RT_TE. Median follow up was 26.4 mo in the entire cohort (range 9.3-43.9) and was shorter in RT_TE (25.7 vs. 28.1 mo in RT_PI). The overall 2-year RF rate was 27% (29/107), with no difference between groups (29.3% vs 23.3%, p=.37). The 2-year rate of PI removal trended higher in the RT _TE group (9.5% vs. 0% RT_PI, p=0.12). Receipt of chemotherapy, hormone therapy, smoking, diabetes and hypertension was well balanced between groups (p=NS). Median time to RF was similar (11.6 mo RT_PI vs 11.1 mo RT_TE). Etiologies for RF differed between groups: CC (9/10) and PI exposure (1/10) in the RT_PI; infection (10/19), CC (7/19), and pain (2/19) in RT_TE. Results from correlative MRI and patient-reported outcome studies and multivariate analysis will be presented.

Conclusion: In this prospective trial, the rate of RF in breast cancer patients treated with VMAT was comparable to historical patients treated with conventional, 3D-conformal RT techniques. Consistent with other published reports, one type of RT timing was not favored over another. Minimizing complications and improving patient reported outcomes remains an important goal, justifying further study of RT techniques in breast cancer patients with reconstruction.

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Risk of Radiation Pneumonitis Following Individualized Modern Radiation Therapy with IMRT, a Breath-Holding Technique and Prone Positioning for Breast Cancer

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Purpose/Objective(s): State of the art techniques for delivering radiation to breast cancer patients have emerged to improve target coverage while limiting traditional toxicities (e.g., heart disease) associated therewith. Despite resource intensiveness and technical difficulties to applying these techniques for all patients, individualized advanced beam delivery is advantageous, especially in patients with anatomic challenges. The present study reports the pulmonary outcomes of women treated with an individualized cardiac-sparing radiation beam delivery approach.
Materials/Methods: Women with breast cancer who received adjuvant RT between 2015 and 2017 were identified from a prospectively collected registry. Patients who received accelerated-partial breast irradiation (n = 114) and who were followed at another hospital (n = 127) were excluded. In a left-sided tumor, the deep inspiration breath hold (DIBH) technique was recommended if the distance between the heart and adjacent chest wall was increased >1cm than that in the free breathing phase. The prone breast technique was attempted in women with large pendulous breasts. When applying IMRT, use of VMAT with two partial arcs, each irradiating between gantry angles of 60°/160° to 190°/310°, was recommended. The primary endpoint was the occurrence of symptomatic radiation pneumonitis (RP). For dosimetric analysis, all planning data were transferred into a commercially available deformable registration algorithm, which was used as a reference system for multiple-plan comparison.
Results: During the study period, 1658 patients received adjuvant RT either with conventional fractionation (23.5%) or hypofractionation (76.5%). The most commonly used technique was VMAT (38.9%), followed by DIBH (33.5%), field-in-field (13.3%), tangential wedge fields (11.4%), prone positioning (2.2%), and reverse-hockey stick technique (0.8%). Including internal mammary nodes (IMN) RT was applied in 38.5%. At a median follow-up of 18 months, RP occurred in 40 patients (2.4%). RP rates were significantly lower for VMAT (0.9%) and DIBH/prone (2.0%), compared to other techniques (5.2%). Differences in RP rates between techniques became more prominent upon subdividing patients according to IMN RT use (no-IMN RT, 1.0% vs. 1.5% vs. 4.7%, $P = .003$; IMN RT, 0.9% vs. 3.2% vs. 6.5%, respectively, $P = .004$). In multivariate analysis, RT technique and IMN irradiation were independently associated with RP risk. In 233 patients with available dosimetric data, RP was significantly associated with increased mean lung dose, V5, V10, V15, V20, and V30, but not V40. Additional dosimetric parameters including mean heart dose, for all patients, will be presented.
Conclusion: This study represents one of the largest, single-institution, retrospective reviews of pulmonary outcomes after adjuvant RT with available modern techniques in women with breast cancer. Individualized radiation beam delivery can optimize pulmonary outcomes, particularly when including IMNs in the treatment target.
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Comparing 10 Year Outcomes in Radiated Patients with Breast Autologous Reconstruction (AR) or Tissue Expander/Implant Based Reconstruction (TE/I)

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Purpose/Objective(s): Post-mastectomy radiation therapy (PMRT) is associated with higher rates of breast reconstruction complications. The optimal approach for reconstruction with PMRT remains indeterminate, as

toxicity profiles vary by technique and timing, and long-term data are limited. We sought to compare rates of complications requiring re-operation (CRR) and reconstruction failure (RF) between upfront autologous reconstruction (U-AR), upfront tissue expander/implant reconstruction (U-TE/I), delayed AR (D-AR), and delayed TE/I (D-TE/I) in pts who received PMRT.

Materials/Methods: Pts who received AR or TE/I, and PMRT between 2000-2008 were identified in an IRB-approved database. Pts underwent either upfront reconstruction on the same day as mastectomy followed by PMRT (U-AR or U-TE/I) or delayed reconstruction following PMRT (D-AR and D-TE/I). CRR was defined as an unplanned return to the operating room due to wound infection, dehiscence, skin and/or flap necrosis, hematoma, or hernia (with AR) and extrusion, leak, or capsular contracture (with TE/I). RF was defined as an unplanned conversion to another reconstruction technique or to a flat chest wall. Cumulative incidence of CRR and RF was calculated using Kaplan Meier method and compared using log-rank test. Logistic regression analysis was used to identify variables associated with CRR and RF.

Results: This study included 230 pts with 233 reconstructions. There were 143 AR (61%) and 90 TE/I (39%), and median follow up was 7.6 years (yrs). Upfront reconstruction was performed in 81% of pts. Age, BMI, active smoking, diabetes, and hypertension were similar between AR and TE/I. Rates of CRR ($p=0.009$) and RF ($p<0.001$) were significantly higher with TE/I compared to AR, overall. Table 1 summarizes the rate of CRR and RF by reconstruction technique and timing. On multivariate analysis, TE/I (OR 2.4; $p=0.007$), BMI ≥ 30 (OR 3.4; $p=0.002$), and active smoking (OR 2.7; $p=0.002$) were significant predictors for CRR, and TE/I (OR 5.4; $p<0.001$) was the only significant predictor for RF. When RF due to wound infection was excluded, the rate of RF was not significantly different between the four groups ($p=0.156$). Most CRR occurred within the first two yrs, while RF could be observed up to ten yrs after upfront reconstruction.

Conclusion: In the setting of PMRT, TE/I reconstruction in the upfront and delayed setting is associated with higher CRR and RF compared to AR. Efforts to minimize RF with TE/I and PMRT should focus on minimizing risks for infection.

Table 1: Rate of CRR and RF by Reconstruction Technique and Timing

CRR					**RF**				
	2 yr	**5 yr**	**10 yr**	**p-value**		**2 yr**	**5 yr**	**10 yr**	**p-value**
U-AR (n=106)	18.9%	19.8%	20.8%	***0.015***	**U-AR (n=106)**	3.8%	4.7%	5.7%	***< 0.001***
U-TE/I (n=82)	32.9%	36.5%	39.0%		**U-TE/I (n=82)**	13.4%	20.7%	24.4%	
D-AR (n=37)	29.7%	33.3%	32.4%		**D-AR (n=37)**	2.7%	5.4%	5.4%	
D-TE/I (n=8)	62.5%	62.5%	62.5%		**D-TE/I (n=8)**	50.0%	50.0%	50.0%	

Author Disclosure: **B. Manyam**: Employee; Vitreo-Retinal Consultants. **C.S. Shah**: Employee; Cleveland Clinic Foundation. Consultant; Impedimed. **N.M. Woody**: None. **A. Juloori**: None. **C.A. Wengler**: None. **S. Valente**: None. **S. Grobmyer**: None. **N. Kundu**: None. **R. Djohan**: None. **R.D. Tendulkar**: None.

Pathogenic Mutations in ATM Enhance Radio-Sensitivity and Local Control in Patients with Primary and Metastatic Breast Cancer

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Purpose/Objective(s): Hereditary alterations in Ataxia-Telangiectasia-Mutated *(ATM)* gene, a key signaling protein in the double-stranded break DNA repair process, is associated with an elevated risk of breast cancer. Here, we sought to define whether pathogenic *ATM* mutations present in breast cancer are associated with response to radiotherapy and exceptional responses to low dose treatment.

Materials/Methods: We screened our institutional database of 21675 patients who have undergone targeted sequencing with a 468-gene panel, and identified 3773 patients with breast cancer, of whom 78 harbored *ATM* mutations. Among the 78 patients, 58 were treated with RT to a total of 105 different sites and were included in this analysis. Nineteen patients (33%, treated to 31 sites) had a pathogenic *ATM* mutation (a truncating/frameshift mutation), whereas 39 patients (67%, treated to 74 sites) had a missense *ATM* mutation of unknown significance. Local control (LC) after RT and toxicity were compared in patients with pathogenic *ATM* mutations versus those with missense mutations.

Results: Median age at time of RT was 52.2 years (range, 32.1-83.6), and median follow up among the entire cohort was 3.2 years. Three-year LC at any irradiated site was 83.3% among patients with pathogenic mutations versus 68.2% in patients with missense mutations (p=0.02). Among the 61 sites treated palliatively (median dose 30 Gy), crude rates of LC were 93.4% in patients with pathogenic *ATM* mutations versus 68.9% in patients with missense *ATM* mutations. Actuarial rates of LC at 3 years were 75% versus 42.0%, respectively (p=0.02). Among the 44 patients treated to the breast or chest wall for localized disease, crude rates of LC were 93.3% versus 79.3%, although actuarial analysis did not demonstrate a statistically significant difference. Patients with pathogenic mutations treated palliatively were more likely to experience lasting symptomatic relief from RT than patients with missense mutations (p=0.009). There were no differences in grade ≥2 acute or late toxicities among the two groups. Exceptional radiation responses were seen in individual patients with pathogenic mutations; one woman with a nonsense truncating mutation and leptomeningeal disease is now without evidence of disease in the central nervous system >10 years after whole brain RT.

Conclusion: Patients with pathogenic *ATM* mutations exhibited higher LC rates than patients with missense *ATM* mutations of unknown significance. There does not appear to be an increase in significant acute or late toxicity after RT for patients with clinically significant somatic *ATM* mutations. Our findings suggest that *ATM* may constitute a novel mutation-based marker of radio-sensitivity in breast cancer and may facilitate personalized treatment in the future.

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Gene Expression Changes Predict Acute and Late Toxicity to Combined PARP1 Inhibition and Radiation (RT) in High Risk Breast Cancer Patients- Results of the Biomarker Analysis of TBCRC 024

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Purpose/Objective(s): Sustained locoregional control of breast cancer is a significant issue in patients with high risk disease. We recently reported the results of a phase I clinical trial describing acute and late toxicity of PARP1 inhibition (PARPi) with concurrent veliparib and RT. The purpose of this study was to determine predictive biomarkers of acute (during treatment) and late (1, 2, and 3 year) toxicity in patients treated with PARPi and RT from that trial. We hypothesized that protein and gene expression changes in skin epithelial cells after concurrent PARPi and RT might be used as predictive biomarkers of toxicity.

Materials/Methods: Acute toxicity was any dose-limiting toxicity defined in the protocol; late toxicity was defined as any CTCAE v4 Grade 3 event, regardless of attribution. Skin punch biopsies from the irradiated field were taken from patients at baseline (pretreatment T=0) and 6 hrs after first fraction of RT alone (T=1). Veliparib was then started and a 3rd punch taken 6 hrs after the second fraction of RT (T=2). RNA was isolated from skin epithelial cells and gene expression assessed using Affymetrix Human Gene ST 2.1 arrays. GSEA and MSigDB software was used for analysis. Significant difference was predetermined as a log2 fold change of+/-1.5 and FDR adjusted p-value <0.05. Protein changes (pγH2AX, PAR, Ki67) were detected using IHC and quantitated using Aperio Digital Path software.

Results: Severe acute and late toxicity rates with combined therapy were 15% (5/33) and 21% (7/33), respectively. Acute toxicity was not a predictor of late toxicity. Indeed, the two were almost mutually exclusive. Gene expression analysis identified 31 genes whose expression was significantly different 6 hrs after RT and 54 genes differed after combined treatment, including genes associated with DNA damage repair (ATM, MDM2, XPC) and proliferation (Ki67, TP53TG1). 67 genes were associated with acute toxicity, including overrepresentation of miRNAs associated with gene repression. Additionally, 63 genes were associated with late toxicity and were associated with metabolism, inflammation, and DNA damage response. There was no overlap in biomarkers of acute and late toxicity. Both pγH2AX and PAR protein levels increased and Ki67 decreased significantly (more than 2 fold for all proteins) with RT and combined therapy (T1 and T2) but were not significantly associated with acute or late toxicity at any time point.

Conclusion: This demonstrates the feasibility of using skin punch biopsy in the irradiated field for biomarker analysis and identification of a number of putative biomarkers of early and late radiation toxicity following combined PARPi and RT treatment. Additionally, for the first time in patient skin punch samples we report (1) gene expression changes in acute responding genes shortly after RT and (2) decreased proliferation after combined treatment. Future trials will validate the utility of these biomarkers for predicting toxicity and will seek to identify biomarkers of treatment efficacy.

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Phase I Trial of Stereotactic Body Radiation Therapy(SBRT) to Multiple Metastatic Sites: A NRG Oncology Study

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Purpose/Objective(s): SBRT to all metastases (mets) is hypothesized to improve survival for oligometastatic breast and other cancers. However, there is scant prospective evidence supporting SBRT safety when multiple mets are targeted. In NRG-BR001 we sought to establish the safety of SBRT dose schedules commonly used to treat a single met, in patients (pts) with 2-4 mets.

Materials/Methods: Eligibility included pts with 3-4 mets or 2 mets within 5 cm amenable to SBRT from breast, lung, or prostate cancer with ECOG performance 0-2. Mets were categorized into 7 anatomic locations: (bone/osseous (BO), spinal/paraspinal (SP), peripheral lung (PL), central lung (CL), abdominal/pelvic (AP), mediastinal/cervical (MC), and liver (L)). The starting dose was 50Gy in 5 fractions (CL, MC), 45Gy in 3 (PL, AP, L), and 30Gy in 3 (BO, SP). The primary endpoint was dose-limiting toxicity (DLT) defined as grade 3-5 CTCAEv4 adverse events (AEs) probably or definitely related to SBRT within 6 months. Six pts were required to evaluate DLTs for each location and a single pt could contribute to multiple mets locations. A dose level was considered safe if DLTs were observed in ≤ 1 of 6 within the location otherwise that anatomic location would undergo dose de-escalation.

Results: From Aug 2014-Dec 2017, 42 pts were accrued. Three pts did not receive protocol therapy, 2 died prior to completion of the DLT period, and one was lost to follow-up, leaving 36 evaluable pts. Twelve, 11, and 13 pts had breast, NSCLC, and prostate cancer, respectively. The median number of mets per pt was 3. There were zero pre-specified DLTs reported for BO, SP, PL, CL, and/or AP locations. At the time of data lock for this analysis, the DLT follow-up periods for MC and L were ongoing.

Conclusion: NRG-BR001 demonstrated that SBRT for patients with 3-4 mets or 2 mets in close proximity in the peripheral lung, central lung, abdomen/pelvic, bone/osseous, and spinal/paraspinal locations is safe. Treatment of pts with multiple mets in these locations has been expanded into ongoing randomized trials NRG-BR002 and LU002.

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Influence of Hypofractionated Radiation Therapy Following Mastectomy on Complication in Breast Cancer Patients Undergoing Two-Stage Prosthetic Breast Reconstruction

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Purpose/Objective(s): To compare the reconstruction-related complication risk between hypofractionated RT and conventional RT and identify a dosimetric predictor for the development of complications.

Materials/Methods: We identified 49 patients received expander placement with acellular dermal matrix immediately after mastectomy, then postmastectomy RT, followed by exchange of the expander for a permanent implant by a single surgeon. Of these patients, 19 underwent conventional 50 Gy RT. The remaining 30 patients underwent hypofractionated RT (mostly, 40.05 Gy/15 fractions), of which 80% received arc-based intensity modulated-RT planning. According to CTCAE v 4.0, grade 1 (faint erythema or dry desquamation), 2 (moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds), and 3 (moist desquamation, in areas other than skin folds) skin reactions occurred during RT in 18 (36.7%), 9 (18.4%), and 3 (6.1%) patients, respectively. The grade 2 or 3 skin reaction rate was lower after hypofractionated RT than after conventional RT (3.3% vs. 57.9%). The primary outcome was any reconstruction-related complication.

Results: The median follow-up was 23.6 months (range, 6.6–60.2 months). Complications following reconstructive surgery at any time after the completion of post-mastectomy RT occurred in 14 of 49 patients (28.6%). The mean time to complication from the date of RT completion was 8.1 months (SD 4.9, range 3.3-18.2). The complication rate was statistically significantly higher in the group receiving conventional RT than in the group receiving hypofractionated RT (52.6% vs. 13.3%, $P = .003$). Higher skin reaction in patients during RT indicates more reconstructive complications they suffered after RT (skin toxicity G0 2/19 (10.5%), G1 3/18 (16.7%), G2 7/9 (77.8%), and G3 2/3 (66.7%), $P = .001$).). ROC analysis showed that D_{max} of chest wall was the best dosimetric predictor for the development of grade 2-3 skin toxicity during RT and reconstruction-related complication after RT. D_{max} differed depending on the fractionation scheme and use of bolus. During the follow-up period, no local

recurrence was found in the chest wall. Six distant metastases with simultaneous regional recurrence (n = 1) were observed.

Conclusion: The hypothesis-generating findings of this study warrant further investigation into the effect of hypofractionated RT on reconstruction-related complication. Rigorous RT-QA program can be critically important component in upcoming randomized phase III trials of hypofractionation (Alliance A221505 and FABREC).

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Central Nervous System

LBA9

Preservation of Neurocognitive Function (NCF) with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy (HA-WBRT) for Brain Metastases: Preliminary Results of Phase III Trial NRG Oncology CC001

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Purpose/Objective(s): Based on preliminary evidence that radiation to the neuroregenerative hippocampal stem cells plays a role in NCF decline, the phase II NRG/RTOG 0933 trial demonstrated memory-preservation following HA-WBRT. The phase III NRG-CC001 trial of WBRT plus memantine without (WBRT+M) or with hippocampal avoidance (HA-WBRT+M) sought to validate these findings.

Materials/Methods: Adult patients with brain metastases were stratified by RPA and receipt of prior radiosurgery/surgery and randomized to WBRT+M versus HA-WBRT+M (30 Gy in 10 fractions). Standardized NCF tests were performed at baseline, 2, 4, 6, and 12 months (mos). The primary endpoint was time to NCF failure defined as decline using the reliable change index on at least one of the following tests: Hopkins Verbal Learning Test-Revised, Trail Making Test, or Controlled Oral Word Association. Cumulative incidence was used to estimate time to NCF failure (death without NCF failure was treated as a competing risk). Between-arms differences were tested using Gray's test. To detect an 11% absolute reduction in 6-month NCF failure, 382 analyzable patients were required for 90% power with two-sided α=0.05. Due to possible non-compliance, the sample size was increased by 25% (510 patients).

Results: 518 patients were randomized from July 2016 to March 2018. Median age was 61.5 years. Treatment arms did not differ in baseline characteristics. Grade≥3 toxicity did not differ (p=0.88). Median follow-up for alive

patients was 6.1mos. NCF testing compliance was 69% at 6mos and 61% at 12mos. Treatment arms did not differ in baseline NCF, overall survival (hazard ratio (HR)=1.13, 95% confidence interval (CI): 0.89-1.44, p=0.31) or intracranial progression-free survival (HR 1.12, 95% CI 0.90-1.39, p=0.33). Time to NCF failure was significantly longer in favor of HA-WBRT+M. The NCF failure rates following WBRT+M vs. HA-WBRT+M were 12.8% (95% CI 8.5-18.0%) vs. 11.2% (7.1-16.3%) at 2mos, 63.0% (55.6-69.5%) vs. 53.7% (46.1-60.8%) at 4mos, and 69.1% (61.8-75.3%) vs. 58.0% (50.2-64.9%) at 6mos (p=0.012). In analyses adjusted for stratification factors, HA-WBRT+M (HR=0.72; 95% CI: 0.56-0.94, p=0.016) and age ≤61 years (HR=0.61, 95% CI: 0.46-0.81, p=0.0006) predicted for longer time to NCF failure. Test for interaction between treatment arm and age was non-significant (p=0.67).

Conclusion: Preliminary analysis confirms our hypothesis that conformal avoidance of the hippocampal neuro-regenerative stem cell niche during WBRT preserves NCF while achieving similar intracranial control and survival. While age independently predicts for NCF, the NCF benefit of hippocampal avoidance does not differ by age.

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Elevated MGMT Gene Expression Is Independently Associated with Worse Overall Survival in NRG Oncology/RTOG 9813: A Phase III Study of Radiation Therapy (RT) and Temozolomide (TMZ) Versus RT and Nitrosourea (NU) in Anaplastic Grade III Glioma

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Purpose/Objective(s): This study sought to determine the prognostic significance of *MGMT* gene expression in NRG Oncology/RTOG 9813.

Materials/Methods: Gene expression data were generated using a transcriptome array on 76 patients from NRG Oncology/RTOG 9813. The *MGMT*-STP27 prediction model was used to calculate *MGMT* promoter methylation status from methylation probe data. Univariate (UVAs) and multivariate analyses (MVAs) were conducted using the Cox proportional hazards model and the log-rank test, to determine the effect of *MGMT* expression as a continuous variable on progression-free survival (PFS) and overall survival (OS). Patient pre-treatment characteristics and treatment assignment were taken into consideration as covariates for the MVAs.

Results: Upon UVAs, elevated *MGMT* gene expression was significantly associated with worse OS (HR = 1.56; 95% CI (1.17-2.08); p = 0.003) and PFS (HR = 1.39; 95% CI (1.06-1.82); p = 0.019). Models with time-varying effects were used for MVAs due to concerns over the proportional hazards assumption and included the following variables: *MGMT* gene expression, *MGMT* promoter methylation, age, *IDH* mutation, surgery, and KPS. Elevated *MGMT* gene expression was significantly associated with worse OS (HR = 1.74 95% CI (1.02-2.97); p = 0.043) for its long-term effect. Similarly for PFS, including *MGMT* promoter methylation, age and *IDH* mutation, elevated *MGMT* gene expression was significantly associated with worse PFS (HR = 2.34 for long-term effect; 95% CI (1.22-4.49); p = 0.01). This effect was also similar when *MGMT* promoter methylation was not included in the MVAs.

Conclusion: Elevated *MGMT* gene expression was found to be an independent prognostic biomarker in anaplastic astrocytomas treated with RT plus TMZ or RT plus NU independent of *MGMT* methylation status. This is the first study, to our knowledge, to identify the significance of *MGMT* gene expression on OS, independent of *MGMT* promoter methylation, in a phase III study of anaplastic glioma patients using rigorous MVAs. Validation of the prognostic significance of *MGMT* gene expression is ongoing as well as our efforts to increase sample size.

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A Phase 2 Trial of Neoadjuvant Temozolomide (TMZ) Followed By Accelerated Hypofractionated Radiation Therapy (AHRT) and TMZ Followed By Adjuvant TMZ in Patients with Newly Diagnosed Glioblastoma (GBM): Long Term Survival and Toxicity Analysis

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Purpose/Objective(s): Purpose: Encouraging results were observed on analysis of a phase II of neoadjuvant temozolomide (TMZ) followed by AHRT and TMZ followed by adjuvant TMZ in patients with newly diagnosed GBM. Here, we report long term outcomes.

Materials/Methods: Fifty patients were accrued: age >18 years, histologically-proven GBM, KPS ≥ 60 and adequate hematologic, renal, and hepatic functions. Three to 4 weeks post-surgery patients started neoadjuvant TMZ for 2 weeks, followed by concomitant AHRT and TMZ followed by adjuvant TMZ. GTV was surgical cavity and/or postoperative contrast-enhancing lesion on MRI. PTV60 included GTV plus 0.5 cm and PTV 40 included GTV plus 2.0 cm. PTV60 received 60 Gy in 20 fractions, while PTV40 received 40 Gy.

Results: From March 2009 and July 2013, 50 patients were accrued with a median age of 60 years. MGMT gene promoter was methylated in 21 patients and unmethylated in 27. Gross total and partial resection were performed in 46, and biopsy in 4 patients. With a median follow up of 71 months for patients at risk, median OS is 22 months with PFS of 13.2 months. At 3 and 5 years, actuarial OS was 34% and 23%, respectively. Methylated MGMT gene promoter patients have OS of 57% and 40.9% at 3 and 5 years, respectively compared to 18.5% and 11.1% for unmethylated MGMT. Eleven patients had reoperation for suspected recurrence, 5 were found to have radiation effects with no evidence of recurrence. The actuarial freedom from necrosis is 82.5% at 78 months, with a plateau after 32.9 months. One patient had a grade 5 hematological toxicity without evidence of disease recurrence at time of death. Another patient developed a grade 4 hepatotoxicity which reversed back to normal after discontinuation of TMZ. As of the date of this report, 10 patients are alive at present with ECOG status of 0 in 4, ECOG 1 in 2, ECOG 2 in 3, and ECOG 3 in one patient. Of the 10 patients 7 are not receiving corticosteroids, while 3 are receiving dexamethasone doses varying between 0.5 mg and 4 mg QD.

Conclusion: With a longer follow up, the initially observed OS was further confirmed, and compares favorably to OS reported by large clinical trials. The long term toxicity continues to be monitored closely, especially for this special group of patients with long survival. Laboratory, in-vitro and in-vivo, experiments are currently underway to further understand the molecular basis of the interactions of neoadjuvant TMZ and AHRT. Future plans are to conduct a phase III randomized clinical trial to compare the current approach versus the standard Stupp's regimen.

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Risk Factors for Progression of Low Grade Glioma Following Gross Total Resection and Observation in the Molecular Era

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Purpose/Objective(s): According to the low risk arm of RTOG 9802, the amount of residual tumor after surgical resection of low grade glioma (LGG) correlates to risk of recurrence. The purpose of this study is to evaluate risk factors in the molecular era for progression in patients with LGG who undergo gross total resection followed by observation.

Materials/Methods: An IRB-approved database of LGG patients was queried for patients with known molecular information who had received gross total resection (GTR) and were initially observed. Patient demographics and tumor factors were evaluated with respect to local recurrence-free survival (LRFS) and overall survival (OS). Univariate and multivariate Cox proportional hazard ratios as well as Kaplan Meier methods were used to evaluate impact on survival outcome.

Results: For the 182 patients diagnosed with LGG between 1985 and 2014, the median age at diagnosis was 29 years (range: 1-73) and 93 (51%) were female. Median follow up was 97 months. Median tumor size was 27 mm. Pathologic diagnosis included 60 (33%) astrocytomas (astro), 82 (45%) oligodendrogliomas (oligo), and 40 (22%) mixed gliomas. One hundred forty-four (80%) patients had GTR confirmed with imaging. One hundred thirty-seven had known 1p status with loss in 36 (26%), 126 had known 19q status with loss in 32 (25%), and 126 had both known 1p and 19q status, with loss of both in 30 (24%). Ninety-eight had known EGFR status with amplified EGFR in 2 (2.0%), 107 had known p53 status with p53 positivity >10% in 37 (35%), and 118 had known IDH status with 58 (49%) mutated. Median time to local recurrence was 10.2 years. LRFS at five and 10 years was 70% (95% CI: 62-78%) and 51% (95% CI: 42-60.), respectively. OS at 5 and 10 years was 97% (95% CI: 95-100%) and 90% (95% CI: 84-96%) respectively. Factors significant for decreased LRFS on univariate analysis were older age at diagnosis (hazard ratio (HR) 1.0; p=.002), oligo histology (HR 2.1; p=.02 vs. astro; HR 2.5; p=.002 vs. mixed), absence of preoperative seizure (HR 2.2; p=.004), presence of preoperative language deficits (HR 2.8; p=.002), IDH mutated status (HR 3.7, p<.0001), and p53 positivity >10% (HR 2.4; p=.005). Only increased tumor size (HR = 1.0, p<0.0001) was significant for decreased LRFS on multivariate analysis, but IDH mutated status (HR = 2.0, p=0.056) approached significance. LRFS in IDH mutated patients at five and 10 years was 57% (95% CI: 43-70%) and 29% (95% CI: 15-43%) respectively, versus 82% (95% CI: 71-94%) and 72% (95% CI: 58-87%) respectively, in IDH wildtype patients.

Conclusion: LGG patients who initially undergo GTR and are observed have prolonged LRFS and excellent OS. In the molecular era, preoperative tumor size remains predictive for LRFS for these low risk LGG.

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Improved Survival Following Immunotherapy in Patients with Lung and Melanoma Primaries Metastatic to the Brain Treated with Upfront Stereotactic Radiosurgery

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Purpose/Objective(s): For patients with lung or melanoma primaries metastatic to the brain, immunotherapy has improved extracranial disease control but results on intracranial disease outcomes after stereotactic radiosurgery (SRS) are not well understood. We sought to evaluate survival, risk of neurologic death and risk of distant brain failure (DBF) and to determine the brain metastasis velocity (BMV) in this patient population comparing those treated with and without immunotherapy.

Materials/Methods: We performed a single institution retrospective analysis of 257 consecutive patients with lung or melanoma primaries metastatic to the brain treated with upfront SRS. 170 of these patients did not receive immunotherapy as part of their treatment and 87 of these patients did. Of the patients that received immunotherapy, 42 (48%) received nivolumab, 24 (28%) received pembrolizumab and 15 (17%) received ipilimumab. 1 (1%) used a combination of nivolumab/ipilimumab and 5 (6%) received other or unknown immunotherapy treatments. BMV was calculated as previously described and compared using the Mann-Whitney U test. The cumulative incidences (CI) of DBF were estimated with death as a competing risk. Overall survival was estimated using the Kaplan Meier method.

