

2019 Best of ASTRO Abstracts

Breast

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Cosmetic Outcome from Post Lumpectomy Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) on the NRG Oncology/NSABP B39-RTOG 0413 Phase III Clinical Trial

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Purpose/Objective(s): The NRG B-39/0413 phase III trial reported that post lumpectomy PBI was not statistically equivalent to WBI, but with an absolute difference for in-breast recurrence at 10 years (y) < 1% it may be a reasonable option for many breast cancer patients (pts). The cosmetic outcome of PBI compared to WBI could be an important determinant for radiation (RT) method selection.

Materials/Methods: NRG B39/0413 substudy addresses QOL and cosmesis. The study was stratified by chemo (CT) use and CT/no-CT groups were analyzed separately for these endpoints. Cosmetic outcome by pt rated global cosmetic score (GCS) and satisfaction, physician (MD) rated GCS, and digital photos (DP) of the breasts were collected at baseline (B), 1 and 3 y after RT. The GCS is a 4 point scale of 1 Excellent (E), 2 Good (G), 3 Fair (F), and 4 Poor (P). Satisfaction scale ranges from 1 totally satisfied to 5 totally dissatisfied. DP were reformatted for consistent image characteristics and centrally scored for GCS by 3 teams of 3 physicians blinded to treatment, breast treated, CT use, and time point. Comparisons between mean differences in treatment arms (μ_d) are based on testing for equivalency of GCS change from B to 3 y, using an α of 0.05. The 95% CI must be completely contained in the bound (bd) to conclude equivalence. MD/DP agreement with pt was assessed.

Results: From Mar 2005 to May 2009, 975 women were enrolled on the QOL substudy; 900 analyzable, 420 (47%) CT and 480 no-CT. There were no significant differences in pt/tumor characteristics for pts analyzable or not. For CT pts, cosmetic outcome from PBI was equivalent to WBI based on pt GCS (bd: -0.35 to 0.35, 95%CI: -0.25 to 0.14; μ_d -0.06); but did not meet equivalence (PBI worse) per MD GCS (bd: -0.42 to 0.42, 95%CI: -0.53 to -0.02; μ_d -0.27). For no-CT pts; cosmetic outcome from PBI was equivalent to WBI based on pt GCS (bd: -0.35 to 0.35, 95%CI: -0.22 to 0.15; μ_d -0.04); but did not meet equivalence (PBI worse) per MD GCS (bd: -0.328 to 0.33, 95%CI: -0.33 to 0.01; μ_d -0.16). Change in mean pt satisfaction from B to 3 y with PBI and WBI was equivalent in the CT and no CT groups. Cosmetic outcome based on DP GCS was worse for PBI in the CT group (bd: -0.37 to 0.37, 95%CI: -0.44 to 0.09; μ_d -0.18) and worse for WBI in the no-CT group (bd: -0.31 to 0.31, 95%CI: -0.01 to 0.42; μ_d = 0.20). For agreement between pts and MD/DP at 3 y, when pt scored E/G or F/P, MD agreements were 88% & 46%, respectively, in the CT group; and 89% & 45%, respectively, in the no-CT group; and DP agreements were 83% & 33%, respectively, in the CT group; and 86% & 31%, respectively, in the no-CT group.

Conclusion: Pt rated cosmetic outcome, based on GCS and satisfaction were equivalent for PBI and WBI. PBI resulted in worse cosmetic outcome on MD rating. On DP central review, cosmetic outcome is worse for PBI in CT treated group and worse for WBI in the no-CT group. MD/DP agreement with pt was high when pt scored E/G.

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Impact of Adjuvant Trastuzumab on Locoregional Failure Rates in the NCCTG N9831 (Alliance) Study

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Purpose/Objective(s): Trastuzumab (H) improves disease-free and overall survival in HER2+ breast cancer (BC) when added to adjuvant chemotherapy. We describe the impact of H on locoregional failure rates (LFRs).

Materials/Methods: 3505 patients (pts) with HER2+ BC were randomized. This analysis included 2763 eligible pts who had lumpectomy (L) or mastectomy (M) with radiotherapy (RT) or M without RT in this 3-arm phase 3 trial of adjuvant doxorubicin (A), cyclophosphamide (C), paclitaxel (T) and H: Arm A) AC→T (n=922); Arm B) AC→T→H (n=988); and Arm C) AC→T+H→H (n=853). RT was given after AC→T concurrently with H. RT was given to all L pts or after M with ≥4 positive lymph nodes (LN+), but was optional for 1-3 LN+. Regional RT to the axilla+supraclavicular fossa and boost were optional; internal mammary RT was not allowed. Median dose was 45.0-50.4 gray (Gy) in 25-28 fractions of 1.8-2.0 Gy fractions. Locoregional failure as first events were compared using competing risk analysis between groups based on treatment arm, ER+, tumor size (<2 cm), local treatment and number of LN+. Since local treatment was not randomized, we also compared LFRs within LN- and 1-3 LN+ subgroups.

Results: Median follow-up is 13.0 years. First site of failure was local only in 96 cases, locoregional in 16, regional in 32, and not specified in 2; 10-year LFR (LFR10) was 4.8% (95% CI 4.1-5.7%). LFR10 was 5.5% (4.3-7.2%), 4.9% (3.7-6.4%) and 2.8% (1.9-4.1%) in Arms A, B and C (A vs B: HR 0.91, p=0.92; A vs C: HR 0.72, p=0.12). For ER+, LFR10 was 3.7% (2.8-4.8%) and 6.1% (5.0-7.4%); HR 0.61, p=0.004) ER-. No difference in LFR was seen by tumor size or number of LN+. Local treatment included: L+RT 1044 (38%), M+RT 1025 (37%), and M 694 (25%). LFR10 was 6.2% (5.0-7.8%), 3.0% (2.1-4.3%) and 5.5% (4.0-7.4%) for L+RT, M+RT and M (L+RT vs M+RT: HR 0.43, p<0.001; L+RT vs M: HR 0.88, p=0.57). Characteristics were similar between L+RT and M patients within the LN- subgroup except for higher tumor grade for L+RT. LFR10 was 3.1% (1.4-6.7%) for L+RT vs 7.2% (4.1-12.4%) for M in this subgroup (HR 1.69, p=0.23). Characteristics were similar between L+RT and M and between M+RT and M pts within the 1-3 LN+ subgroups, except for smaller tumors and lower stage for L+RT, and younger age, higher tumor grade, larger tumors and higher stage for M+RT. In 1-3 LN+, LFR10 for L+RT was 6.5% (4.8-8.9%) vs 4.3% (2.9-6.5%) for M (HR 0.68, p=0.14), and 4.1% (2.4-7.0%) for M+RT (vs M: HR 1.20, p=0.60).

Conclusion: Low 10-year LFRs were seen with small differences based on H use. Use of additional local therapy in pts with 1-3 LN+ did not appear to improve local control. Local therapy studies based on HER2 and other tumor characteristics are important as the role of local therapies continues to evolve in an ever-changing systemic management landscape and should be included in future local therapy trials.

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Post Mastectomy Radiation Therapy in HER2/neu Positive Breast Cancer: Analysis of the HERA trial

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Purpose/Objective(s): Post-mastectomy radiation therapy (PMRT) has been shown in multiple clinical trials to improve local control, distant metastases and overall survival in breast cancer patients. However, it remains unclear whether these findings can be applied to HER-2/neu positive patients in the modern era.

Materials/Methods: The HERA trial (BIG 1-01) is a phase 3 randomized clinical trial that established the efficacy and safety of trastuzumab in HER-2 positive early stage breast cancer. The current study was performed on 1633 trial subjects treated with mastectomy who received adjuvant trastuzumab. The primary goal of the study was to determine the effect of PMRT on loco-regional recurrence (LRR). Hazard ratios were estimated from Cox models and LRR curves were generated by the Kaplan-Meier method.

Results: Our analysis included 940 patients (57.6%) who received PMRT and 693 patients (42.4%) who did not. Patients in the PMRT group received radiation to the chest wall and regional lymphatics. At a median follow up of 11 years, no significant difference in LRR was noted after PMRT in node negative (N0) patients (HR = 1.0 (0.33-2.98), p-value = 0.99). However, patients with N1 disease (1-3 positive lymph nodes) had a LRR of 2.8% in the PMRT group as compared to 9.7% in the no-PMRT group (HR = 0.29 (0.12-0.66), p-value = 0.003). No significant differences in OS were observed according to receipt of PMRT.

Conclusion: PMRT delivery in HER-2 positive breast cancer patients with 1-3 positive nodes decreases the risk of LRR. However, the magnitude of PMRT benefit is lower than historical studies. Future randomized trials are needed to assess the role of PMRT in HER-2/neu positive breast cancer patients.

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Prospective Phase II Clinical Trial of Hypofractionated Radiation in Breast Cancer Patients undergoing Comprehensive Nodal Irradiation for Node Positive Disease

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Purpose/Objective(s): Hypofractionated (HF) breast radiation is equivalent to standard fractionation in the whole breast setting, and is well tolerated in node positive patients without reconstruction. The purpose of this study is to report results from a prospective Phase II clinical trial evaluating HF in a node positive breast cancer population undergoing regional nodal irradiation, including those with reconstruction using implants and/or autologous tissue.

Materials/Methods: Women with stage T1-3 pN+ breast cancer who underwent lumpectomy or mastectomy with axillary surgery and systemic therapy were eligible for enrollment. RT was delivered to the breast/chestwall and regional lymph nodes to a dose of 4005 cGy in 15 fractions with pre-specified dose constraints to targets and organs at risk, with an optional boost of 1068 cGy in four fractions. The primary end point was

designed as a composite of six binary toxicity outcomes (lymphedema, shoulder stiffness, rib fracture, ischemic heart disease, pneumonitis, and brachial plexopathy), with an estimated composite event rate of 40% at 1 year based on historical data. The primary outcome measure was frequency of AE, and a secondary outcome evaluated the rate of expander or implant loss with HF. Toxicity endpoints were evaluated prior to RT and at 6 and 12 month follow-ups. A non-inferiority design with 80% power was used for sample size, and a binomial exact test ($\alpha = 0.05$), was used to estimate AE frequency compared to historical data.

Results: Of the 112 women enrolled from 2016-2018, 104 had follow-up data available out to at least six months with median follow-up of one year. Median age was 52 years (range 31-82 years). For axillary evaluation, 55% of patients underwent sentinel lymph node biopsy alone, and 45% underwent axillary dissection. The primary composite endpoint rate for women with at least six months of follow-up was 26%, less than the pre-determined 40% based on standard fractionation data ($p < 0.01$). Individual AE incidences include lymphedema, defined as an increase in arm circumference of at least 10% in the lower arm and/or the upper arm, (22%) $P < 0.01$; shoulder stiffness (2%), rib fracture (0%), ischemic heart disease (0%), pneumonitis (3%), and brachial plexopathy (2%). For the reconstruction cohort ($n = 38$), 78.4% underwent tissue expander reconstruction, with initial expander placement and later exchange to implant. The remaining 21.6% underwent autologous tissue based reconstruction after radiation. No implants or autologous tissue falls were lost, and 3 patients (7.9%) had implant revisions.

Conclusion: In this prospective Phase II clinical trial of breast HF in patients undergoing regional nodal irradiation including reconstruction patients, approximately one year composite endpoint rates are non-inferior compared to standard fractionation based on pre-determined limits. No implant loss or excessive reconstruction revision was observed. These data support the safety of HF for normal tissues and the reconstructed breast.

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Quantifying the Impact of Regional Lymph Node Irradiation on Lymphedema Risk in Breast Cancer Patients Treated with SLNB or ALND: Long-Term Results from a Prospective Screening Trial

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Purpose/Objective(s): Regional lymph node radiation (RLNR) is a well-established risk factor for breast cancer related lymphedema (BCRL). Results from AMAROS trial have suggested that sentinel node (SLN) + RLNR offered similar 5-year axillary control compared to axillary lymph node dissection (ALND) +/- RLNR for patients with few positive SLNs. The primary method of lymphedema evaluation relied on measuring arm circumference, diminishing its objectivity and extrapolation to nodal management today. In this trial, we used a perometer-based approach to quantify the impact of RLNR in breast cancer patients.

Materials/Methods: Between 2005 to 2018, 2,758 patients who received surgery for breast cancer were enrolled in a lymphedema screening trial (NCT01521741). Similar to AMAROS, patients with bilateral breast cancer, receipt of neoadjuvant chemotherapy or lack of axillary surgery were excluded. Perometry was used to assess limb volume preoperatively in all patients. Breast-cancer related lymphedema (BCRL) was defined as a $\geq 10\%$ relative arm-volume increase arising > 3 months postoperatively. Multivariable Cox proportional hazard model compared the cumulative incidence of BCRL and local failure between different patient's groups. Multiple comparisons with Bonferroni correction were conducted between groups.

Results: Overall median follow-up since diagnosis was 56 months (range: 4.7-195) for the entire cohort and 67.7, 77.5, 53.2 and 53.3 months for ALND+RLNR (N=241), ALND alone (N=117), SLN+RLNR (N=122) and SLN alone (N=1,375) groups, respectively. The 5 years cumulative

incidence rate of BCRL were (37%, 32%, 8.5% and 7.9%) for ALND+RLNR, ALND alone, SLN+RLNR and SLN alone groups, respectively. Multivariate cox models adjusted for age, BMI, surgery and reconstruction types showed that ALND + RLNR group compared to SLN+RLNR group significantly had higher risks for the development of BCRL (HR 5.1, 95% CI 2.4-11.3, p<0.001). Also, ALND alone group had significant higher BCRL risks (HR 4.5, 95% CI 1.9-10.7, p<0.001) compared to SLN+ RLNR. There was no significant difference in terms of BCRL between the ALND + RLNR and ALND alone groups (HR 1.1, 95% CI 0.7-1.8, p=0.5) and between the SLN alone and SLN+RLNR groups (HR 0.4, 95% CI 0.4-1.9, p=0.6). Only 2 patients had axillary failure in ALND+RLNR group, while 1 and 0 patients had this outcome in ALND alone and SLN+RLNR groups, respectively. The multivariable Cox model adjusted for tumor characteristics did not show any significant local tumor control difference between the groups.

Conclusion: In the largest screening trial of breast cancer patients who underwent serial, perometer-based pre- and postoperative arm measurements to date, the 5 years risk of BCRL was significantly lower in patients treated with SLNB and RLNR (8.5%), relative to ALND+/-RLNR (37% and 32%). These confirm AMAROS results and indicate that RLNR should routinely substitute the role of ALND in the regional nodal management of limited volume, sentinel node-positive breast cancer.

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A Prospective Phase I trial of Concurrent Cisplatin (CIS) and Radiation Therapy (RT) in Women with Stage II and III Triple-negative Breast Cancer (TNBC)

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Purpose/Objective(s): Patients with TNBC experience a higher rate of both in breast and regional nodal recurrence. CIS is an effective systemic chemotherapy in TNBC, and is also a radiation sensitizer. This prospective, phase Ib trial was designed to assess safety and toxicity and establish the recommended phase 2 dose of concurrent CIS with adjuvant RT for women with stage II and III TNBC.

Materials/Methods: Eligible patients had stage II or III TNBC. Any prior preoperative or adjuvant chemotherapy was permitted except CIS or carboplatin. Patients receiving preoperative therapy could not have a complete pathologic response. CIS was initiated at 10 mg/m² intravenously once weekly, then escalated in a classic 3 + 3 design by 10 mg/m² at each dose level until a dose of 40 mg/m², or maximum tolerated dose (MTD), was reached. Breast conservation (BCT) and mastectomy (M) patients were accrued in separate parallel cohorts in dose-escalation followed by a 10 patient expansion at the MTD for each group. During the escalation phase, all patients in each dose level were observed throughout the 8-week dose limiting toxicity (DLT) window prior to dose escalation. RT was delivered with conventional once-daily fractionation (1.8-2.0 Gy) to the breast or chest wall to 50-50.4 Gy followed by a 10 Gy lumpectomy site cone down (BCT) or 6-10 Gy incision boost (M) at the discretion of the radiation oncologist. Regional nodal radiation was also at the discretion of the treating physician (46-50.4 Gy).

Results: Fifty-five patients were accrued from 2013-2018. Four experienced a DLT. In the BCT cohort, one patient developed tinnitus at the maximum dose level of 40 mg/m² resulting in a cisplatin delay. This was therefore the BCT MTD. In the M cohort, three experienced a DLT. One patient, receiving 30 mg/m² CIS, was hospitalized for a grade 3 urinary infection. Two additional patients had DLTs at 40 mg/m²: one grade 3 neutropenia, and the other tinnitus, both resulting in delays in CIS. As a result, 30 mg/m² was the MTD for the M cohort. Two patients had breaks in radiation, (one day and three days; both hospitalized for infection). The most common adverse events in both cohorts were dermatitis (45% grade 2, 2% grade 3), leukopenia (15% grade 2, 15% grade 3), fatigue (15% grade 2), nausea (11% grade 2), ototoxicity and thrombocytopenia (each 7% grade 2). Only one patient (BCT cohort at 30 mg/m²) experienced grade 3 radiation dermatitis; there were no grade 4 skin reactions.

CIS was held (16%) or discontinued early (7%) in 13 patients. Median follow-up was 29.1 months. Three-year disease-free survival was 71% in the BCT cohort, and 70% among M patients.

Conclusion: Adjuvant radiation therapy with concurrent CIS is feasible with the MTD of 30 mg/m² and 40 mg/m² IV weekly in M and BCT patients, respectively. Additional study is necessary to determine the long-term benefits of concurrent treatment in this high-risk population.

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Central Nervous System

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Radiosurgery Compared To External Beam Radiotherapy for Localized Spine Metastasis: Phase 3 Results of NRG Oncology/RTOG 0631

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Purpose/Objective(s): This study aimed to compare pain relief between radiosurgery (SRS)/stereotactic body radiation therapy (SBRT) and conventional external beam radiation therapy (cEBRT) for patients with 1 to 3 sites of spine metastases.

Materials/Methods: In this open-label randomized phase 3 study, we enrolled patients with limited spine metastases involving 1-3 separate sites, each site involving up to 2 contiguous spine segments. Minimal epidural lesions at least a 3 mm gap from the spinal cord were included. The study randomly assigned patients to receive either SRS/SBRT 16 or 18 Gy in one fraction to the involved spine segment(s) or cEBRT 8 Gy in one fraction to the involved spine including one additional spine segment above and below the index level. The treatments were performed under robust protocol guidelines with central rapid review. The primary endpoint was pain control, defined as a ³³ point improvement on the Numerical

Rating Pain Scale (NRPS), at the treated spine segment at 3 months post-treatment. The study had 80% power with 352 patients to show a 40% improvement in pain response with 2:1 randomization in favor of SRS/SBRT.

Results: Of the 353 patients, 339 were eligible with 209 randomized to SRS/SBRT and 130 to cEBRT. The baseline mean pain score at the index spine site was 6.06 (standard deviation [SD]=2.61) in the SRS/SBRT arm and 5.88 (SD=2.41) in the cEBRT arm. The 3 month change in pain score at the index site was -3.00 (SD=3.34) in the SRS/SBRT arm compared to -3.83 (SD=2.97) in the cEBRT arm. There was no difference in pain response between SRS/SBRT and cEBRT at 3 months (40.3% vs. 57.9%, respectively, one-sided p=0.99). All the evaluable cases were planned per protocol or with an acceptable variation for delineation of target volume and organs at risk, as well as for dosimetric compliance on both arms. There was no significant difference between the treatment arms in rates of adverse events or in FACT-G, BPI and EQ-5D scores.

Conclusion: SRS/SBRT for spine metastases treating only the involved spine was safely performed without causing any increase in adverse effects, as compared to conventional EBRT treating to one additional vertebral body above and below the metastatic lesion(s). However, pain control at 3 months from the patient's perspective was not improved using SRS/SBRT, due to the lower pain control rate than expected in the SRS arm. **Acknowledgements:** This project was supported by grants UG1CA189867 (NCORP) and the Division of Cancer Prevention from the National Cancer Institute (NCI).

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Prospective Phase I Dose Escalation Study for Neoadjuvant Radiosurgery for Large Brain Metastases

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Purpose/Objective(s): Single session stereotactic radiosurgery (SRS) alone for brain metastases larger than 2cm in maximal dimension results in local control of only 50%. Surgical resection followed by SRS to the resection cavity can result in leptomeningeal failure (LMD). Neoadjuvant SRS followed by resection has been investigated as a dose de-escalation approach with good local control and without LMD. The purpose of this Phase I trial is to determine the maximum tolerated radiosurgery dose (MTD) for neoadjuvant radiosurgery for brain metastases larger than 2cm in maximal dimension.

Materials/Methods: Radiosurgery dose was escalated at 3 Gy increments from currently accepted RTOG dosing; and cohorts of 2-6 patients were treated at each dose. Initially 2 patients were treated at a particular dose and followed for 4 months. If no dose-limiting toxicities (DLT)

were observed the dose was escalated and a new cohort of 4 patients were treated. Patients underwent surgical resection of brain metastases within 2 weeks of SRS and were followed with brain MRIs and neurologic evaluations every 3 months.

Results: A total of 27 patients have enrolled on the trial. Median and mean follow up are 9.2 and 15.2 months, respectively. For tumor size >2.0 - 3.0 cm, 2 patients completed treatment at 18 Gy and 3 patients at 21Gy. For tumor size >3.0 - 4.0 cm, 4 patients were treated at 15 Gy and 9 patients were treated at 18 Gy and 1 patient at 21 Gy. For tumor size > 4.0 - 5.0 cm, 1 patient was treated at 12 Gy and 7 patients at 15 Gy. No DLT have occurred. MTD has not yet been met. Twenty-six patients were evaluable for acute toxicity. Twenty-two patients (85%) had no adverse events related to protocol treatment. Three patients had grade I fatigue or headaches and 1 patient had grade II fatigue possibly related to treatment. No patients have experienced radiation necrosis. 13 patients have died at time of analysis. The 6 and 12 month local control was 94.7% and 94.7%, respectively. Six and 12 month distant brain control was 71.7% and 49.6% respectively. Overall survival at 6 and 12 months was 81.5% and 54.9%, respectively. One patient developed LMD 5 months following SRS. Only one patient has received whole brain radiotherapy.

Conclusion: There are low rates of toxicity for neoadjuvant SRS with dose escalation followed by surgical resection for brain metastases greater than 2 cm in size. MTD has not yet been reached. Early results demonstrate excellent local control with low risk of LMD.

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Significant Preservation of Neurocognitive Function (NCF) and Patient-Reported Symptoms with Hippocampal Avoidance (HA) during Whole-Brain Radiotherapy (WBRT) for Brain Metastases: Final Results of NRG Oncology CC001

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Purpose/Objective(s): NRG Oncology CC001, a phase III trial of WBRT plus memantine (WBRT+M) with or without HA, sought to evaluate the neuro-protective effects of avoiding the hippocampus using intensity-modulated radiotherapy.

Materials/Methods: Patients (pts) with brain metastasis were stratified by RPA class and prior radiosurgery/surgery and randomized to WBRT+M or HA-WBRT+M (30Gy in 10 fractions). Standardized NCF tests were performed at baseline, 2, 4, 6, and 12 months (mos). The primary endpoint was NCF failure, defined as decline using the reliable change index on Hopkins Verbal Learning Test-Revised, Trail Making Test, or Controlled Oral Word Association. Patient-reported symptoms were assessed using the MD Anderson Symptom Inventory Brain Tumor module. Cumulative incidence estimated time to NCF failure (death without NCF failure was competing risk); between-arms differences tested

using Gray's test. Deterioration at each collection time point was tested using a chi-square test. Patient-reported symptoms were assessed using the MD Anderson Symptom Inventory Brain Tumor module and analyzed using mixed effects models and t-tests.

Results: From 7/2016 to 3/2018, 518 pts were randomized. Median age was 61.5 years. Median follow-up for alive patients was 7.9 mos. HA-WBRT+M was associated with lower risk of NCF failure (adjusted HR=0.74, 95% confidence interval (CI): 0.58-0.95, p=0.02). The difference was first seen at 4 months (62.7% HA-WBRT+M vs. 54.5% WBRT+M) and was attributable to improvements in executive function at 4 mos (p=0.01) and encoding (p=0.049) and consolidation (p=0.02) at 6 mos. Age≤61 predicted lower risk of NCF failure (HR=0.60, 95%CI: 0.46-0.79, p=0.0002); non-significant test for interaction indicated independent effects of HA and age on NCF. Patient-reported fatigue (p=0.036), difficulty speaking (p=0.049) and problems remembering things (p=0.013) at 6 mos favored the HA-WBRT+M arm. Imputation models accounting for missing data confirmed NCF results and also favored the HA-WBRT+M arm for patient-reported cognition (p=0.011) and symptom interference (p=0.008) at 6 mos. Toxicity, overall survival, and intracranial progression were not significantly different between the treatment arms.

Conclusion: Hippocampal avoidance during WBRT better preserves neurocognitive function and patient-reported symptoms, while achieving similar intracranial control and survival, and should be considered standard of care for patients eligible to receive WBRT and anticipated to live 4 months or longer. Data analyses for longer-term (12-mo) follow-up are planned for June 2019 and will be presented for the first time at the meeting. Supported by grants UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), DCP from the National Cancer Institute.

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Randomized Phase II Trial of Re-Irradiation and Concurrent Bevacizumab versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma (NRG Oncology/RTOG 1205):Initial Outcomes and RT Plan Quality Report

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University-Bethlehem, Bethlehem, PA, ⁹University of Miami, Miami, FL, ¹⁰University of Kentucky/Markey Cancer Center, Lexington, KY, ¹¹Norton Hospital Pavilion and Medical Campus, Shelbyville, KY, ¹²Massachusetts General Hospital, Boston, MA, ¹³Department of Radiation Oncology at Emory University, Atlanta, GA, ¹⁴University of Michigan, Ann Arbor, MI, ¹⁵Medical University of South Carolina, Charleston, SC, ¹⁶Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Purpose/Objective(s): RTOG 1205 is the first, multi-institutional, prospective randomized phase II trial to evaluate the safety and efficacy of re-irradiation for recurrent glioblastoma using modern radiation therapy (RT) techniques. We report clinical outcomes and results of the RT plan quality review.

Materials/Methods: Eligible patients (pts) were randomized 1:1 to hypofractionated reirradiation (HFRT, 35 Gy in 10 fractions) with concurrent bevacizumab (BEV) IV 10 mg/kg q2 wks vs. BEV alone. Primary endpoint was improved median survival time (MST) with BEV+HFRT. Modality treatment (MT) reviews included evaluation of target volume (TV) and normal tissue (NT) contouring, TV and NT dose volume histogram (DVH) evaluation, RT plan quality score and overall protocol score per protocol guidelines.

Results: From 11/2012 to 4/2016, 182 pts were randomized, of whom 170 eligible pts were analyzed. For the primary endpoint, no difference in MST was observed for BEV+HFRT, 10.1 mos vs. BEV, 9.7 mos, HR=0.98(CI=0.7-1.38, p=0.5) but improved 6-month progression free survival (PFS) rate (54% vs 29%, HR=0.42(CI=0.34-0.5, p=0.001) was demonstrated. Treatment was well tolerated with few study related grade (Gr) 3+ acute adverse events (AEs) (5%) and no delayed Gr 3+AEs. Majority of deaths was due to recurrent GBM. In the BEV arm, salvage radiation was reported in 12 patients. RT planning review was performed for all evaluable patients on the BEV+HFRT arm. For the BEV+HFRT arm, median GTV and PTV were 19 cc (0.4-208 cc) and 53 cc (4-411 cc), respectively. Mean plan conformity index was 1.18 (0.85-2.1). Majority of patients (80%) had previously received RT to the same treatment area. Overall protocol score per protocol guidelines for the HFRT retreatment group was achieved in 60% (38/65 pts) and 70% for the new treatment area group (11/16 pts). Primary RT protocol deviations included geometric miss, exceeded NT tolerance limits and GTV tumor size and inadequate TV minimum dose coverage, etc.