Results: From 2013-2016, 257 patients with lung or melanoma primaries metastatic to the brain and treated with upfront SRS were identified for review. The median age at diagnosis was 66 (IQR: 57-72). Median OS in patients treated with and without immunotherapy was 22.4 and 6.1 months (log-rank $p<0.01$), respectively. Median freedom from neurologic death in patients treated with and without immunotherapy was 24.8 and 10.2 months (log-rank $p=0.04$). The one-year CI of DBF in patients with and without immunotherapy was 57% and 36% ($p < 0.01$). When stratified by primary histology, 1-year DBF rates with and without immunotherapy were 53% vs. 30% for lung ($p<0.01$) and 65% vs 95% for melanoma ($p<0.01$). Of the 115 patients with distant brain failure, median BMV at first failure (BMV1) in patients with and without immunotherapy was 9.0 and 11.4 ($p=0.85$). Median BMV1 was 14.0 and 6.4 in patients who received immunotherapy before and after SRS ($p=0.37$). This difference was most pronounced in lung cancer patients (42.6 v. 6.2, $p=0.14$). Median total BMV over the course of follow-up in patients with and without immunotherapy was 6.8 and 7.3 and 8.0 versus 5.9 in patients who received immunotherapy before and after SRS. Univariate linear regression analysis revealed an association between total number of cycles of immunotherapy and total BMV ($\beta=-1.67$, SE=0.77, $p=0.04$).

Conclusion: These findings suggest that while immunotherapy improves overall survival and decreases neurologic death in lung cancer and melanoma brain metastasis patients, continued progression in the brain remains an issue.

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Preoperative Radiosurgery For Resected Brain Metastases: Updated Analysis of Efficacy and Toxicity Of A Novel Treatment Paradigm

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Purpose/Objective(s): Postoperative (post-op) radiosurgery (SRS) has been proposed as a standard of care for brain metastases (BM) to minimize risk of local recurrence (LR) based on 2 phase III trials. We have previously demonstrated that preoperative (pre-op) SRS is a feasible alternative to post-op SRS and has potential advantages in risk of radiation necrosis (RN) and leptomeningeal disease (LMD) recurrence. The goal of this study was to determine the efficacy and toxicity of pre-op SRS in an expanded patient (pt) cohort with longer follow-up period.

Materials/Methods: The records for pts with BM treated with pre-op SRS and planned surgical resection were reviewed. Pts with classically radiosensitive tumors, planned adjuvant whole brain radiation therapy (WBRT), or no cranial imaging at least 1 month after surgery were excluded. Pre-op SRS dose was based on lesion size and approximately 20% reduced from standard. Surgery generally followed within 48 hours. Overall survival (OS) was estimated using the Kaplan-Meier method. Intracranial event rates were estimated using cumulative incidence with competing risk of death.

Results: The study cohort consisted of 117 pts with 125 lesions treated with single fraction pre-op SRS and planned surgical resection, of which 24 pts were enrolled on an initial prospective trial and an additional 93 consecutive pts were retrospectively reviewed. Most pts had a single BM (70.1%), underwent gross total resection (95.2%), and had non-small cell lung cancer (42.7%), followed by breast (18.8%), melanoma (15.4%), and renal cell (11.1%). Median time from SRS to surgery was 2 days, median SRS dose was 15 Gy, and median gross tumor volume was 8.3 cm^3 (approximately equivalent to 2.5 cm diameter lesion). Median cranial imaging follow-up period was 10.5 months for all pts and 18.7 months for alive pts. The median, 1 and 2-year OS rate was 17.2 months, 60.6% and 36.7%, respectively. The 1 and 2-year rate of cavity LR was 19.9% and 25.1%, distant brain failure (DBF): 45.3% and 60.2%, and LMD: 4.3% and 4.3%, respectively. The 1 and 2-year rate of any RN and symptomatic RN was 5.1% and 8.5%, and 2.6% and 4.8%, respectively. The 1 and 2-year rate of the composite endpoint of cavity LR, symptomatic RN, or LMD was 24.5% and 30.7%, respectively. Three pts (2.6%) experienced grade 3 toxicity: RN requiring surgery (n=1), postoperative wound complications (n=1), and cavity hematoma requiring evacuation (n=1).

Conclusion: This expanded and updated analysis confirms that single fraction pre-op SRS confers excellent cavity local control with very low risk of RN or LMD. Pre-op SRS has several potential advantages compared to post-op SRS including reduced risk of RN due to smaller irradiated volume without need for cavity margin expansion and reduced risk of LMD due to sterilizing tumor cells prior to spillage at the time of surgery. These data will be compared to published post-op SRS results. Based on these results, a randomized trial of pre-op vs. post-op SRS is being designed at this time.

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A Phase II Study of Post-Operative Stereotactic Body Radiation Therapy (SBRT) for Solid Tumor Spine Metastases

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Purpose/Objective(s): In patients with spinal instability, spinal cord compression, or neurologic deficits from spine metastases, the standard of care is surgical decompression/stabilization followed by radiation therapy (RT). Recurrence rates following conventional RT to the post-operative spine remain high. Retrospective data suggests improved local control following spine SBRT in the post-operative setting, however prospective data are limited. The purpose of this study is to prospectively examine the efficacy of post-operative SBRT in patients who have undergone surgical resection of metastatic spine disease. We hypothesize that post-operative SBRT to the spine would be associated with higher local control than historical rates following conventional RT.

Materials/Methods: 35 adult patients with a KPS ≥40 and spine metastases from solid tumors s/p any extent of resection with no prior overlapping RT and target volumes ≤3 consecutive vertebral levels were enrolled. GTV was defined as residual disease on post-operative MRI. The CTV was the GTV, tumor bed, all sites of disease based on pre-operative imaging/operative findings plus the adjacent anatomic compartment. The PTV was a 1-2 mm radial expansion. The spinal cord was defined on T2 weighted MRI or CT myelogram in patients with surgical instrumentation. The cord planning risk volume was the cord plus a 2 mm radial expansion or the thecal sac. All patients received SBRT 30 Gy in 5 fractions. Patients were followed with neurologic exam and CT and/or MRI every 3 months. Neurologic function was assessed at the same time points using the ASIA impairment score. Pain was rated according to the 10 point visual analog scale and MDACC brief pain index. Toxicity was recorded according to NCI CTCAE v4. The primary objective was the rate of radiographic local recurrence at 12 months following completion of SBRT.
Results: Patient characteristics: 26% had radio-resistant primaries; 76% were ASIA E and the remainder ASIA D; the median baseline KPS was 70 (range 50-100). The median prescription isodose line was 61% (range: 53-71) with a median coverage of the PTV of 90.2% (range 85.1-96.2). 31 patients have reached 12 months follow-up. Radiographic and symptomatic local control at 1 year were 90% (95% confidence interval: 74%-98%). The median time to recurrence in these 3 patients was 3.5 months (range 3.4-5.8 months), all had radio-sensitive tumors, and all recurrences included an epidural component. 22.5% of patients developed recurrence or progression within 1 vertebral body of the target. No patients experienced wound dehiscence, hardware failure or radiation induced spinal cord myelopathy. The median time to return to systemic therapy was 0.5 months (range 0-9.4 months).
Conclusion: This prospective study of post-operative spine SBRT demonstrates excellent local control with low toxicity. These data suggest superior rates of local control compared to conventional RT, however a formal comparative study is warranted.
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Dosimetric Predictors of Cognitive Decline in Attention and Processing Speed after Fractionated Brain Radiation Therapy

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Purpose/Objective(s): Neurocognitive decline, including changes in attention/processing speed, can be an unfortunate consequence of brain radiation therapy (RT). The corpus callosum (CC) and right-sided subcortical white matter (WM) are known to subserve this cognitive function. We aimed to determine dosimetric predictors of attention/processing decline at 6 months after fractionated RT in patients with primary brain tumors.
Materials/Methods: Twenty-three patients with primary brain tumors were enrolled on a prospective cohort study. Patients had neurocognitive assessments and high resolution diffusion and volumetric MRI imaging pre-RT and 6 months post RT. Subjects were tested on Delis-Kaplan Executive Function System trail making number and letter sequencing. Reliable change indices accounting for practice effects (RCI-PE) scores were calculated as a normalized measure of cognition change from pre- to post-RT. Practice effects accounts for expected improvements in tasks with repetition. Binary variables decline and substantial decline were defined as RCI-PE <0 and <-1, respectively.

Brain WM regions were segmented using a validated probabilistic diffusion tensor WM atlas. Regions of interest (ROIs) were CC and total right-sided subcortical WM with and without CC. Tumor and edema were censored from ROIs. Data including V_x (structure volume receiving ≥ x Gy) in 5 Gy intervals, minimum, maximum, and mean doses to each ROI were extracted from RT plans. A general linear model on dosimetric/volumetric data was created to identify predictors of decline (significance defined as $p<0.05$).

Results: Most patients (n=15, 62%) had benign or low-grade tumors. Median age at RT was 51 years (range 20-75) and 48% of patients were male. 15 patients (65%) underwent resection pre-RT and 9 (39%) patients received concurrent chemotherapy. Between 60-69% of patients experienced a decline; substantial number and letter sequencing decline was seen in 5 (22%) and 2 (9%) patients, respectively. Minimum dose to CC predicted for substantial letter sequencing decline ($p<0.001$), but there were no significant predictors of number sequencing. In right sided subcortical WM excluding CC, V30 predicted for substantial number sequencing decline ($p<0.001$) while minimum dose ($p<0.001$) and V30-V40 (all $p<0.001$) predicted for substantial letter sequencing decline. Within right-sided subcortical WM including CC, V30 predicted for substantial number sequencing decline ($p<0.001$) while V30-V35 ($p<0.001$) predicted for substantial letter sequencing decline.

Conclusion: In this prospective cohort study, increasing volume receiving 30-40Gy within the right-sided total subcortical WM predicted for decreased attention/processing speed at 6 months after RT. Minimum dose to CC also predicted for decline. This suggests that dose-dependent subcortical WM effects contribute to cognitive decline. Further complex modeling is needed to generate normal tissue parameters for WM structures to guide cognitive sparing brain RT.

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Gastrointestinal

LBA8

Preoperative Chemoradiotherapy Potentially Improves Outcome for (borderline) Resectable Pancreatic Cancer: Preliminary Results of the Dutch Randomized Phase III Preopanc Trial

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Purpose/Objective(s): For patients with (borderline) resectable pancreatic adenocarcinoma standard treatment is resection followed by adjuvant chemotherapy. Previous studies suggest a benefit of preoperative treatment. The aim of this multicenter phase III, superiority, randomized controlled trial is to test the hypothesis that median overall survival of patients with (borderline) resectable pancreatic cancer improves with preoperative chemoradiotherapy.

Materials/Methods: Patients with pathologically confirmed (borderline) resectable pancreatic cancer > 2 cm were randomized between immediate surgery (arm A) and preoperative chemoradiotherapy (arm B), both followed by adjuvant chemotherapy. After diagnostic laparoscopy, the preoperative chemoradiotherapy consisted of 15 daily fractions of 2.4 Gray combined with gemcitabine, 1,000 mg/m^2 on days 1, 8 and 15, preceded and followed by modified courses of gemcitabine. The adjuvant chemotherapy consisted of 6 cycles of gemcitabine in arm A versus 4 cycles in arm B. Primary endpoint was overall survival (OS) by intention to treat, secondary endpoints were (R0) resection rate, disease free survival (DFS), distant metastases free interval (DMFI), locoregional recurrence free interval (LRFI) and toxicity. Accrual took place between April 23, 2013 and July 25, 2017.
Results: In total, 246 patients were included in the intention-to-treat analysis (127 patients in arm A and 119 in arm B). At this analysis, 149 of the 176 required events for the primary outcome were observed. The primary outcome OS was not significantly improved in arm B (median 13.5 vs. 17.1 months; HR 0.74; p=0.074). In arm A, 120/127 patients underwent an exploratory laparotomy, versus 81/119 in arm B. The most common reason not having exploratory laparotomy in arm B was metastatic disease found at laparoscopy or progression during the preoperative treatment. Resection rates were 72% (91/127) in arm A vs. 61% (72/119) in arm B (p= 0.087). However, there was improvement in R0 resection rate (31% vs. 63%, p=<0.001), DFS (median 7.9 vs. 9.9 months; HR 0.71; p=0.023), DMFI (median 10.6 vs 18.4 months; HR 0.64; p=0.013) and LRFI (median 11.8 vs not reached; HR 0.55; p<0.001) after preoperative treatment (arm B). No significant difference was observed in adverse events between both groups (p= 0.28). A subgroup analysis of patients who actually underwent a resection and started adjuvant gemcitabine (61/127 (48%) in arm A and 55/119 (46%) in arm B) was performed which showed a median OS of 19.1 in arm A, compared to 42.1 months in arm B (p<0.001).
Conclusion: Our preliminary data suggest a benefit in outcome of preoperative chemoradiotherapy in (borderline) resectable pancreatic cancer compared to immediate surgery. The final analysis is expected within half a year.
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Capecitabine Plus Oxaliplatin Versus Capecitabine Plus Oxaliplatin with Concurrent Radiation Therapy in the Treatment of Gastric Cancer after D2 Gastrectomy

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Purpose/Objective(s): The role of adjuvant chemoradiation (CRT) in the treatment of gastric cancer patients after D2 resection has not been defined yet. This trial was designed to compare capecitabine plus oxaliplatin (XELOX) versus XELOX combined with concurrent CRT in the treatment of gastric cancer patients after D2 gastrectomy.
Materials/Methods: Patients with histologically confirmed T3-4/N1-3 gastric cancer after D2 gastrectomy were enrolled and randomly assigned to XELOX for 6 cycles (CT arm) or 2 cycles XELOX plus 45 Gy radiation therapy (RT) with capecitabine concurrently, and then followed by another 4 cycles of XELOX after RT (CRT arm). The primary end point was 3-year disease-free survival (DFS), and the secondary end point was 3-year overall survival (OS).
Results: From January 2013 to June 2017, a total of 144 Patients were protocol eligible with 74 assigned to the CT arm and 70 to the CRT arm, respectively. With a median follow up of 25.6 months, the 3-year DFS and OS rates were 76.3% and 79.6% in the CT arm, versus 72.8% and 70.9% in the CRT arm, respectively. The addition of RT did not show significant differences on the DFS (P = 0.868) and OS (P = 0.683). The rate of local recurrence-free

survival and distant metastasis at 3 years were 98.5% vs. 91.7% (p = 0.281) and 18.7% vs. 18.1% (p = 0.606) for the CT and CRT arms, respectively. For patients with positive lymph nodes (84.5%), the 3-year DFS rate was 70.7% and 71.1% in the CT and CRT arms, respectively. The DFS was a bit shorter in the CT arm than in the CRT arm but without statistical difference (p = 0.920). Common grade 3/4 AEs with chemotherapy and RT were leukopenia, neutropenia, thrombocytopenia. All patients finished at least 4 cycles of XELOX with 82.1% and 75.5% patients in the CT and CRT arms finished 5 cycles of chemotherapy.

Conclusion: No significant benefits on DFS and OS of CRT observed in the treatment of gastric cancer after D2 gastrectomy. Addition of RT did not show significant on lowering the risk of local recurrence for gastric cancer patients. Adjuvant CRT needs further investigation with larger populations for gastric cancers patients after D2 gastrectomy.

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A Prospective Study Assessing Early Cardiotoxicity after Trimodality Therapy for Esophageal Cancer

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Purpose/Objective(s): Thoracic radiation therapy (RT) has been associated with the development of late cardiac toxicity. The purpose of this study was to prospectively characterize early cardiac effects of thoracic RT using quantitative and qualitative measures of cardiac structure and function following trimodality therapy for esophageal cancer.

Materials/Methods: We enrolled 11 patients with distal esophageal cancer who were treated with neoadjuvant chemoradiation to 50.4 Gy with concurrent carboplatin and paclitaxel followed by esophagectomy. Ten patients who completed follow-up were included in the analysis. Subjects underwent fasting blood draw and cardiac MRI prior to the initiation of RT and 4-6 months following RT. Quantitative parameters of cardiac function including brain natriuretic peptide (BNP), C-reactive protein (CRP), and troponin levels, as well as right and left ventricular volumes and ejection fractions (EF) before and after RT were compared. Qualitative parameters including stress perfusion, late gadolinium enhancement (LGE), and presence of pericardial effusions were also compared. MRI findings were correlated with the RT plans. Paired and independent *t*-tests were used to determine significance.

Results: Three (30%) patients developed new onset reductions in first pass perfusion and/or LGE involving mid and basal inferior and inferoseptal walls correlating with the high dose regions (> 45 Gy). These structural changes were accompanied by significantly greater increases in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) following radiation , in comparison to the changes in LVEDV and LVESV observed for the remaining 7 patients (p = 0.04 and 0.01, respectively). However, changes in left ventricular EF from pre-RT to post-RT of the 3 patients with notable structural changes did not differ significantly from those of the remaining 7 patients (p = 0.78). 2 patients developed pericardial effusions. Matched-pairs and aggregate analyses of left and right ventricular EF, end-diastolic volume, end-systolic volume, stroke volume, cardiac output, and myocardial mass did not demonstrate significant differences before and after RT. Levels of BNP, CRP, and troponin also did not differ significantly before and after RT.

Conclusion: Cardiotoxicity was observed 3 of 10 patients within 6 months following thoracic RT. Ischemia and fibrosis occurred in the high dose region (> 45 Gy) with corresponding cardiac functional changes in LVEDV and LVESV, suggestive of RT related impaired cardiac filling and/or emptying. Further research is needed to characterize the clinical significance of these changes, as well as discovery of biomarkers that are predictive of them.

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A Randomized Phase II Trial of Neoadjuvant Chemotherapy Compared with Chemoradiotherapy in Locally Advanced Gastric Adenocarcinoma

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Purpose/Objective(s): 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 followed by radical surgery and another postoperative three cycles of SOX. NACRT arm received intensity-modulated radiation therapy with a simultaneous integrated boost (SIB-IMRT) to primary tumor (45.1Gy and 40.04Gy in 22 fractions) concurrently with S-1 followed by surgery and four to six cycles of SOX at the same dosage with NACT arm. The primary endpoint was surgical resection rate.(NCT02301481)

Results: From January 2014 to October 2017, 75 patients were randomly assigned to two arms: 38 in NACRT and 37 in NACT arm. Since two of each arm refused surgery after neoadjuvant treatment (NA), 71 were finally eligible for evaluation. R0 resection rate and D2 lymphadenectomy were performed in 77.8% (28/36) and 92.9% (26/28) in NACRT and 77.1% (27/35) and 96.3% (26/27) in NACT arm. The severe and moderate pathologic responses were significantly achieved with a higher rate of 96.6% (27/28) in NACRT than in NACT arm (66.7%, 18/27, P=0.013), in which 14.3% (4/28) and 11.1% (3/27) had pCR (P=0.724). NACRT arm were observed with much less detected median total number of lymph nodes than NACT (25 vs 37, P<0.001). More grade 1 to 3 myelosuppression including thrombocytopenia (61.3% vs 5.3%, P<0.001), neutropenia (77.4% vs 28.9%, P=0.067) and liver dysfunction (16.1% vs 0, P=0.037) occurred in NACT and NACRT arm had more gastritis (39.5% vs 5.9%, P=0.008) and radiation esophagitis (26.7% vs 0, P=0.001). There were no toxic death or postoperative death in both arms. Postoperative complications were similar in the two treatment groups (NACRT vs NACT, 6.9% vs 7.1%). The compliance with NACRT was 97.4% for radiation and 89.5% for S-1. In NACT arm, 97.3% of patients completed three planned cycles preoperatively. However, only 62.1% and 66.7% completed planned cycles of adjuvant chemotherapy in NACRT and NACT arm. With a median follow-up of 27 months, the 2-year overall survival was not significant difference in all 71 patients (NACRT vs NACT, 75.4% vs 70.1%, P=0.455) and in patients with R0 resection (NACRT vs NACT, 91.3% vs 80.3%, P=0.113). However, patients with R0 resection treated with NACRT were associated with significantly higher disease-free survival (DFS, 87.1% vs 63.9%, p=0.050) and locoregional recurrence free survival (LRFS, 100% vs 79.3%, p=0.014) as compared with NACT.

Conclusion: The design of preoperative concurrent SIB-IMRT with oral S-1 showed better DFS and LRFS with an acceptable toxicity profile, which encouraged future randomized phase III trials comparing NACRT with NACT for resectable or unresectable gastric adenocarcinoma.

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Preoperative Radiation Therapy with a Simultaneous Integrated Boost Compared to Chemoradiotherapy for cT3-4 Rectal Cancer: A Multicentric Randomized Study

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Purpose/Objective(s): Preoperative chemoradiotherapy (CRT) has been established as the standard treatment for T3-4 rectal cancer. As an alternative strategy, we reported previously in a phase II study limited toxicity and high local control (LC) using image-guided and intensity-modulated RT (IG-IMRT) with a simultaneous integrated boost (RTSIB) instead of concomitant chemotherapy. The present multicentric randomized trial (NCT01224392) compared this strategy to CRT. Early and late outcome are reported.

Materials/Methods: cT3-4 rectal cancer patients were randomly assigned to receive either preoperative IG-IMRT 46Gy/23 fractions plus capecitabine 825 mg/m^2 twice daily (CRT-arm) or IG-IMRT 46Gy/23 fractions with a SIB to the rectal tumor up to a total dose of 55.2 Gy (RTSIB-arm). Surgery was performed 6-8 weeks after completion of preoperative treatment. Adjuvant chemotherapy consisted in both arms of 6 cycles capecitabine 1000mg/m^2 twice daily on day 1 to 14, every 3 weeks. Metabolic tumor activity reduction, by measuring the percentage of SUVmax difference on sequential FDG-PET imaging, was the primary short-term endpoint.

Results: A total of 174 patients were randomly assigned to the CRT-arm (n=89) or RTSIB-arm (n=85) between April 2010 and May 2014. Grade 3 acute toxicity was 6% and 4% in the CRT- and RTSIB-arm, respectively. The mean fractional change in SUVmax at 5 weeks after completion of preoperative RT was -55.8% (±24.0%) and -52.9% (±21.6%) for patients in the CRT-arm and RTSIB arm, respectively (p=0.43). There were no significant differences in sphincter preservation (75% vs 68%) and R0 resection rate (98% vs 97%). The pathologic complete response rate (pCR) rate was 24% with CRT compared to 14% with RTSIB (p=0.13). Dworak grade 3-4 rates were comparable between both arms (49% for CRT vs 45% in the RTSIB-arm). Adherence to a full course of adjuvant chemotherapy was low (34% in the CRT-arm and 31% in the RTSIB-arm). After a median follow-up of 48 months, we report a 5-year overall survival (OS) of 76.1% in the CRT-arm vs 74.8% for the RTSIB-arm (p=0.91). There were no differences between treatment arms either for 5-year progression-free survival (PFS) (54.7% for CRT vs 55.4% for RTSIB, p=0.48) and 5-year LC (94.3% for CRT and 93.4% for RTSIB, p=0.42). The absolute incidence of any grade ≥ 3 late gastrointestinal and urinary toxicity was 7% and 5% for CRT whereas 5% and 4% for RTSIB patients, respectively.

Conclusion: The preoperative RTSIB approach was not inferior to CRT in terms of OS, PFS and LC in the current study. Acute and late toxicity did not differ between treatment arms. RTSIB represents a promising alternative to CRT in patients with cardiac comorbidity or other contra-indications for 5-fluorouracil based chemotherapy.

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Efficacy of Preoperative Neoadjuvant Simultaneous Integrated Boost IMRT Radiation Therapy Combined with Preoperative Chemotherapy for Locally Advanced Rectal Cancer: A Prospective II Clinical Study

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Purpose/Objective(s): To evaluate the feasibility, safety and short-term efficacy of preoperative capecitabine and simultaneous integrated boost IMRT-based, followed by a cycle of neoadjuvant capecitabine in patients with locally advanced rectal cancer (LARC).

Materials/Methods: Between March 2015 and July 2016, a total of 43 patients with resectable stage IIor III rectal cancer received capecitabine (825 mg/m2, bid d1-5 weekly) and SIB-IMRT delivering 58.75 Gy (2.35Gy/fraction) to the gross tumor and regional metastatic lymph nodes while simultaneously delivering 50Gy (2.0 Gy/fraction) to the areas at high risk for harboring microscopic disease. One cycle of capecitabine (1250 mg/m2, bid d1-14) was given one week after the completion of neoadjuvant chemoradiation (nCRT), and TME was scheduled 6 to 8 weeks after the completion of nCRT. The primary endpoint included ypCR. Secondary endpoints included acute toxicity, tumor downstaging, surgical morbidity, R0 resection, postoperative complications, sphincter preservation rate, LR, OS, and DFS.

Results: 43 patients completed chemoradiation as the protocol schedule and 40 received surgical resection. 16 (40%) patients had no residual tumor in the surgical specimen. Downstageing of the primary tumor or lymph nodes was observed in 39 (97.5%) patients. Most of the adverse reactions were grade 1/2, Grade 3 diarrhea and radiation dermatitis toxicities were evaluated in two (4.7%) and three cases (7.0%). No grade 4-5 toxicities were observed. Thirty patients underwent sphincter-saving surgery. Postoperative complications included 1 case of ureteral injury and 1 case of intestinal obstruction, no death in perioperative period. Three patients who refused surgery after chemoradiation therapy were excluded from the analysis, included one patient delayed surgery due to anal edema. The 1-year estimated overall survival and disease-free survival rates were 100 and 100% respectively, and no local relapse was found.

Conclusion: The pattern of preoperative SIB-IMRT plus concurrent capecitabine, followed by one cycle neoadjuvant capecitabine is a safe, well-tolerated treatment, gained a good pCR for patients with locally advanced rectal cancer, and the short term outcomes could be promising.

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Predictors of Radiation-Induced Liver Disease in Patients with Hepatocellular Carcinoma Undergoing Proton Beam Therapy

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Purpose/Objective(s): To identify the dose-volumetric predictors for radiation-induced liver disease (RILD) in patients with hepatocellular carcinoma (HCC) who were treated with proton beam therapy (PBT).

Materials/Methods: We retrospectively reviewed 102 HCC patients who underwent PBT between November 2015 and May 2017 in the absence of intrahepatic tumor progression within 4 months of treatment completion. The median cumulative dose was 72.6 GyE (range, 72.6-46.2 GyE), and pretreatment Child-Pugh class A and B were recorded in 90 and 12 patients, respectively. The RILD was defined as elevation of alkaline-phosphatase for more than twice the upper normal limit and non-malignant ascites, Grade ≥3 hepatic toxicity according to Common Terminology Criteria for Adverse Events, version 3.0, or Child-Pugh score worsening by ≥2 within 4 months of PBT completion. The radiation doses were converted to equivalent doses in 2 Gy per fraction (EQD2; $\alpha/\beta = 2$ Gy). Possible correlations of clinical and dose-volumetric parameters with RILD were examined.

Results: Fifteen (15%) patients developed RILD (unrecoverable, $N = 8$; fatal, $N = 3$). Multivariate analysis identified gross tumor volume (GTV, $P = 0.001$), unirradiated-liver-volume (normal liver volume receiving <1 Gy; $P = 0.003$) and Child-Pugh classification ($P = 0.007$) as significantly independent predictors for RILD, and the mean liver dose (MLD) was not associated with RILD development. For the Child-Pugh class A patients with unirradiated-liver-volume ≥500, 499-400, 399-300 and <300 cm3, the incidence of RILD were 0%, 10%, 21% and 46% ($P < 0.001$), respectively. In the Child-Pugh class B group, RILD was recorded in 0%, 25% and 100% patients with unirradiated-liver-volume ≥700, 699-450 and <450 cm3 ($P = 0.010$), respectively.

Conclusion: The unirradiated-liver-volume, not MLD, predicts RILD development in patients with HCC undergoing PBT. Our results suggested the relative and absolute limits of unirradiated-liver-volume being ≥500 and ≥300 cm3 for Child-Pugh class A patients and ≥700 and ≥450 cm3 for Child-Pugh class B patients, respectively.

	Child-Pugh class A					**Child-Pugh class B**			
Unirradiated-liver-volume (cm^3)	≥500 (*N* = 43)	499-400 (*N* = 20)	399-300 (*N* = 14)	<300 (*N* = 13)	*P*	≥700 (*N* = 5)	699-450 (*N* = 4)	<450 (*N* = 3)	*P*
Overall RILD, *N* (%)	0 (0)	2 (10)	3 (21)	6 (46)	<0.001	0 (0)	1 (25)	3 (100)	0.010
Non-recoverable RILD, *N* (%)	0 (0)	1 (5)	1 (7)	3 (23)	0.012	0 (0)	0 (0)	3 (100)	0.005
Fatal RILD, *N* (%)	0 (0)	0 (0)	0 (0)	1 (8)	0.114	0 (0)	0 (0)	2 (67)	0.045

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Circulating Tumor DNA to Predict Surgical Outcome after Neoadjuvant Chemoradiation for Borderline Resectable/Locally Advanced Pancreatic Cancer

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Purpose/Objective(s): Curative resection is possible following neoadjuvant treatment for borderline resectable/locally advanced pancreatic cancer (BR/LAPC), yet there is no method to identify patients in advance who will have a favorable surgical outcome. This study was designed to assess the ability of circulating tumor DNA (ctDNA) measured during neoadjuvant chemoradiation (CRT) to predict surgical outcome for BR/LAPC.
Materials/Methods: 41 patients with newly diagnosed BR/LAPC were enrolled at our institution between 10/2015 - 5/2017. Patients received neoadjuvant FOLFIRINOX followed by CRT: either short-course (n = 10, 25 Gy/5 fractions), or long-course (n = 31, 50.4 Gy/28 fractions). Serum ctDNA was measured at baseline, weekly during CRT, preoperatively, and postoperatively. After extracting DNA from plasma, the BioRad KRAS multiplex droplet digital PCR assay was used empirically to detect the presence of 7 possible KRAS mutations (G12A, G12C, G12D, G12R, G12S, G12V, and G13D), given that >90% of pancreatic ductal adenocarcinomas are expected to harbor KRAS mutations. The following clinical and pathologic outcomes were compiled: CA19-9, CEA, preoperative imaging response assessment, tumor grade, T stage, centrally-reviewed tumor regression grade, R-resection status, pathologically involved lymph nodes, LVI, and PNI.
Results: The median age of the cohort was 66 years (IQR: 59-73 years). Following CRT, 33 (80.5%) were operable. The overall R0-node negative (R0-NN) resection rate was 63.4% for the entire cohort. The rate of R0-NN resection was significantly higher among patients with an undetectable preoperative ctDNA (n = 25) compared to those with a detectable (n = 16) preoperative ctDNA (80% R0-NN vs 37.5% R0-NN, respectively, *Fisher's exact* p = 0.009). On univariate logistic regression, ctDNA status and CA19-9 were significantly associated with R0-NN resection (p = 0.008, and p = 0.0385, respectively), whereas preoperative imaging response assessment and CEA were not associated. On multivariable logistic regression, only ctDNA remained a significant predictor for R0-NN resection when controlling for CA19-9 (p = 0.018). For patients who received surgery, the ctDNA allele fraction was significantly correlated with tumor regression grade (*Pearson* R = 0.35, p = 0.049).
Conclusion: Undetectable preoperative ctDNA is associated with R0-NN surgical outcome in a cohort of patients treated with neoadjuvant CRT for BR/LAPC. Validation of these results is ongoing as we perform next generation sequencing of each patient's primary tumor to design a mutation-specific droplet digital PCR assay for each patient. This approach is worthy of further study to establish guidelines for incorporating ctDNA into clinic with the goal of improving patient selection for surgery.
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DNA Repair Deficiency, Genomic Instability and Immune Profiling in a Phase 1 Study of Locally Advanced Pancreatic Cancer Patients Treated with Veliparib, Gemcitabine and Radiation Therapy

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Purpose/Objective(s): Locally advanced pancreatic cancer (LA) has a dismal prognosis with current treatment modalities. Preclinical studies have demonstrated radiosensitization of orthotopic pancreatic tumors with the PARP-1/2 inhibitor, veliparib. A phase I trial of veliparib (V), gemcitabine (G) and radiation therapy (RT) was conducted to determine the maximum tolerated dose (MTD), safety and clinical activity of this regimen in patients with LA with and without DNA damage repair (DDR) defects.

Materials/Methods: LA patients were treated with weekly G (1000 mg/m2), daily RT (36 Gy/15 fractions) and daily V 20 mg BID for 3 weeks escalated per a novel Bayesian method followed by standard chemotherapy. DAVID was used to interpret differential gene expression. Cox regression model was used to identify DDR pathways associated with survival. Next generation sequencing (NGS) identified genetic mutations involved in DDR, tumor mutation burden (TMB) and microsatellite instability (MSI) status. Blood samples were interrogated for PAR protein and cytokines using an ELISA and electrochemoluminescent array, respectively. The log-rank test was used to evaluate differences in PFS and OS.

Results: 34 patients were enrolled from 2013 to 2016. MTD of veliparib was 40 mg BID with gemcitabine 400 mg/m2 and RT (36 Gy/15). 12 patients experienced DLT (83.3% lymphopenia, 8.3% neutropenia). Median PFS and OS were 10 and 15 months, respectively. Gene expression analysis identified DDR defects in 50% of patients. Median PFS and OS were significantly higher for these biomarker positive patients (17 vs. 8 mos, $p<.01$; 22 vs. 12 mos, $p<.001$, respectively). NGS identified 10 DDR mutations which were not prognostic of outcome. median TMB was 1.8 mut/Mb. A single MSI high patient was identified who was also TMB high (>20 mut/MB) and harbored DDR deficiency by NGS. Lower PAR levels were associated with borderline statistically significant improvements in both PFS and OS ($p<.06$). Higher levels of IL2 and IL12 and lower levels of FLT1 were associated with improved PFS and OS ($p<.05$).

Conclusion: The combination of V, G and RT was well tolerated. DDR alterations were identified in a large proportion of patients and were associated with significantly improved PFS and OS. Whereas most patients were MSS and had low TMB, those with higher levels of pro-inflammatory cytokines were likely to harbor DDR alterations both of which were associated with improved outcomes.

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Genitourinary

LBA5

Short Term Androgen Deprivation Therapy Without or with Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial

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Purpose/Objective(s): To determine in a three-arm randomized trial whether there are incremental gains in freedom from progression (FFP) from the addition of 4-6 months of short-term androgen deprivation therapy (STADT) using antiandrogen plus an LHRH agonist, without or with pelvic lymph node treatment (PLNRT), to prostate bed salvage radiotherapy (PBRT).

Materials/Methods: Patients were randomized to PBRT alone (Arm 1), PBRT + STAD (Arm 2), and PLNRT + PBRT + STAD (Arm 3). The FFP primary endpoint included PSA nadir+2, clinical failure, or death from any cause, with censoring for secondary salvage therapy initiated prior to these events. The sample size provided 90% statistical power to detect a 10% absolute FFP improvement at 5 yr in Arm 2 compared to Arm 1 and a 10% absolute improvement at 5 yr in Arm 3 compared to Arm 2 at an overall alpha level of 0.025. On the third planned interim analysis for efficacy and futility based on 1191 eligible patents with 5 yr minimum follow-up, the treatment arms were compared in a stepwise approach to determine if the Haybittle-Peto (HP) threshold boundary of $p < 0.001$ (one sided) was crossed. Futility evaluation tested the alternative hypotheses at $p < 0.001$. Adverse events were graded using CTCAEv3.0.

Results: There were 1792 patients enrolled from 2008 – 2015. Median follow-up for those living is 5.4 yr. Ineligible patients included 18, 17, and 21 in Arms 1, 2, and 3. The patient and tumor characteristics for the 1736 eligible patients include a median age of 64 yr (range 39-84), black in 13%, baseline Zubrod status of 0 in 93%, seminal vesicle involvement in 15%, pre-radiotherapy PSA of ≤1.0 ng/ml in 89%, Gleason score < 8 in 83%, and pT2 margin positive or pT3 in 72%. Arms 1, 2, and 3 had 5 yr FFP rates of 71.1%, 82.7% and 89.1%. Arm 3 had the highest rate compared to Arm 1 ($p < 0.0001$), exceeding the HP boundary. The hazard ratio (HR) between arms 3 and 1 was 0.44 (95% CI: 0.32-0.59). Arm 3 was then compared to Arm 2, yielding a difference of 6.4% ($p = 0.0063$) and a HR of 0.71 (95% CI: 0.51-0.98). In all eligible patients followed for up to 8 years, there were 45, 38 and 25 patients who developed distant metastasis (DM) in Arms 1, 2 and 3. Without second salvage censoring, the DM hazard ratio for Arm 3 vs Arm 1 was 0.52 (95% CI: 0.32-0.85) and for Arm 3 vs. Arm 2 was 0.64 (95% CI: 0.39-1.06). With IMRT use in 87% of cases, highest late grade 3+ toxicity was observed in 4.3%, 4.9% and 6.0% for renal/genitourinary events and 0.7%, 0.4%, and 1.1% for gastrointestinal events in Arms 1, 2, and 3.

Conclusion: This is the first report of the primary endpoint and is the first randomized trial to show significant incremental improvements in FFP going from PBRT only to PBRT+STAD to PLNRT+PBRT+STAD. The addition of PLNRT resulted in early, meaningful, reductions in failure. Follow-up of patients will further elucidate the magnitude of the differences between arms 2 and 3.

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Patient Reported Outcomes of NRG Oncology/RTOG 0232: A Phase III Study Comparing Combined External Beam Radiation and Transperineal Interstitial Permanent Brachytherapy with Brachytherapy Alone in Intermediate Risk Prostate Cancer

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Purpose/Objective(s): To assess differences in patient (pt) reported outcomes (PROs) between combined external beam therapy (EBT) and transperineal interstitial permanent brachytherapy (B) among pts with intermediate risk prostate cancer (PC). The primary endpoint reported that the addition of EBT to B did not result in superior PFS compared to B alone.

Materials/Methods: Men with intermediate risk PC were randomized to either 45 Gy partial pelvis EBT+B or B alone. The Expanded Prostate Index Composite (EPIC) was used to measure change in PROs from baseline to 4 and 24-mos. EPIC assesses 4 PC-specific PRO domains: bowel, urinary (with 2 subscales; incontinence and irritative/obstructive), sexual, and hormonal. Hormonal domain was excluded as concurrent use was exclusionary and prior neoadjuvant use was low (8%). Scoring is on a Likert scale with responses transformed to 0-100, with higher scores indicating better PC-specific PROs. EPIC change (Δ) domain/ subscale scores were calculated as 4 or 24 mo. score - baseline score. To assess treatment differences, effect sizes (ES) ≥ 0.5 standard deviations (SD) were considered clinically significant and t-tests tested for treatment differences > 0.

Results: 530/579 (92%) eligible pts on study had baseline EPIC: 255 (89%) on EBRT + B arm and 275 (94%) on B arm. There were no significant (sig) differences in baseline characteristics between arms; median age 66, 78% were White and 17% were Black; 89% had GS 7/PSA < 10, 66% were T1 and 96% had Zubrod Performance Status of 0. Grade 3+ toxicities: acute were similar (6%) but late were 13% and 8% for EBT+B and B, respectively. There are no statistically sig differences in any of the baseline mean scores between arms. At 4 mos, mean ± SD of Δ scores for urinary, urinary-irritative, and bowel had sig differences (all $p<<0.0001$) between arms, all in favor of B alone (ES 0.40, 0.44, 0.31, respectively); none for urinary-incontinence, sexual. At 24 mos, sig differences between arms for urinary, urinary-irritative, bowel, & sexual, all in favor of B alone (see Table).

Conclusion: Among men with intermediate risk PC in this study, the addition of EBT to B resulted in poorer urinary, bowel, and sexual PROs, with meaningful effect sizes for urinary and bowel, although not meeting the protocol-defined clinically significant level. This study demonstrates that value-based care strongly supports B over

EBT + B in this population since B has similar PFS, lower toxicity, better patient reported outcomes and ostensibly less cost compared to the combination.

Domain/ Subscale	24 mos Δ mean ± SD		p-value ($\|\mu_B - \mu_{EBT+B}\| > 0$)	Effect Size
	EBT+B	B		
Urinary	-11.2 ± 15.7	-5.6 ± 13.6	0.0002	0.38
Urinary-irritative	-11.9 ± 17.4	-4.8 ± 14.3	<0.0001	0.44
Bowel	-7.1 ± 12.6	-2.4 ± 9.9	<0.0001	0.42
Sexual	-16.7 ± 23.4	-10.6 ± 21.0	0.0072	0.27

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Androgen Receptor Activity and Radiotherapeutic Sensitivity in African-American Men with Prostate Cancer: A Large-Scale Gene Expression Analysis and Meta-Analysis of RTOG Trials

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Purpose/Objective(s): Population data suggests that African-American (AfA) men have an increased mortality from prostate cancer (PCa) compared to Caucasian (C) men. Socioeconomic variables contribute to this disparity, yet intrinsic biological differences remain plausible. Herein, we investigate the interplay of androgen receptor activity (AR-A) and radiotherapeutic sensitivity to provide a molecular rationale to help explain the disparity in outcomes for AfA men with PCa.

Materials/Methods: Transcriptome-wide expression profiles of FFPE tumor samples from 5,831 localized PCa patients were used. Tissue was obtained from a prospective population cohort (n=5,239) and two retrospective cohorts with long-term outcomes (n=592). Predicted radiation sensitivity was measured using the 24-gene post-operative radiation therapy (RT) outcome score (PORTOS). AR-A was defined from the pooled expression of nine canonical AR-target genes. Clinical radiosensitivity was validated using individual patient data from four RTOG trials (92-02, 94-08, 94-13, and 99-10), comprised of 6,011 patients (18.5% AfA). Competing risk adjustments were used for all survival analyses for biochemical recurrence (BCR) and distant metastases (DM).

Results: In men treated by surgery from the prospective cohort, low AR-A tumors were significantly more likely to develop DM (10-year rate: 37% vs 17%, p=0.008). On multivariable analysis after adjusting for Gleason grade, T-stage, PSA, margin status, and lymph node invasion, low AR-A remained independently prognostic for DM (p=0.03). After generating a matched cohort of AfA and C patients, AfA tumors were more likely to have low AR-A (p<0.001). However, AfA tumors had decreased double strand break repair pathway expression (p<0.001) and increased predicted RT sensitivity (p<0.001). This suggests that AfA men may have improved outcomes with RT. To clinically test whether AfA tumors are more radiosensitive, we leveraged four large RTOG trials of men treated with RT. On both unadjusted and propensity weighted cohorts (adjusting for age, performance status, PSA, Gleason grade, T-stage, N-stage, and use/duration of hormone therapy), AfA men had significantly improved outcomes compared to C men (BCR (HR 0.82 [95%CI 0.74, 0.92], p=0.0005) and DM (HR 0.70 [95%CI 0.57, 0.86], p=0.0008)).

Conclusion: Our data suggest that there are population-level differences in AR signaling and DNA repair in AfA and C men's PCa, which transcriptionally suggest that AfA men may harbor more radiosensitive tumors. To our knowledge, this is the first report demonstrating that AfA men may have improved outcomes compared to C men treated with RT, which is consistent with our hypothesis regarding diversity in AR-A, and warrants further investigation.

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10-Year Update of a Randomized Prospective Trial of Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer

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Purpose/Objective(s): We present 10-year disease outcomes of a randomized prospective trial of conventional versus hypofractionated radiation therapy for localized prostate cancer.

Materials/Methods: Between June 2002 and May 2006, men with low- to high-risk prostate cancer were randomized to receive conventionally fractionated intensity-modulated radiation therapy (C-IMRT, 76 Gy in 38 fractions at 2 Gy per fraction) or hypofractionated IMRT (H-IMRT, 70.2 Gy in 26 fractions at 2.7 Gy per fraction) at a single institution. The latter treatment is estimated to have an equivalent dose in 2 Gy fractions of 84.4 Gy assuming an α/β ratio of 1.5. High-risk patients were scheduled to receive 24 months of androgen deprivation therapy (ADT) and some intermediate-risk patients were offered up to 4 months of ADT. The primary end point was the cumulative incidence of biochemical and/or clinical disease failure (BCDF). Biochemical failure (BF) was defined as nadir + 2. In the univariate analyses, Kaplan-Meier estimation was obtained for overall survival (OS) and prostate cancer-specific mortality (PCSM) and cumulative incidence function was estimated for BF and metastatic rate with death as the competing risk. Cox proportional hazard model was done for multivariable analyses (MVA) with adjustment for age, race, ADT, and risk group.

Results: A total of 303 men were randomized to C-IMRT (n = 152) or H-IMRT (n = 151), with 77 men being lost to long-term follow up. Median follow up for the whole cohort was 130 months (range 7 – 181 months). There were 28 (9.2%), 189 (62.4%), and 86 (28.4%) NCCN favorable-, intermediate-, and high-risk patients, respectively. The arms were equally balanced for clinicopathologic factors, except there were more African-Americans in the C-IMRT arm (17.8% vs 7.3%; p = 0.02). ADT was taken by 46.7% and 45% of men in the C-IMRT and H-IMRT arm, respectively (p = 0.97). The median length of ADT treatment was 23.9 and 23.7 months in the C-IMRT and H-IMRT arm, respectively (p = 0.94). On MVA, 10-year BCDF was similar in both arms (25.9% in the C-IMRT arm and 30.6% in the H-IMRT arm; HR 1.42, 95% CI 0.91 – 2.46; Table 1). The two treatment groups also had similar rates of 10-year BF, PCSM, and OS. The H-IMRT arm did have a trend toward higher 10-year metastatic rate (5.3% vs 12.7%; HR 2.12, 95% CI 0.97 – 4.63; Table 1).

Conclusion: H-IMRT demonstrated no differences in disease outcomes when compared to C-IMRT. There was a trend of increased risk of developing metastases in the H-IMRT arm for which further follow up is underway.

Table 1. Disease Outcomes by Treatment Group

	5-year		10-year		MVA		
Outcome	C-IMRT %	H-IMRT %	C-IMRT %	H-IMRT %	HR	95% CI	p-value
BF	9.1%	11.9%	21.2%	25.4%	1.26	0.74 – 2.2	0.4
Metastatic rate	4%	7.3%	5.3%	12.7%	2.12	0.97 – 4.63	0.06
BCDF	12%	17.4%	25.9%	30.6%	1.42	0.86 – 2.32	0.17
PCSM	1.3%	2.7%	2.7%	4%	1.27	0.4 – 4.1	0.69
OS	92.7%	89.4%	78.4%	71.1%	1.43	0.93 – 2.19	0.1

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Long-Term Update of NRG Oncology RTOG 94-08

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Purpose/Objective(s): RTOG 9408 demonstrated that the addition of 4 months of androgen-deprivation therapy (ADT) before and during radiation therapy (RT) improved 10-year overall survival (OS), disease-specific mortality (DSM), biochemical failure (BF), incidence of distant metastases (DM) and local progression (LP) in patients with early, localized prostate adenocarcinoma. The long term update is presented.

Materials/Methods: Patients (pts) with AJCC 4th edition T1b, T1c, T2a or T2b prostate adenocarcinoma and PSA ≤ 20 ng/mL were randomly assigned to RT alone (990 pts) or RT + 4 months of ADT (984 pts). The RT dose was 66.6 Gy administered in 1.8 Gy fractions. The restricted mean log-rank test was used to test the primary endpoint of OS and secondary endpoints of DSM, BF (Phoenix Definition), DM and LP. Due to the non-proportionality of the hazards for OS, a time-varying treatment effect was used in the Cox proportional hazards model. Subset analyses by risk group, race, and age were conducted. Low risk was defined as Gleason score 2-6, PSA ≤ 10 and stage ≤T2a; Intermediate risk was Gleason score 7 or Gleason score 2-6 with either PSA between 10 and 20 or clinical T2b; High risk was Gleason score 8-10.

Results: From 1994 through 2001, 1974 eligible pts were enrolled. The median age at study entry was 71 years. The median follow-up for alive pts was 14.8 years. 194 pts were at risk at 18 years. The incidence of late grade 3, 4 and 5 genitourinary toxicity was 6.2%, 1.4% and 0.1% in the ADT+RT arm and 5.3%, 0.1% and 0 in the RT alone arm. Late grade 3, 4 and 5 gastrointestinal toxicity incidences was 2.5%, 0.2% and 0 for ADT+RT and 1.2%, 0.1% and 0.2% for RT alone. Efficacy results are as follows:

		RT+ADT (at 10 years)	RT alone (at 10 years)	RT+ADT (at 18 years)	RT alone (at 18 years)	Hazard Ratio (HR)	p-value
OS	**(1974 pts)**	**63%**	**56%**	**23%**	**23%**	**0.94**	**0.28**
Low Risk	*(703 pts)*	*69%*	*62%*	*26%*	*31%*	*1.01*	*0.93*

Int. Risk	*(1086 pts)*	*60%*	*53%*	*21%*	*20%*	*0.92*	*0.22*
High Risk	*(185 pts)*	*55%*	*52%*	*19%*	*16%*	*0.88*	*0.48*
Age<=70	*(972 pts)*	*71%*	*64%*	*35%*	*34%*	*0.93*	*0.37*
Age>70	*(1002 pts)*	*55%*	*49%*	*11%*	*14%*	*0.99*	*0.89*
BF		**32%**	**46%**	**37%**	**51%**	**0.66**	**<0.01**
DM		**5%**	**8%**	**8%**	**12%**	**0.66**	**0.01**
LP		**11%**	**16%**	**12%**	**18%**	**0.68**	**<0.01**

In model adjusted for age, baseline PSA, Gleason score, T-stage, N-Stage, and race, OS for RT + ADT was superior to RT alone prior to 10.4 years (HR=1.20, p=0.014) while RT alone was superior after 10.4 years (HR=0.80, p=0.010). OS rates in the ADT+RT and RT alone arms were 62.8% and 55.8% at 10 years and 22.6% and 23.4% at 18 years, respectively.

Conclusion: The addition of short-term ADT to RT improved OS during the 1st 10 years of follow-up but this benefit diminished with long term follow-up. By 18 years, OS was no longer superior with the addition of ADT. BF, DM and LP, however, all continued to show a long-term benefit. Disease-specific mortality continues to be analyzed and will be presented at the meeting.

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International Multicenter Validation of an Intermediate-Risk Subclassification of Men Treated with Radical Treatment Without Hormone Therapy

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Purpose/Objective(s): National Comprehensive Cancer Network guidelines have recently endorsed the Memorial Sloan Kettering (MSK) subclassification of intermediate-risk prostate cancer into favorable (FIR) and unfavorable (UIR) subgroups. These subgroups are often used for decision-making regarding the addition of hormone therapy. However, the subclassification was developed in a heterogeneous cohort of men, many of which received androgen deprivation therapy (ADT), and thus the natural history of hormone therapy naïve FIR and UIR men remains unknown. Herein, we perform the first multi-center validation study across all forms of radical therapy in men with intermediate-risk prostate cancer who did not receive combined hormone therapy.

Materials/Methods: After receiving institutional review board approval from three academic centers, intermediate-risk men treated with radical monotherapy (dose escalated external beam radiation therapy (DE-EBRT), brachytherapy (BT) as monotherapy, or radical prostatectomy (RP)) without the addition of ADT were included. UIR prostate cancer was defined as any intermediate-risk patient with a primary Gleason pattern of 4, percentage of positive biopsy cores ≥ 50%, or multiple intermediate-risk factors (cT2b-c, prostate-specific antigen 10-20 ng/mL, or Gleason score 7). Cumulative incidence curves with competing risk analyses were performed for distant metastasis (DM) and prostate cancer-specific mortality (PCSM).

Results: A total of 2550 intermediate risk men (1044 FIR and 1506 UIR) were included, of which 1149 had RP, 1143 had DE-EBRT, and 258 had BT. The median follow-up for the RP, DE-EBRT, and BT cohorts were 60.4, 70.6, 107.4,months respectively. The 10-year cumulative incidence of DM for FIR vs UIR were 0.6% (95%CI:0.6-0.6) vs. 10.4% (95%CI:6.5-14.3) for RP (p<0.001), 3.4% (95%CI:1.4-5.4) vs. 13.2% (95%CI:9.3-17.1) for DE-EBRT (p<0.001), and 4.4% (95%CI:0.5-8.3) vs. 12.4(95%CI:2.6-22.2) for BT (p=0.025). The 10-year rates for PCSM for FIR vs UIR were 0% (95%CI:0-0) vs. 3.4% (95%CI:1.4-5.4) for RP (p=0.031), 1.3% (95%CI:0-3.3) vs. 5.2% (95%CI:3.2-7.2) for DE-EBRT (p=0.049), and 0.6 (95%CI:0-2.6) vs. 3.0% (95%CI:0-6.9) for BT (p=0.028).

Conclusion: This multicenter international effort has independently validated the prognostic value of the MSK intermediate-risk subgroup classification in men who are hormone therapy naïve across all radical treatment modalities. Our data demonstrates that the current definition of FIR may not be ideal as 3-4% of men still develop distant metastasis at 10 years even with definitive therapy. These results underscore the need for other biomarkers to improve risk stratification, such as the recently reported clinical-genomic risk group classification, and the necessity of studying the differential impact of treatment intensification strategies, such as ADT, among these subgroups.

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Toxicity and Biochemical Outcomes after Dose Intensified Post-Operative Radiation Therapy for Prostate Cancer: A Randomized, Controlled, Phase 3 Trial

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Purpose/Objective(s): There was very little high-level evidence about which radiation therapy (RT) regimen was more effective for prostate cancer after radical prostatectomy (RP). In 2011, we began the randomized, controlled, phase 3 trial to investigate the effect of dose intensified post-operative RT. Patients were randomly assigned to either 66Gy/33f or 72Gy/36f. The aim of current analysis was to compare toxicity, urinary continence recovery and biochemical outcomes.

Materials/Methods: This trial recruited patients who had received RP for a histologically confirmed adenocarcinoma of the prostate, and who had stage pT3-4, positive surgical margins, pN+ or who had rising PSA of 0.2ng/ml following RP. Eligible patients were randomly assigned (1:1) to receive either 66Gy or 72Gy. IG-VMAT techniques was used. The primary endpoint was biochemical progression-free survival (PSA increase of 0.2 ng/ml or greater from the post-RT nadir, a continued rise in PSA despite RT or the initiation of salvage ADT). The second endpoints were acute and late toxicity, and urinary continence recovery. Genitourinary (GU) and gastrointestinal (GI) toxicity was assessed using RTOG-EORTC criteria. Incontinence was assessed by International Consultation on Incontinence Modular Questionnaire Short Form (ICIQ-SF) at start/end of RT and 1 year afterward.

Results: Between Sep. 2011 and Nov. 2016, 144 patients were randomly assigned, 71 to 66Gy group and 73 to 72Gy group. The median follow-up time was 42 months (range: 10-71 mos). 3-year biochemical progression-free survival was 73.8% vs. 76.6% in 66Gy vs. 72Gy group. For acute toxicity no significant differences were seen between the two groups. Acute GU toxicity grade 1 and 2 were reported as 74.6% and 83.6%, 5.6% and 4.4% respectively. Late GU toxicity grade 1 and 2 were 18.3% and 8.2%, 8.5% and 11.0%. Grade 3 GU toxicity was observed in one patient in 72Gy group. For acute GI toxicity, these figures were 78.9% and 84.9%, 11.3% and 8.2%. Late GI grade 1 and 2 were 9.9% and 8.2%, 1.4% and 2.7%. No significant differences between both groups were seen for late GI and GU toxicity. At baseline 48 (33.3%) of patients were incontinent (16.7% mild, 13.9% moderate, 2.8% severe). Of these 48 patients, continence was recovery one year after RT by 33.3% vs. 28.6% with 66Gy vs. 72Gy. 63.0% vs. 66.7% of patients remained stable. Only 2 patients felt more seriously after RT.

Conclusion: Our study suggested that dose-intensified RT was associated with low rates of acute and late grade 2-3 GU/GI toxicity, and had no obviously impact on one-year urinary continence recovery. However, the long-term survival outcomes needed to be further explored.

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Long-Term Outcomes of Stereotactic Body Radiation Therapy for Low and Intermediate-Risk Prostate Adenocarcinoma: A Multi-Institutional Consortium Study

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Purpose/Objective(s): While a growing body of evidence supports the use of stereotactic body radiation therapy (SBRT) for the treatment of low- and intermediate-risk prostate adenocarcinoma (PCa), some trepidation exists regarding its long-term efficacy and safety.

Materials/Methods: Men with low- and intermediate-risk PCa, as defined per the National Comprehensive Cancer Network guidelines, who were enrolled on various institutional phase II trials of SBRT between 2000- 2012 were included in a multi-institutional consortium. Men with multiple intermediate-risk factors, primary Gleason pattern 4 disease, or ≥50% positive cores (if known) were further subclassified as having unfavorable intermediate-risk disease. Biochemical relapse (BCR) was defined as PSA > "nadir +2" or initiation of androgen deprivation therapy (ADT). Toxicity data were scored according to the CTCAE v 3.0 or Radiation Therapy Oncology Group scoring systems.

Results: A total of 1641 men were eligible for analysis, with a median follow-up of 7.1 years. 297 patients (18.1%) had at least 9 years of follow-up. Fractionation schemes ranged from 33.50-40 Gy in 4-5 fractions. 1034 patients (63.0%) had low-risk disease, 444 (27.0%) had favorable intermediate-risk disease, and 163 (9.9%) had unfavorable intermediate-risk disease. 58 patients (3.6%) received short-term ADT. 100 patients (6.0%) experienced BCR, 10 (0.6%) experienced distant metastases, and no patients died of PCa. By Kaplan-Meier analysis, 5- and 10-year freedom from BCR (FFBCR) rates were 97% and 91% in the low-risk group and 94% and 89% in the favorable intermediate-risk group; 5- and 8-year rates (as no 10-year follow-up was available) in the unfavorable intermediate-risk group were and 93% and 85% ($p < 0.05$ by log-rank test). Corresponding 5- and 10-year overall survival rates were 94% and 87% and 96.6% and 90.0% for the low and favorable-intermediate risk groups, and 5- and 8-year rates were and 90.5% and 88.4% in the unfavorable-intermediate risk group ($p < 0.05$ by log-rank test). Toxicity rates are displayed in table 1. Five patients (0.3%) experienced grade 3 acute genitourinary (GU) toxicities and 32 (2%) experienced grade 3 late GU toxicity. One late grade 4 GU toxicity (hemorrhagic urethritis) and one late grade 4 gastrointestinal toxicity (fistula-in-ano) were seen.

Conclusion: To the best of our knowledge, this is the largest analysis of long-term outcomes following SBRT for PCa, and suggest an efficacy and toxicity profile that compares favorably with other radiation modalities, such as conventionally-fractionated radiation therapy and brachytherapy. Offering SBRT in the context of a balanced discussion and shared decision making is appropriate for men with low and intermediate risk prostate cancer.

Table 1. Physician-Scored Toxicity (CTCAE or RTOG)

	Grade 1	Grade 2	Grade 3	Grade 4
Acute GU	344 (20.1%)	145 (8.8%)	5 (0.3%)	0
Acute GI	256 (15.6%)	52 (3.2%)	0 (0%)	0
Late GU	148 (9.0%)	129 (7.9%)	32 (2.0%)	1 (0.1%)
Late GI	86 (5.2%)	52 (3.2%)	2 (0.1%)	1 (0.1%)

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Prospective Immunophenotyping of CD8$^+$ T-cells and Associated Clinical Outcomes of Patients with Oligometastatic Prostate Cancer Treated with Metastasis-Directed Stereotactic Body Radiation Therapy

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Purpose/Objective(s): To prospectively observe CD8$^+$ T-cell immunophenotypic changes in prostate cancer (PCa) patients treated with metastasis-directed stereotactic body radiation therapy (mdSBRT) and correlate these phenotypic changes with clinical outcomes.