Conclusion: Recurrent GBM is a heterogeneous disease with limited therapeutic options. RTOG 1205 confirms the safety of re-irradiation with modern RT techniques. Overall, BEV+HFRT did not demonstrate a benefit in MST but was associated with an improved 6-month PFS. Role of BEV+HFRT should be limited to small volume recurrences especially in previously non-irradiated treatment areas at least 6 months following completion of previous RT. Due to treatment plan complexity, future re-irradiation GBM trials should require real time RT review.

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Comprehensive Prognostic and Predictive Molecular Subgroup Analysis within the High-risk Treatment Arms of NRG Oncology/RTOG 9802: a Phase III Trial of RT versus RT + PCV in High-risk Low-grade Gliomas

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Purpose/Objective(s): NRG Oncology/RTOG 9802, a phase III trial of high-risk low-grade gliomas (LGGs) treated with radiation (RT) with and without PCV after biopsy/surgical resection, was the first phase III study to demonstrate a treatment-related survival benefit for high-risk grade II patients. Using retrospectively collected tissues from NRG Oncology/RTOG 9802, this study is the first to comprehensively evaluate the prognostic and predictive value of the 2016 WHO molecular subgroups in LGGs using prospectively-collected, well-annotated long-term overall survival (OS) data.

Materials/Methods: Immunohistochemistry and/or next-generation sequencing was utilized to determine *IDH1/2* mutation status. Oncoscan and/or 450K array data was utilized to determine 1p/19q co-deletion status. Adjusted and unadjusted Cox proportional hazard models and log-rank tests were used to assess treatment effects on OS and progression-free survival (PFS) by marker status in a post-hoc analysis.

Results: Of the randomized high-risk grade II glioma patients from NRG Oncology/RTOG 9802, 106/251(42%) had sufficient quality DNA for profiling. The 2016 WHO molecular subgroup classification in our study was as follows: 43(41%) were *IDHmut/non-co-deleted*, 37(35%) were *IDHmut/co-deleted*, and 26(24%) were *IDHwt*. Regarding the prognostic multivariate analysis, the three molecular subgroups were significantly different for PFS [HR=0.22; 95% CI 0.12-0.41; p<0.001 (*IDHmut/co-del* vs *IDHwt*); HR= 0.49; 95% CI 0.29-0.85; p=0.012(*IDHmut/non-co-del* vs *IDHwt*)], and for one comparison for OS [HR=0.19; 95% CI 0.09-0.40; p<0.001 (*IDHmut/co-del* vs *IDHwt*); HR= 0.66; 95% CI 0.36-1.22; p=0.186(*IDHmut/non-co-del* vs *IDHwt*)]. The median survival times (MSTs) for the subgroups were 1.9 years (*IDHwt*), 6.9 years (*IDHmut/non-co-del*), and 13.9 years (*IDHmut/co-del*). Regarding predictive analyses, both *IDHmut/non-co-deleted* (MST = 4.3yrs vs 11.4yrs) and *IDHmut/co-deleted* (MST = 13.9yrs vs not reached) subgroups received benefit from the addition of PCV. The *IDHwt* group received no detectable benefit from PCV (MST = 1.9yrs vs 2.1yrs).

Conclusion: This study supports the independent statistical significance of the prognostic 2016 WHO classification relative to historical histopathological characterization and other common clinical variables utilizing samples from a phase III clinical trial with long-term follow-up survival data with limited sample size. Importantly, this post-hoc analysis demonstrates that both IDH-mutant subgroups had longer survival times with the addition of PCV regardless of co-deletion status. FUNDING: U10CA180868, U10CA180822, and U24CA196067. Also, R01CA108633, R01CA169368, RC2CA148190, U10CA180850-01, BTFC, OSU-CCC (all to AC).

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Microstructural Injury to Perisylvian White Matter Predicts Language Decline after Brain Radiotherapy [RT]: Quantitative Analysis of a Prospective Trial

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Purpose/Objective(s): Perisylvian white matter [WM] is involved in language functioning. Impairments in expressive and receptive language are common in brain tumor patients. We hypothesized that changes in volume and diffusion biomarkers, reflecting WM injury, within perisylvian WM would predict for language decline after brain RT.

Materials/Methods: On a prospective trial, 41 patients with primary brain tumors underwent high resolution volumetric brain MRI, diffusion weighted imaging, and neurocognitive testing prior to and 3, 6, and 12 months post RT. Automated image segmentation parcellated WM in bilateral perisylvian regions (WM tracts associated with Broca's Area, Wernicke's Area, and Arcuate Fasciculus [AF] which connects these areas). Tumor, tumor bed, surgical scars and edema were manually censored. At each time point, we quantified volume and diffusion biomarkers of injury (fractional anisotropy [FA]: decrease reflects WM damage; mean diffusivity [MD]: increase reflects WM injury) within each region. Language was assessed with Boston Naming Test [BNT] and Delis-Kaplan Executive Function System Category Fluency subtest [DKEFS CF]. DKEFS CF reliable change indices accounting for practice effects [RCI-PE] were calculated from 0 to 6 months; one sample t-test evaluated for group decline. Associations between RCI-PE scores and covariates were assessed by independent samples t-test, one-way ANOVA, and Pearson correlation. Linear mixed effects [LME] models assessed imaging biomarkers (volume, FA, MD) as longitudinal predictors of language scores while controlling for time. Statistical significance was set at $\alpha=0.05$.

Results: Language performance in DKEFS CF significantly declined at 6 months post RT (mean RCI-PE -0.62, $p<0.01$). Change in language scores was not associated with patient age, sex, highest education level, tumor location, diagnosis, chemotherapy, or antiepileptic treatment. On LME analysis, atrophy ($p<0.01$) and decreased FA ($p<0.01$) within left sided Wernicke's was associated with worse performance on DKEFS CF. Similarly, left Wernicke's atrophy ($p=0.01$) and decreased FA ($p=0.03$) was associated with decline in BNT. Decreased FA of left sided Broca's was a predictor for worse DKEFS CF ($p<0.01$) but only approached significance for BNT ($p=0.09$). Left sided AF atrophy ($p=0.01$), decreasing FA ($p<0.01$), and increasing MD ($p=0.01$) were predictors for worse DKEFS CF. Declining BNT was associated with left AF atrophy ($p<0.01$), decreasing FA ($p=0.01$), and increasing MD ($p<0.01$). Right sided perisylvian tracts did not significantly predict language scores.

Conclusion: Brain tumor patients show significant language decline post-RT. Microstructural injury and atrophy in left sided perisylvian WM tracts predicted for worse language function over time. These regions represent potential targets for dose-avoidance to preserve language function.

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A Single Blind Randomized Controlled Trial of Hippocampal Avoidance on Neurocognitive Outcomes after Conformal Whole Brain Radiotherapy for Brain Metastases: An Initial Analysis

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Purpose/Objective(s): The potential benefit of hippocampal avoidance in preservation of neurocognitive function after whole brain radiotherapy (WBRT) has never been investigated in a prospective blinded randomized controlled trial. The present randomized phase II trial aimed to validate the neuro-protective hypothesis in Mandarin- or Taiwanese Hokkien-speaking patients with brain metastases.

Materials/Methods: Adult patients with brain metastases were stratified by prior radiosurgery and randomized to hippocampal-avoidant conformal WBRT (HA-cWBRT) versus conformal WBRT without hippocampal avoidance (cWBRT) to 30 Gy in 10 fractions. Memantine was

not used during or after WBRT. Standardized neurocognitive test battery (Hopkins Verbal Learning Test-Revised [HVLt-R], Trail Making Test [TMT], and Controlled Oral Word Association [COWA]) was performed at baseline, 1, 2, 4, 6, and every 3 months up to two years by trained independent health professionals. Both clinical trial participants and examiners were blinded to the treatment group assignment. The primary endpoint was the difference in changes of HVLt-R delayed recall at 4 months from baseline between HA-cWBRT and cWBRT.

Results: From March 2015 to November 2018, 70 patients (pts) were enrolled, and 65 pts (33 pts with HA-cWBRT; 32 pts with cWBRT) completed protocol treatment with a median follow-up time of 6.5 months. The median age was 59.5 years old, and the majority (95%) had lung cancer. No differences in age, gender, or baseline neurocognitive function existed between two arms. Twenty-three pts in each arm at 4 months, 15 pts in HA-cWBRT arm and 17 pts in cWBRT arm at 6 months were compliant with protocol neurocognitive test battery. There are no differences in any neurocognitive assessments between two arms at 4 months. At 6 months, pts received HA-cWBRT had favorable perpetuation of HVLt-R total recall (mean \pm standard error of mean [SEM] change of raw score from baseline: $+2 \pm 1.26$ versus -1 ± 0.97 , $p=0.08$), and significantly better preservation of HVLt-R recognition-discrimination index (mean \pm SEM change of raw score from baseline: 0.6 ± 0.54 versus -1.4 ± 0.62 , $p=0.03$) compared to pts had cWBRT. There are no differences in TMT part A or B between two arms at any time point. In pts survived 12 months or longer, it is noteworthy that cWBRT had significantly superior COWA scores than HA-cWBRT.

Conclusion: Initial analysis demonstrates patients received hippocampal-avoidant conformal whole brain radiotherapy without memantine have better preservation in late verbal memory, but not in verbal fluency or executive function. Placebo effect might contribute to the failure of primary endpoint due to unexpected favorable neurocognitive outcomes after conformal WBRT.

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Leucoencephalopathy after Prophylactic Whole Brain Irradiation with or without Hippocampal Sparing: A Long-Term MRI Analysis

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Purpose/Objective(s): Radiation-induced leucoencephalopathy of the brain typically occurs months to years after brain radiation therapy. After whole-brain irradiation most patients will develop leucoencephalopathy of varying degree and the respective cognitive deficits affecting key brain functions such as memory, executive function, attention and concentration. Recently, hippocampal avoidance (HA) has been shown to reduce the negative effects of WBRT. As HA is achieved at the cost of a significantly higher brain dose, we thought to investigate the long-term effects of HA-WBRT on the rate and degree of leucoencephalopathy.

Materials/Methods: Twenty SCLC patients receiving either hippocampus avoidance prophylactic cranial irradiation (HA-PCI) (n = 10) or lateral-opposed field cranial irradiation (non-HA-PCI) (n = 10) were matched on an age-based basis. Pre-therapeutic magnetic resonance imaging (MRI) and regular follow-up MRI starting approximately 6 months after radiation therapy were analyzed. Based on the Fazekas classification, the degree of leucoencephalopathy was scored on T2-Flair MRI in all patients independently and blinded by two radiation oncologists and one neuro-radiologist. In addition, dosimetric parameters for brain parenchyma, including Dmax, Dmean, V26 Gy and V25 Gy, were analyzed. T1 MRI sequences were segmented using Freesurfer 5.3 (Martinos Center, Charlestown, MA, USA). For each patient, 37 bilateral and 11 central/median subcortical structures were segmented and analyzed for volume changes using age-matched two-sided t-tests.

Results: The average age of all patients was 62 years. Significant differences amongst dosimetric and volumetric parameters were observed favoring non-HA-PCI: Dmax ($p = 0.002$) and V25Gy ($p = 0.02$) were higher in the HA-PCI compared to the non-HA-PCI group and HA-PCI patients presented smaller volumes of the medial frontal ($p = 0.04$) and pars orbitalis white matter ($p = 0.05$) compared with 3D-PCI patients. The

Fazekas classification differed significantly ($p = 0.0067$) between the two groups during first follow-up: in the HA-PCI group the mean value of the Fazekas score was 2.0 versus 0.6 in the non-HA-PCI group. Furthermore, a significant increase of the Fazekas score over time after PCI was observed in the HA group comparing pre- and post-treatment MRIs ($p = 0.0011$). This effect was not observed in patients treated without HA.

Conclusion: Although the RTOG 0614 trial reported preservation of short-term neurocognitive function by HA-WBRT, our results demonstrate that long-term radiological changes are more pronounced after HA-PCI compared to 3D-PCI. Although no neurocognitive testing was performed in our patients, the increasing Fazekas score after HA-WBRT could indicate potential negative long-term effects. Long-term neurocognitive investigation from the prospective studies should be performed before HA-PCI is implemented in routine clinical practice.

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Gastrointestinal

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A Pilot Study of Neoadjuvant FOLFIRINOX followed by Chemoradiation for Gastric and Gastroesophageal Cancer: Preliminary

Results and Prognostic Implications of ctDNA

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Purpose/Objective(s): We performed a single-arm pilot study of neoadjuvant FOLFIRINOX and chemoradiation (CRT) with concurrent carboplatin/paclitaxel followed by surgery in patients with locally advanced gastric or gastroesophageal (GEJ) cancer.

Materials/Methods: Patients were enrolled on an NCI sponsored, prospective, single arm study (NCT03279237). Key eligibility criteria included: histologically confirmed T3/4 or lymph node (LN) positive gastric or GEJ adenocarcinoma, ECOG PS ≤ 1 , and life expectancy > 3 months. Extensive LN disease beyond the surgical field (supraclavicular or para-aortic) was permitted if deemed able to be encompassed within the RT field. Pts received neoadjuvant FOLFIRINOX x 8, restaging, CRT (45 Gy for gastric, 50.4 Gy for GEJ) with concurrent C/T, restaging, followed by resection. Serum ctDNA was measured at baseline, prior to CRT, and preoperatively. Tumor genotyping was performed on all pre-treatment specimens to identify mutations in the primary tumor, and mutation-specific droplet digital PCR was used to detect mutation fraction in ctDNA. The primary objective was to determine the rate of completion of FOLFIRINOX x 8 followed by CRT delivered in the preoperative setting. Secondary endpoints included: 1) acute toxicity and 2) pathologic complete response (pCR), and 3) correlation of ctDNA to treatment response. Fisher's exact test was applied to determine predictive value of ctDNA to treatment response.

Results: From Oct 2017 to June 2018, 25 pts were enrolled. Median age was 60 (range:30-76), and 17 pts were male (68%). All pts started FOLFIRINOX, and 23 pts were able to complete all 8 planned cycles. Two pts did not complete the planned 8 cycles due to metastatic progression. Rates of grade 3+ toxicity for overall, gastrointestinal, and hematologic were 28, 12, and 28% respectively. Of the entire cohort, 23 pts started chemoRT and 22 pts completed chemoRT (1 pt died during CRT due to PEA arrest). All 22 pts who completed CRT went for surgical exploration. Of the 22 pts (88%) who went for surgical exploration, 2 pts were found with intraoperative metastases. Thus, in total, 20 (80%) pts underwent surgical resection all with R0 resection. In total, 7 pts had a pCR (35% in resected cohort, 28% in ITT cohort). In the entire cohort, tumor specific mutations were identified in 21 patients (84%) for ctDNA. Of the 21 patients with evaluable ctDNA levels, 3 patients had undetectable ctDNA at baseline (defined as 0) and 18 had detectable ctDNA. Although not significant due to low power, undetectable ctDNA

was associated consistently with higher rate of pCR compared to detectable ctDNA at all-time points (67% vs. 28% at c1D1, p=0.24, 50% vs. 11% at c1D8, p=0.16, and 46% vs. 20% at post-CRT, p=0.6).

Conclusion: Neoadjuvant FOLFIRINOX followed by CRT is feasible with acceptable grade 3+ toxicity. In our small series, the rate of pCR is promising and a follow-up study is currently planned. Although our current study had limited events, ctDNA appears to be a promising predictor of pCR.

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Patterns of Recurrence in the Critics Gastric Cancer Trial: Results from Intention-to-Treat and per-Protocol Analyses

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Purpose/Objective(s): The aim of this study is to describe patterns of recurrence in patients with resectable gastric cancer treated with preoperative chemotherapy, surgery, and postoperative chemotherapy or chemoradiotherapy in the international multicenter randomized phase III CRITICS trial.

Materials/Methods: Event-free survival and patterns of recurrence were determined for 788 patients with adenocarcinoma of the stomach who were randomized to perioperative chemotherapy (CSC), or preoperative chemotherapy, surgery and postoperative chemoradiotherapy (CSCRT). Event-free survival was defined as time from randomization until progressive/recurrent disease (disease progression before surgery, irresectable disease at surgery, or tumor recurrence after potentially curative resection) or death from any cause. Sites of progressive or recurrent disease were categorized as locoregional, peritoneal, distant or occurring at multiple sites. The log-rank test was used to compare event-free survival between the two study arms. Time to first site-specific event accounted for competing risks and was summarized as cumulative incidences. Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed.

Results: Of the 788 patients (393 in the CSC and 395 in the CSCRT arm) included between 2007 and 2015, 636 (81%) patients (310 in the CSC and 326 in the CSCRT arm) underwent surgery with curative intent, and 478 (61%) patients (233 in the CSC and 245 in the CSCRT arm) started postoperative treatment. In the CSC arm 180 (46%) patients and in the CSCRT arm 197 patients (50%) completed the entire treatment. Median follow-up was 6.1 years at the time of analysis and 488 patients experienced an event (240 patients in the CSC arm and 248 patients in the CSCRT arm). Event-free survival rates at 2 and 5 years were 52% vs. 51% and 39% vs. 39% (CSC arms vs. CSCRT arm; stratified log-rank p = 0.94). The 2-year and 5-year cumulative incidences of progressive/recurrent disease were comparable between CSC and CSCRT (ITT analysis). Locoregional recurrence was detected within 2 years in 16% of patients (7% locoregional only + 9% in combination with another site) in the CSC

arm vs. 16% of patients (5% locoregional only + 11% in combination with another site) in the CSCRT arm. The PP analysis showed significant differences in peritoneal events. Significantly less peritoneal metastases were seen in the CSC arm compared to the CSCRT arm.

Conclusion: Cumulative incidences of progressive/recurrent disease were comparable between CSC and CSCRT in the intention to treat analysis. In the per protocol analysis, however, significant differences were seen in peritoneal events. The impact of these findings on outcome will be discussed.

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The Genomic Landscape of Anal Cancer and Its Relationship to Clinical Outcomes: An Exploratory Analysis of NRG Oncology/RTOG 98-11

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Purpose/Objective(s): While precision oncology has yielded remarkable insights regarding targeted therapy and immunotherapy, its relevance for chemoradiation (CRT) remains less well defined. CRT is the standard of care for localized anal cancer (AC). However, the genomic landscape of AC is poorly characterized. We hypothesized that tumor genomic features might be associated with AC prognosis and/or response to CRT.

Materials/Methods: Whole exome sequencing (WES) was performed on tumors from patients (pts) enrolled on NRG/RTOG 98-11, a phase III trial of concurrent radiation therapy (RT) + mitomycin C (MMC)/5FU vs. induction cisplatin/5FU followed by concurrent RT + cisplatin/5FU for localized AC. Mutations were called via MuTect and MutSigCV algorithms and copy number alterations via GATK CNV and GISTIC algorithms with false discovery rate (FDR) correction. These genomic findings were correlated with clinical data.

Results: Of 341 pts in the MMC arm, 64 had tumor DNA available and 62 underwent successful WES. WES of the cisplatin arm is ongoing. Baseline characteristics and clinical outcomes did not differ significantly between MMC cases that did vs. did not undergo WES. Known cancer genes significantly mutated in the MMC arm included the PI3 kinase (PI3K) pathway members PIK3CA (29%, FDR $q=0.001$) and PTEN (6.5%, $q=0.038$); EP400 (18%, $q=0.020$), a chromatin remodeling protein previously implicated in modulation of HPV oncogenicity; and FBXW7 (15%, $q=0.026$), a ubiquitin ligase tumor suppressor also mutated in other squamous cell carcinomas. Median tumor mutational burden was 5.8 non-synonymous mutations per megabase (min-max: 2.9-22.9). Chromosome 3q29 (harboring PIK3CA) was amplified in 50% of samples ($q<0.001$). EP400 mutations were associated with younger age at diagnosis (mean 45.5 y \pm 4.8 vs. 58.6 y \pm 10.6, $p=0.002$); no recurrently mutated cancer

genes were associated with T stage, N stage, or sex. On Cox multivariable analysis with T stage, N stage, and sex, FBXW7 mutations were associated with significantly inferior DFS (HR 2.47 [1.02-5.96], p=0.045) and a trend towards inferior OS (HR 2.61 [0.97-7.04], p=0.058).

Conclusion: These results represent the most comprehensive genomic characterization of AC to date and, uniquely, are contextualized with clinical data from a phase III trial. Clinical-genomic analysis of the MMC arm of NRG/RTOG 98-11 revealed frequent alterations in the PI3K pathway and an association between EP400 mutations and younger age; moreover, FBXW7 mutations were associated with inferior outcomes. WES of the cisplatin arm is ongoing and will provide additional power to detect genomic events and clinical associations. These hypothesis-generating results suggest that profiling clinical trial specimens with modern sequencing-based approaches may help advance genomically-informed, precision oncology approaches for pts treated with CRT.

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ctDNA As a Potential Prognostic Marker for Locally Advanced Rectal Cancer Patients Receiving Neoadjuvant Chemo-Radiation Therapy on Disease-Free Survival (DFS)

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Purpose/Objective(s): Neoadjuvant chemo-radiation therapy (nCRT) plus surgery is the standard treatment for patients with locally advanced rectal cancer (LARC). However, how to predict and select patients who may achieve clinical complete response is still an unsolved issue. We conducted a pilot study to evaluate the potential role of ctDNA as a biomarker to predict treatment outcome. We found that ctDNA clearance was related to TRG level in previous studies. Now we try to explore using ctDNA as a prognostic factor and improve risk stratification in locally advanced rectal cancer (LARC).

Materials/Methods: In this study, we recruited 119 patients with LARC receiving nCRT. 595 serial plasma samples were collected at d0, d15, d25 of radiotherapy as well before and 7 days post surgery. The level of ctDNA was calculated by dynamic monitoring the mutant allele frequency of somatic mutations in plasma. Plasma and tissue samples were subjected to targeted-NGS using a 422 cancer-related genes panel. We followed up patients with concomitant CT until disease progression or death.

Results: Serial samples' data analysis showed detection of pre-treatment mutations after completion of nCRT was significantly associated with worse disease-free survival (DFS) (P<0.05). Patients with ctDNA mutations clearance during nCRT significantly have a better DFS compare with patients with ctDNA non-clearance (P=0.02). The presence of TP53 mutations is predictive of treatment outcome and shows a statistically significant worse DFS (2 years) (54.3% VS 87.0%, P=0.0005). Predictive model based on support vector machine was developed for prediction of pCR achieving a mean AUC of 0.85 assessed by repeated cross validation. Through tracking clonal extinction, persistence and emergence, patients were grouped into four evolutionary subtypes with distinct TRG and DFS.

Conclusion: Our data showed the prognostic value of ctDNA on DFS. In patients treated with nCRT, the presence of ctDNA after completion of nCRT was associated with an inferior DFS (P=0.02). Dynamic monitoring of ctDNA can be used to predict TRG and prognosis in LARC patients receiving nCRT. ctDNA sequencing depicts the evolutionary trajectories of sensitive and resistant clones during nCRT in LARC. CtDNA could potentially be used to guide patient selection for nCRT.

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Patient-Derived Organoids (PDO) As the Potential Model to Predict Treatment Outcome of Rectal Cancer Patients Underwent Neo-Adjuvant Chemoradiotherapy

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Purpose/Objective(s): Recent researches showed patient-derived organoids (PDO) could recapitulate main features of the primary tumors, and could be used as in vitro clinical model to predictive outcome in clinical setting. Here, we have launched the observational investigation to prove whether the PDO radiosensitivity could predict the clinical outcome in locally advanced rectal cancer (LARC) patients (pts) underwent neo-adjuvant chemoradiotherapy (nCRT) in locally advanced rectal cancer (LARC).

Materials/Methods: Primary tumor tissues of LARC pts for PDO culture were collected by rectal biopsy before any treatment. Rectal cancer cells were isolated and cultured following established protocols for PDO culture and expansion. PDOs were exposed to 8Gy X-rays at 246 cGy/min, 5-fluorouracil (10 μ M) and CPT-11 (10 μ M), respectively, and PDO images were captured every 3 days in the following 24 days. PDO radiosensitivity and drugs sensitivity was determined by ROC area changes. Tumor response to neoadjuvant therapy was evaluated according to the pathological tumor regression grading (TRG). Finally, PDO radiosensitivity and drug sensitivity data compared with clinical patients outcome.

Results: We established 34 rectal adenocarcinoma organoids from 40 pts with 85% success rate. RCO data showed 23, 25 and 17 pts' organoids were resistant, while 11, 9 and 13 pts' organoids were sensitive to irradiation, 5-fluorouracil and CPT-11 treatment, respectively. All of the 34 pts received surgery (total mesorectal excision) and got the pathologic TRG data, or achieved clinical complete response (cCR). Clinical data showed 19 pts achieved good response (TRG=0 or 1, or cCR), and other 15 pts had poor response (TRG= 2 or 3). Through comparative analysis, RCO radiosensitivity and drug sensitivity (5-fluorouracil and CPT-11) were concordant with clinical outcome in 76.5% (26/34), 70.6% (24/34) and 70% (21/30) pts, respectively. In consideration of combined treatment in clinic, chemoradiation responses in patients are highly matched to RCO responses, with 86.70% sensitivity, 94.70% specificity, 92.90% positive predict value, 90.0% negative predict value and 91.20% accuracy.

Conclusion: The patient-derived organoids' radiosensitivity correlates to clinical outcome and indicated that organoid model may be used to predict TRG and prognosis in LARC patients receiving nCRT. PDO may be potentially used as a biomarker to for treatment stratification and worth study further.

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Improved Stratification for Risk of Early Metastases by Baseline Circulating Tumor Cell Counts for Locally Advanced Rectal Cancer in Neoadjuvant Setting: an Exploratory Analysis from a Phase III trial

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Purpose/Objective(s): Although local control is improved for locally advanced rectal cancer (LARC) in neoadjuvant setting with total mesorectal excision, the treatment is far from satisfactory since lack of survival benefit and distant metastases (DM, about 25%) remains unsolved. Circulating tumor cells (CTCs) is a prognostic factor in metastatic colorectal cancer. The aim of this study is to investigate whether CTCs may improve the stratification for risk of metastases in patients with LARC.

Materials/Methods: This multicenter, phase II/III randomized trial (NCT02533271) was designed to compare short-term preoperative radiotherapy (SCPRT, 5 Gy x 5 alone) followed by neoadjuvant chemotherapy (4 cycles of XELOX regimen) with preoperative long-term chemoradiotherapy (CRT, 2 Gy x 25 with capecitabine) for middle-lower LARC. The primary endpoint was 3-year disease-free survival. CTCs detected by tumor-selective replication herpes simplex virus-based technology at different stages of treatment was planned for exploratory analysis. Kaplan-Meier method and Cox Proportional Hazards (CPH) model was utilized to analyze the factor associated with DM.

Results: Peripheral blood samples for CTCs detecting were collected from 83 patients before any treatment (Median follow-up = 17 months), and CTCs were present in 76 patients (91.6%) (median CTSs = 3). The baseline characteristics and treatment assignment were well balanced between high risk group and low risk group by CTCs (Partially presented in Table 1, besides, age, gender and TNM stage were comparable between two groups). CTCs risk group was the only significant factor correlated with metastasis-free survival (MFS) (high risk vs. low risk, 61.7 % vs. 89.7% at 18-month, *P*=.006, log-rank test). When most important baseline variables entered the CPH model (Table 2), the CTCs risk group remained independent factor for DM (HR, 4.54; 95% CI, 1.56 to 13.69, *P*=.007), and this ability was shown consistently in subgroup of 62 patients received surgery (HR, 8.42; 95% CI, 1.73 to 40.80, *P*=.008).