Materials/Methods: We prospectively analyzed peripheral blood mononuclear cells (PBMCs) that were isolated – before and at multiple time points after mdSBRT – from 37 patients enrolled between January 2013 and October 2014 with recurrent oligometastatic PCa (≤3 extracranial sites). Immunophenotyping was performed on isolated PBMCs using flow cytometry to identify subpopulations of circulating CD8$^+$ T-cells including Tumor-Reactive ($T_{TR;}$ PD-1$^+$CD11a^{high}), Effector Memory ($T_{EM;}$ CCR7$^-$CD45RA$^-$), Central Memory ($T_{CM;}$ CCR7$^+$CD45RA$^-$), Effector ($T_{EF;}$ CCR7$^-$CD45RA$^+$), and Naïve ($T_{N;}$ CCR7$^+$CD45RA$^+$) T-cells. Univariate Cox proportional hazards regression was used to assess whether changes in these T-cell subpopulations were potential risk factors for death and progression. Kaplan-Meier method was used for survival. Cumulative incidence for progression and new distant metastasis (NDM) was estimated considering death as a competing risk.

Results: Median follow-up was 39 months (IQR 34-43). Overall survival at 3 years was 78.2%. Cumulative incidence for local progression at 3 years was 16.5% and for NDM at 3 years was 67.6%. Androgen deprivation therapy (ADT) was given concurrently with mdSBRT vs. delayed until additional progression for 19 (51%) and 18 (49%) patients, respectively. Concurrent ADT was protective against the risk of NDM (HR 0.44; 95% CI 0.20-0.96; p=0.039). Median time to NDM was 28 (IQR 5-41) vs. 8 (IQR 4-12) months for concurrent vs. delayed ADT, respectively. Seven out of 7 (100%) patients that continue to remain progression-free received concurrent ADT with mdSBRT. An increase in the T_{CM} cell subpopulation between baseline and day 14 after mdSBRT was associated with the risk of death (HR 1.22; 95% CI 1.02-1.47; p=0.033). An increase in the T_{TR} cell subpopulation between baseline and day 14 was protective against the risk of local progression (HR 0.80; 95% CI 0.65-0.98; p=0.032). Relative increases ≥1% in the T_{TR} cell subpopulation between baseline and day 14 were associated with a non-significant protective effect against the risk of any progression, distant or local (HR 0.42; 0.17-1.01; p=0.052).

Conclusion: Prospective CD8$^+$ T-cell immunophenotyping before and after mdSBRT in patients with oligometastatic PCa provided insight into clinical outcomes. An increase in the T_{CM} cell subpopulation was associated with the risk of death. An increase in the T_{TR} cell subpopulation was protective against the risk of local progression. Concurrent ADT with mdSBRT was protective against the risk of NDM. This is the first report to show

that an increase in the T_{TR} cell subpopulation after mdSBRT is associated with PCa disease control, and has implications for combining mdSBRT and adoptive cell transfer therapies. Supported by NCI R01 CA200551.
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Local Failure and Gleason Score 9-10 Disease Independently Predict for Survival Outcomes: A Meta-Analysis of Six Randomized Trials

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Purpose/Objective(s): Emerging data suggest that androgen deprivation therapy (ADT) can act as a radiosensitizer, and the benefit of upfront ADT in high Gleason score (GS) tumors--which has been validated in multiple randomized trials--may be ascribed to improvements in both local and systemic control. Patients with high GS cancers are known to have inferior survival outcomes, which has primarily been attributed to a higher risk of developing distant metastases (DMs) or having micrometastatic disease at presentation. The impact of LF in patients with high GS cancers is unknown. The purpose of the present meta-analysis was to explore whether having GS 9-10 disease and having an LF event were independent predictors of survival outcomes.
Materials/Methods: Individual patient-level data were obtained for patients with GS 8-10 PCa enrolled on three RTOG (8531, 8610, and 9202) and three EORTC trials (22863, 22961, and 22991). An LF event could occur in 4 ways: palpable tumor (all 6 trials), PSA>4 (1 trial), initiation of ADT without DM (1 trial), or urethral obstruction (2 trials). For the purposes of this analysis, LF was only counted if it was identified before a DM was identified. Multivariable Cox proportional hazard models were developed to obtain hazard ratio (HR) estimates of the effect of GS 9-10 vs. GS 8 disease and LF vs. no LF on overall survival (OS) and cancer specific-survival (CSS), after adjustment for ADT duration, age, and T-stage. All analyses were repeated in the subgroups of patients who developed DMs within 3 years ("early DM") or after 3 years ("late DM").
Results: Nine-hundred-and-ninety-two patients (593 GS 8 and 399 GS 9-10) were included, with a median follow-up of 7.1 years for surviving patients. Overall, 22.9% of GS 8 and 26.3% of GS 9 patients experienced LF (HR for GS 9-10 vs. 8 of 1.39, $p<0.05$). LF and GS 9-10 disease were significant predictors of both CSS (HRs 2.23 and 1.69, respectively; $p<0.05$) and OS (HRs 1.32 and 1.31; $p<0.05$). On subgroup analysis, the LF effect for CSS and OS was not significant in patients with early or late DMs, while the GS 9-10 effects for both CSS and OS were significant only in patients who developed early DMs (HRs 1.93 and 2.00; $p<0.05$).
Conclusion: Having GS 9-10 PCa and experiencing a LF are independent predictors of inferior CSS and OS. These results underscore the dual importance of local and systemic control as part of the upfront management of high GS

PCa. Notably, the GS 9-10 PCa effect is most pronounced in patients who develop metastases within 3 years of treatment, suggesting that micrometastatic disease at presentation may be a significant concern. Limitations are that assessment for LF was not uniformly pursued and that the doses of radiation used in the majority of these trials would be considered suboptimal today, such that fewer LF outcomes would be expected in a modern cohort.
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Gynecological Cancer

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Pre-Treatment [F-18]FDG-PET SUV_{max} as a Prognostic and Radiogenomic Marker in Cervical Cancer

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Purpose/Objective(s): We previously identified primary tumor [F-18]fluorodeoxyglucose-positron emission tomography ([F-18]FDG-PET) maximum standardized uptake value (SUV_{max}) as a candidate prognostic marker in cervical cancer patients treated with definitive radiation therapy (RT). We hypothesize that high SUV_{max} is associated with targetable biologic pathways. This work aims to identify and validate a prognostic cut point for SUV_{max} in cervical cancer, and define associated biologic pathways.
Materials/Methods: Two cohorts were used for this study. Cohort 1 consisted of all patients with cervical cancer treated at our institution between 2006-2015 who underwent a pre-treatment [F-18]FDG-PET, were treated with curative intent RT, and completed all prescribed RT (N=331). Cohort 2 consisted of patients enrolled on a prospective tumor banking study with sufficient RNA for whole transcriptome sequencing (N=68). An optimal SUV_{max} prognostic for freedom from progression (FFP) was determined in cohort 1 using outcome-oriented cut point methodology. This SUV_{max} was validated with a bootstrap Cox multivariate analysis (MVA) using 1000 random samplings from cohort 1. SUV_{max}, stage, [F-18]FDG-PET lymph node status, age, and histology were included in the MVA. Stratified Kaplan-Meier (KM) analysis was also performed on cohort 1 subgroups of stage and lymph node status. Gene set enrichment analysis was then performed on RNA samples from cohort 2 to identify pathways associated with high SUV_{max}.
Results: Using cohort 1, the optimal SUV_{max} cut point prognostic of FFP was 11.41 ($p = 0.002$ by log-rank). This was also prognostic for cancer specific survival ($p = 0.02$ by log-rank), but not overall survival. In the bootstrap Cox MVA validation, $SUV_{max} > 11.41$ was a significant prognostic factor for FFP in 46.1% of the cohort 1 samples (median hazard ratio (HR) 1.91), stage in 75.1% (median HR 1.08 for stage II vs. I, 2.23 for stage III vs. I, and 2.57 for stage IV vs. I), and [F-18]FDG-PET positive lymph nodes in 99.1% (median HR 1.30 for pelvic nodes vs none, 3.23 for para-aortic nodes vs. none). On stratified KM analysis, SUV_{max} was prognostic of FFP in stage I cancers ($p = 0.002$), and in patients with positive pelvic nodes on pretreatment [F-18]FDG-PET ($p = 0.006$) and maintained significance on MVA in these subgroups ($p = 0.003$ and 0.03, respectively). Whole transcriptome profiling identified gene sets associated with the NF-κB ($p < 3e\text{-}16$, false discovery rate (FDR) = 7.2e-5) and JAK/STAT3 (p

< 3e-16, FDR = 8.6e-4) pathways, and an inflammatory phenotype associated with immunosuppressive M2 tumor associated macrophages (p < 3e-16, FDR < 3e-16) in tumors with SUV_{max} > 11.41.

Conclusion: Pre-treatment [F-18]FDG-PET SUV_{max} > 11.41 is prognostic in cervical cancer, particularly in stage I cancers and patients with PET-positive pelvic nodes. High SUV_{max} is associated with NF-κB and JAK/STAT3 pathway activation and an inflammatory but immunosuppressive phenotype.

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Global Immune Profiling of Cervical Tumors Reveals a Protective T-Follicular Helper Cell Response Induced by Radiation Therapy

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Purpose/Objective(s): Cervical cancer is a common malignancy worldwide. In the majority of cases it is driven by HPV and thus immune responses are important for the development, progression and treatment of the disease. The primary treatment for locally advanced disease is radiation therapy, which although directed locally, may have a more systemic effect. The first aim of this work is to identify immune response genes that play a role in mediating the survival of patients with the disease. The second aim is to identify the mechanisms by which radiation therapy activates immune pathways. Such knowledge would not only be integral in determining patient prognosis, but would also aid in the development of future therapies.

Materials/Methods: We obtained a comprehensive list of genes annotated to function in the immune response using the Gene Ontology database (GO) (n=636 genes). Utilizing mRNA and survival data from a homogenous patient cohort from The Cancer Genome Atlas (TCGA) (n=49), we wrote an R-based program which performs iterative Kaplan Meier survival analysis for all immune response genes. Additionally, we utilized a machine learning algorithm to quantify immune cell populations in each patient, and identify prognostically significant immune cell types. Lastly, using the Gene Expression Omnibus dataset (NCBI), we defined the role of radiation therapy in activating relevant immune pathways.

Results: The top three cell populations which were indicative of an improved prognosis in cervical cancer were T-follicular helper (Tfh) cells (p=0.005), antibody secreting Plasma B-cells (p=0.005), and B-memory cells (p=0.001). Additionally, secreted chemokine genes involved in the recruitment of additional immune cells to the tumor were the most overrepresented genes via pathway enrichment analysis (p.adj.=0.00001017). The specific chemokine genes which were the most protective were CX3CL1 (p=0.004), CCL21 (p=0.02), IL36B (p=0.01), and CCL24 (p=0.024). Furthermore, CX3CL1 and CCL21 levels were highly associated with increasing Tfh-cell, Plasma cell, and B-memory cell populations via regression analysis. Lastly, we found that radiation robustly induced Tfh migration to cervical cancer tumor parenchyma in matched cervical cancer samples pre- and post-radiation therapy (p=0.03).

Conclusion: Tfh-cells mediate the differentiation of naïve B-cells into either antibody secreting Plasma B-cells, or into B-memory cells. Using large scale databases, we demonstrate that these three cell types are the strongest cell markers of an improved prognosis in cervical cancer. Additionally, our data suggests that chemokine signaling involved in Tfh-cell and B-cell recruitment may play a critical protective role in the immune response to cervical cancer. Lastly, radiation therapy robustly induces Tfh-cell recruitment to the cervical tumor site.

Author Disclosure: **M.R. Waters**: Employee; VCU Medical Center. **D.A. Todor**: None. **E.C. Fields**: None.

Molecular Targeting to Expand the Therapeutic Ratio in Women with Curable Cervical Cancer

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Purpose/Objective(s): Approximately 30-40% of cervical cancer patients treated with radio(chemo)therapy (RTCT) develop recurrence that can be difficult to treat. New approaches for overcoming treatment failures are needed. The CXCL12/CXCR4 chemokine pathway promotes tumor growth and metastasis in various tumor sites and we have observed the pathway is upregulated in RT treated cervical cancers. Plerixafor, an inhibitor of this pathway, is approved clinically and our initial studies showed the addition of plerixafor to RTCT enhanced primary tumor response. The current studies examined: 1. Different ways of sequencing RTCT and plerixafor to maximize efficacy 2. Biomarkers of response to RTCT and plerixafor 3. Effects of plerixafor with RTCT on intestinal toxicity, an important dose-limiting consequence of treatment in these patients.

Materials/Methods: Orthotopic cervix xenografts were treated with RT (30 Gy; 2 Gy/day) and weekly cisplatin (4mg/kg) with or without plerixafor (5mg/kg/day). Plerixafor was administered concurrently with RTCT (3 wks), adjuvantly after RTCT (3 wks) or continuously (6 wks). Biomarker response was evaluated at the end of the concurrent and adjuvant treatments. Tumor growth delay was assessed at later times. Tumor control was assessed after 50 Gy (2Gy/day-5 wks) with cisplatin and plerixafor. Late intestinal toxicity was assessed by histologic examination of the colorectal junction 90 days after treatment.

Results: Plerixafor, whether administered concurrently or adjuvantly, prolonged tumor growth delay following RTCT (30 Gy). Adjuvant plerixafor was associated with longer growth delay. Tumor cure was achieved at a higher RT dose of 50 Gy with RTCT+plerixafor. RTCT alone increased CXCL12/CXCR4 signalling, PD-L1 (immune checkpoint marker) expression and the tumor accumulation of myeloid cells. The addition of plerixafor during or after RTCT abrogated these effects. This suggests: 1) RTCT upregulation of the CXCL12/CXCR4 pathway leads to recruitment of immune populations into the tumor that confer treatment resistance and 2) RTCT-induced increases in PD-L1 expression may promote an immunosuppressed tumor microenvironment that impairs treatment response. Plerixafor reduced RT-related intestinal injury, suggesting a protective effect that may relate to modifications of immune cell infiltrates involved with the mobilization of mesenchymal stem cells from the marrow. Further investigation is needed to assess mechanisms underlying these radio-protective effects.

Conclusion: Adding plerixafor to RTCT blunts RTCT-induced upregulation of the CXCL12/CXCR4 pathway and reduces the increase in tumor-associated myeloid cells. These benefits may apply to other tumors where RT plays a curative role. Plerixafor protects normal tissue from RT injury. Few if any drugs have been identified previously that both improve the effectiveness of RT and prevent side effects. The combination of RT and plerixafor warrants testing in clinical trials to validate these findings.

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Chemoradiation Therapy for Vulvar Squamous Cell Carcinoma: Does p16-Positivity Predict for Better Response Rates and Outcomes?

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Purpose/Objective(s): Vulvar squamous cell carcinoma (VSCC) is a relatively rare malignancy. Human papillomavirus (HPV) has been implicated as a causative factor for a subset of these patients. The purpose of this study is to evaluate if p16-positivity, which is surrogate for HPV infection, predicts for better response rates and survival.

Materials/Methods: A retrospective chart review was undertaken of all women treated with neoadjuvant or definitive chemoradiation (CRT) therapy from 2000-2016 for VSCC at our institution. Available tissue blocks were stained for p16. Each tumor was assigned an H-score according to the College of American Pathologists criteria. P16-positivity was defined as strong immunoreactivity within invasive tumor with an H-score of 200+. P16 +/- groups were compared using Chi-squared and t-test. These were correlated with outcomes via Kaplan-Meier with log-rank technique. Factors which predicted for disease outcomes and overall survival were analyzed via Cox proportional hazards methods. Time to an event was defined as the time from completion of CRT or surgery following CRT if treated neoadjuvantly.

Results: A total of 74 women were identified who had follow-up and specimen available for staining. Median follow up was 14.1 months for all patients (range: 0.4-166.7 months) and 40.6 months for living patients. Thirty-two (42.7%) women had p16+ tumors. Median age was 71.5 years (range: 37-91); for women with p16+ tumors, the average age was 67.8 years vs 70.0 years for women with p16- tumors (p=NS). The distribution of stage between p16-status did not differ. The median maximal vulvar dose was 50.4Gy (range: 33.6-70.2Gy). The complete clinical response (cCR) rate for p16+ tumors was 68.0% vs 34.2% for p16- tumors (p=0.009). The pathologic complete response (pCR) rate for women treated neoadjuvantly was 56.5% vs 29.7% for p16+ vs p16-, respectively (p=0.037). The combined clinical or pathologic complete response (CR) rate was 63% for p16+ and 27.5% for p16- (p=0.004). Two-year vulvar control for women with p16+ tumors was 77.8% vs. 45% for p16- (p=0.010). In women with p16+ tumors who achieved clinical or pathologic complete response, 2-year vulvar control was 90.9% vs 66.7% if p16- and CR (p=0.071). If complete response was not achieved, 2-year control rates were 55.6% vs. 34.9% (p=0.230). No woman with a p16+ tumor developed distant metastases vs. 7 with p16- tumor (p=0.013). OS was not statistically different between p16+/- complete responders (67.3% vs. 71.6%, p=0.719) but non-responders with p16+ tumors had higher 2-year OS compared with p16- tumors (70.0% vs. 22.6%, p=0.161).

Conclusion: This is first study evaluating response to chemoradiation therapy for VSCC based on p16 positivity. P16-positive tumors appear to have better clinical and pathologic response rates and clinical outcomes. Future clinical trials may need to focus on different treatment strategy for p16-negative tumors as they seem to have a worse outcome with lower response rates and higher risk of distant metastases.

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A Prospective Study of IMRT Versus 3D-CRT for Post-Operative Cervical Cancer Patients.

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Purpose/Objective(s): The use of intensity-modulated radiation therapy (IMRT) in postoperative cervical cancer is on the rise, yet there is still some controversy to adopt adjuvant IMRT as standard practice. The purpose of this study is to compare the difference between IMRT and three-dimensional conformal radiation therapy (3D-CRT) especially in quality of life for pelvic radiation of postoperative treatment with cervical cancer.

Materials/Methods: 398 patients were enrolled from Oct 2015 to Oct 2017. They were selected randomly into two groups: IMRT group(*n*=190) and 3D-CRT group (*n*=208). Each patient received a prescribed dose of 45Gy/25F. Radiation dosimetry, the grade 2-4 in GI and GU; the score from functional assessment of cancer therapy scale-cervix (FACT-CX) scale and expanded prostate cancer index composite for clinical practice (EPIC-CP) scale were compared.

Results: (1) There was no significant difference on age, culture level, family economic condition and ratio of radiochemotherapy in two groups (*P*>0.05). (2) Dosimetric comparison: IMRT plans had a significant better conformity index (CI) of PTV compared with 3D-CRT (P<0.05). Compared with 3D-CRT plans, V40 of the small bowel, rectum, bladder, V20 and V10 of bone marrow were all significantly reduced (P<0.05). (3) The incidence of acute grade 2-3 gastriontestinal reaction was significantly high for 3D-CRT group versus the IMRT group (24.0%,15.8%; *P*=0.04). The incidence of acute grade 2-3 urinary toxicity was high for 3D-CRT group versus the IMRT group (25.5%,17.9%),but has no statistically difference *P*=0.07). (4) Quality of life scale: FACT-Cx score were 84.8±16.3 and 71.2±17.9 before and after radiation therapy in 3D-CRT group, 81.8±15.5 and 76.4±14.4 in IMRT group. FACT-Cx score was decreased significantly from beginning of radiation in 3D-CRT group ,it was reached 12.3±4.5,but it was only 5.1±2.3 in IMRT group(*t*=15.530, *P*=0.000). EPIC-CP scale score: EPIC-CP score were 15.4 ± 6.2 and 21.7±7.1 before and after radiation therapy in 3D-CRT group, 15.6 ± 6.9 and 18.4±7.2 in IMRT group. EPIC-CP score was increased significantly from beginning of radiation in 3D-CRT group ,it was reached 6.6±4.1,but it was only 3.1±4.2 in IMRT group(*t*=5.500, *P*=0.000).

Conclusion: IMRT has shown a dosimetric advantage and also provided good quality of life for the postoperative patients with cervical cancer compared to 3D-CRT. Long term follow up will be needed to determine late toxicity and DFS/OS.

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Small Cell Carcinoma of the Cervix: Definitive Chemoradiation for Locally Advanced Disease

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Purpose/Objective(s): Small cell carcinoma of the cervix (SCCC) is a rare neuroendocrine malignancy with no established treatment guidelines informing management. There is limited existing data on patients with locally advanced SCCC treated with definitive chemoradiation (CRT). The present multi-institutional study aimed to assess outcomes of patients treated at seven academic centers in the U.S.

Materials/Methods: Patients with FIGO IB2-IVA SCCC treated with definitive CRT were retrospectively reviewed for sociodemographic, clinical, treatment response, and survival data. Time to recurrence (TTR) was defined as time from first treatment to recurrence. Univariable frailty models examined TTR and time to brain recurrence; multivariable frailty models controlling for FIGO stage and node positivity assessed overall survival (OS) and analyzed interaction effects of chemotherapy agents and number of cycles on OS and recurrence.
Results: 73 patients met inclusion criteria; 41 patients (56.1%) were stage IB2-IIB, 20 patients (27.4%) were stage III, and 10 patients (13.7%) were stage IV. Mean age at diagnosis was 44 (SD: 14.5). 8 patients (16.3%) were HPV positive. 40 patients (58.8%) had pelvic/para-aortic (PA) node disease. 35 patients (52.2%) were treated with cisplatin vs. 28 patients (41.8%) treated with cisplatin and etoposide. 54 patients (74.0%) had brachytherapy (BT). The median follow-up time was 18.7 mo. (IQR: 13.3-47.4). 66.2% of patients recurred; median TTR was 10.4 mo. (95% CI: 7.8-16.5). Recurrence was associated with current smoking (HR: 3.32, p<.01), pelvic/PA node disease (HR: 2.84, p=.01), EQD2 <50 Gy vs. 71-80 Gy (HR: 3.3, p=.07), HPV negativity (HR: 2.4, p=.16) and no BT (HR: 1.5, p=.25). 15.1% of patients recurred in the brain; decreased hazard of brain recurrence was associated with BT (HR: .05, p<.01), EQD2 >75 Gy (HR: .11, p=.04), and receipt of cisplatin and etoposide vs. cisplatin only (HR: .35, p=.23). OS for all patients was 47.9%; factors associated with OS trending toward significance were HPV positivity (HR: .18, p=.10), EQD2 >50 Gy (p=.10), and chemotherapy timing (p=.02), favoring concurrent and adjuvant chemotherapy vs. concurrent only (HR: .49, p=.10). The interaction of cisplatin and etoposide with number of cycles was associated with OS (HR: 0.45, p=.01) and decreased recurrence (HR: .67, p=.07); this effect was not found for cisplatin only (HR: 1.05, p=.59 and HR: 1.04, p=.65, respectively). Patients receiving cisplatin and etoposide demonstrated improved OS (59.3% vs. 44.1%) and a lower recurrence rate (65.2% vs. 73.5%) compared to those receiving cisplatin only.
Conclusion: The present study is the largest study to date specifically analyzing locally advanced SCCC treated with definitive CRT. Patients demonstrated improved outcomes when treated with concurrent and adjuvant chemotherapy, especially with cisplatin and etoposide, EQD2 >75 Gy, and BT. The investigators await longer follow-up and a larger study population to further explore locally advanced SCCC.
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Optimal Adjuvant Management for FIGO Stage III Endometrial Cancer: Is Timing Everything?
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Purpose/Objective(s): The optimal adjuvant management of FIGO Stage III endometrial cancer (EC) remains a source of debate. Initial data from GOG-258 demonstrate that treatment with radiation therapy (RT) prior to chemotherapy (CT) yields a sizable benefit in locoregional control, but is not associated with a survival benefit compared to CT alone. Additionally, treatment with RT prior to CT may be associated with a higher risk of distant metastatic disease, suggesting a detriment to CT delay. The aim of this study was to assess the optimal selection and sequencing of adjuvant therapies in this population.

Materials/Methods: The 2004-2014 National Cancer Database was queried for women with FIGO Stage III EC who underwent hysterectomy Women who received single-agent CT only or <45Gy of regional RT were excluded. Sequence of RT and CT was determined by documented treatment start date(s). To account for immortal-time bias, women with <12 months of follow-up were excluded. A series of observational matched cohort analyses were performed using propensity score-matched cohorts. Additional separate matched cohort analyses were performed for women with Type I (Grade 1/2 endometrioid) and Type II (Grade 3/4 endometrioid, serous, carcinosarcoma, clear cell, and mixed histologies) EC. Kaplan-Meier and multivariable accelerated failure time (AFT) survival analyses were used to calculate absolute and relative survival estimates.

Results: Of the 22,197 women identified, 34.1% (n=7,568) received RT after CT, 9.7% (n=2,165) received RT before CT, 41.1% (n=9,134) received CT alone, and 15.0% (n=3,330) received RT alone. Matched cohorts were well-balanced for all clinical variables. Treatment with RT after CT was associated with significantly longer OS compared to treatment with RT before CT (5-year OS: 68.9% versus 64.5%; TR=1.10, 95% CI=1.06-1.15, P<0.001), as well as compared to CT alone (5-year OS: 65.6% versus 56.1%; TR=1.22, 95% CI=1.19-1.26), or RT alone (5-year OS: 67.6% versus 59.6%; TR=1.19, 95% CI=1.14-1.24, P<0.001). This survival benefit was also seen in the subset analyses of women with Type I EC (5-year OS: 82.5% versus 77.8%; TR= 1.17, 95% CI=1.08-1.26, P<0.001), as well as Type II EC (5-year OS: 58.9% versus 54.4%; TR= 1.06, 95% CI=1.02-1.09).

Conclusion: Accounting for known prognostic factors, women who received CT as the first adjuvant therapy followed by RT experienced significantly longer OS than women who received RT prior to CT or either therapy alone. For women with FIGO stage III endometrial cancer, treatment with CT followed by volume-directed RT (or a sandwich approach) may be the optimal adjuvant multimodality regimen. These data support the inclusion of a CT followed by RT arm in future prospective trials and suggest that RT maintains an important role in the treatment of stage III endometrial cancer.

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Head and Neck

LBA4

NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx

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Purpose/Objective(s): To determine whether radiation with cetuximab has non-inferior overall survival compared to radiation with cisplatin in patients with locoregionally advanced human papillomavirus (HPV)–related oropharynx cancer.

Materials/Methods: Eligible patients were randomized (1:1) to 70 Gy in 6 weeks accelerated (6 fractions/week) with 2 cycles of cisplatin 100mg/m2 every 3 weeks, versus the same radiation with weekly cetuximab. All patients had central laboratory confirmation of HPV status by p16 immunohistochemistry and were stratified by T-stage, N-stage, Zubrod performance status, and smoking history. At final analysis, non-inferiority would be concluded if the overall survival hazard ratio (cetuximab/cisplatin) upper confidence bound was ≤1.45.

Results: From 6/11 to 7/14, 849 patients were randomized, of whom 805 were analyzed. 90% were male with median age of 58. The overall survival hazard ratio was 1.45 (95%CI 1.03-2.05). Estimated 5-year survival rates were 84.6% (80.6-88.6) with cisplatin versus 77.9% (73.4-82.5) with cetuximab. Progression-free survival was significantly worse with cetuximab compared to cisplatin [hazard ratio 1.72 (1.29-2.29); one-sided log-rank p=0.0001] with 5-year estimates of 78.4% (73.8-83.0) with cisplatin and 67.3% (62.4-72.2) with cetuximab. Estimated 5-year local-regional failure/distant metastases rates were 9.9%/8.6% with cisplatin and 17.3%/11.7% with cetuximab. Acute grade 3-4/5 adverse events were 82%/0.8% and 77%/1.3% with cisplatin and cetuximab, respectively. The distribution of grade 3-4 adverse events varied by treatment with anemia, hearing loss, nausea, vomiting, neutropenia, and kidney injury more common with cisplatin, and rash being more common with cetuximab. Long-term severe dysphagia was 4% for the cisplatin arm and 6% for the cetuximab arm. Extensive quality of life measures were collected and will be reported separately.

Conclusion: This study failed to establish the non-inferiority of radiation/cetuximab for patients with locoregionally advanced HPV-related oropharynx cancer. Radiation/cetuximab resulted in inferior overall and progression-free survival. Radiation with concurrent cisplatin remains the standard of care in these patients. Support: This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP), U24CA196067 (NRG Specimen Bank), U24CA180803 (IROC) from the National Cancer Institute (NCI), Eli Lilly and The Oral Cancer Foundation.

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LBA6

Plasma Circulating Tumor HPV DNA for the Surveillance of Cancer Recurrence in HPV-associated Oropharyngeal Cancer

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Purpose/Objective(s): To assess the performance of plasma circulating tumor HPV DNA (ctHPVDNA) as a surveillance blood test in patients with p16 positive oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: A prospective biomarker trial was conducted in 89 patients with p16 positive OPSCC who had no evidence of distant metastatic disease at baseline. All patients received definitive chemoradiotherapy (CRT) with 78 receiving de-intensified CRT on clinical trial (60Gy). Remaining patients received standard CRT (70Gy). All patients had a 3-month post-CRT PET/CT and were thereafter surveilled with clinical examinations every 2 - 4 months for years 1 - 2, then every 6 months for years 3 - 5. Chest x-rays or chest CT's were performed every 6 months. Blood specimens were collected at baseline (58/89), weekly during treatment (30/89), and with each follow-up visit (89) for plasma circulating nucleic acid extraction (Qiagen). Multianalyte droplet digital PCR assays were developed for ultra-sensitive detection of ctHPVDNA -16, -18, -31, -33, and -35 DNA on the Bio-Rad QX200 platform. Additional imaging was obtained if ctHPVDNA became detectable in the blood. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of ctHPVDNA testing at detecting recurrence were calculated. Events were defined as recurrence after the 3-month post-CRT PET/CT.

Results: Clinical characteristics were the following: 89% T0-2, 80% N2, 80% never/≤ 10 pack years. Mean f/u was 19.8 months (range 3.7 – 44.7). Baseline ctHPVDNA was detectable in 51/58 (88%), with a median value of 582 copies/mL (range 8 - 22,579). 53/58 evaluable patients had undetectable ctHPVDNA within 3 months of completing CRT. 73/89 patients in the surveillance cohort had undetectable ctHPVDNA at all timepoints beyond 3 months post-CRT. 16/89 patients developed a positive ctHPVDNA test result with a median interval from CRT of 16.7 months (range 7.8 – 30.4) and a median value of 75 copies/mL (range 9 – 28,369). 8/16 patients who developed a positive ctHPVDNA test result during surveillance were diagnosed with recurrence (0 local, 1 regional, 7 distant). 8 patients currently have detectable ctHPVDNA (range 23 – 28,369 copies/ml) but have no evidence of recurrence and are being monitored with repeat ctHPVDNA and imaging. 0/73 patients with undetectable ctHPVDNA at all follow-up visits have developed recurrence. Sensitivity, specificity, NPV, and PPV of ctHPVDNA testing was: 100%, 90%, 100%, 50%.

Conclusion: Performance of an optimized multianalyte ctHPVDNA blood test for the detection of cancer recurrence was exceptional (NPV = 100%). Future studies should be done to evaluate whether ctHPVDNA testing may improve early detection of cancer recurrence while also reducing costs by targeting radiographic surveillance to the subset of patients who are at greatest risk of relapse.

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Eliminating Post-operative Radiation to the Pathologically Node Negative Neck: Long-Term Results of a Prospective Phase II Study

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Purpose/Objective(s): The volume treated with post-operative radiation therapy (PORT) is a mediator of toxicity and reduced volumes have resulted in improved in quality of life (QOL). In this prospective study we decreased treatment volumes by omitting PORT to the pathologically negative (PN0) contralateral (CL) and/or ipsilateral (IL) neck in patients with tumors of the oral cavity (OC), oropharynx (OPX), larynx (LX), hypopharynx (HPX), and unknown primary (UP). We hypothesized that elimination of PN0 neck PORT would result in > 90% control in the unirradiated neck (UN).

Materials/Methods: Patients with tumors of the OC, OPX, LX, HPX, and UP who underwent surgical resection and neck dissection (ND) with a PN0 neck and high risk features mandating PORT to the primary and/or involved neck were eligible. Our primary objective was to evaluate the rate of control in the UN. Secondary objectives included QOL, local control (LC), regional control (RC), progression free survival (PFS), and overall survival (OS). The CTV1 and CTV2 were treated to 66 Gy and 54 Gy in 33 fractions (fx) or 60 Gy and 52 Gy in 30 fx. Chemotherapy was delivered at the discretion of the treating oncologist. QOL was collected using the MD Anderson Dysphagia Inventory and the University of Michigan Patient reported Xerostomia questionnaire. The study required accrual of 69 patients to achieve 83% power with alpha = 0.10 to show equivalence of reduced volume PORT compared to bilateral neck PORT. LC, RC, PFS, and OS were analyzed via Kaplan-Meier method and mixed modeling was used with Tukey adjustment for multiple comparisons on QOL data.

Results: From 5/2007-9/2013, 73 patients enrolled and 72 were evaluable. Median age was 56 years (range 31-81), 58 (81%) were male, and 47 (65%) used tobacco. Sites included 14 (20%) OC, 37 (51%) OPX, 4 (6%) HPX, 16 (22%) LX, and 1 (1%) UP tumor, with AJCC 7th edition stage III/IV disease in 67 (93%) patients. 51% had T3/4 disease, 59% had N2/3, and 71% of tumors involved or crossed midline. We excluded T1/2 N0-2b lateralized tonsil patients because our policy was to use IL PORT without a required CL ND. 34 patients (47%) received chemotherapy and all completed PORT. Zero patients had CL neck PORT. All but 6 patients had a CL ND; 0/6 had isolated neck failure. At median follow up of 53 mo, there were 2 failures in the PN0 UN; both also had local failures. There were no isolated UN failures. UN control was 97% (95% CI 93.4-100.0%). 5 year actuarial rates of LC, RC, PFS, and OS were 84%, 93%, 60%, and 64% respectively. QOL scores for emotional (Em), physical (Ph), functional (Fxn), and xerostomia (Xe) declined from baseline to time of PORT completion ($p<0.05$). By 24 mo, these scores recovered with no difference from baseline ($P>0.05$), except Xe, for which QOL remained reduced post PORT ($P<0.05$). However, global QOL was improved from baseline 24 mo post PORT ($P=0.04$).

Conclusion: Eliminating PORT to the PN0 neck resulted in excellent rates of control in the UN without adverse effects on global QOL. This trial met the primary endpoint with 97% control in the UN.

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The Influence of Smoking and Age on Pathologic Features and Outcomes in Oral Cavity Squamous Cell Cancer: A Multi-institutional Collaborative Study

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Purpose/Objective(s): To evaluate the impact of smoking and age on the frequency of pathological risk factors and outcomes for surgically staged oral cavity squamous cell carcinoma (OCSCC) in a multi-institutional analysis.

Materials/Methods: A collaborative database of patients with primary OCSCC among 6 academic medical centers encompassing non-metastatic cases diagnosed between 2005 and 2015 was constructed. All cases were treated with surgery +/- adjuvant radiation therapy (RT) +/- concomitant chemotherapy (CRT) according to risk factors. Patients were categorized based on smoking history and age and the resultant groups were compared for demographic data, pathologic features and treatment modalities using t-test and Chi-squared tests. Kaplan-Meier curves and Log-rank *p*-values as well as multivariate analysis (MVA) for recurrence free survival (RFS).

Results: We identified 1055 cases that met our inclusion criteria after excluding 227 patients with unknown smoking history and incomplete records. Median age was 61 years, 60% of cases were men, 88% were Caucasian; and oral tongue (22%) followed by floor of mouth (18%) were the most common sub-sites. The median follow up time was 40 months (15-195 mths). Surgery alone, surgery + RT and surgery + CRT were utilized in 32%, 37% & 31% of cases respectively. Smokers either during or at any point before diagnosis ("Ever Smoked") were 730 cases (69%), whereas "Never Smoked" constituted the remaining 31% (n=325). Smoking was significantly associated with male sex, heavy alcohol use (38% vs 3%) and floor of mouth location (28% vs 6%) ($p<0.001$ for all). Adverse pathologic features were similar in both groups including grade, AJCC stage, lymphovascular (LVI) and extracapsular space invasion (ECE); except for perineural invasion (PNI) that was detected more in smokers (48% vs 37%; $p=0.003$). Three and 5 years RFS were not influenced by smoking (62.8% & 57.7% for Ever Smoked vs. 62% & 56.2% for Never Smoked; $p=0.553$). Even when we further categorized our study population into current (36%), former (33%) and never smokers (31%) similar results were attained both for risk features and RFS and the same occurred within different AJCC stages. RFS for patients younger than 50 years (n=193; 18%) was also not significantly different when compared to older ones 50-70 (n=584; 56%) and > 70 years (n=278; 26%) with 3-year RFS of (67%, 74% & 51%) and 5-year RFS of (64%, 73% & 51%) for the three groups respectively ($p=0.74$). On MVA, classical factors namely higher AJCC stage, PNI, LVSI, ECE and positive final margins were independently associated with worse RFS ($p<0.05$ for all). Both smoking and young age were not associated with any detrimental effect.

Conclusion: In our multi-institutional analysis that included one of the largest cohorts to date for oral cavity squamous cell carcinoma treated with modern modalities with adequate follow up, smoking history and young age did not skew outcomes. Smoking was not correlated with any adverse risk feature except for perineural invasion.

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Validating the AJCC 8th Edition of the Oral Cavity Cancer Staging System: A Multi-institutional Collaborative Study

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Purpose/Objective(s): We conducted a multi-institutional study to interrogate survival outcomes in patients with oral cavity squamous cell carcinoma (OC-SCC) treated definitively grouped according to the AJCC 8th edition staging system and compared them to the 7th edition system for best fit analysis.

Materials/Methods: An IRB approved collaborative database of patients with primary OC-SCC stage I-IVb (AJCC 7th edition) treated with primary surgical resection between 1/1/2005 and 1/1/2015 with or without adjuvant therapy was established from 6 academic medical centers. From a total sample size of 1282 patients, we identified 1037 patients who had sufficient staging data to be included. Survival rates were generated using Kaplan Meier analysis. A Cox proportional hazards model was generated for each staging system and Akaike information criterion (AIC) was calculated for each.

Results: The study population consisted of 647 men (62%), 868 Caucasians (84%) with a median age of 61 and a median f/u of 56 months (1-180). Oral tongue was the most common location (38%), followed by floor of mouth (18%), alveolus (14%) and other. All patients had primary resection, 91% had a neck dissection, 46% had postop radiation therapy alone and 37% had postop chemoradiation. The stage was changed in 388 pts (37%) in the 8th edition, all of whom were upstaged (see Table 1). Relative to stage I, AJCC 8 failed to show a significant difference in survival for stage II (HR 1.2; p=0.63) and stage III disease (HR 1.5; p=0.14), while stages IVa (HR 2.5; p<0.001) and IVb (HR 4.8; p<0.001) demonstrated significantly inferior survival. AJCC 8 5yr OS rates were similar compared to AJCC 7 for stage I (81%) and II disease (77% vs 75%), higher for stage III (72% vs 65%) and stage IVa disease (55% vs 47%), and lower for stage IVb disease (34% vs 44%), respectively. The AIC were smaller for AJCC 8 (5,804 vs. 5,841) indicating better fit.

Conclusion: The AJCC 8th edition upstaged 37% of patients with OC-SCC leading to more uniform representation within each stage. The 8th edition outperformed the 7th edition in distinctiveness, most notably in stage IVa and IVb disease.

Table 1: Distribution of patients according to AJCC stage

	AJCC 8					
AJCC 7						**Total**
	I	II	III	IVA	IVB	
I	80	41	12	-	-	**133**
II	-	69	52	-	-	**121**
III	-	-	112	37	-	**149**
IVA	-	-	-	379	246	**625**
IVB	-	-	-	-	9	**9**
Total	**80**	**110**	**176**	**416**	**255**	**1037**

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Margin Status, Lymphovascular Invasion, and Number of Neck Levels Involved Predict Distant Failure in p16+ Oropharyngeal Squamous Cell Carcinoma (OPSCC) Following Transoral Robotic Surgery (TORS)

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Purpose/Objective(s): Current management paradigms in p16+ OPSCC are exploring de-intensification strategies due to the generally favorable prognosis of p16+ OPSCC and the high morbidity burden of traditional curative treatment. One of the main concerns with this approach is the heterogeneity within p16+ disease and recognition that there are subpopulations at significant risk of disease failure. Therefore, we sought to examine our own outcomes with p16+ OPSCC to identify pathologic factors associated with significant risk of distant metastasis following TORS.

Materials/Methods: We evaluated 424 consecutive patients who underwent TORS resection for p16+ OPSCC between January 2008 to December 2016 at our institution. Overall survival (OS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) were measured from the date of surgery and calculated using the Kaplan-Meier method. The log-rank test was used to compare survival between patient groups. Clinical and pathologic factors associated with DFMS were determined by Cox proportional hazards regression analysis. A two-sided P value of less than 0.05 was considered statistically significant.

Results: Median follow-up was 3.4 years (range 1 day – 7.1 years). Median pack-years was 2 years (range, 0 – 100 years). 120 patients (28.3%) received TORS resection alone, 304 patients (71.7%) received post-operative RT, and 143 patients (33.7%) received adjuvant chemoradiation. The majority of patients were Stage IVA (68.6%) and

tonsillar cancers (55.0%). Median package time from the date of surgery to the completion of RT was 14.3 weeks. For the entire cohort, 3-year OS was 94.6% (95% CI 92.3% - 97.0%), LRF 89.3% (95% CI 86.1% - 92.5%), and DMFS 94.1% (95% CI 91.7% - 96.5%). On multivariate analysis, lymphovascular invasion (LVI) (HR 2.59, 95%CI 1.09 – 6.16, p = 0.031), margin status (HR 1.91, 95%CI 1.12 – 3.24, p = 0.017) and increased number of neck levels involved (HR 1.75, 95%CI 1.16 – 2.65, p = 0.008) were significantly associated with worse DMFS. Patients with and without LVI had a 3-year DFMS of 87.7% and 96.8% (p = 0.001), respectively. The 3-year DMFS for patients with negative, close, or positive margins was 95.4%, 92.7% and 78.7% (p < 0.001), respectively. Patients with zero, one, two, or three neck levels involved had a 3-year DFMS of 98.5%, 95.6%, 91.6%, and 80.6% (p < 0.001), respectively.

Conclusion: This study examines pathologic factors associated with distant relapse in the largest series to date of patients undergoing TORS for p16+ OPSCC. Patients with positive margins, LVI and 3 or more positive neck levels have substantial rates of distant metastasis. These pathologic factors may identify a patient population who may benefit from intensified systemic therapy.

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A Randomized, Placebo (PBO) Controlled, Double-Blind P2b Trial of GC4419 (Avisopasem Manganese) to Reduce Severe Radiation-Related Oral Mucositis (SOM) in Patients with Locally Advanced Squamous Cell Cancer of the Oral Cavity (OC) or Oropharynx (OP)

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Purpose/Objective(s): Intensity-modulated radiation therapy (IMRT) plus cisplatin (CDDP) is established treatment for locally advanced OC/OP cancer, but appx. 70% of patients develop SOM, defined as WHO Grade 3 or 4, which limits patients' ability to eat solids (Gr 3) or liquids (Gr 4, requiring artificial nutrition). An RT-induced burst of superoxide initiates oral mucositis (OM) development. GC4419, a superoxide dismutase mimetic, interrupts this process by potently converting superoxide to H_2O_2. It showed promising reductions of SOM in a published open-label Phase 1b/2a trial (IJROBP 1 Feb 2018). Hypothesis: GC4419 reduces SOM without increasing toxicity or decreasing tumor control of IMRT/CDDP.

Materials/Methods: 223 pts with OC or OP cancers receiving 70 Gy IMRT (≥50 Gy to > 2 oral sites) plus CDDP (qwk or q3wk), were randomized 1:1:1 to PBO, 30 or 90 mg of GC4419, by 60-minute IV infusion, M-F before each RT fraction. OM by the WHO scale was assessed by trained evaluators during RT & for up to 8 wks post RT. Primary endpoint was duration of SOM. Secondary endpoints included incidence & time to onset of SOM, & safety. Efficacy analyses (each active dose v PBO, ITT) proceeded by a sequential, conditional approach; 2-sided α=0.05.

Results: Baseline patient & tumor characteristics were balanced: 86% M, 77% OP, 77% definitive, 82% IVa, 34% T4, 72% HPV+, 38% q3wk CDDP, number of oral sites receiving ≥ 50 Gy [3-4 sites; 53%; 5+ sites, 38%]); as was treatment delivery (median 70 Gy; 6% had RT breaks ≥ 5 consecutive fractions; 80% received ≥ 200 mg/m^2 CDDP; 87% received ≥ 80% of planned GC4419/PBO doses). 90 mg GC4419 reduced SOM across endpoints, including a statistically significant reduction in the primary endpoint of duration (TABLE). Cumulative SOM incidence throughout RT (i.e., through 30, 40, 50 Gy) was also consistently lower with 90 mg GC4419 v PBO. Safety was

comparable across arms with no significant GC4419-specific toxicity; chemotherapy toxicity of IMRT/cisplatin did not appear to be increased. 2-year follow up for tumor outcomes is in progress.

Conclusion: GC4419 90 mg produced a clinically meaningful reduction of SOM; the primary analysis (duration) was statistically significant. Efficacy results with 30 mg were intermediate and did not reach significance. The safety profile was comparable to placebo. Interim tumor control data and exploratory correlative analyses will be presented.

Table 1

	PBO	30mg	90mg	90mg vs. PBO	
N	74	73	76	Relative δ	p=
Duration SOM, median days	19	8	1.5	92%	0.024
Incidence SOM thru 60 Gy	58%	40%	37%	36%	0.010*
Incidence SOM thru last RT	65%	60%	43%	34%	0.009*
Incidence Grade 4 OM	30%	21%	16%	47%	0.045*
Onset SOM, median days	39	47	61	56%	0.080*

*nominal p value, pre-specified secondary endpoint

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Smoking Cessation Had Good Impact on Clinical Outcomes in Patients with Head and Neck Squamous Cell Carcinoma Receiving Curative Chemoradiotherapy

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Purpose/Objective(s): Smoking during curative chemoradiation (CRT) caused rising carboxyhemoglobin concentrations and reduced oxygen supply to radiation therapy sites. Few studies have prospectively examined the effect of smoking cessation on clinical outcomes of radiation therapy. We hypothesized that patients with head and

neck squamous cell carcinoma (HNSCC) who achieved smoking cessation during curative CRT would have lesser complications and lower risks of tumor recurrence.

Materials/Methods: Patients with non-metastatic HNSCC who were smokers at the time of diagnosis (confirmed by carbon monoxide breath test concentrations of ≥ 3 ppm) undergoing curative CRT were prospectively enrolled. Patients were treated with primary curative radiation therapy to a total dose 60-70 Gy in 30-35 fractions. Patients were referred to smoking cessation program before CRT. Successful smoking cessation throughout CRT was confirmed by CO breath test concentrations of < 3 ppm at the end of CRT. Associations between smoking and grade ≥ 3 acute or late toxicities, or permanent tracheostomy were evaluated by Pearson's chi-squared test. Associations between smoking and clinical survivals were evaluated by Kaplan–Meier log-rank tests and Cox proportional hazards regression model.

Results: Sixty-three HNSCC patients (stage IV disease, 68%) were prospectively included. The primary sites were oropharynx (41%), oral cavity (25%), hypopharynx (21%), larynx (6%), and others (7%). Forty-one patients (65%) reached successful smoking cessation throughout CRT. Patients who achieved successful smoking cessation during CRT had a significantly lesser probability of grade ≥ 3 acute toxicities (22% vs. 55%, p = 0.009), compared to patients who continued smoking throughout CRT. With a median follow-up of 33 months, patients who reached successful smoking cessation throughout CRT had a significantly greater probability of recurrence-free survival (3-year RFS 61% vs. 34%, p = 0.026), compared to patients who continued smoking during CRT. Patients who reached successful smoking cessation throughout CRT had a significantly lower rate of permanent tracheostomy (5% vs. 23%, p = 0.032), compared to patients who continued smoking during CRT. In multivariate analysis, despite age, histological grade, primary site, or radiation therapy total dose, initial T4 stage remained significantly poor prognostic factor for tumor recurrence (hazard ratio: 2.7, 95% confidence interval: 1.3-5.6, p = 0.008), while smoking cessation during CRT significantly reduced the risk of tumor recurrence (hazard ratio: 0.4, 95% confidence interval: 0.2-0.9, p = 0.026).

Conclusion: The study showed that smoking cessation during curative CRT reduced treatment-related toxicities and risks of tumor recurrence for HNSCC patients. Efforts should be made to reach smoking cessation during curative CRT, in order to improve the therapeutic efficacy of curative CRT.

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The Long-term Results of Adding Chemotherapy to Intensity-Modulated Radiation Therapy in the Treatment of Stage II Nasopharyngeal Carcinoma - A Multicenter Phase 2 Study

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Purpose/Objective(s): To investigate the role of adding chemotherapy to intensity-modulated radiation therapy (IMRT) for stage II nasopharyngeal carcinoma

Materials/Methods: From May 2010 to Jul 2012, a total of 84 newly diagnosed stage II (AJCC 7th stage system) nasopharyngeal carcinoma patients were entered into this study. All patients were randomized assigned to IMRT alone group (n=43) and IMRT combined concurrent cisplatin (40mg/m2, weekly) group (CCRT group, n=41). The primary endpoint was overall survival (OS), the second primary endpoint were primary lesion control (PLC), regional node control (RNC), disease-free survival (DFS), distant metastasis-free survival (DMFS) and acute toxicities.

Results: With a median follow-up time of 75 months, 4 patients died, 1in IMRT alone group, 3 in CCRT group. The 5-years OS, DFS, PLC, RNC and DMFS were 97.5%，88.7%，93.9%，96.4% and 94.9%. The OS，DFS, PLC, RNC and DMFS of IMRT alone group and CCRT group were 100% vs 94.0% (p=0.25), 90.4% vs 86.6% (p=0.72), 93.0% vs 89.3% (p=0.79), 97.7% vs 95.1% (p=0.54) and 95.2% vs 94.5% (p=0.77). There were 14 patients failed during follow-up, 7 patients in each group. There was more grade 2-4 acute WBC toxicity in CCRT group than in IMRT alone group (p=0.022) , no significant differences of liver, renal, skin and oral mucositis toxicities were observed between IMRT alone and CCRT group.

Conclusion: For stage II nasopharygneal carcinoma, Intensity-moduated radiation therapy is enough.

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5-Year Results of the Prognostic Roles of Serial Post-Intensity-Modulated Radiation Therapy Undetectable Plasma EBV DNA for Non-Metastatic Nasopharyngeal Carcinoma

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Purpose/Objective(s): We previously demonstrated that post-IMRT 8th week and 6th month undetectable plasma EBV DNA were significant prognostic factors of 3-year survival endpoints for non-metastatic NPC. We now presented our 5-year results. (NCT02476669).

Materials/Methods: Patients with previously untreated non-metastatic NPC confirmed by PET-CT and MRI scans were prospectively recruited from 2010 to 2016. They all had plasma EBV DNA measured at baseline, and then 8 weeks and 6 months following IMRT with/without concurrent +/- adjunct chemotherapy. They were staged and treated based on the 7th edition TNM of AJCC/UICC Staging Classification. Covariates including age, sex, ACE-27, pretreatment LDH and plasma EBV DNA were analyzed by Cox regression for prognostic factors of progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS).

Results: 518 patients were prospectively recruited. 71 (13.7%) patients received IMRT alone, while 90 (17.4%) and 357 (68.9%) received concurrent chemoradiation alone and concurrent chemoradiation followed by adjunct chemotherapy respectively. The median pretreatment plasma EBV DNA titers was 494 copies/ml (range 0-175000 copies/ml). After a median follow-up of 5.2 years, 38 (7.3%) and 21 (4.1%) patients still had detectable titers at 8 weeks and 6 months following IMRT. 5-year PFS, CSS and OS in the whole study population were 77.1%, 90.4% and 84.4% respectively. Patients with post-IMRT 8th week and 6th month undetectable plasma EBV DNA titers enjoyed longer 5-year survival endpoints (PFS 79.1% vs. 40.9%; CSS 93.8% vs. 58.8%; OS 85.7% vs. 55.3%; all $p<0.001$), which were also lengthened for those with post-IMRT 6th month undetectable titers (PFS 78.7% vs. 19.0%; CSS 93.4% vs. 39.7%; OS 85.5% vs. 37.5%; all $p<0.001$), compared to those who still had detectable titers at the corresponding time points. They are also the only prognostic factors of these endpoints in multivariable analyses (all $p<0.001$).

Conclusion: Post-IMRT 8th week and 6th month undetectable plasma EBV DNA remained significant prognostic factors after 5 years of follow-up. Additional therapy may have to be considered for those who had persistently detectable plasma EBV DNA after IMRT.

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Hematologic Malignancies

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Definitive and Immediate Salvage Treatment Achieves Durable Response for Relapse Following Primary RT for Follicular Lymphoma: An International Collaborative Study on Behalf of ILROG

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Purpose/Objective(s): We previously reported outcomes for a cohort of patients (pts) with early stage follicular lymphoma (FL) staged by FDG-PET receiving definitive primary radiation therapy (RT) of whom approximately 30% developed recurrence within 5 years. Treatment for relapsed lymphoma after primary RT varies significantly. We sought to report outcomes for pts in this cohort who relapsed.

Materials/Methods: We conducted a multicenter retrospective study of pts who received RT only for stage I-II FL staged by PET-CT meeting inclusion criteria: ≥18 years, grade 1-3A FL, dose ≥24Gy without prior treatment. We analyzed outcome of pts with relapse excluding those with <3 months of follow up from time of failure. Overall survival (OS) and freedom from progression (FFP) were estimated with Kaplan-Meier, and uni- and multivariate analyses with Cox regression. Observation was defined as >6 months from failure without treatment.

Results: Of 512 pts with median follow up of 52 months, 149 developed recurrent lymphoma at a median 23 months (range, 1-143) after primary RT. 137 (91.9%) were distant failures. Histologies included: 90 indolent, 3 FL grade 3B/NOS, 19 diffuse large B-cell lymphoma (DLBCL), and 37 un-biopsied. 109 pts had sufficient follow up (median, 37 months) with 3-year OS of 95.9% from time of relapse. The majority (n=96, 88%) had biopsied (n=73) or presumed (n=23) indolent recurrence and received the following: 57 (59.4%) observation, 20 (20.8%) systemic therapy, 15 (15.6%) RT, and 4 (4.2%) systemic and RT. For indolent recurrences, 3-year FFP or time to next treatment was significantly better for those who received salvage treatment compared with observation, 82.3% vs 57.7%, respectively (p=0.03), with no significant difference in age, gender, localized relapses, biopsy status, or symptoms between subgroups. For those observed, median time to treatment or progression was 21 months (range, 8-56) with 19 receiving salvage treatment and continued observation for the remainder. For all pts with indolent recurrence receiving salvage treatment (n=58), 3-year FFP was 77.9%; 35 were eligible for definitive treatment (RT≥24 Gy, chemotherapy with rituximab, or chemoradiation) with 3-year FFP of 94.4%. 23 received RT<24 Gy or rituximab alone with 3-year FFP of 57.4%. On multivariate analysis, initial observation status was associated with worse FFP (HR=3.22, p=0.03) after adjusting for pt factors at relapse. 9 pts with DLBCL and sufficient follow up received salvage treatment (7 chemotherapy, 2 chemoradiation) for which 6 remain disease free.

Conclusion: Based on this cohort with limited follow up, a significant proportion of patients with relapsed lymphoma after primary RT for early stage FL achieved remission with excellent OS. Pts with indolent recurrence had superior FFP with immediate treatment, and those selected for definitive treatment attained a durable response.

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Tandem Induction Radiation and Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma

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Purpose/Objective(s): Chimeric antigen receptor T cell (CAR-T) therapies targeting lymphoma-specific epitopes have demonstrated efficacy in relapsed/refractory non-Hodgkin lymphoma. Radiation therapy (RT) can be used as bridging therapy for symptomatic progression, and/or as lymphodepletion prior to CAR-T infusion. This tandem sequencing of RT and CAR-T has not been previously reported.

Materials/Methods: Patients enrolled in a phase IIA study evaluating autologous T cells engineered to express CD19-directed CAR (NCT02030834) were divided into no RT or RT prior to infusion groups, including: induction RT (<30 days), prior RT (>30 days but <12 months), and remote RT (>12 months). CAR-T in vivo expansion, toxicity, outcomes were recorded. Median follow-up is defined as time from CAR-T infusion to event or last follow-up (f/u). Descriptive statistics were used with Kaplan-Meier analysis for progression-free (PFS) and overall survival (OS).

Results: Forty-one patients are evaluable: 18 no RT, 5 induction RT, 7 prior RT, and 11 remote RT. Patients included diffuse large B cell (61%), follicular (34%), and mantle cell lymphoma (5%). Induction RT was used to manage symptoms and incorporated into the lymphodepleting regimen in those patients. Patients in the induction RT group began RT after T cell collection, on average 12 days prior to re-infusion (range 7-19); those in the prior RT group received RT 146 days prior to T cell collection (range 99-263). Median f/u time is 674 days for all patients. One-year PFS and OS for each group are: 44 and 65% (no RT), 78 and 100% (induction RT), 0 and 86% (prior RT), and 61 and 90% (remote RT), respectively. Cytokine release syndrome, ≥ grade 3, occurred in 10 of 41 patients overall (24%), but in no patient in the induction RT group (0 of 5). CAR-T expansion and day of peak CAR-T were not affected by RT given at any interval prior to T cell collection or re-infusion.

Conclusion: Induction RT prior to CAR-T infusion does not impact efficacy of therapy, and may be associated with a lower incidence of CRS. Given that RT can both palliate symptoms and be used in lymphodepletion regimens, this tandem approach warrants further exploration and potential consideration in future CAR-T trials.

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In Patients Over 65, Consolidative Radiation for Early Stage Diffuse Large B Cell Lymphoma is Associated with Decreased Hematologic Toxicity and Hospitalizations after RCHOP Compared with RCHOP Alone

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Purpose/Objective(s): SWOG 8736 and ECOG 1484 showed improved outcomes with consolidative radiation (RT) for early stage Diffuse Large B Cell Lymphoma (DLBCL) in the pre-rituximab era. Subset analysis from RICOVER-60 and an interim analysis of the UNFOLDER trial indicate patients with high risk features may benefit from RT. A recent phase III trial in non-bulky early stage DLBCL showed RCHOP to be non-inferior to RCHOP followed by RT for 5 year EFS and OS, but only 1/3rd of patients were over 60. Outcomes for older patients, who may not tolerate full courses of chemotherapy, are unclear as these patients are under represented in most of these clinical trials. The Surveillance, Epidemiology, and End Results (SEER) Medicare Database was used to assess the benefit and toxicity of RT after RCHOP in early stage DLBCL in patients over 65.

Materials/Methods: Patients age >65, diagnosed from 1/1999 to 12/2009, Ann Arbor stage I-II, and who received 2-12 cycles of CHOP or R-CHOP with or without RT were identified. RT had to be completed within 180 days of the end of chemotherapy. Propensity score matching was used to compare overall survival of patients with similar stage, age, comorbidity, extranodal involvement, and cycles of chemotherapy.