Conclusion: We have demonstrated an association between baseline CTCs and early DM for patients with LARC in neoadjuvant setting. This stratification tool may strengthen the pretreatment risk assessment for patients with LARC.

Table 1. Characteristics of patients (n=83)				Table 2. CPH model for DM (n=83)			
Variable	Low risk group CTC≤3,n=43 (No. (%))	High risk group CTC>3,n=40 (No. (%))	<i>P</i>	Factor	HR	95% CI	<i>P</i>
Middle Located Tumor	13 (30.2)	8 (20.0)		Age ≥60	.54	.15 to 1.88	.33
Lower Located Tumor	30 (69.8)	32 (80.0)	.32	Gender	.68	.22 to 2.12	.51
mrEMVI negative	20 (46.5)	18 (45.0)		Tumor lower location	.50	.18 to 1.40	.19
mrEMVI positive	23 (53.5)	22 (55.0)	1.00	EMVI positive	1.40	.49 to 3.94	.53

SCPRT with neoadjuvant chemotherapy	24 (55.8)	18 (45.0)	MRF positive	.84	.29 to 2.40	.74
CRT	19 (44.2)	22 (55.0)	.38 N2 stage by MRI	1.39	.50 to 3.87	.53
Surgery margin positive	1 (2.9)	5 (17.9)	CRT vs. SCPRT+chemotherapy	.75	.29 to 1.97	.56
Surgery margin negative	34 (97.1)	23 (82.1)	.08 CTCs >3	4.54	1.53 to 13.70	.007

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Multicenter Phase II Study of Stereotactic Ablative Radiotherapy for Hepatocellular Carcinoma ≤ 5 cm (KROG 12-02)

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Purpose/Objective(s): To evaluate the efficacy of stereotactic ablative radiotherapy (SABR) for hepatocellular carcinoma (HCC) ≤ 5 cm.

Materials/Methods: A total of 54 patients with unresectable HCC showing an incomplete response after 1-5 sessions of transarterial chemoembolization were enrolled in a phase II clinical trial of SABR from 6 institutions between July 2012 and June 2015. SABR was delivered with a total dose of 60 Gy in 3 fractions within 14 days, with ≥ 48 hour-intervals between each fraction. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiation-induced liver disease (RILD) was analyzed at 2 months. Survival outcomes were analyzed with the Kaplan-Meier method. This trial is registered with Clinical Trials.gov, number NCT01825824.

Results: Forty-eight patients were evaluable with a median follow-up of 41 months (range, 2-61 months). The median tumor size was 2.0 cm (range, 1.0-4.5 cm) and most patients (89.6%) had a single lesion. Thirty-six patients (75%) received TACE ≤ 2 times. Local control rate at 2 and 5 years were 97.4% and 94.7%, respectively. Overall survival rate at 2 and 3 years were 90.9% and 78.3%, respectively. Progression-free survival rate at 2 and 3 years were 50.3% and 27.0%, respectively. One patient experienced non-classic RILD with acute toxicity at 2 month after SABR.

Conclusion: The high-dose SABR for HCC ≤ 5 cm is and effective as evidenced by the high rates of tumor control, overall survival, and acceptable treatment-related toxicity.

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Evaluating the Impact of Combination of Nivolumab and Ipilimumab to Liver/Lung SBRT on Local Control for Colorectal and Pancreatic Cancer: A Pooled Analysis of Two Prospective Trials

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Purpose/Objective(s): Immunotherapy (IO) has emerged as an effective treatment option for many metastatic cancers, however, its role in pancreatic or colorectal cancer is limited to those with microsatellite instability. It has been suggested that radiation (RT) and combination IO may work synergistically to increase the immune system's exposure to tumor antigens, potentiating an abscopal effect. However, the impact of combination IO to stereotactic body radiation therapy (SBRT) on local control of irradiated lesions has not been elucidated.

Materials/Methods: In this study, we combined two prospective phase II single arm studies to compare the impact of SBRT alone (NCT01239381) or with PD-L1/CTLA4 blockade (NCT03104439) on the growth of colorectal and pancreatic liver and lung metastases. Eligible patients had metastatic colorectal or pancreatic adenocarcinoma. Those treated on NCT01239381 received liver SBRT alone (30-50 Gy in 5 fractions), while those on NCT03104439 received combination IO 6 weeks prior to and concurrently with 24 Gy in 3 fractions to liver or lung metastases. Tumor genotyping was performed to assess for KRAS and TP53 mutations. Target lesions were measured on CT scans prior to and following RT. Peak response was measured via modified RECIST criteria as the largest tumor reduction at any time. Wilcoxon Rank Sum tests were performed to evaluate % tumor reduction with regards to combination IO, primary tumor site, metastasis site, and KRAS and TP53 mutation status.

Results: There were 50 eligible patients from NCT01239381 and 41 from NCT03104439, of whom 42 and 39 were evaluable, respectively. Of these 81 patients, 52 and 29 had colorectal and pancreatic cancer, respectively. Of those with molecular analysis, 50% (33/66) had a KRAS mutation and 55% (34/61) had a TP53 mutation. Median follow up was 78 days in the IO arm (driven by distant progression) and 160 days in the non-IO arm (P<0.0001). Mean BED in the IO arm was 43.2 Gy vs. 79.6 Gy in the SBRT alone arm (P<0.0001). Mean target size was 3.8 cm in the IO arm, and 5.0 cm in the SBRT alone arm (P=0.12). There was no difference with respect to overall response rate (38.5% vs. 52.4%, P=0.27) and disease control rate (92.3% vs. 92.9%, P>0.99). There was no significant difference in the % tumor reduction between the IO and non-IO arms (-21% vs. -41%, P=0.08). Among the entire cohort, there was no significant difference in response of irradiated lesion with respect to primary tumor type (P= 0.54), KRAS status (P=.67), TP53 status (P=0.10), or metastatic site (P=0.58).

Conclusion: Despite receiving approximately half the BED dose compared to liver SBRT alone, patients treated with IO and RT had similar response rates, suggesting a potential synergistic effect in the irradiated lesions. Future studies should look to validate these findings and explore optimal RT dose/fractionation schemas in combination with IO. These results support ongoing randomized studies of IO with RT in locally advanced rectal (NRG GI002) and pancreatic (NCT03563248) cancers.

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Genitourinary

LBA 1

Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy: A Secondary Analysis of the NRG Oncology/RTOG 9601 Randomized Phase III Trial

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Purpose/Objective(s): Salvage radiation therapy (SRT) is recommended for men with biochemically recurrent prostate cancer post-radical prostatectomy. RTOG 9601 was a randomized phase 3 clinical trial that demonstrated an overall survival (OS) benefit from the addition of long-term anti-androgen therapy to SRT. However, hormone therapy has well documented side effects and has been shown to increase cardiac event rates, and there remains no evidence of an OS benefit from hormone therapy for men treated with early SRT. Herein, we aim to determine if pre-SRT PSA can serve as both a prognostic and predictive biomarker of benefit or harm from hormone therapy.

Materials/Methods: A secondary analysis of the NRG Oncology/RTOG 9601 double-blind, placebo-controlled randomized trial was conducted (NCT00002874). Patients were treated between 1998-2003 at over 100 centers across North America. Men with adverse pathology (positive surgical margin or pathologic T3 disease) and a PSA of 0.2-4.0 ng/mL were enrolled. Patients were stratified by entry PSA (0.2-1.5 vs >1.5-4.0 ng/mL). Men were randomized to either SRT plus a nonsteroidal anti-androgen (bicalutamide 150mg/day) or placebo for two years. The primary endpoint was OS. Secondary endpoints relevant to the present analysis include distant metastasis (DM) and other-cause mortality (OCM). Subgroup analyses were performed using the pre-specified PSA stratification variable (1.5 ng/mL) including tests for interaction. Competing risk analyses were performed for DM and OCM.

Results: Of 760 patients, 85% (n=642/760) were in the pre-SRT PSA of ≤ 1.5 ng/mL stratum. There was no significant OS benefit with bicalutamide in men with PSA ≤ 1.5 ng/mL (HR 0.87 [95%CI 0.66-1.16]), whereas in men with PSA > 1.5 ng/mL (n=118) OS was significantly improved (HR 0.45 [0.25-0.81]). Interaction test of PSA and hormone therapy benefit for OS was significant (p=0.02). Within the PSA ≤ 1.5 ng/mL subgroup, men with pre-SRT PSA ≤ 0.6 ng/mL (n=389) had increased OCM (sHR:1.94, [1.17-3.20]) from bicalutamide which was greatest in men with PSA 0.2-0.3 (n=148; sHR:4.14 [1.57-10.89]). There was also increased grade 3-5 cardiac events in those treated on the bicalutamide arm (p=0.04). The present subgroup analysis met 8 of 10 criteria for the reliability and credibility of this subgroup analysis.

Conclusion: Pre-SRT PSA is both a prognostic and true predictive biomarker for benefit of hormone therapy with SRT. Long-term anti-androgen therapy did not improve OS in patients receiving early SRT, and may increase OCM. Ongoing trials are enrolling to identify which patients receiving early SRT will benefit from hormone therapy (NRG GU006, NCT03371719).

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GenomeDx. : PFS Genomics. Oversee clinical trials in GU cancers in this cooperative group; Radiation Therapy Oncology Group. **M. Schipper:** None. **H.M. Sandler:** Stock; Advanced Medical Isotope Corporation. **Y. Sun:** None. **W.U. Shipley:** None.

A Phase III Multi-Centre Randomised Trial comparing adjuvant versus early salvage Radiotherapy following a Radical Prostatectomy: Results of the TROG 08.03 and ANZUP “RAVES” Trial

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Purpose/Objective(s): Adjuvant radiotherapy (ART) has been shown to nearly halve the risk of biochemical failure (BF) for high risk post prostatectomy patients. The RAVES trial aimed to test the hypothesis that observation with early salvage radiotherapy (SRT) is not inferior to ART with respect to biochemical failure in patients with high risk disease after radical prostatectomy (RP).

Materials/Methods: Eligible patients needed to have either extraprostatic extension, seminal vesicle invasion (SVI) or positive surgical margins (PSM) and have a postoperative PSA ≤ 0.10 ng/ml. Patients were randomised 1:1 to either ART commencing within 6 months of RP or close observation with early SRT triggered by a PSA level of ≥ 0.20 ng/ml. RT plans were reviewed in real time and utilised 3D CRT or IMRT/VMAT to a dose of 64Gy/32# to the prostate bed alone without androgen deprivation (AD). Primary aim was to exclude a 10% inferiority in Freedom from Biochemical Failure (FFBF) in the SRT arm corresponding to 5-year FFBF rates of 74% (ART) and 64% (SRT) and a hazard ratio (HR) of 1.48. BF was defined as a PSA rise to 0.40 or higher or commencement of AD after RT. Analysis was on an intention to treat basis.

Results: 333 patients were randomised (n=166 ART; n=167 SRT) across 32 institutions in Australia and New Zealand between March 2009 and December 2015. Median follow up was 6.1 years. The Independent Data Monitoring Board recommended that enrolment close early based on interim analyses showing that further recruitment to reach the target of 470 was unlikely to substantially increase power due to an unexpectedly low event rate. Mean age in both arms was 63 years. 16% in ART had a high Gleason Score (8-10) compared with 15% in SRT. SVI was seen in 19% of ART and 20% with SRT. PSM occurred in 66% of ART and 68% of the SRT groups. 84 SRT patients (50.3%) had their PSA rise to 0.2, triggering SRT, of which 80 received SRT. The 5 year FFBF rates were 86% (95% CI [79%, 91%]) in the ART arm compared with 88% (95% CI [82%, 92%]) in the SRT arm. The 8 year rates were 79% with ART (95% CI [68%, 87%]) and 76% (95% CI [65%, 84%]) with SRT. The hazard ratio for the SRT arm was 1.03 (90% CI [0.65, 1.63], p=0.91). The corresponding 90% range in absolute difference between SRT and ART at 5 years was from SRT 5.8% inferior to SRT 5.1% superior. Six percent of patients in the ART arm developed evidence of local, regional or distant failure by 8 years compared with 5% in the SRT group. The grade 2+ GU toxicity rate was lower in the SRT arm (OR 0.34, 95% CI [0.17, 0.68], p=0.002) with no significant difference in grade 2+ GI toxicity rate (OR 0.48, 95% CI [0.047, 4.88], p=0.53).

Conclusion: Similar FFBF rates were shown between ART and SRT, but we did not meet the protocol defined level set for non-inferiority. SRT spares approximately half of men from pelvic radiotherapy, and is associated with significantly lower levels of GU toxicity.

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Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy with Brachytherapy Boost: Comparison of Outcomes in A Multi-Institutional Analysis of 4,086 Patients with High-Risk Prostate Cancer

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Purpose/Objective(s): The optimal treatment strategy for patients with high-risk prostate cancer (PCa)--defined as lesions associated with PSA>20, clinical T stage≥3, or Gleason grade group (GG) 4-5 disease--remains highly controversial. The National Comprehensive Cancer Network guidelines recommend external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT, 2-3 years), EBRT with a brachytherapy boost (EBRT+BT) with ADT (1-3 years), and radical prostatectomy (RP) with or without postoperative therapy as standard options. We hypothesized that EBRT+BT would be associated with improved outcomes compared with EBRT or RP in general, but restriction to patients receiving standard-of-care and/or multimodality treatment (i.e., appropriate ADT and postoperative radiotherapy, respectively) would reduce this benefit.

Materials/Methods: Four-thousand-and-eighty-six patients with high-risk PCa treated between 2000-2013 across ten institutions were included. Patients were stratified into six treatment groups: RP alone (378), RP with postoperative therapy (233, "MaxRP"), EBRT with <2 years ADT (1211), EBRT with ≥2 years ADT (744, "MaxEBRT"), EBRT+BT with <1 year ADT (915), and EBRT+BT with ≥1 year ADT (605, "MaxEBRT+BT"). Fine-Gray competing risks regression models with the inverse probability of treatment weight (IPTW) were used to compare distant metastasis (DM) and prostate cancer specific mortality (PCSM) outcomes across groups. Propensity scores included age-at-treatment, initial PSA, clinical T stage, and GG as covariates.

Results: The overall median follow-up was 6.6 years (interquartile range, 3.9-9.5 years). Seventy-five percent had GG 4-5 disease, 33% had PSA>20, and 23% had clinical T stage≥3. Prior to treatment substratification, EBRT+BT was associated with significantly improved DM and PCSM outcomes over RP and improved DM outcomes over EBRT. EBRT was associated with improved PCSM but not DM outcomes over RP. When limiting the comparison to patients receiving "optimal" treatments, MaxEBRT+BT was associated with improved DM outcomes compared with MaxRP or MaxEBRT, but PCSM outcomes were not different. MaxEBRT was associated with improved time to DM, but not time to PCSM, when compared with MaxRP.

Conclusion: While limited by the retrospective study design, these results underscore the critical importance of postoperative treatment after RP and use of appropriate duration of ADT with EBRT. The conserved, albeit blunted, benefit of EBRT+BT even after accounting for optimal treatment warrants further investigation. Table 1. Subdistribution Hazard Ratios from Competing Risk Models

Comparison	DM	PCSM
All EBRT vs All RP	1.19 (0.99-1.44)	0.52 (0.38-0.70)*
All EBRT+BT vs All RP	0.18 (0.14-0.24)*	0.37 (0.27-0.50)*
All EBRT+BT vs All EBRT	0.15 (0.13-0.19)*	0.71 (0.55-0.91)*
MaxEBRT vs MaxRP	0.42 (0.30-0.60)*	0.70 (0.36-1.38)
MaxEBRT+BT vs MaxRP	0.16 (0.11-0.25)*	0.88 (0.46-1.70)
MaxEBRT+BT vs MaxEBRT	0.39 (0.27-0.57)*	1.26 (0.84-1.90)

*p<0.05

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Development and Validation of the First AJCC Compliant Clinical Staging System for Localized Prostate Cancer: Results from a Multicenter International Study

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Purpose/Objective(s): The American Joint Committee on Cancer (AJCC) Precision Medicine Core recently established criteria to evaluate prediction models for incorporation into staging. All previously developed models for localized prostate cancer were excluded from the AJCC 8th edition, primarily because endpoints other than survival were used, and staging was devised through expert opinion. We therefore sought to develop the first AJCC compliant staging system for use in localized prostate cancer.

Materials/Methods: Eligible patients had T1-4N0-1M0 prostate cancer treated between 1992-2013 with radical prostatectomy (RP) or radiotherapy (either external beam (EBRT) and/or brachytherapy with or without androgen deprivation therapy (ADT)). Over 50 centers provided data, including centers in the USA, Canada, and Europe, and across academic, community, and Veterans Affairs medical centers. Patients with M1 disease or PSA>200 ng/ml, and those with preoperative ADT were excluded. The final cohort was randomly split into training and validation sets. An *a priori* statistical plan was utilized, and statisticians were blinded to the validation cohort until a locked training model was developed. The primary endpoint was prostate cancer-specific mortality (PCSM) treating non-cancer death as a competing-risk. Model discrimination (C-index), calibration, and overall performance (Integrated Brier Score R-squared (IBSR2)) were assessed at 3-, 5-, 10- and 15-years with 10-year results reported below.

Results: A total 19,684 men were included, of which 12,421 were treated with RP, 5942 with EBRT, and 1321 with brachytherapy (+/-EBRT). Median follow-up was 72 months (range, 1-289 months), and 4078 were followed for at least 10 years. Novel cut points and groupings were identified that are not currently used in existing prognostic systems, including age, PSA, and percent positive cores. In the new score model, nine tiers were identified (Stage Ia-c, IIa-c, and IIIa-c), and predicted 10-year PCSM ranged from 0.3% to 40%. In the validation set, 10-year discrimination for the new system (C-index 0.796) were superior to the AJCC 8th edition (0.757); overall performance (IBSR2 0.048) was also improved over AJCC 8th edition (IBSR2 0.035). The new staging system was also superior to AJCC 8th edition across primary treatment modality (surgery, EBRT, brachytherapy), age, and race.

Conclusion: Using a large, diverse international cohort treated with standard curative treatment options with long term follow up, we have developed and validated the first AJCC compliant clinical staging system for prostate cancer that is superior in each metric to the current AJCC 8th edition and is ready for AJCC committee evaluation.

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Patient Reported Acute Toxicity in PACE-B, an International Phase III Randomised Controlled Trial Comparing Stereotactic Body Radiotherapy to Conventionally Fractionated or Moderately Hypofractionated Radiotherapy (CFMHRT) for Localised Prostate Cancer

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Purpose/Objective(s): External beam radiotherapy (EBRT) is one of several curative treatment options for localised prostate cancer (LPCa). Moderate hypofractionation of EBRT (2.5–3Gy per fraction (f)) has been shown non-inferior to conventional 2 Gy/f by multiple large randomised controlled trials (RCTs). Low and comparable rates of clinician reported acute toxicity have been reported in the Stereotactic Body Radiotherapy (SBRT) and CFMHRT treated groups in PACE-B. This study reports patient reported outcomes (PRO) for bladder and bowel, related to acute toxicity.

Materials/Methods: PACE (NCT01584258) is a phase III, open-label, multiple-cohort RCT. Patients eligible for the PACE-B cohort had LPCa, stage T1-T2, \leq Gleason 3 + 4, PSA \leq 20 ng/mL and were either unsuitable for surgery or chose EBRT. Randomisation was 1:1 between SBRT (36.25Gy/5f over 1-2 weeks (wks)) or CFMHRT (78Gy/39f over 7.5 wks or 62Gy/20f over 4 wks, determined by centre's standard schedule). Androgen deprivation therapy was not allowed. PRO metrics included: Expanded Prostate Cancer Index Composite 26 (EPIC-26) at baseline, 2, 4, 12 wks post radiotherapy (RT); International Prostate Symptom Score (IPSS) at baseline, 2, 4, 8, 12 wks post-RT. The proportion of patients with EPIC-26 change scores (baseline to 12 wks) greater than minimum clinically important differences (MCID) in each subdomain (urinary incontinence (UI) 8 points, urinary obstructive (UO) 6 points, bowel 5 points) are reported. IPSS total scores were categorised as none, mild, moderate, severe and compared between SBRT and CFMHRT at 12 weeks. Comparisons between SBRT and CFMHRT were based on chi-squared tests with $p < 0.01$ considered statistically significant.

Results: Between 07/12/2012 and 04/01/18, 38 centres randomised 874 pts: 431 received CFMHRT; 414 SBRT. Patient and disease characteristics were similar between CFMHRT and SBRT: mean age: 69.5 vs 69.3 years; Intermediate risk: 91.4% vs 92.5%; T-stage \geq T2b: 51.7% vs 56.6%; Gleason Score 3+4: 80.7% vs 85.5%; PSA 10-20 ng/mL: 30.9% vs 31.6%. EPIC MCID deteriorations, for CFMHRT vs SBRT, occurring by subdomain were: UI 67/326 (20.6%) vs 51/323 (15.8%), $p=0.12$; UO 108/313 (34.5%) vs 105/306 (34.3%), $p=0.96$; bowel 91/322 (28.2%) vs 90/323 (27.9%), $p=0.91$. Proportion of patients with baseline none/mild/moderate/severe IPSS symptoms were CFMHRT: 5.4%/51.1%/37.3%/6.2% and SBRT: 4.5%/54.5%/35.6%/5.4%. At 12 weeks no differences were seen in IPSS scores between CFMHRT and SBRT: 2.8%/57.9%/36.8%/2.5% vs 3.4%/54.8%/36.7%/5.1% ($p=0.34$, test for trend).

Conclusion: These data corroborate the prior clinician-reported acute toxicity findings for bladder and bowel outcomes, with no significant differences in key PRO measures.

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Accelerating Prostate Stereotactic Ablative Body Radiotherapy (SABR): Efficacy and Toxicity of a Randomized Phase II Study of 11 Versus 29 Days Overall Treatment Time (PATRIOT Study; ClinicalTrials.gov NCT01423474)

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Purpose/Objective(s): The experience and use of stereotactic ablative body radiotherapy (SABR) for the treatment of prostate cancer is increasing. Reported regimens differ in time, dose, and fractionation. We report an update of a multicentre, Canadian randomized phase II study to investigate the impact of overall treatment time on efficacy, PSA kinetics and late toxicity. The quality of life data has been published previously.

Materials/Methods: Men with cT1-2b (no MRI staging used), Gleason ≤ 7 , and PSA ≤ 20 ng/mL prostate cancer were randomized 1:1 to 40 Gy in 5 fractions delivered every other day (11 days) vs. once per week (29 days) using gantry-based SABR and gold-seed based image guidance. Late toxicity (≥ 6 mo) was graded by RTOG criteria; biochemical failure (BF) was defined by nadir ≥ 2 ng/ml. Cumulative incidence of BF, use of salvage therapies, late GI and GU toxicities were calculated. PSA nadir, time to PSA nadir, PSA response rate at 4 years (4yPSARR), overall survival (OS), cause specific survival (CSS) and metastases-free survival (MFS) are also presented.

Results: A total of 152 men (13%, 58%, 29% with low, favorable intermediate and unfavorable intermediate prostate cancer) from 3 centres were randomized (77 to 11d arm; 75 to 29d arm); median follow-up was 62 months. Results are described for 11d vs. 29d. Of baseline characteristics, only median IPSS was different: 4 vs 7 ($p=0.02$). 5% and 4% used short-term androgen deprivation. There were 1 (1.3%) vs 3 (2.7%) late grade 3+ GI toxicities ($p=0.36$) and 5 (6.7%) vs 2 (2.7%) late grade 3 GU toxicities ($p=0.44$). Median PSA nadir was 0.1 ng/ml in both arms (median time to nadir 54mo). 4yPSARR were 76 vs 82% ($p=0.42$). 2 and 5 patients had BF (5-year failure rate 3.0 vs 7.2%, $p=0.22$); 0 and 4 patients received salvage therapy ($p=0.04$). 5-year OS and CSS was 95.8% and 98.6% with no difference between arms ($p=0.49$, $p=0.15$). 0 vs 3 patients developed metastases; 5-year MFS 100% vs 95.8% ($p=0.08$)

Conclusion: Prostate SABR was well tolerated and effective in the medium term. There were no differences observed in toxicities, BF, PSA kinetics or survival outcomes between the 11 and 29 day regimens.

Outcome	11 day arm n=77 (%)	29 day arm n=75 (%)	p-value
Baseline median IPSS	4	7	0.02
Androgen deprivation therapy use	4 (5.2%)	3 (4.0%)	ns
Late grade 3+ GI toxicity	1 (1.3%)	3 (2.7%)	0.36
Late grade 3 GU toxicity	5 (6.7%)	2 (2.7%)	0.44
Median PSA nadir	0.1	0.1	ns
4yPSARR	76%	82%	0.42
5-year cumulative BF	2 (2.6%)	5 (7.2%)	0.22
Use of salvage therapy	0 (0%)	4 (5.3%)	0.04
5-year MFS	100%	95.8%	0.08

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High Dose-Rate Prostate Brachytherapy as Monotherapy: a Single Fraction May Not be Enough

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Purpose/Objective(s): Fractionated high dose-rate (HDR) brachytherapy as monotherapy provides high cancer control rates for men with low and intermediate risk prostate cancer. Based on radiobiological modelling, a single fraction of 19 Gy was predicted to provide similar outcomes. Our purpose is to report clinical and biochemical control rates with 19 Gy x 1 or 13.5 Gy x 2 in a single centre randomized trial.

Materials/Methods: Eligible patients had NCCN low or intermediate risk disease, a prostate volume < 60 cc, International Prostate Symptom Score (IPSS) of 18 or less and no use of androgen deprivation therapy. Patients were randomized to receive either 19 Gy HDR as a single fraction (1F), or 27 Gy in 2 fractions one week apart (2F). Treatment was delivered using an out-patient ultrasound-based technique. Relative dosimetry was similar between arms with median prostate V100, V150, V200 and D90 of 97%, 35%, 11.4% and 110%, respectively. Follow-up with toxicity assessment, physical examination and serum prostate specific-antigen (PSA) level occurred at week 6, week 12, every 3 months for the first year, every 6 months until year 5, and annually thereafter. Biochemical failure was defined as nadir + 2 ng/ml. Rising PSA was investigated with CT, MRI, bone scan and in some cases PSMA PET. Local recurrence was confirmed by biopsy.

Results: A total of 170 patients were randomized between June 2013 and April 2015: 87 to 1F and 83 to 2F arms. Median age was 65 years, median PSA was 6.3 ng/ml and 72% had Gleason 7 cancer. NCCN low, favourable intermediate and unfavourable intermediate was present in 28%, 49% and 23%, respectively, with similar distribution between arms. Median follow-up was 51 months (range 24-68 months). PSA decreased more rapidly in the 2F arm, with median PSA at 5 years of 0.75 and 0.21 ng/ml in the 1F and 2F arms, respectively. Clinical or biochemical failure occurred in 22 patients – 20 in the 1F arm and 2 in the 2F arm, with a 5-year biochemical disease-free survival of 74.5% and 97.3%, respectively (Log Rank p=0.002). Most recurrences were local (16/20) in the 1F arm, while only one of the recurrences in the 2F arm had a local component. The 5-year cumulative incidence of local failure was 25.7% in the 1F and 2.6% in the 2F arm (p<0.0001). Of the local failures, 14 underwent salvage treatments: 7 with brachytherapy, 6 with prostatectomy and 1 with HIFU. On Cox analysis, biochemical failure was not associated with clinical stage, risk group, Gleason or baseline PSA. Distant metastases-free survival was 98% at 5 years.

Conclusion: Despite linear quadratic considerations, single fraction 19 Gy is inferior to two fractions of 13.5 Gy, which appears to be highly effective. Single fraction 19 Gy is associated with an unacceptable rate of local failure. As recurrence is predominantly at the site of initial bulk disease, further dose escalation either focally to the dominant nodule or to the whole gland may be considered in a clinical trial.