Results: 1541 patients were identified. Median age was 75. 818 (59.3%) of patients were stage 1. 1206 (78.3%) received RCHOP. 470 (30.5%) received RT. Median number of cycles of chemotherapy received were 4, 3, 6, and 3 for CHOP, CHOP RT, RCHOP and RCHOP RT, respectively. In patients treated with CHOP, RT was associated with improved overall survival on univariate analysis (HR 0.75 (0.56-1.00), p=0.048; 5 year OS 68.7 vs 63.7%). Propensity score matching was not feasible for CHOP vs CHOP RT due to small sample size. When comparing RCHOP and RCHOP RT, RT patients were more likely to have stage I disease (69.8 vs 54.4%, p<0.001), extranodal disease (46.4% vs 39.6%, p=0.031), and receive fewer cycles of chemotherapy (p<0.001), with no difference in age or comorbidity score. RCHOP RT was associated with less febrile neutropenia (p=0.026), thrombocytopenia or neutropenia (p=0.020), and hospitalizations (p<0.001). Using propensity score matching, RT was not associated with improved OS (HR 0.86 (0.65-1.13), p=0.279).

Conclusion: Medicare patients over age 65 who received consolidative RT after RCHOP chemotherapy for DLBCL experienced less febrile neutropenia, thrombocytopenia or neutropenia, and had fewer hospitalizations than patients treated with RCHOP alone. Consolidative RT was associated with equivalent survival. Ongoing clinical trials will further help elucidate which risk factors are indications for consolidative RT, and which patients will benefit from radiation.

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Involved-Site Radiation Therapy for H. Pylori-Independent Gastric MALT Lymphoma: 26 Years of Experience with 178 Patients

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Purpose/Objective(s): Gastric mucosa associated lymphoid tissue lymphoma (GML) is often associated with *Helicobacter pylori* (*H. pylori*) infection. Eradication of *H. pylori* is effective for up to 80% of patients. For *H. pylori*-independent GML, treatment options include surgery, immunotherapy, chemotherapy and radiation therapy (RT). The purpose of this study is to investigate the efficacy and safety of involved site radiation therapy and routine endoscopic surveillance, hypothesizing that radiation is highly effective for *H. pylori*–independent GML and most patients are curable with RT alone.

Materials/Methods: A single institution database at a tertiary referral cancer center was queried for patients with *H. pylori*-independent GML treated with radiation between 1991 and 2017. Prior to treatment, pathology was confirmed by hematopathology experts and patients underwent staging with either computed tomography scan,

positron emission tomography, endoscopic ultrasound, or a combination of techniques. All patients received involved site radiation therapy to the stomach. The clinical treatment volume (CTV) included the stomach and first part of the duodenum. Perigastric lymph nodes and other parts of the duodenum were also included in CTV if involved with disease. Response was assessed by follow up endoscopies (EGDs) within 10-12 weeks following RT with multiple biopsies at frequent intervals, as well as appropriate radiographic imaging. Survival analysis was calculated using the Kaplan Meier estimator and toxicity was graded according to CTCAEv4 criteria.
Results: There were 178 patients identified (56% female). Median age was 63 years (range 25-91 years). Eighty-eight percent of patients presented with stage I disease; 6% were stage II and 6% were stage IV. Median RT dose was 3000 cGy over 20 fractions. Post treatment EGD with biopsy was obtained in 173 patients, of which 95% demonstrated a complete pathologic response. Intriguingly, 4 patients had abnormal posttreatment EGD biopsies that spontaneously resolved. One patient experienced grade 3 toxicity. Over a median follow up of 9 years, 8% experienced local failures and 10% developed distant sites of disease. Eighty-three percent of patients remained lymphoma free. Five and 10-year overall survival estimates from all causes were 97% and 84%, respectively.
Conclusion: RT is a highly effective, safe treatment for GML with excellent overall survival and very rare acute or late treatment related toxicities. Spontaneous resolution of abnormal post treatment biopsies offers an intriguing window into histologic responses to radiation. Favorable outcomes from this large retrospective sample of patients provide credible and compelling support for the use of RT for *H. pylori*-independent GML as standard of care.
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Successful Management of Diffuse Large B-Cell Lymphoma Involving the Mesentery with Volumetric Image Guided Intensity Modulated Radiation Therapy

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Purpose/Objective(s): Due to the potential for unpredictable motion of mesenteric masses, there may be reluctance to administer radiation therapy (RT) for diffuse large B- cell lymphoma (DLBCL) with mesenteric nodal involvement. We report the outcome of patients treated with RT to mesenteric adenopathy with involved site radiation therapy (ISRT), intensity modulated radiation therapy (IMRT) and daily CT image guidance.
Materials/Methods: Patients treated for DLBCL with RT to the mesentery between 2011-2017 were reviewed. Eligible patients had RT for consolidation or definitive treatment targeting all sites of evident disease. Clinical and treatment characteristics were analyzed for an association with local control (LC), progression free survival (PFS) and overall survival (OS).
Results: 24 patients were eligible for analysis. At diagnosis, the median age was 52 years (39-77), and 54% (n=13) had stage I/II DLBCL. All patients received frontline chemotherapy (ChT) (R-CHOP, n=20; dose adjusted R-EPOCH, n=4) with a median of 6 cycles. Salvage ChT for refractory DLBCL was given prior to RT in 46% (n=11) and autologous stem cell transplantation was administered in 13% (n=3) before RT. At the time of RT, PET-CT imaging revealed 5PS of 1-3 in 46% (n=11), 5PS of 4 in 12% (n=3) and 5PS of 5 in 42% (n=10). All patients received IMRT, daily CT imaging and ISRT. The median RT dose was 40 Gy. After RT, relapse or progression occurred in 22% (n=5). 2 patients progressed, 2 relapsed, and one had a residual avid mass in-field that has been followed for 12 months without additional therapy. Disease relapse/progression occurred locally (within field) for 2

patients, distant (outside of the abdomen) in 1 patient, and combined distant and local in 2 patients. The median time to local failure, PFS, and OS were not reached. At a median follow up of 37 months, the 3-year LC, PFS and OS rates were 81%, 76% and 96% respectively. Among patients treated with consolidative RT after successful frontline ChT (n=9), 3-year PFS was 100%, compared to 64% for patients with a history of chemorefractory DLBCL (n=16, p=0.07). Comparing patients with 5PS 1-3 after ChT to those with 5PS 4-5, there was no difference in time to local recurrence, PFS, or OS (p= 0.27, 0.31, 0.10). 4 of the 5 relapses occurred in patients with 5PS of 5 prior to RT. Patients with 5PS of 5 (n=10) had a median of 3 lines of ChT prior to RT and 3-year PFS of 56%, compared to 1 prior line of ChT and 3-year PFS of 92% for those with 5PS of 1-4 (n=14, p=0.098). 2 deaths occurred due to DLBCL (n=1) or myelodysplastic syndrome (n=1).

Conclusion: Patients with DLBCL involving the mesentery can be successfully treated with image-guided IMRT and ISRT. Outcomes for patients treated with combined modality therapy for chemosensitive disease are excellent. Even among patients with highly refractory and heavily pretreated DLBCL with a 5PS of 5, RT offers disease control in roughly half of patients.

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MO_43_2798

Concurrent Radiation and Biological Therapy is Safe in Multiple Myeloma

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Purpose/Objective(s): The management of multiple myeloma (MM) has evolved in the modern era partially owing to the increasing number of biological therapeutics. Bortezomib, Daratumumab and Carfizomib have become standard of care treatments for MM. Nonetheless radiation continues to be an important treatment in the management of painful lytic lesions from MM. There is a concern for increased toxicity of treatment when given concurrently with biologicals. The goal of this study is to evaluate the side effect profile of radiation therapy while patients are concurrently being treated with biological agents.

Materials/Methods: We conducted a retrospective study based on data collected from patients receiving radiotherapy at our institute from 2007 to 2017. A total of 130 patients (279 treatment sites) were included in this study with a median follow up time of 14 months. Patients had to be receiving a biological agent at least within one month prior to start and up to one month post receiving radiation therapy. Generalized estimating equations were used to assess difference in the probability of onset of acute side effects (within 4 weeks of treatment), sub-acute side effects (during 4 weeks and 6 months of treatment) and hematological events (Grade 3 or higher anemia, need for PRBC transfusion, need for platelet (Plt) transfusion and need for neupogen) between patient groups receiving or not receiving concurrent biological agents with RT. A compound symmetric covariance structure was assumed to control for intra-subject correlation. Linear mixed models were used to estimate the change in blood counts before and after treatment while adjusting for pre-treatment values.

Results: The mean age of all the patients in our cohort was 63.1 years (SD: 8.7), with 53 (58.9%) males and 37 (41.1%) females. The mean KPS score of all the cohort was 76. Further patient demographic information can be found in table 1. No significant difference in incidence of acute [OR = 1.65, 95% CI, (0.87, 3.13), p = 0.1270] or subacute [OR = 0.90, 95% CI, (0.40, 2.04), p = 0.8068] toxicities was found between patients with or without biological agents concurrently with RT. Furthermore, no significant difference in incidence of anemia and

Neupogen requirement was noted between patients with or without biological agents concurrently with RT. However, patients receiving biological agents were more likely to have PRBC transfusion [OR = 5.05, 95% CI, (1.09, 23.44), $p<0.05$] and Plt transfusion [OR = 2.26, 95% CI, (1.01, 5.06), $p<0.05$].

Conclusion: Our study did not detect any significant toxicity rates from palliative radiation while patients were concurrently receiving biological agents. Palliative radiation therapy may be safely administered while patients are concurrently being treated with biological agents, without any major adverse effects. Biological therapies do not need to be held during RT.

Table 1

Treatment Site	Number of Patients
Spine	49
Pelvis	23
Skull	18
Shoulder	6
Arm	6
Dose (Gy)	Number of Patients
≤ 20Gy	54
20-30Gy	31
≥ 30Gy	17

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Lung Cancer

LBA3

Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

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Purpose/Objective(s): We previously observed that LCT improves progression free survival (PFS) in patients with oligometastatic NSCLC after front-line systemic therapy without progression (Gomez et al, Lancet Oncol 2016). Here we report the final analysis of this trial, including the mature secondary endpoint of OS.

Materials/Methods: Patients were enrolled from 3 institutions (MD Anderson Cancer Center, London Health Sciences Center, University of Colorado) and met the following eligibility criteria for randomization: 1) stage IV NSCLC, 2) ≤3 metastatic lesions, 3) ECOG performance status of 2 or less, and 4) no progression after standard front-line systemic therapy. Front-line therapy was four or more cycles of platinum doublet therapy or 3 or more months of EGFR or ALK inhibitors for patients with EGFR mutations/ALK rearrangements, respectively. Patients were then randomized in a 1:1 fashion to receive either standard maintenance therapy/observation (MT/O arm) versus LCT, defined as radiation or surgery to all remaining active sites of disease followed by MT/O (LCT arm). The primary endpoint was PFS, with secondary endpoints including OS, toxicity, and time to appearance of a new lesion. Kaplan-Meier estimates of survival endpoints were obtained, with differences assessed utilizing the log-rank test. Statistical tests were two-sided, and p-values<0.10 were deemed to be significant. At a 10% type I error and a 90% power to detect an improvement in PFS from 4 months (MT/O) to 7 months (LCT), the trial was designed to enroll 94 patients.

Results: The trial was closed by the MD Anderson DSMB after the accrual of 49 patients, due to a benefit detected in PFS; these results have been previously reported at a median follow-up of 12.4 months. For this analysis. median follow-up time for censored patients at the last known date alive is 38.8 months (range 28.3-61.4 months). The PFS benefit was durable, with a median of 14.2 months in the LCT arm (95% CI 7.4,2 4.3) vs. 4.4 months in the MT/O arm (95% CI 2.2, 8.3; p=0.014). The extended follow up also demonstrated a benefit in OS for patients in the LCT arm, with a median OS of 41.2 months (95% CI 18.9, NA) vs. 17.0 months in the MT/O arm (95% CI 10.1, 39.8; p=0.017). No additional Grade 3 or higher toxicities were observed in either arm. Time to new lesion failure trended towards significance with a median of 14.2 months in the LCT arm (95% CI 5.7, 26.2) vs. 6.0 months in the MT/O arm (95% CI 4.4, 8.3; p=0.11).

Conclusion: To our knowledge, this study represents the first randomized data showing an OS benefit for local ablative therapy in patients with oligometastatic NSCLC that do not progress after front-line systemic therapy. Ongoing phase II/III trials will assess the effect of LCT in larger populations and with the incorporation of novel therapeutic agents (immunotherapy, targeted therapy).

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LBA10

PACIFIC: Overall Survival with Durvalumab versus Placebo after Chemoradiotherapy in Stage III NSCLC

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Purpose/Objective(s): In the global, Phase 3 PACIFIC study (Antonia 2017; NCT02125461), Durvalumab significantly improved progression-free survival (PFS) versus placebo in Stage III, unresectable NSCLC patients without progression after concurrent chemoradiotherapy (CRT) (stratified HR, 0.52; 95% CI, 0.42–0.65; P<0.001). This was the first major advance in this disease setting for many years. Here we report the second primary endpoint of overall survival (OS) for PACIFIC.

Materials/Methods: Patients (any PD-L1 tumor status) with WHO PS 0/1 who received ≥2 cycles of platinum-based CRT were randomized (2:1) 1–42 days post-CRT to Durvalumab 10 mg/kg IV Q2W or placebo up to 12 months, stratified by age, sex, and smoking history. Primary endpoints were PFS from randomization (blinded independent central review; RECIST v1.1) and OS (interim analysis reported). Secondary endpoints included time to death or distant metastasis (TTDM) and PFS2 (time to second progression) from randomization and safety. Time to first/second subsequent therapy or death (TFST/TSST) were supportive assessments for PFS/PFS2.

Results: Between May 2014 and April 2016, 713 patients were randomized; 709 received treatment (Durvalumab, n=473; placebo, n=236). As of March 22, 2018 (data cutoff), median follow-up duration was 25.2 months (range, 0.2–43.1). After discontinuation, 41.0% and 54.0% in the Durvalumab and placebo groups received subsequent anticancer therapy; overall, 8.0% and 22.4% received additional immunotherapy. Durvalumab significantly improved OS versus placebo (stratified HR 0.68, 99.73% CI, 0.469–0.997; P=0.00251), with the median not reached (NR; 95% CI, 34.7 months–NR) and 28.7 months (95% CI, 22.9–NR), respectively. Durvalumab improved OS in all pre-specified subgroups. Updated PFS remained similar (stratified HR 0.51, 95% CI, 0.41–0.63), with medians of 17.2 and 5.6 months with Durvalumab and placebo, respectively. Durvalumab improved updated TTDM (stratified HR 0.53, 95% CI, 0.41–0.68), and PFS2 (stratified HR 0.58, 95% CI, 0.46–0.73), TFST (stratified HR 0.58, 95% CI, 0.47–0.72) and TSST (stratified HR 0.63, 95% CI, 0.50–0.79). Within the Durvalumab and placebo groups, 30.5% and 26.1% had grade 3/4 any-causality AEs, 15.4% and 9.8% discontinued due to AEs, and no new safety signals were identified; any-grade (grade 3/4) pneumonitis/radiation pneumonitis occurred in 33.9% (3.6%) and 24.8% (3.0%). Exploratory analyses characterizing outcome based on features of previous CRT will be presented.

Conclusion: Durvalumab demonstrated statistically significant and clinically meaningful improvement in OS compared with placebo, supported by secondary endpoints such as PFS2. PACIFIC is the first study to show a survival advantage following CRT in this locally advanced NSCLC population, providing compelling evidence for the unprecedented benefit of durvalumab treatment as the standard of care.

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Pfizer. Travel Expenses; AZ, Elekta, Pfizer. contribute ideas, discuss, meet, decide etc; IASLC. contribute ideas, discuss, decide, meet etc; ESTRO/ACROP guideline committee, ESTRO. contribute ideas, discuss, decide, sit in meetings; ERS-EACTS-ESTS-ESTRO. contribute ideas, sit in meetings, disc. **D. Spigel**: None. **D. Daniel**: None. **A. Villegas**: Speaker's Bureau; Gilead, Seattle Genetics, AstraZeneca. **D. Vincente**: None. **R. Hui**: Honoraria; MSD, Novartis. Advisory Board; AstraZeneca, MSD, Roche, BMS, Novartis. **J. de Castro Carpeno**: None. **S. Murakami**: None. **L. Paz-Ares**: Advisory Board; Lilly, MSD, BMS, AstraZeneca, Novartis, Roche, Incyte, Celgene, Pfizer, Merck, Takeda. **M. Özgüroğlu**: None. **T. Kurata**: Research Grant; AstraZeneca. Honoraria; AstraZeneca. **A. Chiappori**: Research Grant; BMS, Novartis. Speaker's Bureau; Genentech, Takeda, Merck, BI, Celgene. Advisory Board; AstraZeneca, BMS, Novartis. **K. Lee**: None. **M. de Wit**: Research Grant; AstraZeneca. Speaker's Bureau; AstraZeneca. **L. Poole**: Stock Options; AstraZeneca. **C. Wadsworth**: Stock Options; AstraZeneca. **P.A. Dennis**: Stock Options; AstraZeneca. **S.J. Antonia**: Employee; H Lee Moffitt Cancer Center. Research Grant; Novartis. Advisory Board; BMS, Novartis, Merck, CBMG, Boehringer Ingelheim, AstraZeneca/MedImmune, Memgen, FLX Bio.

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A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-Small Cell Lung Cancer. Japan Clinical Oncology Group (JCOG0403): Long Term Follow-up Results

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Purpose/Objective(s): The purpose of JCOG0403 was to evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) in patients with both operable and inoperable T1N0M0 non-small cell lung cancer (NSCLC) (UICC 6th ed., 2002). The patient accrual started in 2004, and the three and five year follow-up results were published in 2015. This is the updated report with a 10-year follow-up period for the operable population.
Materials/Methods: The eligibility criteria included clinical T1N0M0 NSCLC, operable patients assessed by thoracic surgeons. Operability was recategorized by the study coordinator after registration and before the primary analysis. The prescription was 48 Gy at the isocenter in 4 fractions over 4-8 days. The primary endpoint was the three-year survival and the secondary endpoints included overall survival (OS), progression-free survival (PFS), local-progression free survival (LPFS), event-free survival (EFS), toxicity, and patterns of failure.
Results: Between July 2004 and May 2007, 65 operable patients were registered in this study from 15 institutions and 64 eligible patients were included in efficacy analysis. The patient characteristics were: male 45, female 20; median age 79 (range 50-91); and adenocarcinomas 40, squamous cell carcinomas 21, others 4. All patients completed the protocol treatment. At the last follow-up in February 2017 (median follow-up is 5.2 years), 20 patients died with disease, 24 patients died with other disease, 1 patient with treatment-related death, 2 died with unknown reason and 17patients still alive. Follow-up images of all patients were centrally reviewed by September 2017. The median survival was 5.6 year (95% CI: 4.1 – 7.1 year).The 3, 5, 10-year survival were 76.5% (95% CI: 64.0% - 85.1%), 54.0% (95% CI: 41.0% - 65.4%) and 23.8% (95% CI: 13.7% - 35.5%), respectively. The 10-year PFS, LPFS, and EFS were 19.1% (95% CI: 9.8% - 3.7%), 20.9% (95% CI: 11.1% -32.8%), 13.7% (95% CI: 6.0% - 24.6%), respectively. The 3, 5, 10-year local control rates were 85.4% (95% CI: 73.8% - 92.1%), 85.4% (95% CI: 73.8% - 92.1%) and 85.4% (95% CI: 73.8% - 92.1%), respectively. To date, a total of 27 failures were observed

including 9 with local failure, 11 with regional nodal failure and 11 with distant metastases. Grade 3 toxicity was observed in 6 patients: chest pain in 1 (1.5%), dyspnea in 4 (6.2%), hypoxia in 1 (1.5%), and pneumonitis in 2 (3.1%). No grade 4 or 5 toxicity was observed.

Conclusion: Long term results confirmed the efficacy and safety of the previous result. SBRT has a potential to be an alternative to surgery for operable T1N0M0 NSCLC and deserves a further evaluation. To further improve the tumor control, a randomized phase III study investigating higher dose prescribed to the 80% isodose line is underway (JCOG1408).

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Systemic Therapy with Stereotactic Body Radiation Therapy (SBRT) for Early-Stage Non-Small Cell Lung Carcinoma (NSCLC): A Multi-institutional Analysis

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Purpose/Objective(s): For patients with early-stage NSCLC, SBRT generally yields favorable local tumor control, but regional and distant failures occur in up to 20-30% of patients. Although adjuvant systemic therapy (ST) is often recommended for early-stage NSCLC with large tumors after surgery, there is a lack of evidence supporting the use of ST with SBRT. We used a multi-institutional database to evaluate the association between ST use and disease and survival outcomes for patients with early-stage NSCLC treated with SBRT.

Materials/Methods: We conducted a retrospective cohort study using a multi-institutional, academic-community practice database, including consecutive patients with biopsy-proven T1-3N0M0 NSCLC treated with definitive SBRT from 2006 – 2015 at 114 sites. Patient cohorts were defined as those who received SBRT+ST or SBRT alone. Group characteristics were compared with Chi-square, Wilcoxon rank-sum, and logistic regression. Local, regional, and distant failure (LF, RF, and DF) were analyzed with multivariable competing risks regression with Fine and Gray's proportional subhazards models. Progression-free and overall survival were analyzed with the Kaplan-Meier method and Cox regression. Competing risks regression was performed with 2:1 nearest-neighbor propensity score matching on clinical risk factors.

Results: Of 1,328 patients included, 54 (4.1%) received SBRT+ST. The most common ST regimen was a platinum doublet (n=38; 70.4%), followed by erlotinib (n=8; 14.8%), single agent chemotherapy (n=3; 5.6%), or unknown regimen (n=5; 9.3%). Compared with SBRT patients, SBRT+ST patients were younger (median age: 71 v 78, P<.001), had larger tumors (>2 cm: 38.9% v 21.5%, P=.003), and higher T-stage (T2-3: 42.6% v 22.4%, P=.001). Median follow-up in living patients was 24 months. Compared with the SBRT cohort, the SBRT+ST cohort had significantly less DF (3.7% v 13.0%, P=.04) and RF (0% v 10.4%, P=.01), but not LF (7.4% v 10.4%, P=0.48). On multivariable analyses, SBRT+ST was independently associated with reduced DF (HR: .22, 95%CI: .05 - .88, P=.03) and overall failure (HR: .34, 95%CI: .15 - .76, P=.009) (RF not evaluable, as there were no events in the SBRT+ST cohort), with trend for improved progression-free (HR: 0.72, 95%CI: 0.49 – 1.06, P=.09), but not overall survival (HR: .78, 95%CI: .52 – 1.18, P=.24). After propensity score matching on size, T-stage, performance and smoking status, histology, and age, the SBRT+ST cohort had reduced DF, RF, and overall failure (each P<.05).

Conclusion: This multi-institutional study shows improved regional, distant, and overall disease control in patients receiving adjuvant systemic therapy with SBRT for early stage NSCLC, despite the increased prevalence of larger

and higher-stage tumors in this cohort. Prospective study is being planned to evaluate this hypothesis in high-risk subgroups.

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An Externally Validated Nomogram for Predicting Distant Metastasis after Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer: Implications for Adjuvant Systemic Therapy

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Purpose/Objective(s): SBRT is a standard treatment option for patients with early stage NSCLC who are considered medically inoperable. While SBRT is associated with excellent local control, distant metastases (DM) represent the primary pattern of failure. Adjuvant systemic therapy has not traditionally been used in this patient population due to medical comorbidities. With the advent of immunotherapy that may be better tolerated, there has been a renewed interest in identifying patients that may derive benefit. We developed and internally validated a nomogram to predict the likelihood of DM after SBRT for early stage NSCLC which was then externally validated.

Materials/Methods: Our institutional registry of patients treated with lung SBRT was queried for patients with early stage NSCLC treated with definitive intent from 2003-2017 and 1002 patients were identified for analysis to develop the model. A large dataset from an external institution was used to similarly identify patients and 737 patients were used for the model validation cohort. Random Survival Forest was used as an exploratory phase to assess importance, interactivity, and overall predictive ability with respect to distant failure for 14 variables. A Fine-Gray competing-risks regression model was then formulated where apparent interactions/non-linear relationships were examined with likelihood-ratio (LR) tests. Backward variable selection was then implemented to reduce to a parsimonious model. The concordance probability (C-index) of the final model was internally validated with 10-fold cross validation.

Results: The median overall survival was 1.71 years internally and 1.92 years externally. Median follow-up was 18.3 months and 21.1 months. The 1-year incidence of distant failure was 16% and 12.1% in the internal and external cohorts, respectively. The results from the random forest suggest that tumor size and PET SUV are the most important predictors of distant failure. The 1-year cumulative incidence (CI) of DM was 18.5% for PET SUV $\geq$4.1 vs 8.4% for <4.1. 1-year CI for tumor size >3 cm was 26% vs 12.6% for $\leq$3 cm. The median time to distant failure was 0.86 years internally and 1.1 years externally. The final nomogram included tumor size, histology, PET SUV, age, KPS, and active smoking status, and had a cross-validated C-index of 0.62. The nomogram provides predictive value for probability of DM at 1-year between 10 and 70%.

Conclusion: This novel nomogram with external validation can be used to predict the 1-yr risk of DM after SBRT for pts with early-stage NSCLC, accounting for the competing risk of death. This nomogram may help define patient subsets for stratification in future clinical trials to help identify who may benefit from adjuvant systemic therapy after SBRT to reduce the incidence of distant failure and disease-related death.

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Local Control Analyses of Pulmonary Oligometastases Treated By Stereotactic Body Radiation Therapy (SBRT) from a Multi-institutional Survey in Japan

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Purpose/Objective(s): This study aimed to investigate local control (LC) rate and to identify affecting factors for LC of pulmonary oligometastases treated by SBRT using large data sets from a multi-institutional nationwide survey in Japan.

Materials/Methods: A total of 1374 patients with 1545 targets from 68 institutions were collected. Eligibility was as follows: SBRT for pulmonary oligometastases was performed between 2004 January and 2015 June, biological effective dose (BED10) was 75 Gy or more. Local recurrence of thoracic primary tumor was excluded and all extrathoracic lesions were controlled at the time of SBRT. Cumulative LC rate was calculated using Kaplan-Meier method and the 95% confidence interval (95% CI) was calculated using Greenwood's formula. Cox proportional hazards model was applied for LC analyses and variables with a p-value of < 0.20 in univariate analyses were put in multivariate analysis (MVA).

Results: The median targeted tumor diameter was 1.5 cm (range, 0.3-6.5), and the median overall treatment time (OTT) of SBRT was 7 days (range, 3-81). Dose calculation algorithm was divided into type B (51.7%) which was equivalent of Analytical Anisotropic Algorithm, type C (9.3%) which was equivalent of Monte Carlo Algorithm and type A (34.8%) which was older generation algorithm than both. The median heterogeneity correction considered BED10 around isocenter was 126.9 Gy (range, 76.8-352.7). Primary sites were separated into lung (29.1%), colorectum (25.3%), genitourinary (13.5%), head and neck (8.6%), esophagus (8.5%) and others. Median follow-up period was 24.2 months (range, 0.1-143.7). Local recurrence occurred in 222 tumors and median time to local recurrence was 12.4 months (range, 2.9-98.7). Estimated 1-year, 3-year and 5-year LC were 92.0% (95% CI, 90.4-93.4%), 81.3% (95% CI, 76.7-83.6%) and 78.5% (95% CI, 75.6-81.2%), respectively. The result of MVA (n=785) showed that maximum diameter of targeted tumor (per 1cm increase; Hazard ratio [HR], 1.320; p=0.023), dose calculation algorithm (type B vs. type A; HR, 0.541; p=0.012), OTT (per 10 days prolonged; HR, 0.564; p=0.022) and primary site of metastases were significantly associated with LC. In regard to primary sites, colorectum showed significantly lower LC rate compared to lung (HR, 2.837; p<0.001), genitourinary (HR, 6.473; p<0.001), head and

neck (HR, 4.879; p<0.001) and others (HR, 2.478; p=0.005), genitourinary showed significantly better LC compared to colorectum (HR, 0.154; p<0.001) and esophagus (HR, 0.291; p=0.020) but the others showed no significant association. BED10 showed the tendency (per 10 Gy increase; HR, 0.924; p=0.102).

Conclusion: To procure excellent LC rate, the use of type A algorithm should be avoided, the strategy of tumor diameter and primary sites should be considered and higher BED with longer OTT might help.

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Local Ablative Therapy Improves Survival in Patients with Synchronous Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated with First-Line EGFR-TKIs

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Purpose/Objective(s): The aim of the current study was to investigate whether consolidation local ablative therapy (LAT) can improve the survival of patients with stage IV EGFR-mutant NSCLC who have oligometastatic disease treated with first-line EGFR-TKI therapy.

Materials/Methods: Patients with stage IV EGFR-mutant NSCLC and no more than five metastases at diagnosis in 2 months were enrolled. All patients were treated with first-line EGFR-TKIs. Consolidation LAT included radiation therapy or surgery. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier curves.

Results: From October 2010 to May 2016, 145 patients were enrolled, including 51 (35.2%) who received consolidation LAT to all oligometastatic sites (All-LAT group), 55 (37.9%) who received consolidation LAT to either primary tumor or oligometastatic sites (Part-LAT group), and 39 (26.9%) who did not receive any consolidation LAT (Non-LAT group). The median PFS in All-LAT, Part-LAT, and None-LAT group were 20.6 months, 15.6 months, and 13.9 months, respectively (P<0.001). The median OS in All-LAT, Part-LAT, and None-LAT group were 40.9 months, 34.1 months, and 30.8 months, respectively (P<0.001). The difference was significant between All-LAT group and Part-LAT or Non-LAT group but was not significant between Part-LAT and Non-LAT group. The median OS was significantly improved with consolidation LAT for primary tumor (40.5 versus 31.5 months, P<0.001), brain metastases (38.2 versus 29.2 months, P=0.002), adrenal metastases (37.1 versus 29.2 months, P =0.032). Adverse events (Grade≥3) due to radiation therapy included pneumonitis (7.7%) and esophagitis (16.9%).

Conclusion: The current study demonstrated that consolidation LAT to all sites was a feasible option among patients with EGFR-mutant oligometastatic NSCLC during first-line EGFR-TKI treatment, with significantly improved PFS and OS compared with consolidation LAT to partial sites or observation alone.