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A Biochemical Definition of Cure Following Brachytherapy for Prostate Cancer: A Multi-Institution International Study

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Purpose/Objective(s): 14,496 patients with localized prostate cancer from 7 participating international institutions were treated with low-dose-rate (LDR) brachytherapy (BT), either alone as monotherapy (n=11,578), combined with androgen deprivation therapy (ADT) (n=1,965), combined with external beam radiotherapy (EBRT) (n=498), or combined with both ADT and EBRT (n=455). The objective was to determine whether a population can be defined that is *cured* based on long-term outcomes at 10 and 15 years after LDR BT using a surgical definition of biochemical failure, PSA \leq 0.2, as a biomarker.

Materials/Methods: Analysis was based on PSA measured at 4 years (minimum follow-up of 3.5 years, range 3.5-4.5 years, n=9,011) post-treatment in patients who have not experienced clinical failure (CF). PSA measurements prior to the interval of interest were excluded, as were patients who failed clinically prior to the interval. Kaplan-Meier (KM) analysis was carried out using CF (local, distant, or regional) as endpoint for each of 4 PSA categories: PSA \leq 0.2 ng/ml, PSA >0.2 to \leq 0.5 ng/ml, PSA > 0.5 to \leq 1.0 ng/ml, and PSA>1.0 ng/ml. Results were validated through analysis of a prospective phase II trial of LDR BT alone for patients with intermediate-risk localized prostate cancer.

Results: The patients were distributed by risk category as 39% low-risk, 52% intermediate-risk, and 9% high-risk. The results of KM analysis are set out in the table below (95% CI in parentheses): The association of treatment success with PSA range was highly significant (p<0.0005). Over 2600 patients remained in follow-up beyond 10 years and >350 beyond 15 years; 93% maintained PSA \leq 0.2 10-15 years post-treatment. Analysis of the phase II study of LDR BT alone (all intermediate risk) showed that 99.4% of patients with a PSA \leq 0.2 were NED at 10 years post-treatment, with 95% CI (95.8%-99.9%).

Conclusion: Patients with a PSA \leq 0.2 ng/ml at 4 years post-treatment following LDR BT have >99% chance of remaining disease-free beyond 10 years. As this applies to more than 80% of patients in this study and has been validated in a prospective clinical trial cohort, we suggest that PSA \leq 0.2 ng/ml be adopted as the biochemical definition of cure for LDR BT patients with \geq 4 years follow-up.

PSA range	Number of patients in PSA range after 4 years	%NED @ 10 y (238 CFs)	%NED @ 15 y (195 CFs)
PSA \leq 0.2	7407	99.3(99.0-99.5)	98.2(97.2-98.8)
0.2<PSA \leq 0.5	811	96.0(93.8-97.4)	86.8(78.4-92.1)
0.5<PSA \leq 1.0	306	88.6(83.0-92.4)	81.9(70.7-89.2)
PSA>1.0	487	61.0(54.6-66.8)	50.1(40.7-58.8)

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Hypo-Fractionation in Muscle-Invasive Bladder Cancer: An Individual Patient Data (IPD) Meta-Analysis of the BC2001 and Bcon Trials

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Purpose/Objective(s): There are two radiotherapy (RT) fractionation schedules used in the UK for treatment of MIBC: 64Gy in 32 fractions (f) given over 6.5-weeks and a hypo-fractionated schedule of 55Gy in 20 f over 4-weeks. Using an α/β ratio of 10, the EQD2 of 55Gy/20f is only 58.4Gy but the biological effect may be greater than this if the α/β is lower and the shorter overall treatment time reduces the effects of repopulation. The long term outcomes of several studies suggest that response, survival and toxicity of the two schedules are comparable, but there is no published direct comparison. This work was aimed to assess whether 55Gy/20f is non-inferior to 64Gy/32f in terms of invasive loco-regional control (ILRC) (pre-specified non-inferiority (NI) margin hazard ratio (HR)=1.25), and late bladder and bowel toxicity in MIBC patients (pre-specified NI margin for absolute difference 10%). Secondary endpoints included overall survival.

Materials/Methods: Individual patient data (IPD) were obtained from two prospective multicenter randomized controlled trials: BC2001 (NCT00024349), which assessed addition of chemotherapy to RT, and BCON (NCT00033436), which investigated adding hypoxia-modifying therapy to RT. In both trials fractionation schedule (64Gy or 55Gy) was according to local standard practice. One-stage IPD meta-analysis models both for time to event (ILRC/OS) and binary outcomes (toxicity) were used. Trial differences and clustering due to within-center correlation were accounted for in the models, as well as adjustment for randomized treatment received, baseline imbalances and potential confounding from relevant prognostic factors.

Results: 782 patients (456 BC2001 326 BCON; 376 64Gy 406 55Gy) were included (mean age 72 years, 80% stage T1/2); median follow-up was 120 months. Both trials showed consistent benefit in ILRC by the addition of a radiosensitiser (combined HR 0.65, 95% confidence interval (CI) [0.49, 0.87]). Patients who received 55Gy had a 29% lower risk of invasive ILRR than those who received the 64Gy schedule (adjusted HR=0.71, [CI 0.52, 0.96]); this benefit was seen when analysis was restricted to patients receiving RT alone (adjusted HR 0.72 [CI 0.49-1.05]). No differences in OS were found (adjusted HR=0.87, CI [0.72, 1.06]). The 2 fractionation schedules had a similar toxicity profile, with a difference in absolute risk of experiencing a grade 3 or 4 late bladder or rectum symptom of -3.82%, CI [-11.88%, 4.24%]).

Conclusion: In this IPD meta-analysis, the hypo-fractionated 55Gy/20f schedule was non-inferior to conventionally fractionated 64Gy/32f in terms of ILRC, OS and late toxicity. Superiority of 55Gy over 64Gy was shown for ILRC but not OS. Results indicate that hypo-fractionated RT is a safe and effective alternative to conventional RT in the primary treatment of MIBC.

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Gynecologic

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Patterns of Recurrence and Survival in the Randomized Portec-3 Trial of Chemoradiotherapy for High-Risk Endometrial Cancer

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Purpose/Objective(s): Women with high-risk endometrial cancer (HREC) are at increased risk of recurrence. The PORTEC-3 trial investigated the benefit of adjuvant chemotherapy during and after radiation therapy (CTRT) versus pelvic radiation therapy alone (RT) for women with HREC. In the present analysis we updated outcomes, focusing on patterns of recurrence, and survival and on results for serous cancers.

Materials/Methods: Women with HREC (FIGO-stage I grade 3 with deep myometrial invasion and/or LVSI; stage II or III; or serous/ clear cell histology) were randomized (1:1) to CTRT (two cycles of cisplatin 50 mg/m² in week 1&4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m² at 3-week intervals) or RT alone (48.6 Gy in 1.8 Gy fractions). The co-primary endpoints were overall survival (OS) and failure-free survival (FFS). Secondary endpoints vaginal, pelvic and distant recurrence were analyzed according to first site of recurrence. The Kaplan-Meier method, log-rank test and Cox regression analysis were used according to intention-to-treat, and competing risk methods for FFS and recurrence. Analysis of the primary endpoints was adjusted for the stratification factors (participating group, lymphadenectomy, stage of cancer and histological type). PORTEC-3 is registered with ISRCTN (ISRCTN14387080) and ClinicalTrials.gov (NCT00411138).

Results: 686 women were enrolled between 2006 and 2013; 26 were excluded for immediate informed consent withdrawal or ineligibility, leaving 660 patients in the final analysis, 330 CTRT and 330 RT. Median follow-up was 72.6 months (IQR 59.9-85.6). 5-year OS was 81.4% vs 76.1% for CTRT vs RT [HR 0.70, 95% CI 0.51-0.97, p=0.034], and 5-year FFS was 76.5% vs 69.1% [HR 0.70, 95% CI 0.52-0.94, p=0.016]. Women with serous cancers had significantly lower OS compared with other histologies (62.0% vs 81.9% at 5 years), while 5-year OS for serous

cancer was 71.4% with CTRT vs 52.8% with RT [HR 0.48, 95% CI 0.24-0.96, p=0.037], and 5-year FFS was 59.7% vs 47.9% [HR 0.42, 95% CI 0.22-0.80, p=0.008]. For women with stage III disease an absolute 5-year OS improvement of 10% (HR 0.63, 95% CI 0.41-0.99, p=0.043) and FFS improvement of 12.5% at (HR 0.61 (95% CI 0.42-0.89, p=0.011) was found with CTRT. Distant metastases were the first site of recurrence in the majority of patients, 21.4% (CTR) vs 29.1% (RT) (p=0.047), and most patients received chemotherapy for recurrence. Survival after recurrence was 1.2 vs 1.4 years (p=0.7). Pelvic control was high in both arms with isolated vaginal or pelvic recurrence in only 1.2%.

Conclusion: This updated analysis with median FU of 6 years showed a significantly improved OS and FFS with combined adjuvant chemotherapy and radiation therapy for HREC. The largest improvement was found for women with stage III and/or serous cancers. Shared decision making remains essential to weigh the costs and benefits for individual patients.

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IMRT Improves Late Toxicity Compared to Conventional RT: An Update on NRG Oncology-RTOG 1203

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Purpose/Objective(s): To determine if there is a reduction in patient-reported adverse events (AEs) or differences in disease outcome with intensity-modulated radiation therapy (IMRT) compared to conventional 4-field pelvic radiation (CRT).

Materials/Methods: Patients with cervical and endometrial cancer who received postoperative pelvic radiation were randomly assigned to CRT or IMRT. The primary endpoint was change in patient-reported acute gastrointestinal (GI) AEs from baseline to 5 weeks measured by the bowel domain of Expanded Prostate Cancer Index Composite (EPIC). Change in EPIC score was calculated such that a negative change score indicated a decline in function from baseline. Secondary endpoints included a comparison of patient-reported GI AEs using PRO-CTCAE GI question set, urinary AEs using the urinary domain of EPIC, and QOL using the FACT-G. A Wilcoxon test was used for non-normal data. Log-rank tests were used for survival data and Gray's test was used for time to failure data in the presence of competing risks (death without a failure).

Results: There were 289 patients enrolled between 2012 and 2015; 10 patients were found to be ineligible, leaving 279 eligible patients. Median follow-up for all patients was 37.8 months. There were no differences in overall survival (HR=0.76, 95% CI:0.32-1.79, p=0.53), disease-free survival (HR=1.39, 95% CI:0.82-2.35, p=0.21), or local-regional failure (2-year rate of 2.6%, 95% CI:0.7-6.9, IMRT vs. 1.4%, 95% CI: 0.3-4.6,

CRT, $p=0.81$). There was no statistically significant difference in mean change in EPIC Bowel summary score at 1 and 3 years between arms. At 1 year post-RT there was no significant difference in the mean change in EPIC Urinary summary score between the arms. At 3 years post-RT, however, the CRT arm showed a worsening in the mean change score compared to 1-year post-RT (-1.7 at 1 year vs. -6.0 at 3 years), signifying a decline in urinary function with further follow-up, while the IMRT arm continued to show improvement from 1 year to 3 years post-RT (-1.8 to 0.5, respectively). This improvement in the IMRT arm compared with the CRT arm at 3 years is statistically significant (mean change score of 0.5, $SD=13.0$ vs. -6.0, $SD=14.3$, respectively, $p=0.005$). At 1 year post-RT, the CRT arm experienced more high-level diarrhea frequency measured by the PRO-CTCAE (5.8% IMRT vs. 15.1% CRT, $p=0.042$). There was also a significant difference at 1 year in the number of women having to take antidiarrheal medication 2 or more times a day (1.2% IMRT vs. 8.6% CRT, $p=0.036$). These differences in GI AEs disappeared at 3 years post-RT.

Conclusion: We previously reported that IMRT reduces acute patient-reported GI and GU AEs compared with CRT. This analysis shows that IMRT also reduces patient-reported GI AEs and urinary AEs at 1 and 3 years of follow up, respectively. Additionally, there is no difference in treatment efficacy with IMRT, although further followup is needed.

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Nomograms Predicting Overall Survival in Locally Advanced Cervical Cancer treated by Image Guided Brachytherapy: a Retro-EMBRACE study

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Purpose/Objective(s): To present a nomogram for prediction of overall survival (OS) in locally advanced cervical cancer pts (LACC) undergoing definitive radiochemotherapy (RCT) including image guided adaptive brachytherapy (IGABT).

Materials/Methods: 720 pts with LACC treated with RCT including IGABT in 12 institutions (median follow-up 56 mths) were analyzed; 248 deaths occurred. Based on literature and expert knowledge, 13 candidate predictors for OS were a priori chosen. Missing data (7.2%) were imputed by multiple imputation and predictive mean matching. Univariate analyses (UA), multivariable Cox regression model (m-Cox) for OS stratified by center were applied to test for statistical significance and display the effect size with hazard ratios (HR). Stepwise selection of predictive factors with the Akaike information criterion (AIC) was used to obtain a predictive model and to construct a nomogram for OS

predictions 60 months from diagnosis. This was internally validated by concordance probability as a measure of discrimination and a calibration plot (both corrected for optimism using bootstrap cross-validation).

Results: 13 potential predictive factors were evaluated; 10 reached statistical significance in UA (table 1) while histopathology, parametrial involvement and hydronephrosis did not reach significance. Four factors were confirmed significant with m-Cox, through the predictive model (AIC), seven factors selected to develop the nomogram, with satisfactory calibration and useful discrimination (concordance probability $c=0.74$).

Conclusion: This is the first nomogram to predict OS in LACC patients treated with IGABT. In addition to previously reported factors such as age, FIGO stage, corpus involvement, chemotherapy delivery, overall treatment time (OTT) and lymph node involvement, response to EBRT and chemotherapy (volume of CTV_{HR} at first BT) seems to be an essential outcome predictor. These results may facilitate individualized patient counseling during the treatment. **Table 1:** *Significant results ($p<0.05$), +Highly significant results ($p<0.001$), Hazard Ratio (HR), Confidence Interval (CI)

Variable		UA HR and 95% CI	m- Cox HR and 95% CI	Stepwise selection (AIC) HR
Age	linear squared	1.02 [1.01, 1.03] ⁺	0.95 [0.89, 1.02] 1.00 [1.00, 1.00]	0.93 1.001
Hemoglobin (diagnosis)	g/dl	0.86 [0.79, 0.94] ⁺	0.98 [0.88, 1.08]	-
FIGO Stage	2B vs.1A,1B,2A	1.73 [1.16, 2.57]*	1.62 [0.98, 2.67]	1.50
	3A,3B,4A,4B vs.1A,1B,2A	4.15 [2.76, 6.25] ⁺	3.24 [1.80, 5.83] ⁺	2.53
Tumour width (MRI)	mm	1.02 [1.01, 1.03] ⁺	1.00 [0.99, 1.01]	-
Corpus involvement	yes vs. no	1.48 [1.10, 1.98]*	1.17 [0.85, 1.60] ⁺	1.20
Lymph nodes	N1 vs. N0	1.47 [1.13, 1.89] ⁺	1.46 [1.10, 1.94]*	1.40
Concurrent chemo.	yes vs. no	0.52 [0.39, 0.69] ⁺	0.59 [0.40, 0.87]*	0.64
OTT	months	1.02 [1.01, 1.03] ⁺	1.01 [1.00, 1.02]	1.01
CTV_{HR} Volume (BT)	cm ³	1.02 [1.01, 1.02] ⁺	1.01 [1.01, 1.02] ⁺	1.02
CTV_{HR} D90	Gy	0.97 [0.96, 0.98] ⁺	0.99 [0.98, 1.00]	-

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Purpose/Objective(s): To evaluate sexual activity and vaginal functioning in patients treated in the prospective, observational, multi-center EMBRACE study (An international study on MRI-guided brachytherapy in locally advanced cervical cancer).

Materials/Methods: From 2008-2015, 1416 patients from 22 centers were included in EMBRACE and treated with combined external beam radiotherapy ± chemotherapy and image-guided adaptive brachytherapy following the GEC-ESTRO recommendations. Sexual outcomes were prospectively assessed using the EORTC-QLQ-CX24 questionnaire at baseline (available for 1027 patients) and follow-up (FU) every 3 months year 1, every 6 months years 2-3, every 12 months thereafter (available for 1044 patients with no evidence of disease). Sexual activity was analysed longitudinally, and defined as frequent sexual activity if reported to some degree in ≥50% of FU and as occasional if reported in <50%. Crude incidence rates of vaginal functioning problems during sexual activity (dryness, shortness, tightness and pain) at baseline and during FU were calculated if reported as “quite a bit” or “very much” (substantial symptoms). Association between vaginal shortening and tightening was evaluated with Spearman’s rank correlation, pooling observations over all FU (N=2669).

Results: After the diagnosis of cancer, but prior to treatment, 230/1027 (22.4%) of patients reported some degree of sexual activity. During FU (median 36 months), 433/1044 (41.5%) patients reported no sexual activity, 128 (12.3%) occasional and 483 (46.3%) frequent sexual activity. Prior to treatment, vaginal dryness, shortening, tightening and pain during intercourse were reported by 7.1%, 2.9%, 4.8% and 10.5% of patients, respectively. During follow-up these sexual functioning problems (crude incidence) increased to 38.4%, 36.4%, 34.2% and 33.5%, respectively. The median sexual enjoyment over all FU for individual patients was “quite a bit” / “very much” in 55.6%. Vaginal shortening and tightening during intercourse were significantly correlated (Spearman’s rho 0.661; 19% tightening alone, 25% shortening alone, 56% both).

Conclusion: More than half of the patients responding to the EORTC questionnaire are sexually active after treatment and the majority report frequent sexual activity. Sexual functioning problems are reported in around one third of patients and sexual enjoyment is compromised in almost half of sexually active patients. This underlines the importance of efforts directed towards prevention of vaginal morbidity and sexual rehabilitation after treatment.

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Comparison of Concurrent Cisplatin Chemoradiotherapy Plus Adjuvant Chemotherapy Versus Concurrent Chemoradiotherapy Alone in Locally Advanced Cervical Cancer

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Purpose/Objective(s): According to NCCN guidelines, concurrent chemoradiation (CCRT) is the standard care for locally advanced cervical cancer (LACC) patients, but the benefit of adjuvant chemotherapy (ACT) after CCRT for LACC patients is still controversial. This study is designed to answer the question by comparing the efficacy and toxicities of concurrent chemoradiation (CCRT) with adjuvant chemotherapy (ACT) (CCRT+ACT) versus concurrent chemoradiation (CCRT) alone in LACC.

Materials/Methods: Patients with stage IB2, IIA2, IIB-IVA (2009 FIGO staging) cervical cancer were recruited from June 2013 to June 2018 at 4 cancer centers in China. The patients were randomly assigned to two arms: CCRT +ACT and CCRT alone. All patients were treated with IMRT (external-beam radiotherapy up to 50.4 Gy) with concurrent cisplatin, followed by intra-cavitary brachytherapy. The chemotherapy consisted of concurrent cisplatin (40 mg/m² weekly) during IMRT, and 3 cycles of adjuvant CT with TP (docetaxel 75 mg/m², day 1, and cisplatin 25 mg/m², day 1-3 or carboplatin AUC 4-5, day 1) every 3 weeks. The primary endpoint was progression free survival (PFS), and the secondary endpoints included overall survival (OS), locoregional recurrence rate, distant metastasis rate, and toxicities. Survivals were calculated with Kaplan-Meier method. The differences between survivals were calculated with Log-rank test. Toxic effects were analyzed using the χ^2 test. All statistical tests were two-sided.

Results: A total of 176 patients were recruited in the study and 161 were eligible for intent-for-treat analysis. 82 patients were assigned to the CCRT+ACT arm and 79 in the CCRT alone arm. With a median follow-up of 60.1 months, the 5-year PFS and OS of all the patients were 68.32% and 72.05%, respectively. The 5-year PFS was 75.61% in the CCRT+ACT arm, and was 60.76% in the CCRT arm. There was significant difference in PFS between the two arms (P=0.043). The 5-year OS was 76.83% in the CCRT+ACT arm and was 67.09% in the CCRT arm. There was no significant difference in OS between the two arms (P=0.169). There was significant difference between the CCRT+ACT and CCRT arms in distant recurrence (p=0.048), but not in locoregional recurrence rate (p=0.752). There were significantly higher acute systemic side effects in the CCRT+ACT arm, especially the incidence of grade 3-4 hematologic and gastrointestinal reactions (P=0.000). Most of locoregional recurrence and distant metastases occurred with staging IIB-IVA patients in the CCRT alone arm.

Conclusion: Adjuvant chemotherapy after concurrent cisplatin chemoradiation for LACC patients improves PFS but not improves OS. It reduces distant metastasis but is correlated with poorer response to locoregional recurrence. There were more significant toxicities during adjuvant chemotherapy but it was well tolerated by patients. Further research and longer follow up is needed, especially for the staging IIB-IVA LACC patients.

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Definitive External Beam Radiation Therapy with Stereotactic Body Radiation Therapy Boost for FIGO Stage IB - IIB Cancer of the Cervix: Minimum 5-Year Disease Control, Toxicity and Quality of Life Outcomes From a Phase 2 Trial

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Purpose/Objective(s): SBRT for cancers of the cervix may offer an alternative to brachytherapy for those patients who are not candidates for brachytherapy procedures. SBRT dose-fractionation schedules may be selected to approximate those of HDR in order to achieve similar radiobiologic dosing, while SBRT technique eliminates the need for applicator placement and sedation. Herein, we report health-related quality of life, toxicity and disease control outcomes of a prospective, phase II trial of SBRT for primary cervical cancers.

Materials/Methods: Eligible patients included those with (1) pathologically confirmed cervical squamous cell carcinoma or adenocarcinoma; (2) FIGO stage IB, IIA or IIB disease; (3) technical or medical contraindication to brachytherapy; and (4) primary GTV < 125 cc following induction therapy. Induction therapy consisted of external beam radiotherapy (EBRT) to a minimum dose of 45.0 Gy encompassing primary tumor and regional pelvic lymphatics. All patients received weekly cisplatin-based chemotherapy concurrent with EBRT. SBRT boost treatment planning then followed, and GTV delineation was aided by co-registration of the boost planning CT set to a post-EBRT MRI. A boost dose of 40.0 Gy was prescribed to the primary tumor and delivered over a 10-day schedule of 5 fractions of 8.0 Gy each. Assessments included (1) disease response was determined pathologically by 3-month post-therapy biopsy and radiographically by biannual PET/CT imaging for 2 years; (2) acute and chronic toxicities were assessed using the National Cancer Institute's CTCAE v3 toxicity scales; and (3) quality-of-life was scored using FACT-G measurements.

Results: Fifty-five patients with FIGO stage IB - IIB cervical cancer have been treated since June 2007 and have been followed for a median of 72.0 months (range, 60 – 132 months). Stage distribution was as follows: 6/55 FIGO stage IB1, 18/55 FIGO stage IB2, 3/55 FIGO stage IIA1, 6/55 FIGO stage IIA2 and 22/55 FIGO stage IIB. Post-SBRT biopsy at 3 months was negative for 52 of 55 patients, or 94.5%, for all patients. At 5 years, estimated local control by combined pathologic and radiographic (i.e., PET SUVmax < 2.5) criteria at the SBRT treatment site is 92.3% for all patients. No NCI CTCAE grade 3 or greater urinary or bowel toxicities have been observed to date. Urinary frequency was the most common grade 1 – 2 acute toxicity, observed for 43.2% of patients. Post-treatment FACT-G overall scores at 2 years were statistically superior compared to pre-treatment assessments and for the following domains: physical, emotional and functional well-being.

Conclusion: At a minimum followup of 5 years, SBRT offers an effective and well-tolerated boost modality for selected FIGO stage IB - IIB cervix cancer patients otherwise contraindicated for brachytherapy. To our knowledge, this prospective phase 2 study reports the largest cohort of cervical cancer cases treated with curative intent using boost SBRT.

Author Disclosure: C.A. Mantz: None.

Stage III Uterine Serous Carcinoma: Improved Outcomes in the Modern Era with Multi-Modality Treatment

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Purpose/Objective(s): To examine patient outcomes of stage III uterine serous carcinoma (USC) in a modern and prior treatment era. We hypothesized that contemporary treatment incorporating external beam radiotherapy (EBRT) is associated with improved outcomes.

Materials/Methods: We performed a retrospective review of FIGO (2009) stage III USC patients who received radiotherapy as a component of treatment at our institution between 1/2003-5/2018. Fifty patients were identified and divided into two cohorts: 20 comprised the early cohort (2003-2010), for whom vaginal brachytherapy (VB) was considered the radiotherapy modality of choice per institutional standard. Thirty were included in the modern cohort (2011-2018), for whom EBRT was considered. Patient, tumor, and treatment characteristics were compared using

χ^2 tests for categorical variables and *t*-tests for continuous variables. Recurrence free survival (RFS) and overall survival (OS) were analyzed with Kaplan-Meier estimates, the log-rank test, and Cox proportional hazards.

Results: There were no differences in clinicopathologic characteristics between the two cohorts. All patients underwent complete surgical staging and 3-7 cycles of carboplatin/paclitaxel chemotherapy. The modern era differed from the early era in the increased use of volume-directed EBRT as opposed to VB alone (33.3% vs 5.0%, $p=0.048$). Reasons for non-use of EBRT in the modern era included patient refusal, poor performance status, or enrollment on clinical protocols not permissive of EBRT. Other management differences between the cohorts included increased use of minimally invasive surgery (56.7% vs. 25%, $p=0.027$), sentinel node sampling (26.7% vs. 0%, $p=0.012$), CT imaging in the perioperative period (63.3% vs. 30%, $p=0.044$), and HER2/neu testing (96.7% vs. 55%, $p=0.001$). Median follow-up for the early and modern eras was 37.27 months and 33.23 months, respectively. The early and modern treatment era 3-year RFS was 33% and 64% ($P=0.039$), respectively, while the 3-year OS was 55% and 90% ($P=0.034$). There were no vaginal recurrences in either time period. In the early and modern eras, 50% and 23% of patients, respectively, had a regional nodal component of recurrence ($p=0.051$). Of the 11 patients who received EBRT, only one patient had a regional nodal recurrence (9%), whereas among the 39 patients who received VB only, 16 patients (41%) had a recurrence with a regional nodal component ($p=0.048$).

Conclusion: Modern era treatment was associated with improved RFS and OS in patients with stage III USC. Regional nodal recurrences were significantly reduced in patients who received EBRT. EBRT should thus be considered for locoregional control, which becomes even more valuable as the prognosis for this population continues to improve in the modern era.

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Regional Control and Dose-Response for Chemoradiotherapy in Locally-Advanced Endometrial Cancer

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Purpose/Objective(s): Endometrial cancers are primarily managed with surgery which includes lymph node staging or debulking of any involved lymph nodes. Currently, there is limited data for nodal control of involved nodes with (chemo) radiotherapy (CRT). The goal of the current study is to assess nodal control with CRT for locally-advanced endometrial cancers managed with preoperative CRT followed by hysterectomy.

Materials/Methods: From July 1999-November 2018, 105 patients with \geq clinical stage II endometrial cancer treated with pre-operative CRT followed by extrafascial hysterectomy were retrospectively reviewed. Patients not completing therapy ($n=6$) or receiving CRT at outside institutions were excluded ($n=4$). Limited nodal dissection after CRT was performed if nodal disease persisted on imaging or was seen intraoperatively. PET/CT was performed for initial nodal staging in 80 (84%). The CTV included pelvic nodes up to the common iliac for node-negative and para-aortic lymph nodes up to the renal vessel for node-positive patients. Involved nodes most commonly received a simultaneous integrated boost of 55Gy in 25 fractions \pm 4-6Gy sequential boost for nodes >2 cm.

Results: Of the included 95 patients, 55 (58%) had clinically positive lymph nodes: 17 (31%) pelvic only, 5 (9%) para-aortic only, and 33 (60%) pelvic + para-aortic. The median number of positive nodes was 4 [interquartile range (IQR): 2-7] with a total number of 300 positive nodes. Nineteen (20%) patients had limited nodal dissection with a median of 3 (IQR:2-5) nodes dissected. At a median follow-up of 25 months (IQR: 9-46), the 3-year regional control was 91% (95%CI: 85-98%). In clinically node-negative patients, 2 (5%) developed isolated recurrence out-of-

field in the para-aortic region. In clinically node-positive patients, failure in involved nodes occurred in 4 (7%) and in prophylactic treated nodal regions in 4 (7%), 3 of which had synchronous nodal failure at both sites. Regional recurrence was higher in patients with lymph nodes ≥ 2 cm (3-year regional control 100% < 2 cm vs. 72% ≥ 2 cm, $p=0.005$) and nodal maximum SUV (100% < 10.6 vs 76% ≥ 10.6 , $p=0.045$). For the 300 clinically-involved lymph nodes, the median size was 1.2cm (IQR: 0.8-1.7). The 3-year involved nodal control rate was 96% (95%CI: 93-99%). Involved nodal failure was higher in type-II histology (3-year control 100% type-I vs 90% type-II, $p=0.002$), lymph nodes ≥ 2 cm (98% < 2 cm vs 84% ≥ 2 cm, $p=0.007$), and by radiation dose (75% for < 55 Gy, 98% 55Gy in 25 fractions, and 89% > 55 Gy, $p=0.03$).

Conclusion: This is largest study looking at regional control rates of involved lymph nodes with CRT. Despite a high burden of clinical involvement and low rates of dissection, nodal failure is low following neoadjuvant CRT, suggesting efficacy of CRT. A dose of at least 55Gy in 25 fractions is suggested for clinically involved nodes, with consideration of higher dose or alternative strategies in non-endometrioid histologies and bulky nodes ≥ 2 cm.

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Head and Neck

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Detectable HPV ctDNA in Post-Operative Oropharyngeal Squamous Cell Carcinoma Patients is Associated with Progression

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Purpose/Objective(s): Circulating tumor DNA (ctDNA) as a cancer biomarker may assist in detection, risk stratification, treatment assessment, and surveillance. There are limited data on the rates of detectability and ctDNA kinetics in the post-operative (post-op) setting for patients with Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC). We aimed to investigate ctDNA detectability rates by post-op risk category and association with prognosis in this population.

Materials/Methods: Prospectively collected serum samples from 29 treatment-naïve HPV-OPSCC patients were first tested for assay validation. 7 HPV negative OPSCC patients were included as a control. A cohort of 46 post-op HPV-OPSCC patients were identified with serum collection post-op but before adjuvant therapy. Serum was analyzed in a blinded fashion for E6/E7 HPV ctDNA for these 82 samples using a previously described ddPCR multiplex assay (HPV 16, 18, 31, 33). HPV ctDNA detectability was compared statistically across groups. Estimates of progression-free (PFS) and overall survival (OS) were made using the Kaplan-Meier (KM) method. Associations of patient and tumor characteristics with recurrence were assessed using a univariate Cox proportional hazards regression model.

Results: Prior to treatment, ctDNA was detectable in 27 of 29 patients for a sensitivity of 93%. None of the 7 HPV-negative patients had detectable ctDNA for a specificity of 100%. Post-op serum was collected at a median of 25 days (range 11-46) after surgery. Post-op ctDNA was detectable in 43% (20/46) of patients: 47% (18/38) of patients with high-risk features (ENE or R1) compared to 25% (2/8) of patients with intermediate-risk features ($p=0.25$). All detectable were HPV type 16. Median follow-up for the post-op HPV-OPSCC cohort ($n=45$) was 20 months (1 patient not completing adjuvant therapy by time of analysis was excluded). Eleven patients (24%) recurred: locoregional ($n= 5$) or

distant (n=6); 64% (7/11) of patients who recurred had detectable ctDNA compared to 35% (10/34) in patients who did not recur (p=0.1). Detectable ctDNA was significantly associated with 24-month PFS (45% vs. 84%, p=.04) and OS (80% vs. 100%, p=.02). Univariately, T4 tumors (HR: 14.3, p<0.01), >4 lymph nodes (HR: 5.5, p<0.01), and detectable ctDNA (HR 3.31, p=0.05) were positively associated with disease recurrence.

Conclusion: HPV ctDNA is a highly sensitive and specific means of determining HPV-status prior to treatment and remains detectable for many patients post-op. Detectable ctDNA was significantly associated with worsened PFS and OS. Risk stratification using a complement of ctDNA and historical risk factors may be instrumental in improved patient selection for treatment intensity decision making for patients with HPV-OPSCC and warrants further study.

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NRG-HN002: A Randomized Phase II Trial for Patients with p16-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer

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Purpose/Objective(s): NRG-HN002 was designed to select the arm(s) achieving acceptable progression-free survival (PFS) without unacceptable swallowing-related quality of life [MD Anderson Dysphagia Inventory (MDADI)] in patients with p16+, non-smoking-associated, locoregionally advanced oropharyngeal cancer.

Materials/Methods: Eligible patients had stage T1-2N1-N2bM0 or T3N0-N2bM0 (AJCC 7th edition) oropharyngeal squamous cell carcinoma and ≤10 pack-year smoking history. p16 immunohistochemistry was centrally confirmed. Patients were stratified by unilateral vs bilateral radiation and randomized (1:1) to either 60 Gy of intensity modulated radiation therapy over 6 weeks + Cisplatin (IMRT+C) at 40 mg/m² weekly vs 60 Gy of modestly accelerated IMRT alone over 5 weeks. For the expected 2-year PFS of 91%, assuming a binomial distribution, 140

randomized eligible patients per arm were required for 80% power and 10% 1-sided type I error rate. For swallowing acceptability, the required mean 1-year MDADI composite score was ≥ 60 .

Results: NRG-HN002 accrued 10/2014-2/2017. Of 316 patients enrolled, 306 were randomized and eligible. Among randomized eligible patients, 84.0% were male, 52.6% had tonsil primary, 62.4% had T2-3 disease, 75.5% had N2 disease, and 80.1% had bilateral IMRT. 97.7% completed 60 Gy IMRT. Of 157 patients receiving Cisplatin, 80.9% had ≥ 5 cycles and 72.6% had ≥ 200 mg/m². There were 15.1% grade 4 and 64.5% grade 3 acute (≤ 180 days after the end of treatment) toxicities on the IMRT+C arm as compared to 2.0% grade 4 and 50.3% grade 3 on the IMRT arm. There were 1.3% grade 4 and 20.0% grade 3 late toxicities on the IMRT+C arm as compared to 1.4% grade 4 and 16.7% grade 3 on the IMRT arm. There was no grade 5 toxicity reported. Nine patients withdrew consent and 5 did not have 2-year assessments, leaving 292 patients analyzable for PFS. At 2.6 years of median follow-up, the 2-year PFS estimate for the IMRT+C arm was 90.5% (95% CI 84.5-94.7%) with $p=0.0350$ thus rejecting the null hypothesis of 2-year PFS $\leq 85\%$. For IMRT, the 2-year PFS was 87.6% (95% CI 81.1-92.5%) with $p=0.2284$ thus failing to reject the null hypothesis. At 1 year, useable and timely MDADI completion rates were 77.1% and 71.1% in the IMRT+C and IMRT arms, respectively. Both arms passed the MDADI threshold, with 1-year means of 85.30 (95% CI 82.53-88.07) and 81.76 (95% CI 78.98-84.54) in the IMRT+C and IMRT arms, respectively. Estimated 2-year OS rates were 96.7% (95% CI 93.9-99.5%) for IMRT+C and 97.3% (95% CI 94.6-99.9%) for IMRT.

Conclusion: The IMRT+C arm met the acceptability criteria for both 2-year PFS and 1-year MDADI. The IMRT alone arm did not meet the PFS acceptability criterion. Higher rates of grade ≥ 3 acute toxicity were reported for IMRT+C. Rates of late grade ≥ 3 toxicity and estimated 2-year OS rates were similar.

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Reduction of Radiotherapy Dose to the Elective Neck in Head and Neck Squamous Cell Carcinoma; Update of the Long-Term Tumor Control of a Randomized Clinical Trial

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Purpose/Objective(s): A multicenter prospective randomized controlled trial was performed to investigate whether dose reduction to the elective nodal volume (PTVelect) in head and neck squamous cell carcinoma (HNSCC) reduces radiation-induced dysphagia, primary endpoint, without compromising tumor control, secondary endpoint. In this abstract, we report on the long-term follow-up of the secondary endpoint.

Materials/Methods: Patients with non-metastatic HNSCC were treated with primary (chemo)radiotherapy (RT) including irradiation of the bilateral elective neck. Patients were randomized (1:1) between the standard arm, irradiation to PTVelect up to an equivalent dose of 50 Gy and the experimental arm, irradiation to

PTVelect up to an equivalent dose of 40 Gy. The primary tumor and involved nodes were treated according to the standard of care up to an equivalent dose of 70 Gy (PTV high dose). (NCT01812486) Secondary endpoints were overall survival (OS), local recurrence (LR), regional recurrence (RR) and distant metastasis (DM). OS was estimated using Kaplan-Meier method and compared with log-rank test. LR, RR and DM were assessed using competing risk method and compared with Pepe and Mori's test. RR were projected on the initial RT planning computed tomography studies to identify the localization of recurrence. **Results:** Between 2008 and 2011, 200 patients were enrolled. Median follow up was 7.6 years (IQR 6.6-8.7). The 5 year (5Y) OS was 56.5% (CI95% 45.7;65.9) in the 40 Gy arm versus 49.6% (CI95% 39.0;59.2) in the 50 Gy arm (p=0.56). In the reduced 40 Gy arm, 5Y-LR was 17.2% (CI95% 10.4;25.4) versus 13.8% (CI95% 7.7;21.5) in the standard 50 Gy arm (p=0.39); 5Y-RR was 14.0% (CI95% 7.9;21.8) versus 7.5% (CI95% 3.3;14.0) (p=0.10) and 5Y-DM rate was 12.9% (CI95% 7.1;20.6) versus 24.4% (CI95% 16.3;33.5), respectively (p=0.07). Majority of RR in the 40 Gy arm (9 of 13) were projected in the PTV high dose and 2 RR were seen outside the treated RT volume (Table 1). Only 2 RR occurred in PTVelect irradiated up to 40 Gy which was the same number as RR occurring in the 50 Gy PTVelect. **Conclusion:** At 5 years of follow-up, no statistically significant differences regarding OS, LR, RR nor DM were observed between both treatment arms. This study is underpowered to undoubtedly demonstrate non-inferiority and to change the standard of care to 40 Gy. However, since only two RR in the PTVelect in both treatment arms were observed, reducing the dose to PTVelect appears safe and these results support further research in de-escalating the dose to the elective neck.

40 Gy				50 Gy			
Recurrence	n=13			Recurrence	n=7		
PTV high dose	9	IRR	5	PTV high dose	5	IRR	1
		LRR	2			LRR	1
		RR + DM	2			LRR + DM	1
						RR + DM	2
PTV elect	2	IRR	1	PTV elect	2	IRR	1
		RR + DM	1			LRR + DM	1
Outside planning volume	2	LRR	2				

Table 1: Regional recurrences classified according to the treatment arm (LRR: Locoregional recurrence; IRR: Isolated regional recurrence)

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Stem Cell Sparing IMRT for Head and Neck Cancer Patients: A Double-Blind Randomized Controlled Trial

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Purpose/Objective(s): Head and neck cancer patients treated with radiotherapy often suffer from xerostomia. Critical for the radiation response of the parotid glands are the parotid gland stem cells, mainly located in the main salivary gland ducts (van Luijk, 2015). Reducing dose to these High Stem Cell Density (HSCD) regions may prevent xerostomia. This double-blind randomized controlled trial (RCT) aimed to determine the impact of dose reduction to the HSCD regions on parotid gland stimulated salivary flow (FLOW12M) and patient-rated xerostomia 12 months (XER12M) after treatment.

Materials/Methods: Patients with HNC treated with definitive bilateral radiotherapy (70 Gy in 35 fractions) with or without systemic treatment were eligible for the study. Target volumes and organs at risk (OARs) were delineated according to international guidelines. The parotid gland

HSCD regions were contoured using in-house made software. Next, for every patient a standard parotid gland sparing IMRT plan (ST-IMRT) was generated. Second, a HSCD region sparing IMRT (HSCD-IMRT) plan was generated by reducing dose at the HSCD region as much as possible while keeping the whole mean parotid gland dose the same. Finally, patients were randomized between ST-IMRT (arm 1) and HSCD-IMRT (arm 2). Primary and secondary end-points were FLOW12M and XER12M, respectively.

Results: The study population was composed of 102 patients. 54 were assigned to receive ST-IMRT (arm 1) and 48 HSCD-IMRT (arm 2). The mean parotid gland dose was similar in both arms (contralateral: 24.2 and 23.8 Gy ($p = 0.801$) for arm 1 and 2, and ipsilateral: 31.7 and 30.8 Gy ($p = 0.659$), respectively). HSCD region sparing significantly reduced the dose to the HSCD region (contralateral: 16.4 to 12.6 Gy ($p = 0.007$) for arm 1 and arm 2, respectively, and ipsilateral: 25.0 to 17.4 Gy ($p = 0.005$), respectively). Baseline xerostomia and other OARs (oral cavity and submandibular glands) dose were similar in both arms. Compared to baseline, FLOW12M was reduced with 16.8% and 8.5% ($p = 0.621$) for arm 1 and arm 2, respectively and XER12M was 50.0% and 45.9% ($p = 0.720$), respectively. Multivariate analysis showed that the mean ipsilateral HSCD region dose and baseline xerostomia (none vs. any) were the most important predictors for XER12M. Analysis on the development of xerostomia and sticky saliva during day and night time, revealed that xerostomia during the day at 6 to 24 months was significantly lower in arm 2 compared to arm 1. For sticky saliva, during the day and night only the first 12 weeks after start treatment less sticky saliva was observed for arm 2 compared to arm 1.

Conclusion: In this double-blind RCT, stem cell sparing IMRT did not significantly improve salivary flow or reduce xerostomia 12 months after radiotherapy. However, the ipsilateral HSCD region dose was the most important dosimetric predictor for xerostomia, suggesting that dose to the HSCD region is more important for the development of xerostomia than dose to the entire parotid gland.

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Cost-Effectiveness of Screening for Nasopharyngeal Carcinoma with Serology or Plasma Epstein Barr-Virus DNA in High-Incidence Populations Globally

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Purpose/Objective(s): The incidence of nasopharyngeal carcinoma (NPC) exhibits marked geographic variation globally and is intimately associated with endemic Epstein-Barr Virus (EBV) infection. Although most patients present with locoregionally-advanced disease, several population-level screening trials using blood-based EBV assays have successfully detected most cases in the asymptomatic period. Given the rarity of NPC, it is uncertain whether screening could be cost-effective, and what the optimal screening program might be. We therefore sought to define the cost-effectiveness of three blood-based screening strategies in high-incidence regions globally, and hypothesized that screening of men and women in both high-incidence and middle-income countries could be cost-effective. **Materials/Methods:** Using incidence data from 340 cancer registries in 69 countries, we selected 42 high-incidence populations in 15 countries with a lifetime NPC incidence exceeding 0.25%. We developed a decision-analytic model comparing three previously-tested annual screening strategies (EBV DNA PCR + endoscopy + MRI, PCR + endoscopy, and ELISA serology + endoscopy) to no screening. Transition probabilities and stage distributions were based upon screening trials. Clinical outcomes were extracted from trial data and the AJCC 8 update, and microcosting was performed using WHO-CHOICE methods. One-way and probabilistic sensitivity analyses were performed to study the impact of age, gender, utilities, and costs. A willingness-to-pay (WTP) threshold was set at twice the local per-capita GDP. **Results:** Among the 42 selected populations, screening with PCR + endoscopy + MRI, PCR + endoscopy, and ELISA + endoscopy decreased NPC-specific mortality by 62%, 53%, and 72%, respectively. These strategies thereby improved 5-year NPC-specific survival from 74% in an unscreened population to 91%, 89%, and 94%. In the base case scenario, screening with PCR + endoscopy + MRI was cost-effective at the WTP threshold in 40% of selected populations, compared to 38% with PCR + endoscopy and 67% with

ELISA + endoscopy. The addition of MRI to PCR was marginally more cost-effective than endoscopy alone, but was associated with small improvements in 5-year NPC-specific survival (2%). Among populations with a lifetime incidence exceeding 0.60%, screening was always cost-effective. Moreover, screening in many middle-income and most high-income countries was also cost-effective. Sensitivity analysis informed the optimal age at first screening in each region, as well as the screening of women. Probabilistic sensitivity analysis was in close agreement with base case analyses. **Conclusion:** We observed significant reductions in NPC-specific mortality with the use of blood-based screening in high-incidence populations globally. Despite economic differences and the rarity of NPC, these strategies were cost-effective in most high-incidence regions, and could be extended to both adult men and women, generally beginning at age 40.

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A Pilot Study of Stereotactic Body Radiotherapy (SBRT) Combined with a PD-L1 Antibody Durvalumab (D) and a CTLA-4 antibody Tremelimumab (T) To Treat Metastatic Anaplastic Thyroid Cancer (ATC)

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Purpose/Objective(s): The prognosis of metastatic ATC is dismal and there are very limited treatment options. The thyroid is one of the most immunogenic organs in the body. PD-L1 is commonly expressed on ATC tumor cells and PD-1 in the inflammatory cells in the ATC microenvironment. However, antibodies to PD-1 as single agents have a poor record in this disease. Therefore, we designed this pilot study to add T to D and together with SBRT to augment their effects in hope to improve survival.

Materials/Methods: This study evaluated the addition of T (75 mg every 4 weeks up to 4 doses) to D (1500 mg every 4 weeks). SBRT 9Gy x 3 fractions was given within the first 2 weeks of treatment to produce an “abscopal” effect. Major inclusion criteria: Metastatic ATC; ECOG PS 0-2; No prior immunotherapy; Last anti-cancer treatment > 7 days prior to starting study. Primary objective 1-year overall survival with target of ≥ 2 out of 12 patients.

Results: 12 patients were accrued. Male – 50%; Median PS 1; Median Age – 71 (49-82); Prior radiation to neck (75%); Prior chemotherapy (75%). MSI-High was noted in 2/11 subjects. BRAFV600E mutation in 3/12 subjects. There were 0 confirmed responses and only 1 subject with SD for 4 cycles or longer. Median time on treatment was 11 weeks (1-28+ weeks). MSI status did not affect treatment response. MSI-High patients were on treatment before progression for 8-14 weeks. Median overall survival was 14.5 weeks with only one person alive past 1 year. Neither the presence of a BRAF or p53 mutation appeared to affect either outcome.

Conclusion: T/D with SBRT was not active in metastatic ATC. Future studies looking at other novel immunotherapy combinations in ATC should be evaluated. Biopsies done on study are being analyzed and will be presented.

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Radiotherapy vs. Trans-Oral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma (OPSCC): Results of a Randomized Trial

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Purpose/Objective(s): The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has risen rapidly, due to an epidemic of human papillomavirus (HPV) infection. Radiation therapy (RT) has historically been the standard treatment, but transoral robotic surgery (TORS) has surpassed RT in the US as the most common approach, based on assumptions of reduced toxicity or improved quality of life (QOL). No randomized trials have previously compared these treatments.

Materials/Methods: The ORATOR trial (NCT01590355) enrolled patients with T1-T2 N0-2(≤4 cm) OPSCC amenable to TORS. We randomly assigned patients, stratified by p16 status, to RT (70 Gy/35 fractions, or as chemoradiotherapy [CRT] if N1-2) vs. TORS (± adjuvant RT or CRT based on pathology). The primary endpoint was a definitive comparison of swallowing QOL at 1-year using the MD Anderson Dysphagia Inventory (MDADI), powered to detect a 10-point improvement (a clinically-meaningful change [CMC]) in the TORS arm. Secondary endpoints included adverse events (AEs), other QOL outcomes [including EORTC Head and Neck-35 (H&N-35) scale and other scales], overall and progression-free survival (OS, PFS). Herein we report primary and secondary outcomes with a post-hoc analysis of outcomes by treatment intensity.

Results: Between 2012 and 2017, 68 patients were randomized (n=34 in each arm), at 6 centres in Canada and Australia. Median age was 59 years; 87% were male. Primary tumors sites were palatine tonsil (74%) or base of tongue (26%). Arms were well-balanced for baseline factors, including p16 status (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p=0.042), but not meeting the definition of a CMC. For other QOL metrics, outcomes were similar at 1-year. Percutaneous feeding tube rates at 1-year were 3% (n=1) vs. 0% respectively. Rates of treatment-related grade ≥ 2 AEs were similar (91% vs. 100%, p=0.24), with more neutropenia, hearing loss, constipation and tinnitus in the RT arm and more trismus in the TORS arm (all p<0.05). There was one TORS bleeding-related death. The arms were similar in OS (p=0.88) and PFS (p=0.63). Longitudinal QOL analysis over time confirmed the statistical superiority of RT in the MDADI scores (p<0.001), with average differences below the threshold of a CMC. In the RT Arm, 1-year MDADI scores based on treatment intensity were as follows: RT alone 89.5 ± 6.2; CRT alone 88.0 ± 11.5 RT; RT/CRT with salvage surgery 68.0 ± 7 (ANOVA p=0.044). In the TORS arm, the 1-year MDADI scores by treatment intensity were: TORS alone 82.8 ± 10.5; TORS with RT 78.5 ± 11.0; TORS with CRT 80.4 ± 19.6 (ANOVA p=0.760).

Conclusion: RT had superior swallowing QOL scores at 1-year compared to TORS, but the difference was not a CMC. Toxicity patterns differed between the arms. Patients with OPSCC should be counselled on the advantages and disadvantages of both modalities.

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A Phase II Trial of Alternative Volumes of Oropharyngeal Irradiation for Deintensification (AVOID): Omission of the Resected Primary Tumor Bed for Squamous Cell Carcinoma of the Oropharynx

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Purpose/Objective(s): Treatment of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) with initial surgical resection followed by adjuvant radiotherapy yields high cure rates, but can cause long-term toxicity. This phase II trial evaluated whether omitting high dose radiation to the resected primary tumor bed while targeting only the regional neck nodes, could maintain high local control rates while reducing late sequelae.

Materials/Methods: Eligible patients were those appropriate for adjuvant RT after surgical resection for p16-positive, pathologic stage III-IVa (7th edition) p16-positive OPSCC. Pathologic inclusion criteria included: T1-T2 disease, any N1-2, negative resection margins, and no perineural or lymphovascular invasion. Patients received 60-66 Gy RT over 30-33 fractions to the regional nodes of the bilateral neck, with active omission of high-dose RT to the resected primary tumor bed. Concurrent chemotherapy was given for patients with extranodal extension. The primary end point was 2-year locoregional control.

Results: Sixty patients were enrolled. Thirty-two (53%) received intensity-modulated radiation therapy (IMRT), 27 (45%) received proton therapy, and 1 (2%) received a 50:50 hybrid IMRT:proton plan. Average follow-up was 2 years, with local control of 98%, regional control of 100%, distant control of 97%, and overall survival of 100%. Median dose delivered to the avoided primary site was 37 Gy (40 Gy for IMRT, 34 Gy for proton RT, p = 0.03). There was only 1 local recurrence, occurring 9 months after completion of RT, which was successfully salvaged via surgical resection. Two (3%) patients experienced post-RT primary site tissue necrosis, both of whom experienced complete resolution with conservative management. Percutaneous endoscopic gastrostomy (PEG) tube dependence rates were: 0 patients (0%) during RT, and 1 patient (2%) at time of last follow-up.

Conclusion: Avoidance of radiation to the resected primary tumor bed appears safe in well-selected patients with HPV-associated OPSCC. This approach resulted in a low rate of treatment-associated complications, and is worthy of further study as a strategy for deintensification.

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Recurrence and Quality-of-Life Following Elective Nodal Volume and Dose De-Escalation for Oropharyngeal and Laryngeal Cancer:

Initial Results from the Infield Trial

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Purpose/Objective(s): The required elective nodal dose and volumes for head and neck intensity-modulated radiotherapy (IMRT) have largely been extrapolated from conventional radiotherapy fields. The combination of CT and PET-CT imaging with surgically established patterns-of-nodal-spread provides an opportunity to meaningfully reduce the elective dose and volume, with a significant gain in acute and long-term morbidity. In this prospective phase II study, we investigated the efficacy and tolerability of reduced elective nodal volume and dose in oropharyngeal and laryngeal squamous cell carcinoma.

Materials/Methods: Patients with newly-diagnosed squamous cell carcinoma of the oropharynx and larynx were eligible for enrollment; only stage I-II glottic larynx were excluded. In collaboration with a nuclear radiologist, each lymph node was characterized as involved or suspicious based on anatomic and PET criteria. Lymph nodes whose cross-sectional diameter was at least 17 mm and/or nodes with FDG uptake greater than the adjacent blood pool were considered suspicious. For oropharynx cancer, only involved nodal stations plus one adjacent station (and retropharynx) were treated to 40 Gy in 20 fractions. In larynx patients, at least bilateral levels II and III were treated to 40 Gy, with level IV treated only if level III was involved. Involved and suspicious nodes were then boosted with 30 Gy and 24 Gy in 15 fractions, respectively. The primary gross tumor and clinical target volumes were irradiated to 70 and 64 Gy, respectively, in the same fractionation. Concurrent chemotherapy was required for stage T3N0-1 and IVA/B patients. The primary endpoint of the study was solitary elective volume recurrence, with secondary endpoints including patterns-of-failure and patient reported outcomes.

Results: A total of 72 patients completed treatment on this trial from January 2017 through November 2018. The study was composed of 19 larynx and 53 oropharyngeal patients, 77% of whom were p16-positive. The stages at presentations were 5, 17, and 50 stage I-II, III, and IV, respectively, with 8% and 92% treated with accelerated radiotherapy and chemoradiotherapy, respectively. Average contralateral mean parotid and SMG doses for non-N2c patients were 16.5 Gy and 36.7 Gy, respectively. With a median follow-up of 11.9 months for surviving patients, there have been **no** recurrences in the 40 Gy or untreated elective nodal stations. Gastrostomy was placed in 32 (44%), with median removal after 2.9 months for disease-free patients; only one disease-free patient is still dependent. At 3 months, the mean composite MDADI score was 79, and the mean EORTC HN35 dry mouth and sticky saliva scores were 59 and 40, respectively.

Conclusion: Preliminary results suggest that elective dose and volume reduction is oncologically sound for oropharyngeal and laryngeal cancer treated with IMRT, with promising quality-of-life outcomes. Longer follow-up is needed to confirm these results.

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Randomized Clinical Trial on 7-days-a-week Postoperative Radiotherapy vs. Concurrent Postoperative Radio-chemotherapy in Locally Advanced Cancer of the Oral Cavity/Oropharynx

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Purpose/Objective(s): It has been demonstrated that postoperative radio-chemotherapy (p-RTCT) in high-risk squamous cell head and neck cancer may provide superior loco-regional control compared to conventionally fractionated postoperative radiotherapy. However, the combined treatment was associated with a substantial increase in adverse effects and improvement in overall survival was not demonstrated in some series.

It has been also demonstrated that accelerated 7-days-a-week postoperative radiotherapy (p-CAIR) may provide superior loco-regional control compared to postoperative conventionally fractionated radiotherapy among the patients with cancer of the oropharynx/oral cavity. Therefore, we performed a randomized clinical trial on p-CAIR vs. p-RTCT to compare the outcomes in both schedules.