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Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET): Results of A Randomized Trial

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Purpose/Objective(s): The oligometastatic paradigm suggests that patients with a limited number of metastases may be curable if all sites of disease are eradicated with ablative therapies, such as surgery or radiation. However, randomized evidence in support of this paradigm is lacking. We assessed the impact of delivering stereotactic ablative radiotherapy (SABR) on survival, oncologic outcomes, toxicity, and quality of life (QOL) in patients with a controlled primary tumor and up to five oligometastatic lesions.

Materials/Methods: We enrolled patients who had a controlled primary malignancy with 1-5 metastatic lesions, all of which were amenable to SABR, with good performance status (ECOG 0-1) and life expectancy >6 months. We stratified by the number of metastases (1-3 vs. 4-5) then randomized in a 1:2 ratio between palliative standard of care (SOC) treatments [Arm 1] vs. SOC plus SABR to all metastatic lesions [Arm 2]. The primary endpoint was overall survival (OS). A randomized phase II screening design was employed with a two-sided alpha of 0.20 (wherein a p-value <0.20 designates a positive trial) to provide an initial comparison of these two treatment strategies. OS was compared using the stratified log-rank test based on Kaplan-Meier (KM) estimates. Secondary endpoints included progression-free survival (PFS), toxicity, and QOL (assessed using the FACT-G). All analyses herein were pre-specified and intention-to-treat.

Results: Between Feb 2012 and Aug 2016, 99 patients were randomized (33 in Arm 1, 66 in Arm 2) at centres in Canada, Scotland, the Netherlands, and Australia. Median age was 68 (range 43-89) and 59% were male. The most common primary tumor types were breast (n=18), lung (n=18), colorectal (n=18) and prostate (n=16). Most patients (n=92) had 1-3 metastases. There were no significant differences in baseline factors between arms. Median follow-up was 27 months. Median OS was 28 months in Arm 1 (95% CI 19-33 months) vs. 41 months in Arm 2 (95% CI: 26 months to 'not reached'; stratified log-rank p=0.09). Median PFS was 6.0 months in Arm 1 (95% CI: 3.4-7.1 months) vs. 12 months in Arm 2 (95% CI: 6.9-30 months; p=0.001). Grade ≥2 adverse events related to treatment occurred in 9% in Arm 1 and 30% in Arm 2 (p=0.022). The most common grade ≥2 toxicities in the SABR arm were fatigue (n=10), dyspnea (n=9), muscle and joint pain (n=7), bone pain (n=6) or pain not otherwise specified (n=7). There were 3 treatment-related grade 5 events in Arm 2, due to deaths from radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural hemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1). There were no differences in overall mean FACT-G scores at 6 months (82.5 in Arm 1 vs. 82.6 in Arm 2; p=0.992), or in any of the physical, social, functional, or emotional QOL subscales (all p>0.4).

Conclusion: SABR was associated with an improvement in OS, meeting the primary endpoint of this trial, and PFS was doubled. Grade ≥2 toxicities were more common with SABR, but no differences were seen in QOL. (NCT01446744)

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Optimized Survival Evaluation to Guide Bone Metastases Management: Developing an Improved Statistical Approach

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Purpose/Objective(s): In managing bone metastases, estimation of life expectancy is central for individualizing patient care given a range of radiation therapy (RT) treatment options. With access to larger volume and more complex patient data and statistical models, oncologists must develop methods for optimal decision support. Yet including more covariates may not improve predictions; studies show simple survival models of 2-3 variables perform nearly as well as 6-8 variable models in metastatic populations. Approaches incorporating many covariates should also identify complex interactions and manage missing data. To address these issues, we applied a statistical learning approach, random survival forests (RSF), to predict survival for patients with bone metastases using up to 26 predictor variables. We then compared our method to two simpler, validated Cox regression models.

Materials/Methods: For 397 patients evaluated in RT consultation for bone metastases from 1/2007 to 1/2013, data for 26 readily available clinical variables was collected. Primary outcome was time from consultation to death. Patients were randomly assigned to training (n=306) and validation sets (n=91). The training set was used to build a RSF model. To establish relative utility of our RSF model, we performed Cox regressions per Chow's 3-item Survival Prediction Score (SPS) and Westhoff's 2-item tool (W2). Predictive accuracy of the 3 models was compared using time-dependent area under the curve (tAUC). We obtained internal estimates of tAUC using the .632+ bootstrap method for the training set and external estimates for the validation set.

Results: Patient mean age was 62 years (SD 13). Median survival was 227 days. Table 1 shows tAUC at select time points by survival model. Using both internal and external tAUC estimates, RSF predictions out-performed simpler models at all times, with greatest difference at 30 days and performance most similar at the 1-year prediction horizon. For the RSF model, variable importance was greatest for performance status, blood cell counts, histology, age, recent chemotherapy, time from diagnosis, RT site, and neuraxis compromise.

Conclusion: For patients with bone metastases, our RSF model substantially improved survival predictions versus relatively simpler traditional models. As such, we have developed a web platform to facilitate ease of data entry and display predicted patient survival probabilities from our RFS to guide in selection of appropriate RT regimens. Our future work aims to further optimize estimates through inclusion of time-dependent covariates to better reflect the dynamic nature of health status and through investigation of deep learning models.

Table 1: Estimates of tAUC by time and survival model

	Training set			Validation set		
Days from consultation	**RSF**	**SPS**	**W2**	**RSF**	**SPS**	**W2**
30	**0.90**	0.82	0.83	**0.90**	0.82	0.80
180	**0.84**	0.80	0.81	**0.80**	0.77	0.74
360	**0.84**	0.80	0.83	**0.74**	0.70	0.72

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Patient Reported-Quality of Life in Oligometastatic Cancer Treated with SBRT: Interim Report of a Phase II Multicenter Clinical Trial

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Purpose/Objective(s): Oligometastatic disease has emerged as a potentially curable state in the process of cancer progression where aggressive local therapy renders improved oncologic outcomes. Stereotactic body radiation therapy (SBRT) can deliver highly-conformal, doses of radiation to the target lesions while minimizing dose to normal surrounding tissues in an approach that can be integrated with systemic therapy for patients with a limited number of metastatic lesions. Herein we report the initial oncologic outcomes and patient-reported quality of life (PR-QoL) from a phase II multicenter trial for patients with recurrent oligometastatic disease.

Materials/Methods: Patients with a pathologically proven-diagnosis of a solid malignancy with recurrent oligometastatic disease (1-5 metastases ≤3 organs) were prospectively recruited between 2011-2017. SBRT dose and fractionation was dependent upon the lesion location and tumor size consistent with ablative doses of radiation. Patient follow-up occurred within 6 weeks of completion of SBRT and every 3 months for 3 years. Patients received FACT-G questionnaire at baseline and at each follow-up to assess for PR-QoL. Total Fact-G scores were compared to baseline using Wilcoxon signed rank test. Median follow-up was calculated by reverse Kaplan-Meier method. Overall survival (OS), local progression-free survival (LPFS), and distant progression-free survival (DPFS) were calculated using Kaplan-Meier estimation to either date of last follow-up/death or local/distant failure.

Results: We enrolled 147 patients with recurrent oligometastatic cancer. Median age at time of enrollment was 66.4 years (IQR: 59.9-74.6). The most common primary tumors included: lung (21.8%, NSCLC: n=29, SCLC: n=3), colorectal adenocarcinoma (21.1%), and head & neck (12.2%, SCC: n=11). Patients were treated with SBRT to either 1 (70.7%), 2 (19.0%), 3 (6.8%), 4 (0.7%), or 5 metastatic sites (2.7%). In a median follow-up of 41.3 months (IQR: 14.6-59.0), the median OS was 42.3 months (95% CI: 27.4-infinity) with 5-year OS of 43%. Median OS was 26.8 months (95% CI: 8.1-45.4), 54.4 months (95% CI: incalculable), and 19.8 months (95% CI: 1.8-16.2) for lung,

colorectal, and H&N. At 5-years LPFS and DPFS were 75% and 17% respectively. Acute grade 2+ and grade 3+ toxicity was 7.5% and 2.0%, respectively and late grade 2+ and grade 3+ toxicity both 1.4%. Acute grade 3 toxicity included dyspnea (n=1), dermatitis (n=1), and anemia (n=1). Late toxicity included grade 3 ureter obstruction (n=1) and grade 4 small bowel obstruction (n=1). There was no significant change in quality of life at completion, 6 weeks, 3, and 9 months after treatment. At 6 and 12 months patients were found to have statistically significant improvement in PR-QoL.

Conclusion: This multi-center prospective phase II study demonstrates SBRT for recurrent oligometastatic cancer is a feasible and tolerable treatment option with minimal acute and late grade 3+ toxicity, and initially associated with improved PR-QoL.

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Phase III Multi-Center, Prospective Randomized Trial Comparing High Dose Single Fraction Radiation Therapy to a 3-Fraction SBRT Regimen in the Treatment of Oligometastatic Human Cancer

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Purpose/Objective(s): Pre-clinical and clinical evidence have shown that high single dose radiation therapy (SDRT) is associated with superior tumor control compared to multi-fraction (MF) regimens, due to SDRT's ability to engage a microvascular response interfering with the ability to repair radiation damage to tumor cell DNA. The primary objective of this study was to compare local control rates with either a single dose of 24Gy versus 27Gy in three 9Gy fractions in patients with oligometastatic disease. A secondary objective was to compare toxicity outcomes between the two cohorts.

Materials/Methods: A total of 174 patients were enrolled at three institutions. 155 patients (75 randomized to the SDRT and 80 to the MF regimen) were assessable for treatment-related toxicities having met protocol criteria. A total of 117 patients with 154 treated lesions, were evaluable for the local disease control end point. Eligibility criteria for enrollment included ≤5 metastatic lesions documented on imaging studies, and no prior radiation therapy to the treated site. Eligible lesions were limited to non-mobile targets (osseous or lymph node metastases). Potential candidates whose target lesions were adjacent to critical organs, precluding treatment with SDRT due to the risk of treatment-induced complications, were excluded. Patients were followed every 6 months for a minimum of 2 years, and imaging evaluation of the treated site at 12 and 24 months post-treatment was mandatory. Responses were measured using standard RECIST criteria. For the assessment of toxicity, a minimum follow-up of 6 months was required. Median follow up was 39 months (range, 11-85).

Results: Lesions treated with SDRT demonstrated a significantly lower incidence of local disease progression (LR) compared to those treated with MF ($p<0.0005$). The 3-year incidence of LR was 6.1% of the lesions compared to 23% for the SDRT and MF regimens, respectively. A reduction in distant metastatic (DM) progression was noted among those treated with SDRT compared to the MF regimen The 3-year incidence of DM progression was 4.1% compared to 17.5% for the SDRT and MF regimens, respectively($p<0.02$). There was no significant difference in grade 3+ toxicity between the two arms (SDRT: 10.7%; MF: 5%; $p=0.24$). The specific incidence of grade 3+ pain, peripheral neuropathy and bone fractures for the SDRT regimen was 5.3%, 2.7% and 1.3%. The corresponding

incidence for these toxicities for the MF regimen was 1.3%, 0% and 2.5%. No overall survival differences were observed between the arms.

Conclusion: The study provides Level 1 evidence that SDRT was associated with superior tumor control outcomes compared to a standard 3-fraction regimen in a cohort of patients with oligometastatic osseous/nodal disease. SDRT was well tolerated, rendering comparable toxicity outcomes to a current standard-of-care hypofractionated SBRT treatment regimen.

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Celiac Plexus Radiosurgery, a New Modality for Cancer Pain Management – Final Results of a Phase II Clinical Trial

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Purpose/Objective(s): Many patients with upper-abdominal malignancies suffer from a characteristic syndrome of severe lower back pain radiating to the epigastrium, thought to be caused by involvement of the celiac plexus. Contemporary approaches (opioids, celiac blocks, systemic chemotherapy) are often inadequate. We hypothesized that ablative radiation delivered to the celiac plexus would alleviate pain levels.

Materials/Methods: We performed a single-institution prospective clinical trial to evaluate a novel therapeutic approach: stereotactic radiation therapy focused on the celiac plexus. Eligibility criteria included typical celiac-pain syndrome, significant pain despite opioid usage (Numerical Rating Scale, NRS > 4/10), prognosis > 8 weeks, ECOG 0-3. Evaluable patients were defined as those completing treatment per protocol and completed at least one post-treatment visit. Exclusion criteria included previous abdominal RT. The anterolateral aspect of the aorta from D12 to L2 was used as a surrogate marker for the celiac plexus; primary tumor was irradiated according to physicians' discretion. Radiation dose was originally 9 Gy*5, and later amended to a single fraction 25 Gy, both using VMAT. A dose-painting technique was used to limit dose to duodenum. The primary endpoint was pain-relief 3 weeks post-treatment, measured using NRS. Secondary endpoints included pain at 6 weeks, analgesic use, toxicity (CTCAE v4.03), and pain interference with seven daily activities as evaluated by the 'Brief Pain Inventory' (BPI) instrument before and after radiation therapy. Analgesic use was not restricted.

Results: Twenty-one subjects were evaluable: 2 received 9Gy*5, 19 received 25Gy*1. The median age was 65 (range 37-83 years) with a Median ECOG of 1, 86% had pancreatic cancer. Median volume of celiac plexus was 30.8 cc, median dose to celiac plexus was 25 Gy. All patients reported decreased celiac pain: median pain level prior to RT was 6/10 (IQR 5-7.5) and reduced to 2.3/10 NRS score (IQR 0.9-3.3) ($p < 0.0005$ compared to baseline) at 3 weeks (primary endpoint), and to 1.8/10 (IQR 0-3) ($p < 0.0005$ compared to baseline) at 6 weeks' post-treatment. 76% of patients reported a significant decrease of pain at primary endpoint (two point decrease), and in one third of patients the celiac pain had been eliminated entirely during follow-up. Toxicity was minimal and limited to grade 1-2 (2 patients reported mild worsening of pain immediately following treatment, some limited nausea/vomiting). Median daily morphine equivalent dose consumption decreased (NS). A significant improvement was noted in all evaluated measures of quality of life.

Conclusion: Celiac plexus radiosurgery is well tolerated, substantially decreases pain, and improves quality of life amongst patients with advanced upper-GI cancer. An international multicenter phase II trial is currently accruing.

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Quality of life: A Prospective Randomized Trial of Palliative Volumetric Arc Therapy (VMAT) Versus Conformal Radiation Therapy (CRT)

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Purpose/Objective(s): VMAT spares normal tissues from high/intermediate radiation (RT) doses but increases the volume of tissues receiving low doses of RT as compared to CRT. We hypothesized that palliative VMAT would induce less acute quality of life (QOL) detriment than CRT.

Materials/Methods: This phase 2 trial randomized patients to palliative RT using VMAT or CRT to 1 painful site of metastatic disease in the trunk. Eligible patients were able to complete questionnaires (EORTC QLQ C30 and SF-BPI) and were expected to live >3 months. Patients were ineligible if their KPS<50, they had prior radiation to the same site, there were planned changes in analgesics or cancer therapy within 7 days of the RT. Treating physicians could choose 8Gy in 1 fraction or 20Gy in 5 fractions, a choice used to stratify randomization. The primary endpoint was EORTC QLQ C30 global QOL subscales at 1 week post-RT (QOL at 4 weeks was a secondary endpoint). Paired t-test was used to compare the effect of RT to all patients. Wilcoxon signed-rank test (2-tailed) was used to compare changes in QOL. Only clinically important (≥10 point) QOL differences are reported.

Results: From July 2014-November 2017, 72 patients were accrued. Three patients did not receive RT, 12 did not return 1 week post-RT. There were 55 and 46 evaluable patients at 1 and 4 weeks post-RT, respectively. The most common diagnoses were NSCLC, breast, and prostate cancer. Median overall survival was 9 months. Median pain level was 7/10 at baseline and 5/10 at 1 and 4 weeks post-RT ($p<0.0001$ and $p=0.0013$). Median time from consultation to RT was 6 days. Baseline characteristics (KPS, pain, QOL subscales and time to 1st RT fraction) were balanced between the groups. At 1 week post-RT, global QOL subscale was not significantly ($p=0.46$) different between VMAT vs. CRT, but VMAT induced significantly ($p= 0.027$) less nausea and vomiting than CRT. At 4 weeks post-RT, VMAT induced significantly ($p=0.048$) less global QOL deterioration. At 4 weeks, patients who received VMAT maintained better role ($p=0.022$) and social ($p=0.018$) functions, but reported more diarrhea symptoms ($p=0.033$) than patients treated with CRT. Patient age, gender, RT dose, PTV size and target location (abdomino-pelvic vs. thoracic) were not associated with global QOL changes at 4 weeks.

Conclusion: Palliative VMAT appears to induce less QOL detriments than CRT at 4 weeks post-RT. VMAT reduced iatrogenic nausea and vomiting, which was partially offset by an increase in diarrhea.

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Integrating Radiation Oncology into Inpatient Interdisciplinary Rounds with Medical Oncology and Palliative Care

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Purpose/Objective(s): In an academic tertiary care setting, we have developed a multidisciplinary palliative care team, which includes members of radiation oncology, medical oncology, and palliative care, that performs daily inpatient rounds. We look to examine the impact this initiative has had on recommendations for radiation therapy, patient length of stay, and for those patients recommended radiation treatment, treatment completion rates.
Materials/Methods: Multidisciplinary palliative care rounds (MPCR) were initiated in July 2017. We retrospectively reviewed all medical records for patients treated at this inpatient facility from 1/2017 – 12/2017, and recorded demographic data, treatment details, and length of inpatient stay after a radiation oncology consultation. We compared the 6 month baseline data prior to the initiative (1/17-6/17) with that from the 6 months immediately following (7/17-12/17) using Chi-square and two sample, two tailed t-tests.
Results: 176 inpatients received radiation therapy during this 12 month interval. There was a 35% increase in number of inpatient radiation treatment courses in the 6 months after development of MPCR as compared to the 6 months prior (104 treatment courses post-MPCR versus 77 treatment courses pre-MPCR). Number of fractions recommended was not different (mean of 6.1 fractions pre-MPCR versus mean of 5.5 fractions post-MPCR, p=0.37). The median number of fractions recommended for both time periods was 5. There was a trend towards increased recommendation of single fraction RT (7 courses pre-MPCR versus 16 courses post-MPCR, p=0.16). Early treatment terminations, defined as patients who received less than the prescribed number of treatments, was not different (11.7% pre-MPCR versus 13.5% post-MPCR, p=0.72). There was, however, a trend towards decreased length of stay (median of 14 days pre-MPCR versus median of 12 days post-MPCR, p=0.36). **Conclusion:** We found that multidisciplinary palliative care rounds are feasible and result in changes in practice patterns of palliative care patients. There was a large increase in the number of patients treated with radiation therapy and a trend towards decreased length of stay. This likely is due to better recognition of indications for palliative radiation therapy as well as improved communication between the treatment teams. While the median number of treatments recommended was 5, we did see a trend toward increased recommendation of single fraction treatments. Longer term follow-up is needed to confirm these findings.
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Variation in Use of Palliative Radiation in Lung Cancer Patients with Bone Metastases by Health Care Market

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Purpose/Objective(s): Palliative radiation therapy (PRT) is an effective option for relieving pain from bone metastases. Based on randomized studies suggesting equivalent pain relief from shorter courses of treatment, national guidelines advocate for shorter courses of PRT. Though these guidelines address *how* PRT should be given, they do not address *when* PRT should be considered. We sought to measure variation in the use of PRT among Medicare patients with bone metastases at diagnosis.

Materials/Methods: Using data from SEER-Medicare, we identified patients over age 65 diagnosed with metastatic non-small cell lung cancer (NSCLC) from 2010-2013 who had bone metastases at diagnosis. We calculated the proportion of patients who received PRT within one year of diagnosis by Health Service Area (HSA), representing a geographic health care market. HSAs with at least 20 patients diagnosed during the study period were included in the analysis. A multivariable generalized linear mixed model with logit link was used to identify associations between patient and HSA characteristics and likelihood of receipt of PRT.
Results: Among 20,517 patients diagnosed with metastatic NSCLC, 6,681 (33%) had bone metastases at diagnosis. Of these, 51% received PRT within the first year. Among 80 HSAs with at least 20 patients in the cohort, use of PRT ranged from 30% to 82% (median 51%, 33%-66% 5%ile-95%ile). Patient factors associated with PRT use included younger age group (overall p<.01), female gender (OR 1.3, p<.01), married status (OR 1.45, p<.01), and race (white vs black vs other, OR 1.0 vs 0.76 vs 0.92, overall p<.01). HSA factors associated with PRT use included greater per capita Medicare spending (OR 1.13/$1000, p<.01), median household income (OR 1.11/$1000, p<.01), and density of hospitals with pain and/or palliative care services (4^{th} vs 1^{st} quartile, OR 1.58, overall p<.01).
Conclusion: We identified substantial variation in the use and intensity of PRT among lung cancer patients with bone metastases. Patient living in HSAs with higher Medicare spending and greater financial and pain/palliative care resources were more likely to receive PRT. This suggests a potential opportunity to better optimize use of PRT.
Author Disclosure: **A.B. Chen**: None. **A.M. Cronin**: None. **D. Schrag**: None.

Patient Safety

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Analysis of Retrospective Versus Prospective Peer Review in a Multisite Academic Radiation Department
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Purpose/Objective(s): Our multisite academic radiation department transitioned from weekly retrospective to daily prospective peer review to improve plan quality and decrease the rate of plan revisions after treatment start. We review our initial experience regarding deviation patterns and time from simulation to treatment start.
Materials/Methods: In all, 798 patients with 1124 plans were reviewed: 611 plans weekly from 7/12 to 10/18/17 and 513 plans daily from 10/16/17 to 1/12/18. In the weekly era, plan review primarily occurred after treatment start (5.6% prospectively reviewed) and was based on screenshots of beam arrangement, dose distribution, and dose-volume histograms. In the daily era, plan review was performed in a treatment planning system with emphasis on prospective timing of review (75.4% prospectively reviewed). Brachytherapy, stereotactic radiosurgery, and most emergent plans were not reviewed prospectively. Plans were assessed for appropriateness of treatment intent, dose-fractionation, simulation, modality, contours, target coverage, and risk to critical structures. Deviations were major if plan revisions were recommended prior to the next fraction and minor if modifications were suggested but not required for that course. All physicians and representatives from dosimetry and physics were required to attend. Categorical variables were compared using chi-squared tests of independence; means were compared using independent t-tests.
Results: Overall, 76 (6.8%; 31 major) deviations were noted. Rates of any deviation were increased in the daily era (8.6% vs 5.2%, p = 0.031) and with prospective review (9.7% vs 5.0%, p = 0.003), with higher rates of major deviations in the daily era (4.1% vs 1.6%, p = 0.016 major; p = 0.542 minor) and with prospective review (5.0% vs 1.4%, p = 0.001 major; p = 0.347 minor). In the subset of plans excluding brachytherapy, stereotactic radiosurgery, and boosts not specifically resimulated (N = 844), mean working days between simulation and treatment was similar across eras (5.55 days vs 5.53 days, p = 0.923) but was increased with prospective review (6.04 days vs 5.22 days, p

= 0.001). Deviations (N = 76) were addressed at a higher rate in the daily era (84.1% vs 31.3%, p < 0.001) and with prospective review (85.4% vs 34.3%, p < 0.001). The rate of plan revisions after treatment start due to peer review was not related to era (11.4% vs 25.0%, p = 0.136) but was decreased with prospective review (7.3% vs 28.6%, p = 0.030). The rate of plan revision recommendations not followed was numerically decreased in the daily era (4.5% vs 15.6%, p = 0.100) and with prospective review (4.9% vs 14.3%, p = 0.154).

Conclusion: Daily peer review with emphasis on prospective plan evaluation was related to increased rates of deviations recorded and corrected without a prolonged interval between simulation and treatment. Daily prospective plan review is feasible in a multisite academic setting and is an integral part of our process improvement strategy for excellence in patient care.

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Knowledge-Based Error Detection in External Beam Physician Orders Using Association Rules

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Purpose/Objective(s): The physician orders for external beam radiation therapy (EBRT) are associated with top-level treatment decision parameters including prescription dose, number of treatment fractions, treatment modality, treatment positioning, image guidance, etc. Physician order errors manifest as wrong values of individual parameters or logical inconsistencies between multiple parameters, which are difficult to detect even to human experts without going through many data and documentations. The purpose of this work is to investigate an association rule based approach to error detection in physician orders. The goal is to catch those errors earlier so to avoid the costly re-simulation and re-planning.

Materials/Methods: Clinical physician orders for patients who received EBRT treatments from 2008 to 2017 at author's institution. A total of 3059 individual single-prescription orders for nine disease sites – brain, breast, lung, pelvic, pelvis, prostate, spine, TBI, extremely – were acquired. Each order includes disease attributes and prescription parameters. Seven disease attributes were considered as conditions - site, tumor stage, nodal stage, metastatic stage, intent, laterality and previous treatment. Errors were detected on the four prescription parameters - total dose, fractions, technique and modality. The Apriori algorithm was employed to extract frequent item sets from the historical physician orders. The association rules were generated by arranging items in each frequent item set as antecedent items and consequent items. The active association rules were selected according to their support and confident scores. The error detection tool raises an error flag if a new physician order breaks any active association rules. 10 percent of physician orders were randomly chosen and errors (wrong values in prescription parameters) were added manually for testing the performance of the method.

Results: 257 active association rules were selected on average for each individual disease sites. The mean values of true positive and false positive rates of error detection were 92.38% and 10.23% respectively for single-prescription cases of nine disease sites.

Conclusion: The wrong value of individual physician order parameters and logical inconsistence between physician order parameters could be detected by applying association rules with high positive rate, which could be further improved by optimizing the association rule discovery algorithm. The association rules are human expert understandable and verifiable, and linked directly to historical physician orders. Association rule discovery algorithm can naturally handle physician orders with missing values existing in more than 50% physician orders. The approach supports incorporation into independent error detection tools for assisting manual double-checks on physician orders. The success of the method here also gives promise to further scaling to include patient setup parameters and all treatment sites.

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Hazardous Attitudes: Physician Decision Making in Radiation Oncology

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Purpose/Objective(s): The Federal Aviation Administration assesses hazardous attitudes (HA) among pilots using the HA Scale, a 30-item questionnaire that quantifies HA such as macho, antiauthority, worry, resignation, and impulsivity, and has demonstrated the association of these attitudes with aviation risk. An association of HA scale and risk has been previously demonstrated in surgeons. The purpose of this study was to assess the influence of HA and other factors in treatment decision making among radiation oncologists (RO).

Materials/Methods: The HA Scale was adapted for RO and the anonymous survey was sent to 809 RO in the cities housing the top 25 cancer centers. Participants completed this scale, gave treatment recommendations in four cases designed to assess willingness to prescribe radiation (RT) courses with a higher biologically equivalent dose (BED), and were queried about their preferred option in routine practice in patients who mirror the focus of a Choosing Wisely campaign. Physician-reported demographic and treatment decision data were dichotomized in order to identify factors associated with higher BED treatment and compliance with Choosing Wisely recommendations using univariable (UVA) and multivariable (MVA) logistic regression analyses.

Results: 139 responses (17.1%) were received, 103 of which were eligible for analysis. Of the respondents, 61 (60%) were male and 41 (40%) were female, and ages were evenly distributed. Eighty-five were from academic centers (83%). Median scores for macho, antiauthority, worry, resignation, and impulsivity were all below aviation thresholds for hazard (15, 9, 15, 12, & 15, respectively). On UVA, age >50 (odds ratio [OR] 3.65; 95% confidence interval [CI] 1.39-9.56], p=.008) and experience >5 years (OR 3.18, 95%; CI 1.08-9.37, p=.036) were associated with an increased likelihood of recommending higher BED RT, while HA and other demographic factors did not demonstrate an association. On MVA, responders >50 years old with >5 years experience were 4.45 times more likely to recommend higher BED RT (95% CI 1.32-15.0, p=.016). The macho attitude was negatively associated with compliance with Choosing Wisely recommendations (OR 0.12; CI 0.03-0.4; p=.001). Physicians who reported an experience of RT retreatment of the supraclavicular fossa without complication were more likely (OR 5.2, CI 1.55-17.61, p=.008) to recommend retreatment in medically unfit patients if they felt the complication was avoided due to careful planning rather than chance.

Conclusion: To our knowledge this is the first study to examine and classify physician attitudes in the field of radiation oncology. RO did not display high levels of HA. However, the macho attitude was associated with nonadherence to Choosing Wisely recommendations. Other factors, such as increasing age and experience were associated with a higher propensity to recommend higher BED RT. This work lays the foundation for further efforts to identify factors associated with physician decision making in RO.

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Use of Relational Coordination Scale to Assess Perceptions of Physician Teamwork Skills by Clinical and Administrative Staff

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Purpose/Objective(s): The quality of relationships within a healthcare setting has been shown to impact quality of care and quality improvement success. Delivery of care in radiation oncology requires physicians to work with a variety of providers such a nurses and therapists. Physicians may have differing perspectives as to the quality of their working relationships than do their counterparts, with physicians often estimating those as more positive. We hypothesized that patterns of communication and relationships between team members and physicians could be meaningfully evaluated.

Materials/Methods: The Relational Coordination Scale is a validated instrument for assessing quality of communication and relationships, and measures teamwork on 6 dimensions: timeliness, accuracy, problem solving, shared goals, shared knowledge and respect. Each dimension is rated on a 5-point scale. We asked dosimetrists, nurses, physicists, therapists, and administrative staff to anonymously rate 15 attending physicians within a radiation oncology department using the RC scale.

Results: Of 135 staff invited, 67 (52%) completed the survey over 2 months. IRB approval (exempt status) was received. For each dimension, we measured rates of physicians being positively rated (above midpoint on the scale, i.e. 4-5/5). Analysis of variability of positive responses by respondent group revealed highest variability reported by administrative staff for Completeness of work, by dosimetry for Timeliness, by nursing for Timeliness, by physics for Timeliness, and by therapists for Completeness. Overall, timeliness was rated with the greatest variability across individual physicians (mean positive rating 43 - 99%). Nurses were found to give higher ratings to physicians on timeliness compared to administrative staff, physics, and therapy (F [4, 75] = 3.18, $p < .02$). We also compared individual physicians by percentage of positive ratings for each dimension and respondent group. Aggregating on dimensions across respondent groups displayed variations across physicians, as well as some individual physicians receiving lower ratings across multiple dimensions and respondent groups, indicating gaps in communication and teamwork.