Materials/Methods: Between September 2007 and October 2013 111 patients were enrolled and randomly assigned to receive 63 Gy in 1.8 Gy fractions 7-days-a-week (n=57, p-CAIR) or 63 Gy in 1.8 Gy fractions 5-days-a-week with concurrent cisplatin 80-100 mg per square meter of body-surface area on days 1, 22 and 43 of the radiotherapy course (p-RTCT). It represents approximately 40% of the intended trial size, that was closed prematurely due to slowing accrual. Only high-risk patients with squamous cell cancer of the oropharynx/oral cavity, considered fit for concurrent treatment were enrolled.

Results: After a median follow-up of 5.4 years, the rate of locoregional control did not differ significantly between treatment arms (p=0.18, HR=0.56, 95%CI 0.24-1.31), the actuarial 5-year locoregional control tended, however, to favor p-RTCT (81%) vs. p-CAIR (62%). There was no difference in overall survival between treatment arms (p=0.90, HR= 1.03, 95% CI 0.57-1.87), the actuarial 5-year OS was 63% for p-RTCT vs 59% for p-CAIR. The actuarial 5-year incidence of second cancer was 8% in p-CAIR and 9% in p-RTCT. The incidence and severity of acute mucosal reactions did not differ significantly between treatment arms. Hematological toxicity of p-RTCT was, however, considerably increased compared to p-CAIR with only 51% of the patients receiving complete three courses of concurrent chemotherapy. No apparent differences in late toxicity were observed.

Conclusion: While the conclusions from this study are limited due to its underpowered size, concurrent postoperative RTCT tended to improve locoregional control rate as compared to p-CAIR. This, however, did not transferred into improved overall survival. Postoperative RTCT was associated with a substantial increase in hematological toxicity that negatively affected treatment compliance in this arm.

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Hematologic Malignancies

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PET-Guided Treatment of Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase 3 Trial HD16 by the GHSG

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Purpose/Objective(s): Combined modality treatment (CMT) consisting of two cycles of ABVD and 20 Gy of involved-field radiation therapy (IFRT) is widely accepted standard of care for early-stage favorable Hodgkin lymphoma (HL). Recent clinical research suggests that metabolic response assessment after two cycles of chemotherapy using FDG-PET (PET-2) can predict the individual outcome and PET-2 negativity might allow reducing the overall treatment intensity. In this study, we assessed whether omitting consolidating radiation therapy in patients with negative PET-2 is feasible without loss of efficacy as determined by progression-free survival (PFS). Furthermore, we analyzed the prognostic impact of PET-2 among patients receiving CMT.

Materials/Methods: Between November 2009 and December 2015, we recruited patients with newly diagnosed, early-stage favorable HL aged 18–75 years from Germany, Switzerland, Austria, and the Netherlands for this double-blind, randomized, parallel-group phase 3 trial. Patients were randomly assigned to receive standard CMT with 2x ABVD and 20 Gy IFRT or PET-guided treatment, whereby IFRT was restricted to those patients with a positive PET after 2xABVD.

Results: A total of 1150 patients were enrolled; 628 patients with negative PET-2 were eligible for the per-protocol non-inferiority analysis and were treated with CMT (n=328) or ABVD alone (n=300). With a median follow-up of 47 months, the estimated 5-year PFS was 93.4% (90.4–96.5) with CMT and 86.1% (81.4–90.9) with chemotherapy only (difference 7.3%, 95% CI 1.6%–13.0%). The hazard ratio was 1.78 with a 95% CI ranging from 1.02 to 3.12, including the non-inferiority margin of 3.01. The PFS difference primarily resulted from a significant increase in disease recurrences with in-field recurrence rates of 2.1% vs. 8.7% (p=0.0003); there was no relevant difference regarding out-field recurrences (3.7% vs. 4.7%, p=0.55). Estimated 5-year overall survival in the per-protocol population was 98.1% (96.5–99.8) with CMT and 98.4% (96.5–100.0) with ABVD. 693 patients assigned to receive CMT were eligible for the analysis of the PET objective and had a negative (n=353) or positive (n=340) PET-2. With a median follow-up of 46 months, estimated 5-year PFS was 93.2% (90.2–96.2) among PET-2-negative and 88.1% (83.8–92.3) among PET-2-positive patients (p=0.035). When using the more common liver cutoff (Deauville score 4) for the definition of PET-2 positivity, the difference became more pronounced (5-year PFS 93.1% [90.7%–95.5%] vs. 80.1% [71.2%–88.9%], p=0.0004).

Conclusion: In early-stage favorable HL, radiation therapy cannot be safely omitted from standard CMT without a clinically relevant loss of tumor control in patients with negative PET-2. PET positivity after 2xABVD represents a risk factor for PFS in HL patients treated with standard CMT, particularly when a Deauville score of 4 is considered as cutoff for positivity.

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Long-Term Outcomes for Patients with Limited Stage Follicular Lymphoma: An Update of a Population-based Study

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Purpose/Objective(s): Follicular lymphoma (FL) is the most common indolent lymphoma and most frequently presents as advanced stage disease. Radiotherapy (RT) is integral in the treatment of limited stage FL and potentially curative. However, given the long natural history, mature follow-up is needed to accurately define the relapse risk. We previously reported on the long-term outcome of 237 patients with limited stage FL treated with curative intent RT with a median follow-up of 7.3 yr. Herein, we report the outcome with now a median follow-up of 13.1 yr and also re-evaluated the impact of involved node with margins ≤ 5 cm (now known as involved site RT (ISRT)) on relapse rates.

Materials/Methods: Patients diagnosed with stage 1A/IIA, grade 1–3A FL from 1986–2006 and treated with curative-intent RT alone were previously identified. Computed tomography scans but not positron emission tomography scans were used for staging. RT was categorized as IRRT vs. ISRT; IRRT encompassed the involved lymph node (LN) group plus ≥ 1 adjacent, uninvolved LN group(s) and ISRT covered the involved LN(s) with margins ≤ 5 cm. Survival rates with standard errors were calculated using the Kaplan-Meier method and comparisons made using the log-rank test. Cox regression was used for multivariable analysis (MVA).

Results: Of the 237 patients, 48% were men, 54% were >60 yr old at diagnosis, 76% had stage IA disease, 12% had grade 3A disease, 19% had LN size ≥ 5 cm, and 7% had elevated lactate dehydrogenase. IRRT was used in 60% and ISRT in 40%. Median follow-up was 13.1 yr (range, 0.3–28.9 yr) and 80% were followed for over 7 yr. Freedom-from-progression (FFP, unrelated deaths censored) was 65.9 \pm 3.1% at 5 yr, 49.5 \pm 3.4% at 10 yr and 43.8 \pm 3.6% at 15 yr. Five-year progression-free survival (PFS, all deaths counted) was 61.8 \pm 3.2%, 10-yr PFS was 40.1 \pm 3.2% and 15-yr

PFS was 28.0±3.1%. Overall survival was 86.5±2.2% at 5 yr, 70.9±3.0% at 10 yr and 57.2±3.2% at 15 yr. Of the 124 first relapses, 11 (9%) occurred beyond 10 yr and 3 (2%) occurred beyond 15 yr. First failures were distant alone in 107 patients (45%), in-field alone in 4 patients (1.6%) and both distant and in-field in 11 patients (4.6%). Of the 95 patients treated with ISRT, only one (1%) had a first failure that was regional-only (i.e., out-of-field but would have been covered by an IRRT approach). Ten-year FFP was 45.9±4.3% after IRRT and 55.4±5.4% after ISRT (P=0.26). On MVA, RT field size did not impact FFP; significant factors for FFP included only sex and stage, with hazard ratio [HR]=1.5 for male vs. female (P=0.028), HR=3.7 for LN size ≥5 cm vs. complete excision (P=0.007), and HR=2.7 for nodal size <5 cm vs. complete excision (P=0.032).

Conclusion: In patients with limited stage FL, disease recurrence was uncommon after 10 yr and rare after 15 yr. At 15 yr, 44% of patients remained disease-free, confirming that a cure is possible. Reduction of RT fields to ISRT did not appear to impact relapse risk in the long-term.

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Radiotherapy in Early-Stage Gastric MALT: Improved Survival without Increased Cardiac Death

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Purpose/Objective(s): Radiotherapy (RT) is an effective treatment for localized gastric mucosa-associated lymphoid tissue (MALT) lymphomas unresponsive to antibiotic therapy. Unfortunately, RT to the stomach can lead to significant doses of RT to the heart. RT to the heart is a known risk factor for late cardiac disease. We analyzed the Surveillance, Epidemiology, and End Results (SEER) database to evaluate overall outcomes and death related to heart disease in patients with stage I gastric MALT. We additionally compared that population to those treated with RT for orbital MALT to further evaluate the relationship between RT and death related to heart disease.

Materials/Methods: The SEER database was queried to identify adult patients with stage I gastric or orbital MALT lymphoma treated between 1993 and 2014. The relationship between treatment modality (RT, chemotherapy, combination, and no treatment) and overall survival (OS), MALT-specific survival (MSS), and Heart-specific survival (HSS) was assessed using Kaplan-Meier survival and multivariate Cox proportional hazards analyses.

Results: A total of 2,996 patients with gastric MALT and a median follow-up time of 5.6 (interquartile range, 2.4 – 9.9) years were included. 27.5% of patients received RT alone, 12.1% chemotherapy alone, 3.9% chemoradiotherapy, and 56.5% none /unknown treatment (including antibiotic therapy). Patients with gastric MALT who received chemotherapy alone exhibited worse OS (HR 1.67, 95% CI 1.32 – 2.10, p < 0.001) and MSS (HR 2.10, 95% CI 1.36 – 3.23, p = 0.001) compared to those treated with RT alone. Although the HSS appeared worse in patients with gastric MALT following chemotherapy alone (HR 1.56, 95% CI 0.92 – 2.66, p = 0.10, **Table**) compared with RT alone, it was not statistically significant. When comparing orbital (n = 1,629, median follow-up = 6.0 years) and gastric MALT patients receiving RT (with or without chemotherapy), there was no significant difference in HSS (HR = 0.80, 95% CI = 0.49 – 1.31, p = 0.38).

Conclusion: We demonstrate improved survival among patients with stage I gastric MALT treated with RT without an increased risk of cardiac death. Gastric MALT patients treated with RT had similar HSS to orbital MALT patients treated with RT. While we are unable to analyze the incidence of non-fatal cardiac toxicity, these results nonetheless suggest that RT should remain first-line in the management of early-stage gastric MALT not treatable with antibiotic therapy. **Table 1.** Multivariate Cox Proportional Hazards Analysis for Heart Disease Related Death

Treatment Type	Incidence (per 1,000 person-years)	95% CI	Hazard Ratio*	95% CI	P value
No Treatment	12.2	10.3 – 14.4	1.74	1.15 – 2.63	0.01
CRT	7.8	3.7 – 16.3	1.40	0.61 – 3.20	0.46
RT Alone	5.9	4.0 – 8.6	–	–	–
Chemo Alone	11.1	7.7 – 16.1	1.56	0.92 – 2.66	0.10

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Patterns of Failure Following Chimeric Antigen Receptor T-cell (CAR-T) Therapy

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Purpose/Objective(s): Axicabtagene ciloleucel (axi-cel) is a chimeric antigen receptor T-cell (CAR-T) therapy that can elicit a complete and durable response in patients with refractory B-cell lymphomas. Patterns of failure in patients receiving axi-cel CAR-T have not been previously characterized and may provide insights as to the potential role for local therapy to improve overall efficacy of CAR-T therapy.

Materials/Methods: Patients with disease progression following CAR-T therapy at our institution from May 2015 to April 2018 were reviewed retrospectively. Patient disease burden and lesion-specific disease characteristics were quantified by pre-treatment PET/CT and compared to serial post-treatment images to characterize patterns of recurrence, including timing and location of recurrent disease. Progression of existing pre-treatment disease sites was considered a local failure, while the development of new, non-overlapping disease sites was considered distant failure. Univariate and multivariate survival analyses were used to identify pre-treatment patient and lesion-specific risk factors for disease progression.

Results: Twenty-six patients with disease progression following CAR-T therapy were included for analysis. Median age was 58.5 (range, 31-80). Patients had either diffuse large B-cell (n=22) or transformed follicular lymphoma (n=4). The 3-month disease-free survival was 35% with all patients progressing by 6 months. All but one patient (96%) recurred at a previously involved disease site (i.e. had a component of local failure), with 12 (46%) patients exhibiting strictly involved-site progression and 13 (50%) having both involved-site and distant progression at time of recurrence. Only one patient (4%) had an isolated distant failure. Of the 243 distinct disease sites identified on pre-treatment imaging, nearly half (n=115, 47%) had progressed at time of overall treatment failure. Site-specific factors associated with increased risk of local failure included SUV max ≥ 10 (HR 2.06, $p < 0.001$), cross-sectional area $\geq 2\text{cm}^2$ (HR 2.22, $p < 0.001$), metabolic volume $\geq 20\text{cc}$ (HR 1.51, $p = 0.04$), and presence of clustered lesions (HR 1.76, $p < 0.001$). All 17 lesions with pre-treatment radiographic evidence of necrosis progressed on CAR-T therapy by the time of overall patient failure ($p < 0.001$). There was no difference in failure rates in nodal vs. extranodal disease ($p = 0.62$).

Conclusion: In patients who failed CAR-T therapy, nearly all recurred at previously involved disease sites by 6 months. Disease sites with high metabolic activity and lesions $\geq 2\text{cm}^2$ in cross sectional area or $\geq 20\text{cc}$ in metabolic volume are at an increased risk of progression following CAR-T therapy. All necrotic lesions progressed at the time of failure. Disease sites with high-risk features may benefit from localized bridging treatments, such as involved-site radiotherapy, to improve overall CAR-T efficacy and may warrant further investigation.

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Is Radiotherapy Adequate Treatment for Patients not in Complete Metabolic Response after First-Line Chemotherapy for DLBCL?

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Purpose/Objective(s): Failure to achieve complete metabolic response (CMR) on 18-FDG PET/CT at the end of chemotherapy (CT) in diffuse large B cell lymphoma (DLBCL) is associated with poor prognosis. Patients (pts) are usually considered for salvage CT and autologous stem cell transplant if fit. However salvage often fails and is not suitable for a substantial proportion of pts. A subset of these pts have localised uptake that can be treated with radiotherapy (RT) but the efficacy of RT in this situation is not established. This study aims to assess the efficacy of salvage RT after incomplete response to first line CT and identify factors that may predict its efficacy.

Materials/Methods: We performed a retrospective review of DLBCL pts who had residual FDG uptake on PET/CT after first line CT and subsequently received RT. Eligibility included: treatment with curative intent, RCHOP or similar, post-CT PET/CT Deauville score (DS) 4 - 5, RT ≥30Gy within 8 weeks. End points included: relapse rate, pattern of relapse, response to RT and overall survival (OS).

Results: We included 44 pts treated March 2011-August 2018 with median follow up (FU) of 29.3 months (1.6-90.8). Table 1 shows pt, disease and treatment characteristics. 45.5% were stage 3-4. 88.7% received RCHOP/RminiCHOP with median of 6 cycles. DS was 4 and 5 in 77.3% and 22.7%. During FU 14 (31.8%) pts relapsed/progressed. 10 (71.4%) relapsed outside the RT volume, 1 (7.1%) inside and 3 (21.4%) relapsed in both. Progression occurred relatively early with a median time from RT of 4.0 months (0.8-51). Of those who relapsed, 6 received salvage CT and 3 are alive with median FU of 50.8 months (26.9-90.7) . 13 pts died, 11 of lymphoma and 2 of unrelated causes. Median OS is 75 months (1.6-90.8). PET/CT scans were performed after RT in 40/44 (90.9%) of pts. Half achieved CMR, 10 had DS 4 and 10 DS 5. The risk of relapse was related to the post RT PET status. 9/10 (90%) of pts with DS5 relapsed compared to 1/10 (10%) with DS4 and 4/20 (20%) of pts with CMR. Relapse risk was also related to the pre RT DS. Relapse occurred in 5/10 (50%) pts with DS 5 compared to 9/34 (26.5%) with DS 4. There was no difference in relapse rate according to RT dose (30/30.6 vs ≥36Gy).

Conclusion: RT seems to be an adequate treatment for a substantial proportion of pts not achieving CMR following initial CT with more than half remaining in long term remission. Pts with post CT DS 4 had a better outcome after RT.

Table 1 Patient and treatment characteristics Male Female	n (%) 22 (50) 22 (50)
Median Age /years (range)	65.5 (21-89)
Histopathology Germinal centre (GC) Non GC THRLB-CL PMBCL NOS	16 (36.3) 10 (22.7) 2 (4.5) 6 (13.6) 10 (22.7)
Stage 1 2 3-4	4 (9.1) 20 (45.5) 20 (45.5)
IPI 0-1 2 3 4-5	16 (36.4) 11 (25) 9 (20.5) 8 (18.2)
Median no of cycles (range) R miniCHOP RCHOP/RCEOP RGCVP/RCVP COPADM-R	6 (3-8) 9 (20.5) 31 (70.5) 3 (6.8) 1 (2.3)

End of CT DS 4 5	34 (77.3) 10 (22.7)
RT dose (Gy) 30/30.6 36 40	17 (38.6) 18 (40.9) 9 (20.5)

Author Disclosure: **J.L. Brady:** None. **G. Mikhael:** None.

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Quality of Life Improvement Following Low-Dose Total Skin Electron Beam Therapy in Patients with Mycosis Fungoides or Sezary Syndrome

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Purpose/Objective(s): Total skin electron beam therapy (TSEBT) has proved to be a safe and effective treatment for cutaneous T-cell lymphomas. Here, we report our experience applying low-dose TSEBT to patients with mycosis fungoides (MF) or Sezary syndrome (SS). We examined the impact of this treatment on patient quality of life and outcome.

Materials/Methods: Forty-four patients with MF or SS received 48 TSEBT courses with a median dose of 12 Gy (range, 12–24) within the past eight years at our institute. Patient and treatment characteristics for these cases, as well as the impact of TSEBT on quality of life and duration of response, were retrospectively analyzed and compared.

Results: The median modified Severity Weighted Assessment Tool score before the start of TSEB was 44 (mean: 57, range: 7–160). The overall response rate was 88%, with a complete response (CR) rate of 33%. Five patients (10%) had near CR (< 1% body surface area). Pruritus improved significantly in 84% of the patients treated (CR rate, 35%). The median follow-up period was 13 months. The median duration of response (DOR), progression-free survival (PFS), and overall survival (OS) for the entire cohort were 10 months, 9 months, and 20 months, respectively. Patients who received maintenance treatments had a longer DOR (13 months vs. 6 months, respectively; $P = 0.1$), PFS (9 months vs. 3 months, respectively; $P = 0.01$), and OS (51 months vs. 18 months, respectively; $P = 0.15$). Meanwhile, patients presenting CR had a noticeably longer PFS (13 months vs. 7 months, respectively; $P = 0.05$). Patient-reported symptom burden was measured with Dermatological Life Quality Index and Skindex-29 questionnaires. The mean symptom reductions were 6 ± 8 ($P = 0.005$) and 21 ± 24 ($P = 0.002$), respectively. In the Functional Assessment of Cancer Therapy-General assessment, significant improvements in both the emotional ($P = 0.03$) and social ($P = 0.08$) domains were observed after TSEBT. In univariate analyses, various clinical and hematological parameters were found to be significant. In a multivariate analysis, only CD30+ MF was associated with improved DOR ($P = 0.05$) and PFS ($P = 0.05$), while disease stage appears to potentially impact OS ($P = 0.06$).

Conclusion: Taken together, these results indicate that maintenance of TSEBT improves the PFS of patients with MF or SS. In addition, TSEBT improved disease symptoms and significantly improved emotional and social domains of patients' quality of life.

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Accelerated Fractionated Compared to Conventional Fractionated Salvage Radiation Therapy Improves Outcomes in Salvage Chemotherapy Refractory Diffuse Large B-Cell Lymphoma

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Purpose/Objective(s): To evaluate the role of accelerated fractionated salvage radiation therapy (SRT) in patients with diffuse large B-cell lymphoma (DLBCL) refractory to salvage chemotherapy in preparation for high dose chemotherapy (HDT) and autologous stem cell transplant (ASCT). Relapsed/primary refractory patients who are also salvage chemotherapy refractory are usually not considered eligible for HDT and ASCT. Conventional and accelerated fractionated salvage radiation therapy was used with the goal of making salvage chemotherapy refractory patients eligible for HDT and ASCT. We compared patients receiving two different radiation therapy fractionation schedules.

Materials/Methods: We reviewed the medical records of 38 consecutive patients at one institution with DLBCL who were refractory to salvage chemotherapy and underwent salvage radiation therapy (SRT) from 2003-2018. Twenty-two patients underwent accelerated fractionated SRT (most commonly 3600 cGy in 20 twice daily 180 cGy fractions) and sixteen patients underwent conventional fractionated SRT (most commonly 3600 cGy in 20 daily 180 cGy fractions). Patients were excluded if they had a complete response to salvage chemotherapy or if they underwent a course of radiation therapy with fraction size <150 cGy.

Results: We evaluated 26 males (68%) and 12 females (32%) with a median age of 62 (range: 13-80) at the time of SRT. Twenty-four patients (63%) had primary chemotherapy refractory DLBCL having never achieved a remission and were also refractory to salvage chemotherapy, while 14 patients (37%) were refractory to salvage chemotherapy in the setting of a relapse. Twenty-three patients (61%) had progressive disease and 15 patients (39%) had no response or a partial response at the conclusion of salvage chemotherapy. Twenty-two patients (58%) underwent high dose chemotherapy and proceeded to HDT and ASCT. The percentage of patients that underwent ASCT who received accelerated fractionated SRT compared to conventionally fractionated SRT was not statistically different (59% vs 56%, p=0.86). Accelerated fractionation compared to conventional fractionation was associated with a significant improvement in complete response (CR) rate (86% vs 50%, p=0.015) and 2-year disease free survival (59% vs 19%, p=0.031). There was a trend towards a significant improvement in 2-year loco-regional control (82% vs 56%, p=0.052); however, 2-year overall survival (59% vs 63%, p=0.96) was not significantly different.

Conclusion: In patients with DLBCL who were refractory to salvage chemotherapy, the use of salvage radiation therapy was associated with a high rate of conversion to ASCT eligibility in a group of patients that are frequently ineligible for ASCT. The use of accelerated fractionation compared to conventional fractionation SRT was associated with a significantly improve CR rate and DFS. Prospective trials are needed to further identify the patients that would derive the most benefit from accelerated fractionated SRT in this setting.

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Lung

The Incidence and Location of Brain Metastases Following HA-PCI Compared with Standard PCI in Small Cell Lung Cancer (SCLC) : A Phase III Trial

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Purpose/Objective(s): The multicenter randomized phase III trial NCT01780675 investigated memory functioning and safety after PCI with or without hippocampus sparing in Small Cell Lung Cancer (SCLC). This study focuses on the safety and reports the incidence and location of brain metastasis.

Materials/Methods: Patients with stage I-IV SCLC were randomized to standard PCI or hippocampus avoidance PCI (HA-PCI), in both arms 25 Gy/ 10 fractions was given, using IMRT or VMAT. Dose objective in the HA-PCI arm: mean dose in the right and left hippocampus ≤ 8.5 Gy (biological dose ≤ 6.1 Gy for $\alpha/\beta=2$ Gy) and $D_{1\%}$ hippocampus ≤ 10 Gy, D_{max} PTV < 28.75 Gy (115%) and $V_{115\%}$ PTV $\leq 1\%$. Neurocognitive functioning was assessed by a neuropsychological test battery at baseline, 4, 8, 12, 18 and 24 months after the irradiation. Primary endpoint: decline in the Hopkins Verbal Learning Test -Revised (HVLt-R) total recall at 4 months, where a decline of 5 or more out of a possible 36 points was considered a failure. Secondary endpoints: other cognitive outcomes, quality of life, structural brain damage on MRI at baseline, 4 and 12 months, circulating biomarkers and evaluation of the incidence and location of brain metastases.

Results: From April 2013 until March 2018 a total of 168 patients were randomized in 10 centers in the Netherlands and Belgium. The median follow-up time was 24.6 months. Median age was 64 years, 51% was female, and WHO performance score at baseline was 0-1 in 93%. The stage distribution was comparable in both arms (70% stage I-III- and 30% stage IV). All patients had a baseline MRI, on which 3 patients had brain metastases and were ineligible. All patients received 25 Gy in 10 fractions. A total of 23 patients developed brain metastases: 15 in the standard PCI group and 8 in the HA-PCI group. In 16 out of the 23 patients the brain metastases were asymptomatic. In nine patients and five patients the brain metastases were detected on the MRI at 4 and 12 months respectively (asymptomatic in 8/9 and 4/5). In 15 patients the brain metastases were multiple and 8 patients a single metastases was diagnosed. None of the patients developed a single brain metastasis in the hippocampus or avoidance region. In one patient with multiple metastases, the hippocampus avoidance region was involved.

Conclusion: This randomized phase III trial investigated the safety and reports on the incidence and location of the brain metastases after treatment of HA-PCI compared to standard PCI. With a median FU of 24.6 months, there was no significant difference in the incidence of brain metastases between standard PCI and HA-PCI. None of the patients developed a single brain metastases in the hippocampus or hippocampus-avoidance region.

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Phase III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for SMALL-CELL LUNG Cancer.

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Purpose/Objective(s): Clinical evidence suggests that radiation dose received by the hippocampus during whole brain radiotherapy may play a role in radiation-induced neurocognitive decline. To prospectively evaluate the neurocognitive (NC) benefit of hippocampal sparing (PCI-HA), we have developed a phase III clinical trial (PREMER) to test hippocampal sparing during PCI.

Materials/Methods: 118 patients undergoing PCI were randomized to receive PCI (n=60) or PCI-HA (n=58). The hippocampus was contoured, and hippocampal avoidance regions were created using a 5-mm volumetric expansion around the hippocampus. Linear accelerator –based intensity-modulated radiotherapy and Volumetric Modulated Arc Therapy treatment plans were generated for a prescription dose of 25 Gy in 10 fractions. The main objective was NC function at 3 months assessed by Free and Cued Selective Reminding Test (FCSRT). The FCSRT is a well-validated and reliable assessment of memory, including encoding, retrieval, and retention of new information over time.

Results: These treatment modalities spared the hippocampus, with a D100 of 8.4 ± 2.0 Gy and a maximum dose of 14.5 ± 3.3 Gy. There was a decline in free delayed recall in PCI vs PCI-HA arm at 3 months (21.7 vs 5.1%; p 0.01; OR 5 [IC 95% 1.36-18.87]) at 6 months (32.6 vs 7.3%; p 0.008; OR 6.1 [IC 95% 1.60-23.29]) and at 12 months (18.5 vs 3.8%; p 0.09; OR 5.7 [IC 95% 0.61-52.42])

Conclusion: There was a significant decline in memory in PCI group. Further investigation to assess its impact on long-term follow-up is in progress.

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A Prospective Single Arm Phase I/II Study: Consolidative Ipilimumab and Nivolumab with Thoracic Radiotherapy after Platinum Based Chemotherapy for Patients with Extensive-Stage Small Cell Lung Cancer

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Purpose/Objective(s): Patients with extensive stage small cell lung cancer (ES-SCLC) typically receive first line treatment with platinum doublet chemotherapy (CT). Consolidative thoracic radiotherapy (TRT) has also been shown to improve outcomes for patients with ES-SCLC. We hypothesized that the addition of ipilimumab (IPI) and nivolumab (NIVO) after TRT would improve the 6 month progression free survival (PFS, primary endpoint) and 12 month overall survival (OS, secondary endpoint) for patients with ES-SCLC and stable disease or better after at least 4 cycles of platinum CT.

Materials/Methods: This prospective single arm Phase I/II study enrolled 21 patients. Eligible patients demonstrated stable disease or better following platinum CT. Study therapy included consolidative TRT to a total dose of 30Gy in 10 fractions targeting any residual primary tumor

and all initially involved regional lymph node stations. Two weeks after TRT, patients received concurrent IPI (3mg/kg) and NIVO (1mg/kg) every 3 weeks for 4 planned doses followed by NIVO monotherapy (480mg) every 4 weeks until progression or up to 1 year. Archival tissue from initial diagnosis (n=15) and peripheral blood (n=20) were collected at serial time points for research purposes.

Results: The study planned to enroll up to 52 patients but was discontinued early due to a planned interim analysis after 21 patients had enrolled. The initial 6 patient safety lead in demonstrated an acceptable toxicity profile with the study therapy. The 6 month (mo) PFS estimate was 24% (95% CI: 9%-43%). The median PFS estimate was 4.5 mo (95% CI: 2.7-4.6). The median PFS follow up for those patients who have not progressed is 11.1 mo. The 12 mo OS estimate was 47% (95% CI 25%-66%). The median OS estimate was 11.7 mo (95% CI: 4.7-16.0). The median OS follow up for patients who remain alive is 14.4 mo. 52% of patients had at least 1 grade 3 or higher immune related adverse event (IRAE) possibly or definitely attributable to study therapy. Grade 3 pulmonary and GI IRAEs possibly or definitely attributable to study therapy were recorded in 19.1% and 23.8% of patients respectively. The only grade 4 IRAE toxicity was thrombocytopenia. One patient died without progression at 4.6 mo due to lung aspergillosis infection secondary to steroid and infliximab therapy delivered for treatment of study related grade 3 diarrhea.

Conclusion: Consolidative IPI and NIVO after platinum based CT and TRT demonstrated a toxicity profile consistent with the known AEs attributable to IPI and NIVO. The study regimen did not significantly improve the 6 mo PFS compared to historic estimates. The OS estimate at 1 year compares favorably with historic estimates. Biomarkers including tissue PD-L1 and estimation of tumor mutational burden, as well as flow cytometric characterization of the peripheral T cells and myeloid cells at baseline and during the treatment course will be presented.

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Accelerated Hypofractionated CRT Followed by SABR Boost (HyCRT-SABR) for Locally Advanced Unresectable NSCLC: A Prospective Phase II Radiation Dose-Escalation Study

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Purpose/Objective(s): To report on a completed Phase II prospective trial of Image-guided Hypofractionated CRT followed by dose-escalated (DE - 3 cohorts) SABR boost (HyCRT-SABR) for locally advanced unresectable NSCLC. Primary endpoint was to determine the maximal tolerated dose (MTD) or deliver a total dose of 75 Gy in 15 fractions (fx) with 3 weekly infusions of carboplatin-paclitaxel.

Materials/Methods: HyCRT-SABR was conducted at a single academic institution under local IRB/DSMB governance. All patients received an initial 10 fx of 4 Gy with CT, followed by 3 sequential cohorts of at least 7-15 patients of 5 Gy x 5, 6 Gy x 5, 7 Gy x 5 [total dose 65 gy in 15 fx – (LOW); 70 gy in 15 fx (INT); 75 Gy in 15 fx (HIGH)]. Study was designed to end if the rate of dose limiting toxicities (DLTs) within 90 days from treatment is $\geq 33\%$. MTD was defined as the immediately prior dose cohort. PET-CT/4DCT was performed for treatment planning with an ITV approach. In the first 40 Gy, PTV was defined as ITV + 5 mm. A repeat PET-CT/4DCT was performed at fx 8 or 9, with an adaptive re-plan

for the SABR boost. In the boost, ITV was the target volume (no PTV margin). Treatment was completed in 3 weeks without unintended breaks between initial vs. adaptive SABR boost. An intention-to-treat analysis was performed. Local control (LC), overall survival (OS) and progression-free survival (PFS) rates were estimated using the Kaplan-Meier method and survival rates compared using the log-rank test. Acute and late (≥ 90 days) toxicities were prospectively scored.

Results: The study did not reach DLT endpoint, and all 3 cohorts of DE were completed. From 2010 – 2018, a total of 28 patients were enrolled and treated on protocol. All patients had stage II or III NSCLC by AJCC 7th edition. Only one subject received consolidation durvalumab (end of enrollment period in 2018). Overall median f/u time was 18 months (mos), and for the 10 surviving patients it was 27 mos. Median OS for all patients was 27 mos, with 1 and 2-year OS rates of 78% and 52%. Median PFS was 12 mos, with 1 and 2-year PFS rates of 48% and 25%. 1, 2, 3-year LC rates were 91%, 82%, 82%. No statistical differences were seen in LC, PFS, and OS by LOW, INT, and HIGH dose cohorts ($p = ns$). Overall cumulative incidences of non-hematological rates of acute and late \geq grade 3 toxicities were 11% and 7%. Numerically, there were higher rates of acute and late pulmonary \geq grade 3 toxicities in HIGH vs. LOW+INT cohorts (22% vs 0%, $p=1$; 11% vs 0%, $p=.3$). However, there were no differences in the rates of acute and late esophageal \geq grade 3 toxicities in HIGH vs. LOW+INT cohorts (0% vs 5%, $p=1$; 0 vs 5%, $p=1$).

Conclusion: MTD was determined to be 70 Gy in 15 fx. OS of 27 mos in this study is similar to the 60 Gy arm of RTOG 0617 and CRT alone arm in PACIFIC (29 mos). HyCRT-SABR appears effective, convenient, and well-tolerated. With improvement in OS by adding durvalumab to standard CRT, this HyCRT-SABR regimen appears promising as a back-bone treatment to test and integrate immunotherapy.

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Left Coronary Artery Dose Exposure Predicts Major Adverse Cardiac Events in Coronary Heart Disease Negative Lung Cancer Patients

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Purpose/Objective(s): Validated cardiac dose constraints to predict radiotherapy (RT)-associated Major Adverse Cardiac Events (MACE) in patients with non-small cell lung cancer (NSCLC) are lacking. We sought to identify cardiac substructure dose variables predictive of MACE (myocardial infarction, cardiac death, revascularization, heart failure).

Materials/Methods: Retrospective analysis of 449 consecutive locally-advanced NSCLC patients treated with thoracic RT and without pre-existing coronary heart disease was performed. Cardiac chambers (left and right atria, ventricles), coronary arteries (left main, left anterior descending [LAD], left circumflex [LCx], right, posterior descending), and whole heart were manually delineated in MIMvista according to published contouring guidelines. Mean (Gy), max (Gy), and volume (%) receiving X Gy dose (VX Gy, in 5 Gy increments to 70 Gy) were obtained for each structure. Receiver operating curve (C-index) and cut-point analyses were performed. Cumulative incidence estimates and Fine and Gray regressions were adjusted for non-cardiac death as a competing risk.

Results: The median delivered mean heart dose was 12.3 Gy. After a median follow-up of 33 months, 24 patients developed ≥ 1 MACE (1-year cumulative incidence, 2.5% [95% CI 1.3-4.2]). Baseline Framingham risk was low or moderate in 51% and high in 49%. The best-performing dose parameter (C-index) and cut-point by substructure was LCx V15 Gy (.76) <15%, LAD V15 Gy (.76) <23%, left ventricle V15 Gy (.73)

<3%, posterior descending mean (.70) <2 Gy, whole heart V20 Gy (.69) <24%, right ventricle mean (.69) <4 Gy, left main V20 Gy (.69) <82%, while both atria and right coronary artery were ≤ 65 . Specifically, a LCx V15 Gy $\geq 15\%$ vs. $<15\%$ (sensitivity 83%, specificity 64%) corresponded to an 8-fold increase in 1-year MACE cumulative incidence (5.4% [95% CI 2.6-9.5] vs. 0.7% [95% CI 0.2-2.4], respectively; $P < .001$). Similarly, a LAD V15 Gy $\geq 23\%$ vs. $<23\%$ (sensitivity 83%, specificity 63%) corresponded to a 14-fold increase in 1-year MACE cumulative incidence (5.7% [95% CI 2.9-9.8] vs. 0.4% [95% CI 0.0-1.9], respectively; $P < .001$). Adjusting for baseline Framingham risk, both LCx and LAD V15 Gy were associated with a significantly increased risk of MACE (adjusted hazard ratio, AHR [1.02%, 95% CI 1.01-1.03]; $P < .001$) and (AHR [1.03%, 95% CI 1.02-1.04]; $P < .001$).

Conclusion: Despite the competing risk of cancer-specific death in NSCLC patients, left circumflex V15 Gy $\geq 15\%$ and left anterior descending V15 Gy $\geq 23\%$ confer an 8- and 14-fold increase, respectively (5% absolute for each), in the 1-year cumulative incidence of MACE in patients without baseline coronary heart disease. These newly identified left coronary dose-volume thresholds are worthy of further study for validation as critical cardiac substructure dose constraints for RT planning are currently lacking.

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The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R): Real-World Data on Elderly Stage III Non-Small Cell Lung Cancer Treated with Definitive Chemoradiation

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Purpose/Objective(s): The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R) is a national lung cancer registration that started in 2013 for patients treated with radical or curative intent radiotherapy. For elderly patients with locally advanced non-small cell lung cancer (NSCLC), real-world data is essential to be able to balance treatment toxicity and treatment outcome. The aim of this study is to analyze definitive chemoradiation (CRT) in elderly patients above 75 years of age with stage III NSCLC.

Materials/Methods: All patients receiving primary thoracic radiation treatment with radical or curative intent for (primary or recurrent) stage I-III lung cancer are included in this population-based study. Information is collected on patient, tumor and treatment characteristics, as well as the incidence and severity of acute toxicity. Descriptive statistics were used to compare patients ≤ 75 years with patients > 75 years who were treated for stage III NSCLC between 2017 and 2018 with sequential chemoradiation (seqCRT) or concurrent chemoradiation (cCRT). cCRT is scored in case radiotherapy started within 30 days after the start of chemotherapy. We studied toxicity as well as mortality within three months after the end of radiotherapy.

Results: Out of all 20 Dutch departments of radiation oncology, 19 centers participate in the registry. A total of 1.523 NSCLC stage III patients were treated with CRT. 18% of these patients were >75 years (mean 79 years), and 45% of these patients was treated with cCRT while for the ≤75-year group (median 65 years) 67% was treated with cCRT. Good performance (WHO 0-1) for patients ≤75 years was 87% vs. 81% in case >75 years old. Acute 3-month toxicity (grade ≥3) was scored in 18% of the younger patients and in 15% of the older patients. The 3-month mortality rate calculated after the end of radiotherapy was 5% for the younger patients and 9% for the patients >75 years of age. Comparing concurrent vs sequential CRT showed for the younger patients grade ≥3 toxicity and mortality within three months of 18% and 4% for cCRT and 18% and 7% for seqCRT respectively. For the elderly, the grade ≥3 toxicity and mortality was 18% and 9% for cCRT and 14% and 8% for seqCRT respectively.

Conclusion: This Dutch audit provides real-world data for stage III NSCLC patients treated with CRT. Only 44.8% of the elderly were treated with cCRT while this was 67.2% for the younger patients. The acute grade ≥3 toxicity was identical in both cCRT groups. The overall three months mortality after the end of radiotherapy was 5% in the younger patients versus 9% in the elderly.

		Non-Elderly n=1.300	Elderly n=223	p-value
Age	Mean (SD)	63.97 (7.7)	78.71 (2.5)	<0.01
Gender	Male	53.2%	70.0%	<0.01
WHO	0-1	86.6%	80.7%	0.01
Clinical stage (TNM-8)	IIIA - B - C	45.6 - 43.5 - 10.9%	50.7 - 40.8 - 8.5%	0.30
Chemoradiation	Concurrent	67.2%	44.8%	<0.01
	Sequential	22.8%	47.5%	
	Missing	10.0%	7.6%	
Toxicity	Grade ≥3	17.5%	15.2%	0.16
Mortality	<90 days	4.5%	8.5%	0.02

Table 1. Patient, tumor, and treatment characteristics of all stage III patients included in de database

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Palliative Care

LBA 3

Primary outcomes of a phase II randomized trial of Observation versus stereotactic ablative Radiation for OLigometastatic prostate CancEr (ORIOLE)

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Purpose/Objective(s): Mounting evidence supports complete metastatic ablation for oligometastatic cancer but the relevance of this approach to oligometastatic prostate cancer (OMPC) remain an area of active study. Importantly, biomarkers to determine patients who benefit most from complete ablation are unknown. We hypothesize that stereotactic ablative radiation (SABR) will improve oncologic outcomes in men with OMPC.

Materials/Methods: In this phase II randomized trial, men with recurrent hormone-sensitive OMPC (1-3 radiation fields) were stratified by primary management (radiotherapy vs surgery), PSA doubling time, and prior androgen deprivation therapy and randomized 2:1 to SABR or observation (OBS). The primary endpoint was progression at 6 months by PSA ($\geq 25\%$ increase and \geq nadir + 2 ng/mL), conventional imaging (RECIST 1.1 criteria or new lesion on bone scan), or symptomatic decline. Tissue, liquid and imaging correlative studies were obtained and analyzed as biomarkers.

Results: From 5/2016-3/2018, 54 patients were randomized. Progression at 6 months was observed in 19% of patients in the SABR arm and 61% of patients in the OBS arm (ITT, $p=0.005$). Median progression-free survival (PFS) was not reached for men treated with SABR and 5.8 months for men who underwent OBS (HR 0.30, $p = 0.0023$). Of 35 patients in the SABR arm who received PSMA-based PET/CT imaging at baseline and 6 months, those with total consolidation of radiotracer-avid disease were less likely to develop new lesions at 6 months (16% vs 63%, $p = 0.006$) and had significantly longer median PFS (unreached vs 11.8 months, $p = 0.003$) and distant metastasis-free survival (DMFS) (29 vs 6.0 months, $p = 0.0008$). No grade III or higher toxicity was observed. Deep sequencing of T-cell receptor DNA identified significantly more clonotypic expansions ($p = 0.03$) between baseline and day 90 with SABR than with observation, greater peripheral baseline clonality was correlated with progression at 180 days in the SABR arm only, and clusters of similar expanded T-cell receptors were identified in 3 patients after SABR. Analysis of circulating tumor DNA (ctDNA) is in progress.

Conclusion: SABR for OMPC affords significant benefits in freedom from progression at 6 months and PFS. In fact, the PFS for patients treated with SABR still has not been reached and is well over one year. Total consolidation of disease identified by PSMA-PET with SABR provides a substantial advantage in DMFS (4.8 times greater) when compared to subtotal consolidation. SABR also induces a systemic adaptive immune response and baseline clonality was associated with predictive response to SABR. These results underline the importance of prospective randomized investigation of the oligometastatic state with concurrent collection of imaging and biological correlates.

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Pilot Assessment of the BMET Decision Support Platform: A Tool to Improve Provider Survival Estimates and Selection of Prognosis-Appropriate Treatment for Patients with Symptomatic Bone Metastases

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Purpose/Objective(s): Previously, we developed the BMET random survival forests model, which uses 27 covariates to estimate survival in patients seen in consultation for palliative radiotherapy (RT) to symptomatic bone metastases. In the present study, we conducted a pilot assessment of the clinical utility of this model and an associated decision support platform (DSP).

Materials/Methods: To facilitate clinical use of the BMET model, we constructed a DSP that (1) collects covariate data and displays a patient-specific predicted survival curve, and (2) provides case-specific, evidence-based recommendations for RT, open surgery, systemic therapy (ST), and hospice referral in the care of symptomatic bone metastases. Five trainee and 5 attending physicians in Radiation Oncology participated in the DSP assessment. A total of 55 patient cases were randomly selected from the 397 patients used to build the BMET model; each predicted survival curve displayed as part of the DSP was refitted leaving the case patient out. Relevant case data including BMET covariates were summarized and presented to physicians at 2 times: without and then with use of the DSP (separated by a 3-week washout). At each time, physicians were asked to estimate patient survival in the 12 months following RT consultation; their confidence in and likelihood of sharing this estimate with the patient (increasing 1-10 scales); recommendations for open surgery, ST, and hospice referral; and preferred RT regimen (0, 1, 5, 10, or >10 conventional fractions or stereotactic RT). Wilcoxon signed-rank test evaluated paired survival estimates and rating scales, and McNemar's test compared accuracy of survival estimates at clinically relevant binary time points.

Results: Assessment completion rate was 96%. Pre- vs. post-DSP, physicians' estimates of survival were mean 7.9 (SD 3.6) vs. 6.9 (SD 3.7) months, respectively, $p < 0.001$. There was a significant reduction in overestimation of true minus estimated survival time, with a mean difference of -2.1 (SD 4.1) vs. -1 month (SD 3.5), $p < 0.001$. This improvement was observed across training level. Accuracy of survival predictions were significantly improved at binary time points of < 3 (72 vs. 79%, $p < 0.001$), ≤ 6 (64 vs. 71%, $p = 0.007$), and ≥ 12 months (70 vs. 81%, $p < 0.001$). Median ratings of confidence in and likelihood of sharing prognosis each increased from 6 to 8, both $p < 0.001$. There was greater concordance in matching use of 1-fraction RT with true survival < 3 months (70 vs. 76%, $p = 0.001$) and < 10 fraction RT with true survival < 12 months (55 vs. 62%, $p = 0.006$). Improvements noted in hospice referral, ST, and surgical interventions were not statistically significant.

Conclusion: In this pilot study, use of the BMET-DSP significantly improved physician accuracy in estimating survival and increased prognostic confidence, likelihood of sharing prognosis, and use of prognosis-appropriate RT regimens in the care of symptomatic bone metastases. These data support future multi-institutional validation of the DSP.

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Rapid Access Multidisciplinary Bone Metastases Clinic Decreases Financial Toxicity for Patients Undergoing Palliative Radiation

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Purpose/Objective(s): A rapid access bone metastases clinic (RABC) was instituted at MD Anderson Cancer Center (MDACC) to allow consult, simulation and treatment in <6 hours for patients with painful bone metastases. Patients referred to the RABC underwent multidisciplinary evaluation with orthopedics and radiation oncology. “Financial toxicity,” distress due to out-of-pocket costs associated with a treatment, is an important factor when assessing the implementation of new radiation methods. Our goal was to determine whether RABC decreased financial toxicity for MDACC patients over traditional treatment.

Materials/Methods: Patients referred for consideration by RABC between April 2018 and January 2019 were surveyed. Patients were asked to estimate out of pocket costs for radiation treatment (including prescriptions, copays, hotels, travel costs and miscellaneous expenses) and overall cost burden of treatment. Out of pocket costs for patients treated in RABC (N=31) and out of RABC (n=18) were compared. To eliminate time bias, this group was then screened to only compare patients receiving 8Gy in 1 fraction through the RABC (N=27) or outside the RABC (N=8). Travel distance was computed using hometown distance from MDACC. Local patients were those with travel distance <100 miles. Wilcoxon rank-sum test was used to make comparisons between groups. Finally, patient self-assessment of cost-burden on a scale of 1 to 10, with 10 being “very satisfied”, was analyzed for those treated in RABC (N=33) and out of RABC (N=23).

Results: Median out of pocket cost was significantly lower for RABC patients vs. non- RABC patients treated in one fraction (\$500 [IQR \$200-\$1,200] vs. \$3,500 [\$625-\$17,500]; p=0.037). Median travel distance was not significantly different for patients treated in RABC vs. out of RABC (229 [40-380] vs. 133.5 [8.25-620]; p=0.33). Travel distance was directly correlated with out of pocket cost (R²=0.2; p=0.006). Overall patient satisfaction with cost burden was high regardless of treatment setting (10 [8-10] vs. 10 [10-10]; p=0.543).

Conclusion: The establishment of a rapid access bone metastases clinic at MDACC significantly decreased overall financial toxicity for patients receiving palliative radiation. Increased financial toxicity was associated with longer travel distance for palliative radiation. Implementation of a similar model in local community centers offers an opportunity to further decrease financial toxicity for patients receiving palliative radiation.

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A Prospective Randomized Phase II Trial of Single-Fraction versus Multi-Fraction Stereotactic Spine Radiosurgery for Spinal Metastases: An Initial Analysis

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Purpose/Objective(s): The optimal schedule of spinal stereotactic radiosurgery (SSRS) for patients with limited spinal metastases is not well established and has never been investigated in a prospective randomized trial. The present randomized phase II study aimed to compare 2 SSRS schedules to determine which results the lowest rate of grade 3 or higher protocol-specified adverse events at 4 months.

Materials/Methods: Patients with biopsy-proven non-hematogenous malignancy and limited un-irradiated spine metastases not requiring upfront spine surgery were eligible. Patients were randomized to receive either 16 Gy in 1 fraction or 24 Gy in 3 fractions on every other day. This study was designed to detect a protocol-specified adverse event rate > 20% at a 10% significance level (1-sided) and 90% power. Secondary analysis included time to treatment failure, which was defined as presence of grade 3 or higher adverse events or unequivocal local progression of treated spine(s) indicative of re-irradiation or surgical intervention. Designating the preferable of the 2 schedules was based on rules of protocol-specified adverse events and treatment failure rate for each arm.

Results: Between November 2015 and October 2018, 50 patients (pts) were enrolled for SSRS to 75 metastatic spinal lesions, including 41 lung cancer, 2 breast cancer, 2 head and neck cancer, 2 liver cancer, 2 prostate cancer, and 1 colon cancer. The median age was 62 years old (range 36-79). There were 1 cervical, 41 thoracic, 31 lumbar, and 2 sacral sites for SSRS. Twenty-six patients were randomized to the single-fraction (SF) arm, and 24 patients were randomized to the multi-fraction (MF) arm. The median follow-up time was 11.73 months (range 0.67-39 months). At 4 months, none of the 25 evaluable patients in the SF arm experienced any protocol-specified grade 3 or higher toxicity, but 1 out of the 21 evaluable patients in the MF arm underwent surgical intervention due to progressive compression fracture. During longer follow-up, 2 patients in the SF arm and five additional patients in the MF arm developed treatment failure. The median time to treatment failure was 13.5 months for SF arm, and 8 months for MF arm. The one-year treatment failure rate was significantly worse in the MF arm (SF 5.6% versus MF 14.3%, p=0.04).

Conclusion: Both SF and MF SSRS seem safe and the SF arm has met its primary endpoint. The interim analysis suggests 16 Gy in single fraction might be the preferable SSRS schedule and warrants longer follow-up as well as further investigation.

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Improving the Palliative Patient Journey in Radiation Oncology

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Purpose/Objective(s): Radiotherapy (RT) has an important role in the symptomatic relief and improvement in the quality of life for patients with bony and soft tissue metastases. We hypothesised a streamlined palliative care pathway by removing the need for a simulation computed tomography (sCT) scan. The aim of this study was to investigate the use of the patient's diagnostic CT (dCT) dataset to produce palliative 3D conformal radiotherapy (3D-CRT) treatment plans.

Materials/Methods: The impact on dose distribution of Hounsfield Units (HUs) variance from different dCT sources, patient position and couch curvature was assessed retrospectively. From 150 patients treated with palliative 3D-CRT, a sample of 92 diagnostic datasets covering the most common treatment sites were used. A slab geometry phantom was created in the treatment planning system to compare the dosimetric impact of variance in HU. Dosimetric evaluations were undertaken by comparing the clinical plan calculated with fixed monitor units on the dCT. The integration of dCT treatment planning into the palliative care path was done prospectively. Patients booked for palliative RT (1 to 5 fractions), and a dCT acquired within the last 4 weeks, were included. The dCT had to encompass the area of interest and have a complete field of view including body contours. Patients were then simulated as per standard department protocol, but in the dCT position. Treatment was dual planned on the dCT and the sCT and delivered with daily image guidance as per routine treatment.

Results: The mean HU for vertebra (n=12), femoral head (n=17), lung (n=22) and soft tissue (n=41), was 185±50, 416±125, -741±91, and 59±41 respectively. From tissue slab phantoms, dose differences due to HU variation resulted in lung HU changes that impact dosimetry in the order of 3-5% for 6MV. In patient dCTs, uncertainty in dose calculation due to HU variation in the lung was in the order of 2.5-5% for 10MV and 1.5-3.5% for 18MV which needs to be considered when calculating on diagnostic scans since the higher the energy, the less impact change in HU has on dose. From the retrospective analysis, the most suitable treatment sites for the application of dCT planning were the abdomen, lumbar or thoracic spine, pelvis and sacrum. Of the first 35 patients planned and treated with dCT, 28 plans used 18MV, 6 plans 6MV and one plan 6/18MV mix. A curved full body vac-bag was designed to enable better replication of the posterior body curvature in dCTs for treatment. Dosimetric evaluations were made between the dCT and pre-treatment cone beam CT in 32 patients, with the planning target volume (PTV) dose difference being <2% in 29 patients.

Conclusion: 3D-CRT plans for patients with bony and soft tissue metastases can be produced using dCT, eliminating the need for the sCT. This was demonstrated to be feasible and has been implemented as a standard clinical care pathway, with major implications for improving the care journey for patients with metastatic cancer.

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Single-Fraction Stereotactic versus Conventional Multifraction Radiation for Predominantly Non-Spine Bone Metastases: A

Randomized Phase II Trial

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Purpose/Objective(s): There lacks a consensus for the optimal radiotherapy dose and fractionation including the role for stereotactic body radiation therapy (SBRT) in treatment for bone metastases. The purpose of this randomized trial was to assess the efficacy of dose escalated SBRT vs standard multi-fraction (SMF) radiation therapy for the alleviation of pain in patients with predominantly non-spine bone metastases.

Materials/Methods: We performed the first, prospective randomized phase II trial at a single institution from September 2014 to June 2018 enrolling patients with radiologically confirmed painful bone metastases. Patients were randomly assigned by a 1:1 ratio to receive either single SBRT (12 Gy if ≥4 cm or 16 Gy if <4 cm lesion) vs SMF with 30 Gy delivered in 10 fractions. The primary endpoint evaluated was progression of pain defined as worsening pain score (by at least 2 categories by MDASI survey), >50% increase in dose of opioid medication, re-irradiation rate, and pathologic fracture. We used international consensus criteria to assess overall pain response (sum of CR+PR) taking into account MD Anderson Symptom Inventory (MDASI pain score) and MED for daily analgesic consumption. We hypothesize SBRT was non-inferior to SMF using a Hazard ratio of 1.5. **Results:** Among evaluable patients who received treatment per protocol, the single-fraction group had more pain responders (CR+PR) at 2 weeks (62% vs. 36% multifraction, $P=0.01$), at 1 month (62% vs 36%, $P=0.01$), at 3 months (72% vs. 49% multifraction, $P=0.03$), and at 9 months (77% vs. 12% multifraction, $P=0.03$). Local progression-free survival rates were higher in the SBRT group at 1 year (100% vs. 90.5% multifraction) and at 2 years (100% vs. 75.6%) ($P=0.01$). There was no difference in toxicity or MDASI symptoms score after SBRT or SMF. **Conclusion:** Delivering higher single SBRT dose appears to be non-inferior and an effective treatment

option for patients with painful bone metastases. For evaluable patients, SBRT demonstrated a higher rate of pain response (CR+PR) compared to SMF, therefore should be considered for patients with longer expected survival.]]]

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Quality of Life Outcomes after Stereotactic Ablative Radiotherapy (SABR) vs. Standard of Care Palliative Treatments: A Secondary Analysis of the SABR-COMET Randomized Trial

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Purpose/Objective(s): The use of SABR in patients with oligometastases has been associated with improvements in progression-free survival and overall survival. Quality of life (QoL) is of substantial importance in the metastatic setting, since treatments have historically been considered palliative-intent. However, randomized data assessing the longitudinal QoL impact of SABR in the oligometastatic setting are lacking. Herein we report longitudinal QoL outcomes from the SABR-COMET randomized trial.