Conclusion: The relational coordination scale revealed variations in perceptions among support staff about teamwork and communication skills of radiation oncologists, particularly on completeness of work and timeliness of communication. We have utilized these data as part of evaluation of workflow and annualized feedback for physicians, towards targeted improvement of nontechnical skills in coordinating and working with staff.

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High Volume Incident Learning System Use is Associated with Durable Improvement in Patient Safety Culture Over 5 Years

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Purpose/Objective(s): Incident learning systems (ILS) require substantial time and effort to maintain and risks staff burnout and ILS disuse. Understanding the permanence of ILS benefits to safety culture and the relationship between staff ILS engagement and safety culture are important considerations for resource allocation for safety initiatives. Here we assess the durability of ILS-associated safety culture improvements and ILS engagement at five years.

Materials/Methods: Prior to initiating the ILS in 2012, a survey assessing patient safety culture was sent to all staff to establish a baseline. The survey draws from the validated AHRQ Hospital Survey on Patient Safety Culture. The same survey was collected annually for the subsequent five years through 2017. Key aspects of safety culture, including overall patient safety grade, were analyzed using chi-square test to compare baseline rate of positive scores (4-5 on 5-point Likert scale) to the post-ILS 5-year average. ILS engagement was measured by self-reported number of ILS entries submitted by respondents in the previous 12 months.

Results: The annual safety culture survey response rate was ≥68% each year (range 68-81%). High-volume reporting was sustained over five years (4673 reported events; average of one ILS entry per patient). Significant increases in positive responses pre vs post-ILS were observed in responsibility and self-efficacy ($p < 0.001$), feedback ($p < 0.01$), teamwork ($p<0.01$), and open communication and punitive concerns ($p = 0.02$). The percent awarding the department an "excellent" safety grade increased from 16% to 28% (5-year mean). Overall patient safety grade of good or excellent was significantly improved (69% vs 85% 5-year mean, $p = 0.03$). The percent of self-reported ILS engagement increased significantly ($p < 0.001$).

Conclusion: Comprehensive high volume incident learning is associated with significant improvements in patient safety culture and improved ILS engagement over 5 years, offering further evidence for the broader adoption of such safety initiatives by other institutions.

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Radiation and Cancer Biology

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Integrated Molecular Subtyping of Clinical Metastasis: Implications for Defining a Curable Oligometastatic State

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Purpose/Objective(s): The oligometastasis hypothesis suggests a spectrum of metastatic virulence where some metastases are limited in number and organ involvement and potentially curable with focal therapies. A subset of patients with metastatic colorectal cancer (CRC) achieves prolonged survival after resection of liver metastases consistent with oligometastasis. Here, we characterized the molecular determinants of CRC liver metastases (CRCLM) as they relate to clinical outcomes following resection.

Materials/Methods: We integrated next-generation DNA and RNA Sequencing, microRNA expression, and microsatellite instability (MSI) analysis of 121 clinically annotated *de novo* CRCLM. Molecular data were incorporated with clinicopathological variables to identify patients who achieved favorable outcomes following hepatic resection.

Results: Molecular features of primary CRC are reflected in liver metastases, but are not predictive of clinical outcomes. By contrast, integrative transcriptional analysis revealed three robust molecular subtypes of CRCLM associated with distinct outcomes. Metastases exhibiting MSI-independent immune activation predicted the most favorable survival. Subtypes with adverse clinical outcomes demonstrated *VEGFA* amplification in concert with (i) stromal, mesenchymal, and angiogenic signatures, or (ii) exclusive *NOTCH1* and *PIK3C2B* mutations with E2F/MYC activation. An expression-based classifier independently validated to identify patients with favorable clinical outcomes following resection of limited CRCLM. Integration of molecular subtypes and clinicopathologic risk stratification distinguished low-, intermediate-, and high-risk patients with 10-year overall survivals of 94%, 45% and 19%, respectively.

Conclusion: This is the first integrated analysis to define the molecular subtypes of metastasis as they relate to clinical outcomes. Molecular subtypes of CRCLM complement clinical risk stratification to provide a framework for integrated classification and treatment of metastatic disease and support the biological basis of curable oligometastatic CRC. These concepts may be applicable to many patients with metastatic cancer.

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Association of Circulating Tumor Cells (CTCs) and Genomic Signatures in Prostate Cancer Patients

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Purpose/Objective(s): Intermediate and high-risk prostate cancer patients who are candidates for radiotherapy (RT) are very heterogeneous. Genomic classifiers add to clinical-pathologic risk factors and have the potential to become integral to risk stratification. Since circulating tumor cells (CTCs) are determinate of metastasis and genomic predictors of CTCs are not yet understood in this population, we investigated the associations of CTC counts with several genomic classifiers in patients enrolled in a randomized Phase II radiotherapy clinical trial (BLaStM, NCT02307058).

Materials/Methods: CTCs were enumerated in blood samples from 31 patients using a microfilter system. The number of single CTCs, CTC clusters and their sum were recorded. Several gene signatures were investigated. Decipher® (metastatic risk), PORTOS (predictor of RT response) and PAM50 (predictor hormone response, which includes gene expression-based "intrinsic" subtypes: luminal A, luminal B, HER2-enriched, and basal-like), were quantified in tissue obtained by MRI-Ultrasound fused biopsies. A high-density gene expression microarray processed at a biosciences laboratory was used. A Poisson regression model with demographic and disease characteristics variables (PSA, Gleason Score (GS), T stage, %tumor in biopsies, age, race/ethnicity) were used in the univariable analysis (UVA). Multivariable analysis (MVA) included the statistically significant variables, where each biomarker was examined, along with chosen covariates for association with CTC counts in a one-at-a-time manner.

Results: CTCs were evident in over 70% of patients tested. The single cell and cluster median values in 8 mL of blood were 33 (range 0-343) and 4 (range 0-26). In MVA, several of the signatures were associated with total CTC number (single cells and clusters). When the biopsy core containing the highest Gleason score (GS) and %tumor

were analyzed, the significant relationships included PORTOS (RR 6.00; p<0.001), PAM50_basal (RR 2.21; p<0.001), and Decipher (RR 1.16; p=0.048). Since multiple biopsies were analyzed for gene expression, when the cores with the highest signature value were selected, PORTOS surged (RR=47.10; p<0.0001) in the MVA. Despite the relatively small sample size, the results indicate a strong signal related to radiation sensitivity. NCCN risk categories were not significantly related to CTC counts or gene signatures.

Conclusion: Determinants of prostate cancer lethality in intermediate to high-risk prostate cancer are poorly understood. Our results show an association between tumor gene expression alterations and CTC number, indicating that genes linked to radiation sensitivity have a role in early metastatic risk.

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The Influence of the Pretreatment Host Immune Inflammatory State and Response to Radiation Therapy in High Risk Adenocarcinoma of the Prostate: A Validation Study From NRG Oncology/RTOG 0521

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Purpose/Objective(s): The host immuno-inflammatory state, as reflected by elevation in C-Reactive Protein (CRP), has been shown in several retrospective series to be associated with poor outcomes following radiation therapy (RT). We conducted a validation study using prospectively banked serum specimens from the phase III clinical trial RTOG 0521 which evaluated the addition of docetaxel to androgen suppression and RT for high risk prostate cancer.

Materials/Methods: Patients enrolled on RTOG 0521 had serum samples banked for future biomarker validation. This study was designed to validate previous findings showing an association between elevations in CRP levels and shorter biochemical failure-free survival after RT. CRP levels were measured in pre-treatment samples using a widely available, clinical grade assay. A panel of serum immuno-inflammatory cytokines were also measured including: monocyte chemotactic protein-1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-γ), IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17A, IL-23, and tumor necrosis factor (TNFα). The primary endpoint examined in this *a priori* designed validation study was disease-free survival (DFS), defined as the time from randomization to the development of biochemical failure, local

progression, distant metastases, or death from prostate cancer, whichever occurred first. Additional endpoints included correlation with cytokine levels and toxicity events attributed to RT, namely: pollakiuria ≥ grade (g) 2, cystitis ≥ g 2, diarrhea ≥ g 2, erectile dysfunction (ed) ≥ g 2, proctitis ≥ g 2.

Results: Of 563 patients who enrolled in RTOG 0521, 202 had banked serum samples available. In the subsample, median age was 66 years (range 48-83), 90% of patients were white and 10% African-American. There was not an association between CRP and DFS ([HR]=1.06 per one log increase in CRP, 95% CI: 0.78 - 1.43, p=0.72). Pre-treatment IL-10 was significantly associated with DFS following co-variate adjustment (HR=1.59, p=0.02 per one log increase). Pretreatment levels of IFN-γ, IL-2, IL-13, IL-23 were negatively associated with g 2 or higher pollakiuria (OR=0.68, 0.75, 0.76, and 0.78, respectively, all $p<0.05$) and IL-12 and IL-13 were positively associated with g 2 or higher cystitis (OR=2.04 and 1.55, respectively, $p<0.05$).

Conclusion: Elevation in host inflammatory state, as reflected by CRP, was not associated with a poorer DFS following RT. Higher baseline levels of IL-10 were associated with lower rates of DFS. Elevated pretreatment levels of IL-12 and IL-13 were also associated with higher rates of cystitis. These data support an interaction between the host pretreatment immune inflammatory state on outcomes following RT. Anti-inflammatory medical intervention in patients with prostate cancer, in association with RT, may be worthy of future investigation. Acknowledgements: Supported by Institutional Research Grant # 14-247-29-IRG from the American Cancer Society

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Clonal Expansion of Antigen Specific T-Cells during Radiation Therapy for HPV Associated Cervical Cancers Is Regulated By the Vaginal Microbiome

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Purpose/Objective(s): Cervical cancers are known to be highly radiation sensitive; however, the rate of response to treatment is variable and poor responders are more likely to recur. The microbiota of colon cancers has been reported to play a role in response to chemotherapy and immune activation. We hypothesized that the cervical microbiome may impact radiation response and T-cell expansion. To address this, we completed prospective serial T-cell receptor (TCR) and microbiome sequencing of 30 patients with CCa throughout chemoradiation (CRT).
Materials/Methods: Patients with newly diagnosed CCa were enrolled on a prospective study to characterize changes in the TCR profile and vaginal microbiome during CRT. Cervical samples were obtained from 30 patients before and during (weeks 1, 3 and 5) radiation. TCR profiling was performed through ImmunoSEQ to amplify and sequence the TCR CDR3b regions. Total unique templates, clonality, maximum productive frequency (MPF) and MPF of the top 10 clones (MPF10) were quantified. Disease response was categorized as exceptional response (ER), standard response (SR) or poor response (PR) based on week 5 MRI and 3 month PET/CT. Microbiome was characterized via 16S rDNA sequencing. Shannon diversity index (SDI) was used to compare microbiome diversity. Impact of specific microbial species were assessed using Linear Effect Size (LEFSe) analysis.
Results: Among all patients, the total templates (p=0.22), sample clonality (p=0.3) and MPF (p=0.07) were similar among SR, ER and PR at baseline. At week 5, total templates was similar among all groups (p=0.13); however, ER samples demonstrated higher clonality (ER median 0.05 [0.04-0.06] vs SR median (0.01 [0.009-0.02]; p=0.02). MPF10 decreased over time for PR/SR and increased over time for ER, with a higher fold change in MPF10 from week 3 to week 5 for ER (1.51 [1.10-2.61]) vs PR (0.60 [0.30-0.94]; p=0.02) or SR (0.80 [0.54-1.10]; p=0.03). Alpha diversity of the cervical microbiome was similar among responders (SR/ER) and non-responders (PR); however, distinct genus-level differences existed between SR/ER and non-responders PR, with enrichment of *Porphyromonas* in SR/ER and enrichment of *Lactobacilli* in PR. A *Lactobacillus*:*Porphyromonas* ratio (LPR) >= 1 (N=7) vs. LPR <1 (N=23). A *Lactobacillus*:*Porphyromonas* ratio (LPR) >= 1 was associated with decreased RFS (12.3 months vs NR; p=0.004) with failure rate of 43% (3/7) versus 4% (1/23) noted in the low LPR (<1; N=23). High LPR at baseline was also associated with decreased fold change in MPF10 by week 5 (p=0.015).
Conclusion: Exceptional responders to radiation treatment are more likely to have clonal expansion of antigen specific T-cells within CCa. Predominance of vaginal Lactobacillus is associated with poor radiation response and lack of clonal T-cell expansion. Loss of E6/7 expression driven by lactobacillus may provide a mechanism to account for this observation. Further validation will be needed prior to development of interventions targeting the local tumor microbiome.
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Genetic Profiling of Oligodendrogliomas (IDH Mutated and 1p19q Co-deleted) Treated with Adjuvant Radiation Therapy or Observation Informs Prognosis

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Purpose/Objective(s): Recent international sequencing efforts have allowed for the molecular taxonomy of low-grade gliomas (LGG)(The Cancer Genome Atlas (TCGA), 2015). Based on clinical and pathological factors, patients with resected oligodendrogliomas are usually treated with adjuvant radiation or observed. We sought to analyze TCGA gene expression and copy number datasets on oligodendrogliomas patients treated with adjuvant radiation or those observed to discover prognostic markers and pathways.

Materials/Methods: Our cohort consists of patients with oligodendroglioma in the TCGA dataset (accessed through http://www.cbioportal.org/). mRNA expression, copy number, and clinical information was taken from the TCGA "Brain Lower Grade Glioma" provisional dataset. Survival modeling and ANOVA analysis was performed using the R packages "plsRCox" and "survival". 10-fold bootstrap, cross-validation was performed using the "rms" and "pec" packages.

Results: From 530 potential LGG dataset patients, 164 were included in our analysis with oligodendroglioma or oligoastrocytoma, and both IDH mutation and 1p19q codeletion. Out of our cohort of 164 patients, 137 had documentation of treatment, with 65 receiving adjuvant radiation (median dose 5,940 cGy) and 62 observed. In the cohort that received adjuvant radiotherapy, expression of members of the PDGFRA module (GSTA4, CXXC4, KLRC3, DSCAM, OLIG2, SOX4, SOX8) was associated with shorter progression-free survival (HR=7.8, $p < 0.02$, median C-index=55.3%). This increased risk was not seen in patients who were observed (HR=0.86, p=0.83). In addition, expression of circadian clock genes (CSNK1E, CRY2, PER1) was also associated with shorter progression-free survival (HR=4.9, $p < 0.03$, median C-index=68.6%)) when treated with radiation versus observation (HR=0.33, p=0.11). Median progression-free survival in the radiotherapy cohort positive for the circadian gene signature was 64 months versus 97.2 months for those negative for the signature. Within the observation cohort, expression of genes in the polycomb repressive complex-2 (EZH1, EZH2, SUZ12, EED, and RBBP4) was associated with poor progression-free survival (HR=1.65, $p < 0.008$, median C-index=68.5%)). This risk was abrogated in the adjuvant radiation cohort (HR=1.03, p=0.55). Decreased expression of genes targeted and down-regulated by this complex also was associated with shorter progression-free survival (Chi-sq=7.4, $p < 0.007$ median C-index=66.3%).

Conclusion: We identified genes in the PDGFRA and circadian signaling pathways that are associated with poor prognosis in patients with IDH mutated and 1p19q codeleted oligodendroglioma treated with adjuvant radiotherapy. These patients would be potential candidates for treatment intensification. We also identified a PRC-2 gene signature for patients who were more likely to progress on observation. This potentially identifies a cohort who would benefit from upfront adjuvant radiotherapy.

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Personalizing Prescription of Radiation Therapy Utilizing Genomic Markers of Radiosensitivity

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Purpose/Objective(s): In previous studies, we developed the radio-sensitivity index (RSI) and genomic adjusted radiation dose (GARD) to capture genomic heterogeneity and personalize radiation therapy (RT) prescription. We hypothesize that the current one-size fits-all paradigm to RT prescription is inefficient for individual patients given observed distributions of tumor RSI across large cohorts of patients. We demonstrate a workflow for clinical use of genomic features in RT prescription.

Materials/Methods: We assessed tumor genomics in a cohort of 1229 patients with non-small lung cancer (NSCLC,Cohort 1) using RSI. To model the impact of genomic heterogeneity on RT dose prescription, we utilized a cohort of 60 NSCLC patients treated with surgery and postoperative RT (45 – 70 Gy, median 54 Gy,Cohort 2). For all analyses, expression data (Affymetrix Hu-RSTA-2a520709) were used to calculate RSI. Using RSI, we derive a patient specific alfa to calculate GARD. Previously we demonstrated that lung cancer patients in cohort 2 who achieved a GARD >= 33 had an improved local control (HR=3.4, 1.3, 9.1 p=0.02). We defined the personalized RSI/GARD RT dose prescription (RxRSI) as the physical dose in Gy required to achieve the GARD threshold of 33. We integrated GARD into the planning workflow of a commercial treatment planning system to create personalized genomic radiation treatment plans (pGRT) using standardized plan optimizations for both standard of care (SoC) and RxRSI doses. RxRSI plans were evaluated against standard planning criteria and normal tissue constraints, and compared with SoC prescription plans using biological effective voxel based dose scaling.

Results: In cohort 1, RSI demonstrated a bimodal distribution, indicating a uniform treatment dose may be sub-optimal. A similar heterogeneity was observed in cohort 2, (RSI (IQR: 0.25, 0.40), GARD (IQR: 24.7, 38.62)) where we calculated a personalized RxRSI dose for each patient. In 24% of cohort 2, RxRSI dose was lower than the prescribed dose by more than 10%, with median RxRSI at 47Gy. In 60% of the cohort, RxRSI dose was greater than prescribed dose by more than 10%, ranging from 62Gy to 95Gy. pGRT planning achieved both desired target coverage for RxRSI and normal tissue constraints for patients under 74Gy, with esophageal dose falling below clinically acceptable levels for 80% of plans at 88Gy and above.

Conclusion: One-size fits-all RT dose prescription may be sub-optimal for some patients given the genomic heterogeneity observed. Using a clinically-validated model (RSI/GARD) we identify that in up to 84% of patients the prescribed dose and personalized RxRSI did not match, suggesting that there is a large opportunity to optimize dose with genomics. A novel pGRT function within a commercial system can effectively optimize plans to present a choice between a personalized RxRSI and SoC treatment plans for consideration. To our knowledge this is the first demonstration of a feasible clinical approach to precision medicine in radiation oncology.

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Intelligent 4D CT Sequence Scanning (i4DCT)

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Purpose/Objective(s): Respiration-correlated or 4D CT imaging is an integral part of treatment planning in 4D radiotherapy. However, clinical 4D CT protocols and image data often suffer from severe artifacts due to insufficient projection data coverage for image reconstruction at the desired breathing phases. The present work proposes a novel sequence mode 4D CT imaging protocol (i4DCT) that builds on intelligent selection of beam on/off periods during scanning to fulfill projection data coverage requirements. Protocol characteristics are evaluated and compared to standard clinical sequence mode and spiral 4D CT (seq4DCT, spiral4DCT).

Materials/Methods: Core blocks of i4DCT are (S1) an initial breathing signal-driven learning phase; (S2) online respiratory-controlled sequence mode scanning; and (S3) rescanning based on rapid breathing record analysis. S1 is required to select patient-specifically optimized scan protocol parameters (e.g. gantry rotation time). S2 covers real-time analysis of the breathing signal to appropriately switch on/off projection data acquisition even during irregular breathing. After acquisition of projection data for the clinically requested z range, S3 corrects for residual projection data coverage issues by automated quality assurance testing of the data and direct rescanning at max. *k* respective z positions. Protocol evaluation was based on 189 breathing records acquired during spiral 4D CT scanning for radiotherapy treatment planning (acquisition period: 2013-2017). For each patient, i4DCT, seq4DCT (Pan, Med Phys 31: 333-40) and spiral4DCT (Siemens Somatom) scanning was simulated. Evaluation measures were projection data coverage (PCov: z position-specifically covered fraction of mean breathing cycle peak-to-peak amplitude during 4D CT beam-on time); rate of failure (#$Fail_{pat}$: patients with PCov < 0.5 for at least one z position; #$Fail_{tot}$: overall numbers of PCov failures); and required imaging dose and total patient on couch time after starting 4D CT scanning (T_{OC}).

Results: i4DCT reduces the number of z positions with PCov failures (#$Fail_{total}$) and respective data gap image artifacts by 85% and 82% compared to seq4DCT and spiral4DCT without and by 90% and 92% for 5 allowed rescanned z positions. Simultaneously, the dose to the patient is reduced by 13% (with rescanning: 7%) compared to spiral4DCT. T_{OC} is increased by 45% and 55% compared to spiralCT; cf. table.

Conclusion: We proposed a novel 4D CT scanning approach that reduces data gap-related artifacts by up to >90%; interestingly, compared to current 4D CT protocols and for the considered cohort (larger fraction of fast breathing patients), i4DCT simultaneously reduced the imaging dose. Longer T_{OC} (prolongation by 45-55 s, compared to common 100 s T_{OC}) appears tolerable given the significant image quality improvement.

	spiral4DCT	**seq4DCT**	**i4DCT**	**i4DCT$_{rescan}$**
#Fail$_{pat}$	69	66	20	14
#Fail$_{tot}$	170	139	25	16
Dose	100% (reference)	82%	87%	93%
T_{OC}	100% (reference)	103%	145%	155%

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Virtual Bronchoscopy-Guided Dose Response Modeling of Airways to Mitigate Radiation Induced Airway Injury in Lung Sabr

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Purpose/Objective(s): Preserving post-treatment lung function is an important consideration in lung stereotactic ablative radiotherapy (SAbR). An important yet poorly understood toxicity in lung SAbR is radiation injury to the individual segments of the airway tree, especially the peripheral elements, which are essential for gas conduction to and from the alveoli. Here, we use virtual bronchoscopy to spatially map central and peripheral airways for individual patients, and estimate the radiation dose response for these airway segments as quantified by the dose-dependent probability of airway collapse.

Materials/Methods: Under IRB approval, pre- and post-SAbR diagnostic-quality CT scans were retrospectively collected from three lung cancer patients. For each patient, the pre and post-SAbR bronchial trees were segmented using a research version of a commercially available virtual bronchoscopy software (Archimedes, Bronchus, San Jose, CA). The post SAbR bronchial tree was deformably registered (MIM Vista) to the pre SAbR tree to identify airways that had collapsed post-treatment. The airways were imported as RTStructs into a commercial treatment planning system and doses received by individual airway segments from the clinical RT plan were computed. In a previous multivariate analysis, we had shown that airway collapse was closely associated with max point dose(Dmax) and airway diameter. Accordingly, logistic regression was utilized to fit a dose-response curve as a function of segmental collapse based on Dmax to and mean diameter of individual airways.

Results: A total of 648 airway segments were segmented and analyzed. The min, max and median diameters were 3.2, 24.4 and 4.14 mm respectively. We limited our study to the airways with diameters 3-6 mm since larger airways (>6 mm) did not show collapse even at the highest dose level. The collapse of smaller diameter airways (3-6 mm) was significantly correlated with D_{max} and airway diameter ($P<0.001$ for both). The probability of collapse of the small airways as function of dose is represented in the table below. Our estimated dose response curve exhibited a 78% accurate prediction rate for airway collapse across all diameters.

Airway diameter	Dose (Gy) for various probabilities of collapse			
	30%	40%	50%	70%
3-4 mm	1	1.43	10.40	29.14
4.1-5 mm	15.88	25.65	34.62	53.36
5.1-6 mm	40.10	49.87	58.84	77.57

Conclusion: Using virtual bronchoscopy guidance, we demonstrated the feasibility of spatially mapping and quantitatively estimating the radiation dose response of individual segments of the airway tree. Beyond the present scope, such improved understanding of radiation injury to airways will enable current and future novel treatment planning strategies to minimize airway injury and thereby better preserve post-SAbR respiratory function.

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Functional Liver Image-Guided Hepatic Therapy (FLIGHT) with Hepatobiliary Iminodiacetic Acid (HIDA) Scans: Predictors of Functional Dosimetric Improvements

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Purpose/Objective(s): Hepatobiliary iminodiacetic acid (HIDA) scans provide global and regional assessments of liver function that can serve as a functional map for stereotactic body radiation therapy (SBRT) planning. We hypothesize that patients with worse liver function and/or prior liver directed therapy (LDT) may derive a larger benefit from functional liver image-guided hepatic therapy (FLIGHT) compared to standard planning due to increased heterogeneity in liver function.

Materials/Methods: This study included patients at a single institution who underwent HIDA prior to SBRT. Two plans, standard and FLIGHT, were generated. FLIGHT beam arrangements and plans were optimized with priority given to avoid higher-functioning liver as defined by HIDA. The planning goal was to increase the functional residual capacity of the liver receiving <15 Gy (FRC_{15}HIDA), with a >5% improvement considered significant. The following dosimetric endpoints were compared for FLIGHT vs. standard plans using paired t-tests: FRC_{15}HIDA, mean liver dose, effective uniform dose (EUD), and functional EUD (FEUD). Pearson correlation was used to evaluate whether improvements in FRC_{15}HIDA were associated with baseline Child-Turcotte-Pugh (CTP), global HIDA, and/or liver/planning target volume (PTV) ratio. Dosimetric improvements in CTP A vs. B patients and those with vs without prior LDT (surgery, SBRT, or catheter-based therapies) were compared using independent t-tests.

Results: Standard and FLIGHT plans were created for 33 patients, including 6 who are enrolled on a prospective FLIGHT trial. Compared to standard planning, FLIGHT improved FRC_{15}HIDA, mean liver dose, EUD, and FEUD ($p \leq 0.001$); 12 had >5% improvement in FRC_{15}HIDA (mean 4.7%, range -3.8-20.2%), and 24 had >5% improvement in mean liver dose. The improvement in FRC_{15}HIDA were not correlated with CTP or global HIDA (p>0.1). The improvement in CTP A (n=20) vs B (n=13) was 5.5% vs 3.4% (p=0.347), HIDA ≤3.0%/min/m^2 (n=20) vs >3%/min/m^2 (n=13) was 3.7% vs 6.2%, and prior LDT (n=19) vs no LDT (n=14) was 6.1% vs 3.6% (p=0.252). Liver/PTV correlated with FRC_{15}HIDA improvement (r= -0.353, p=0.044): those with vs without ≥5% improvement had liver/PTV 18.1 vs 37.0 (p=0.009). The improvement in mean liver dose in CTP A vs B was 14.9% vs 8.8% (p=0.073).

Conclusion: FLIGHT with HIDA led to improvements in all analyzed dosimetric parameters. There was individual variation in the extent of benefit based on regional variations in liver function. Patients with worse baseline liver function as assessed by CTP and HIDA and those with prior LDT did not derive a significantly larger benefit from FLIGHT planning suggesting that modifications in addition to FLIGHT may be necessary to increase the therapeutic ratio in patients at high risk for toxicity. Patients with lower liver/PTV ratios derived larger benefit in FRC_{15}HIDA suggesting that consideration of the function of the remnant liver in this population may be important.

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Modeling of Locoregional Control in Hepatocellular Carcinoma after Stereotactic Body Radiation Therapy by Integrating Clinical and Immune Cell Profiles

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Purpose/Objective(s): Locoregional control (LRC) is associated with long-term outcomes in patients with hepatocellular carcinoma (HCC) who receive liver SBRT. The purpose of the current study is to develop new models for predicting LRC and to evaluate the role of clinical factors and circulating immune cells in predicting post-SBRT response.

Materials/Methods: Data from 146 HCC patients who received SBRT from 2005-14 were analyzed retrospectively. Tumor doses (median prescribed = 49.8 Gy, delivered in 3 or 5 fractions) were bio-corrected to 2 Gy equivalents (EQD2) using the LQ-L model. Circulating immune cell (lymphocytes, neutrophils, platelets) profiles (ICPs), red blood cell counts, and their changes during and after treatment were retrieved from the patients' laboratory records. The locoregional failure rate was 54.7% with a median follow-up and time-to-failure of 11 months and 6 months, respectively. Actuarial models based on machine learning algorithms were developed for predicting LRC. These models were based on variable shrinkage analysis with Cox proportional hazard (Lasso-Cox) and ensemble methods with Random survival forests (RSF). Relative variable importance was assessed in Lasso-Cox by hazard ratios (HR) and in RSF by the Gini impurity index. To avoid overfitting pitfalls, the bootstrap 0.632+ resampling method was used to validate prediction, and performance was measured using the concordance statistic (c-index).

Results: When modeling with only clinical variables for LRC, the Lasso-Cox selected in descending HR significance order: *previous recurrences, age, Child Pugh, ALBI,* and *cirrhosis* as relevant factors, achieving an average bootstrap c-index = 0.538 (95% CI: 0.496-0.564). The RSF achieved an average bootstrap c-index = 0.687 (95% CI: 0.666-0.704) with *previous recurrences, Child Pugh, age, ALBI, gender, tumor mean dose, tumor volume* as the top important factors according to their Gini impurity index. The addition of ICPs, available in about half the population, yielded an average bootstrap c-index = 0.569 (95% CI: 0.496-0.67) using Lasso-Cox with *pre-treatment hematocrits, ALBI,* and changes in *lymphocyte* and *neutrophil counts* as statistically significant variables according to their HRs ($p<0.05$). Whereas the RSF, with immune cells included, achieved the best performance overall with an average bootstrap validated c-index = 0.696 (95% CI: 0.638-0.751). Changes in *lymphocytes* and *platelets counts, pre-treatment hematocrits, neutrophil counts, ALBI,* and *age* were the most important factors according to the Gini impurity index ranking.

Conclusion: Machine learning methods based on RSF can provide a robust framework for estimating locoregional failure risk in HCC patients post-SBRT. The predictive power improves by including immune cells profile and their changes during treatment. These new LRC models can be used to personalize and guide new regimens for combining local (SBRT) and systemic (chemo- and/or immuno-) therapy in HCC patients.

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