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 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 standard of care (SOC) treatment [SOC Arm] vs. SOC plus SABR to all metastatic lesions [SABR Arm]. Due to the wide variety of tumor sites and treatment targets included, QoL was measured using a general tool, the Functional Assessment of Cancer Therapy – General (FACT-G), which includes 4 subscales: Physical Well Being, Social/Family Well Being, Emotional Well Being, and Functional Well Being. A 5-point decline in the total FACT-G scale, or a two-point decline on a subscale, is generally considered a clinically meaningful change (CMC). QoL changes over time and between groups was assessed with linear mixed modeling.

Results: Ninety-nine patients were randomized (33 in Arm 1, 66 in Arm 2). Median age was 68 (range: 43-89) and 60% 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. Median follow-up was 26 months. Because of the inferior survival of the SOC arm, as previously reported, the time for attrition in QoL respondents to <10% of subjects was shorter in the SOC vs SABR arm (30 vs. 42 months). In the whole cohort, QoL declined over time after randomization: there were significant declines in total FACT-G score over time compared to baseline (p<0.001), due to declines in physical and functional subscales (both p<0.001), with no declines in social and emotional subscales. However, the magnitude of declines were small, and CMCs were not seen at most time points. Comparison between arms showed no differences in QoL between the SABR and SOC arms in total score (p=0.42), or in the physical (p=0.98), functional (p=0.59), emotional (p=0.82) or social (p=0.17) subscales.

Conclusion: For patients with oligometastases, average QoL declines slowly over time regardless of treatment approach, although the changes are small in magnitude. The use of SABR, compared to SOC, was not associated with a QoL detriment. This suggests that QoL changes are due to underlying disease processes over time. (NCT01446744)

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Pre-Treatment and Early Post-Radiotherapy PET Metabolic Metrics Predict Probability of Local Relapse in Oligometastases

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Purpose/Objective(s): To assess pre-treatment and early post-treatment Positron Emission Tomography (PET) standardized metrics as predictors of long-term local outcomes of single dose radiation therapy (SDRT) and hypofractionated stereotactic body radiotherapy (SBRT) in extracranial oligometastatic lesions.

Materials/Methods: Between November 2011 and July 2018, 559 lesions in 169 consecutive patients were treated in a phase II study of oligometastasis-directed ablative radiotherapy using a PTV prescription dose of 24Gy SDRT, or a non-toxic 3x9Gy SBRT schedule when 24Gy was unfeasible due to dose/volume serial organs constraints. A total of 427/559 (76%) and 132/559 (24%) lesions were treated with SDRT and SBRT respectively. SUV_{max} values were computed pre-treatment, at 3 and 6 months post-treatment, and at 6 months intervals thereafter. Tumor response was scored according to PERCIST criteria, confirmed by morphologic imaging. Correlations of baseline SUV_{max} and its decline (ΔSUV_{max}) with actuarial local relapse free survival (LRFS) were analyzed by Cox proportional regression.

Results: at a median follow-up of 32.4 (range 6 - 74.3) months the actuarial 5-year LRFS was 92% for 24 Gy SDRT and 38% for 3 x9Gy SBRT, respectively ($P < .0001$). A total of 70/559 lesions (12%) developed recurrences within the irradiated region, 24/427 (6%) and 46/132 (34%) for SDRT and SBRT, respectively. Baseline SUV_{max} value of 10.2, a statistically calculated optimal cut-off point, significantly dichotomized the probability of LRFS, yielding 86% vs 63% ($P = .001$) probability for <10.2 and ≥ 10.2 , respectively. The respective values for the SDRT- and SBRT-treated lesions were 93% vs 92% ($P = .29$) for 24Gy SDRT, and 63% vs 31% ($P = .03$) for 3x9Gy SBRT. A ΔSUV_{max} decline of $>75\%$ was associated with 86% actuarial 5-year LRFS vs. 72% for $\Delta SUV_{max} \leq 75\%$ ($P < 0.0001$) for the entire cohort, differing for 24Gy SDRT (96% vs 88%; $P = .007$) and 3x9Gy SBRT (66% vs 30%; $P < .0001$), respectively. A multivariate Cox analysis confirmed ΔSUV_{max} as the only independent covariate in predicting LRFS. Bivariate analyses using permutations of baseline SUV_{max} and ΔSUV_{max} at three months categorized the probability of 5-year actuarial LRFS, yielding 93% for lesions with <10.2 SUV_{max} at baseline and $>75\%$ ΔSUV_{max} decline post-treatment, 77% for lesions with one adverse PET metric, and 53% for both adverse (>10.2 SUV_{max} and $\leq 75\%$ ΔSUV_{max}) PET metrics, respectively ($P < .0001$). For 3x9Gy SBRT-treated lesions alone the respective probabilities were 90% vs 42% vs 11% ($P < .0001$), respectively.

Conclusion: A combination of pretreatment and early post radiation PET metabolic metrics can be used to generate of a nomogram for use in clinical decision-making on whether to re-treat areas at high risk of local failure adjuvantly, when early and definitive tumor ablation is deemed critical for cure of oligometastatic disease. An approach to prospectively study this hypothesis is currently under consideration.

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A Volumetric Dosimetry Analysis of Vertebral Body Fracture Risk after Spine Stereotactic Radiosurgery

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Purpose/Objective(s): Vertebral compression fractures (VCF) are a complication of spine stereotactic radiosurgery (sRS). It is currently unclear how the heterogeneity of radiation dose delivered to a vertebral body affects the occurrence of VCF. In this study, we sought to analyze how volumetric dosimetry and clinical factors were associated with the development of VCF.

Materials/Methods: We evaluated 173 spinal segments undergoing single fraction sRS in 85 patients from a retrospective database at a single tertiary care institution. Vertebral bodies were contoured and detailed dosimetric variables were collected. Competing risk models were used to evaluate the effect of clinical and dosimetry variables on the risk of VCF. Sensitivity analysis was performed to obtain cutoffs of 90% sensitivity.

Results: Our primary endpoint was development of post-sRS VCF. Fractures were noted in 21/173 vertebrae (12.1%); of these, 12 were de novo and 9 were progressive. The median time to fracture was 11 months. Median follow up time was 14.2 months. In total, 69 vertebral bodies were lumbar, 82 were thoracic, and 22 were cervical. The median prescribed dose for both groups was 18 Gy (IQR 16-18). On multivariable analysis, the percentage of vertebral body volume receiving >20 Gy (HR 1.04, p=0.03) and >24 Gy (HR 1.10, p=0.04) were significantly associated with increased risk of VCF. No other patient or dosimetric variables were found to be significant on multivariable analysis. Sensitivity analysis revealed that the percentages of vertebral body volume receiving >20 Gy and >24 Gy required to obtain 90% sensitivity for predicting vertebral body fracture are 24% and 0%, respectively.

Conclusion: sRS treatment plans that permit increased doses of >20 Gy and >24 Gy to larger vertebral body volumes are associated with increased risk of VCF. In order to minimize the risk of post-sRS VCF, the percentage of vertebral body volume receiving >20 Gy and >24 Gy should be less than 24% and 0%, respectively. These results may help guide clinicians in treatment planning for patients at high risk for VCF following sRS.

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Patient Safety

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Optimizing Efficiency and Safety in External Beam Radiotherapy Using Automated Plan Check (APC) Tool and Six Sigma Methodology

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Purpose/Objective(s): To develop and implement an Automated Plan Check (APC) tool using a Six Sigma methodology with the aim of improving safety and efficiency in external beam radiotherapy.

Materials/Methods: The *Six Sigma* Define-Measure-Analyze-Improve-Control (DMAIC) framework was used by measuring defects stemming from treatment planning that were reported to the departmental incidence learning system (ILS). The common error pathways observed in the reported data were combined with our departmental physics plan check list, and AAPM TG-275 identified items. Prioritized by Risk Priority Number (RPN) and severity values, the check items were added to the APC tool developed using a treatment planning system programming interface. At 9 months post-APC implementation, the tool encompassed 89 check items, and its effectiveness was evaluated by comparing RPN values and rates of reported errors. To test the efficiency gains, physics plan check time and reported error rate were prospectively compared for 20 treatment plans.

Results: The APC tool was successfully implemented for external beam plan checking. FMEA RPN ranking re-evaluation at 9 months post-APC demonstrated a statistically significant average decrease in RPN values from 129.2 to 83.7 ($p < 0.05$). After the introduction of APC, the average frequency of reported treatment-planning errors was reduced from 16.1% to 4.1%. For high-severity errors, the reduction was 82.7% for prescription/plan mismatches and 84.4% for incorrect shift note. The process shifted from 4σ to 5σ quality for isocenter shift errors. The efficiency study showed a statistically significant gain in plan check time (10.1 ± 7.3 minutes, $p = 0.005$) and decrease in errors propagating to physics plan check (80%).

Conclusion: Incorporation of APC tool has significantly reduced the error rate. The DMAIC framework can provide an iterative and robust workflow to improve the efficiency and quality of treatment planning procedure enabling a safer radiotherapy process.

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Quality Assurance of Contouring for NRG Oncology/RTOG 1308 Clinical Trial Based on Automated Segmentation with Deep Active Learning

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Purpose/Objective(s): High quality data for clinical trials requires that contours are generated in compliance with definitions in protocol. The current NCI-funded Imaging and Radiation Oncology Core (IROC) workflow includes manual review of the submitted contours, which is time-consuming and subjective. In this project, we developed an automated quality assurance (QA) system based on a segmentation model trained with deep active learning to detect contouring errors automatically and improve the current clinical workflow.

Materials/Methods: The study used data that included a golden atlas with 36 cases from ‘Lung CT Segmentation Challenge 2017’ and 110 cases from NRG Oncology/RTOG 1308, which was divided into three groups: the first 70 cases enrolled were used as the candidate set, the following 40 cases were randomly assigned to a validation set (20 cases) and a test set (20 cases). The OARs included heart, esophagus, spinal cord, left and right lung. The proposed QA system was based on automated segmentation that consisted of four steps. First, we trained a convolutional neural networks (CNN) segmentation model with the golden atlas, even though it does not represent the whole population. This deficiency is overcome with the second step where we selected quality images from the candidate set to be added to the training set for fine-tuning of the model. The image selection strategy was based on the representativeness, defined with a parameter combined with the ‘uncertainty’ and ‘accuracy’ (quantities for image segmentation performance evaluation). We utilized the top 30% samples from the candidate set from the ranking of the representativeness and repeated the first two steps twice. Third, after the fine-tuning, we evaluated the accuracy of the segmentation model on the

validation set, of which the contours were verified for its accuracy. The metrics included Dice and Hausdorff distance. The mean and standard deviation (σ) of the two metrics for each OAR were calculated and the QA passing criteria were set with a threshold of mean $\pm 1.96\sigma$. Finally, we applied the fine-tuned CNN model and the decision criteria to the test set to assess the performance of the QA system. The quantitative metrics included balanced accuracy, sensitivity, specificity and the area under the receiving operator characteristic curve (AUC).

Results: The proposed QA method achieved promising contour error detection, with balanced accuracy of 0.96, 0.95, 0.96, 0.97 and 0.97, sensitivity of 0.95, 0.98, 0.96, 1 and 1, and specificity of 0.98, 0.92, 0.97, 0.94 and 0.94, AUC of 0.96, 0.95, 0.96, 0.97 and 0.94, for heart, esophagus, spinal cord, left and right lung, respectively. The CT slices with error-containing contours can be detected for further evaluation.

Conclusion: We have created a system that can automatically detect contour errors for multi-center clinical trial quality assurance. The implementation of such a system in clinical trials can provide consistent and objective evaluations with much reduced investigator intervention.

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Reducing Treatment Delays with a Modified No-Fly Policy

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Purpose/Objective(s): Delays in the start of radiation treatment potentially affect the timeliness of treatment for cancer patients. The purpose of this work was to assess the impact of changing the scheduling time point from the date of the initial CT simulation to that of approval of the treatment plan on these delays.

Materials/Methods: The treatment planning workflow in our department has been coordinated electronically since 2008 using quality checklists, oncology information systems, and an in-house whiteboard. Patients were traditionally scheduled for their treatment to be initiated a set number of days following CT simulation. Approximately 10% of treatments were observed to be delayed annually following the implementation of a no-fly policy (NF1). Per this policy for safety reasons treatment starts were proactively delayed or interlocked respectively when high-risk planning tasks were either delayed or incomplete. Analyses of underlying causes in our incident learning system indicated that certain delays in planning process steps were not necessarily predictable at the time of CT simulation. We changed the time point to schedule treatment initiation to coincide with plan approval instead to mitigate the uncertainties associated with knowing upfront the likelihood of such delays, and modified our relevant no-fly policy rules accordingly (NF2). In order to assess the impact of changing the scheduling time point we extracted metadata from our whiteboard for computation of fraction of IMRT treatment starts that were delayed, timeliness of planning tasks, as well as turnaround intervals between CT simulation and treatment start. We compared findings for NF1 (2010-2014) with those for NF2 (2015-2018).

Results: Compared with NF1, the fraction of treatment starts that were delayed due to planning issues fell from 10.1% to 1.3% (p-value 0.004) in NF2. Those delays that were proactively enforced due to planning task delays fell from 8.2 to 0.0%. No statistically significant difference was observed in treatment starts interlocked for incomplete work or missing documentation. Timeliness of task completion improved statistically significantly for plan uploads and second physics checks but not for contours. The turnaround from CT simulation to treatment start increased from 10.6 to 11.1 days (p-value 0.001). The interval between pre-planning peer review of contours and treatment start increased from 8.3 to 8.4 days, however this change was not statistically significant.

Conclusion: Changing the time point for scheduling treatment starts from the CT simulation date to the date of plan approval has led to significant reduction in treatment start delay rates resulting from delays in the planning process. The no-fly culture continues to prevent potentially unsafe treatment starts by maintaining the integrity of forcing functions, while enabling greater flexibility in meeting planning task deadlines, yet has not increased the overall time to initiate therapy following pre-planning peer review.

Author Disclosure: **L. Potters:** None. **H. Chou:** None. **A. Kapur:** ; ASTRO.

A Blinded, Prospective Study of Problematic Plan Detection During Physician Chart Rounds

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Purpose/Objective(s): Departmental physician chart rounds (CR) is a major quality assurance (QA) step in the radiation oncology workflow. However, there is minimal evidence as to the effectiveness of CR in detecting problematic treatment plans (PP). We performed a prospective, blinded study of the rate of detection of PP at CR to clarify the effectiveness of this QA step.

Materials/Methods: Twenty treatment plans with a simulated error (identical in nature to that reported to the Radiation Oncology Incident Learning System) were generated by a resident physician, a physicist and a dosimetrist. These PP were inserted randomly into our weekly CR over 9 weeks. PP were sorted into 2 major categories: poor plan quality (n=18) or problem with imaging used for planning (n=2). Poor quality plans were further classified as: wrong target identified (n=6), normal structures not spared (n=4), inadequate target coverage (n=3), dose and fractionation pattern incorrect (n=3), or previous treatment not considered (n=2). Detection of PP was noted, as was length of CR, and number of plans presented. Detectability and severity of PP were assessed in accordance with the American Association of Medical Physicists Task Group-100 (TG-100) report through modified delphi process of 3 raters. We analyzed our data using descriptive statistics and univariable logistic regression with odds ratios (OR). Analysis was performed using statistical software.

Results: The median length of CR over the study period was 60 mins (range 42-79) and the median number of cases presented per week was 45 (range 38-50). A median of 2 PP were presented weekly (range 1-4). In 75% of PP, the TG-100 severity score was >7 (potentially serious toxicity or tumor underdose), and in 75% of PP the detectability score was <7 ($\geq 95\%$ likelihood of detection). The detection rate of PP was 55% (11/20). Detection rates varied by problem type: 100% for previous treatment not considered, 75% for normal structures not spared, 67% for dose and fractionation pattern incorrect, 50% for wrong target identified, 50% for problem with imaging used for planning, and 0% for inadequate target coverage plans. Rate of detection decreased as length of CR increased, with detection of 70% of PP presented within the first 20 minutes, 67% of PP between minutes 20-40, and 29% of PP after 40 minutes of CR (OR: 0.42, 95%CI: 0.14 – 1.2, p=0.11). The detection rates increased during the study period, with 33% of PP detected in weeks 1-5, and 73% of PP detected in weeks 6-9 (5.3, 95%CI: 0.78 – 36, p=0.08). Detection rates varied by role (64% of total detections made by attending physicians, 27% by residents, 9% by dosimetrists).

Conclusion: Problematic plan detection at chart rounds is an imperfect process. Larger studies are needed to confirm the observation that detection rates decrease with longer durations of CR. Higher detection rates were observed as more PP were detected in the study period, which suggests a greater level of focus can be encouraged by the insertion of PP into routine CR.

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MO_41_3430**Establishing a Radiation Oncology Quality Surveillance Program**

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Purpose/Objective(s): Veterans Health Administration's (VHA) National Radiation Oncology Program (NROP) has established a quality surveillance program (VA-ROQS) evaluating its radiation oncology practices against metrics established in partnership with ASTRO. VA-ROQS provides comprehensive assessments through continuous, passive, electronic scoring of patient treatments.

Materials/Methods: The VA-ROQS pilot examined 1567 cases, serially selected to include intermediate-risk or high-risk carcinomas of the prostate (CAP), stage IIIA/B non-small cell lung cancer (NSCCa) or limited-stage small cell lung carcinomas (SCCa). Data, collected from the electronic medical records (EMR), treatment management (TMS) or planning (TPS) systems were curated to score 19 Quality Metrics (QM) for lung tumors and 26 QM for prostate cancers. Tumor site panels comprised of nationally-recognized experts identified QM as currently expected, aspirational or for surveillance. Panels selected 34 additional measures based upon dose-volume criteria. Case scores, aggregate scoring and scores relative to other centers were delivered to VHA providers via a Web Portal.

Results: Overall, the pass rate for 45 QM was 82.4%. Pass rates for prostate and lung cases were 87.2% and 78.0%, respectively. While aspirational CAP QM for quality of life determinations at consult and at follow-up scored below 50% for 12 and 17 centers, respectively, survivorship care plans and bone health assessments scored uniformly low. Two measures, treatment options discussed for intermediate risk CAP and frequency of follow-up evaluations, varied widely among the practices. QM passing scores for lung cancer assessments were similar among all centers with the exception of the following: addressing smoking cessation, evaluating implanted cardiac devices, motion management, prophylactic cranial irradiation, and follow-up frequency scored <68%. QM identified as aspirational by the panelists included three for treatment timeliness, which passed in >60% of cases. Collection of molecular markers and clinical trial participation scored low. Panels recommended 34 QM related to dose-volume (QMDVH). Mean pass rates were >90% for 10 of the 16 GU-QMDVH, but only 3 of 18 LU-QMDVH. Mean pass rates exceeded 80% for the other LU-QMDVH with the exception of the brachial plexus dose, 53% pass rate, and three ipsi-lateral lung QMDVH, passing in <30% of cases.

Conclusion: The VA-ROQS pilot shows the feasibility of defining and scoring a detailed set of QM for those common tumor presentations for which substantial clinical data exist. Focusing on intermediate and high-risk CAP, stage IIIA/B NSCCa and limited stage SCCa, panels were able to form consensus QM. Moreover, the data necessary to evaluate these metrics were successfully abstracted from electronic sources setting the stage for continuous, remote, fully-electronic peer-reviews. QM derived and evaluated in this way offer a personal pathway for performance improvement.

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Biology

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Sensitive Detection of Microsatellite Instability (MSI) in Liquid Biopsies from Early Stage Colon Cancer Patients using Nuclease-based Enrichment and Standard-Marker or NGS based approaches

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Purpose/Objective(s): The role of MSI in colorectal cancer (CRC) is well characterized, and tumors are classified as MSI-High or MSI-Stable by screening specific microsatellites. MSI-H reflects mismatch repair deficiency, is predictive for CRC therapy outcome in chemotherapy and immunotherapy and has a higher 5-year survival. While tumor testing is the gold standard, a convenient approach to screen for MSI before and during cancer treatment is screening circulating DNA (liquid biopsy) using a blood draw. However, using electrophoresis or next generation sequencing for MSI detection presents challenges at low levels of MSI due to polymerase slippage ('stutter') that generate high false positive rates at positions of homo-polymers. The purpose of this study was to test a new approach for enrichment of altered micro-satellites prior to DNA-amplification thereby reducing stutter from wild-type alleles and facilitating detection of MSI.

Materials/Methods: The method employs a double-strand-DNA-specific nuclease and overlapping oligonucleotide probes interrogating multiple micro-satellite targets ('NaMe-PrO', nuclease-assisted minor-allele enrichment with probe-overlap). Following DNA denaturation, the probes form double-stranded regions with their targets, thereby guiding nuclease digestion to selected sites. Microsatellite indels create 'bulges' that inhibit digestion, thus subsequent amplification yields DNA with microsatellite alterations enhanced at multiple targets. We first validated the method by evaluating 5 MSI targets simultaneously, NR27, NR21, NR24, BAT25 and BAT26 using DNA from tumor biopsies and circulating-DNA from colorectal cancer patients.

Results: The technique detected microsatellite alterations down to 0.01% altered allele frequency, thus improving detection sensitivity by > 100-fold relative to current approaches. Next, a clinical study was performed. We screened microsatellites in circulating DNA from groups of early stage colon cancer patients with known MSI status in the tumor. Combination of NAME-PRO with capillary electrophoresis demonstrated 100% sensitivity (10/10) and 90% specificity (9/10) in detecting MSI status in the blood. Finally we show the potential of a modified version of this method to enrich thousands of microsatellite indels over the genome, instead just on the established 5 MSI targets. This development opens the door to the possibility of early cancer detection for MSI positive tumors, or for application in detecting minimal residual disease in liquid biopsies with unprecedented sensitivity.

Conclusion: Detection of MSI in the blood of early stage colon CA patients is feasible using novel methods that allow increased sensitivity. We anticipate application of this highly- multiplex-able method either with standard 5-plex reactions or with NGS-based detection of MSI on thousands of targets to enable sensitive detection in tumors and liquid biopsies.

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FOXO1 Inhibition as a Therapeutic Strategy for Radiation Fibrosis

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Purpose/Objective(s): Radiation fibrosis (RF) is a long-term consequence of radiation, affecting up to 70% of radiotherapy patients. The pathogenesis of this condition is complex, involving inflammatory, epigenetic, and genetic alterations which promote excessive extracellular matrix (ECM) accumulation, ultimately leading to tissue dysfunction and patient morbidity. We previously demonstrated that a shift from fatty acid oxidation (FAO) to glycolysis is a predominant and sustained alteration in RF, and that transplantation of adipose-derived stromal cells (ADSCs) can restore metabolic homeostasis while reducing fibrosis severity. We hypothesized that epigenetic regulation of metabolism may be central to the development and treatment of RF. Our objectives were to investigate DNA methylation patterns in ADSC-treated RF *versus* irradiated control tissue to identify and target alterations specific to the reversal of RF.

Materials/Methods: Genome-wide methylation profiling was performed on the murine tissue using reduced representation bisulfite sequencing, and the HOMER motif discovery algorithm was then used to identify differentially methylated targets associated with RF reversal. FOXO1 was identified as a novel metabolic target, and its pharmacological inhibition was examined using a TGFB1-activated fibroblast model. The propensity of FOXO1 inhibition to modulate metabolism and the expression of key fibrotic markers was assessed using Western blotting and qPCR. Finally, the therapeutic potential of FOXO1 inhibition was investigated in a murine RF model.

Results: ADSCs induced hypermethylation at the DNA binding motif of FOXO1 ($p < 0.01$). FOXO1 inhibition therapeutically restored the expression of key FAO genes ($p < 0.05$), while decreasing the expression of fibrotic proteins such as collagen and fibronectin *in vitro*. Furthermore, FOXO1 inhibition reduced the severity of murine skin fibrosis *in vivo* ($p < 0.05$). Western blotting revealed that FOXO1 may interact with the prostaglandin E2 pathway to regulate ECM expression.

Conclusion: In summary, ADSC transplantation promoted the recovery of RF, providing insight into epigenetic alterations which are specific to RF reversal. This enabled the discovery of FOXO1, a regulator of metabolism that demonstrates promise as a novel therapeutic target for RF *in vitro* and *in vivo*. Moreover, by identifying a potential convergence of the FOXO1 and prostaglandin E2 pathways, a mechanism through which FOXO1 may regulate RF has been established. Future work will include an in-depth investigation of the epigenetic regulation of key genes in these pathways. This work will lead to a deeper understanding of RF pathogenesis while proceeding toward a novel therapeutic strategy for the treatment of this condition.

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***De Novo* Purine Synthesis Is a Targetable Vulnerability That Confers Radiation Resistance and Inferior Patient Survival in IDH-Wild Type Diffuse Glioma**

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Purpose/Objective(s): We sought to understand how metabolic phenotypes mediate RT resistance in isocitrate dehydrogenase wild type diffuse glioma (IDHwtGBM) to define genomic-independent *metabolic* radiosensitization strategies.

Materials/Methods: Steady state metabolomics and clonogenic survival curves were performed in 23 IDHwtGBM cell lines during exponential growth. Relationships between metabolites and RT resistance were determined using metabolic pathway analysis and Spearman correlations. γ H2AX foci were enumerated using immunofluorescence. Patient-derived IDHwtGBM neurospheres were grown under stem cell conditions. Treatment of GBM xenografts was with RT (2 Gy x 5), mycophenolate mofetil (MMF, 120 mg/kg x 6 doses) or the combination.

Results: Increased abundance of metabolites involved in purine metabolic pathways (guanine and inosine) was positively correlated with RT resistance, while increased abundance of those involved in energy production (e.g., glycolysis and lipid metabolism) was negatively correlated ($p < 0.05$ for all). RT resistance was also associated with the ability to repair γ H2AX foci after RT but not targetable transcriptionally-defined pathways, cell-cycle distribution or proliferation rates. Supplementing purine-poor radiosensitive IDHwtGBM cell lines with cell-permeable purine precursors (nucleosides) decreased γ H2AX foci staining 2-3 fold following RT and protected cells from RT (enhancement ratios 0.6-0.8). Mycophenolic acid (MPA), an inhibitor of *de novo* guanine synthesis, depleted GTP by 90%, increased RT-induced γ H2AX staining 2-3 fold and radiosensitized multiple purine-rich IDHwtGBM cell lines and neurospheres (enhancement ratios 2-3). These effects were rescued by exogenous nucleosides. Inhibition of *de novo* pyrimidine synthesis using teriflunomide had no effect on radiosensitivity or γ H2AX resolution. Treatment with MMF (an FDA-approved, orally-bioavailable prodrug of MPA) modestly slowed GBM xenograft growth *in vivo* (increased median tumor tripling time from 8 to 11 days), significantly sensitized tumors to RT (tumor tripling time not reached) and depleted intratumoral GTP 3-fold

when combined with RT. In 232 patients from the Pan-Cancer Atlas with newly diagnosed IDHwtGBM, increased expression (>median) of *IMPDH1*, the rate limiting enzyme in *de novo* guanine synthesis and target of MPA, was associated with inferior overall survival (HR 0.59, 95% CI 0.43-0.81, p=0.001). Increased expression of the rate limiting enzymes of *de novo* pyrimidine or adenine synthesis were not associated with inferior survival (HR 1.3, 95% CI 0.96-1.77 or HR 1.5, 95% CI 1.09-2.04).

Conclusion: RT resistance in IDHwtGBM is mediated in part by elevated purine levels, which can be overcome by inhibition of *de novo* purine synthesis. Because many of the genomic drivers of IDHwtGBM stimulate *de novo* purine synthesis, its inhibition represents a promising metabolic strategy to radiosensitize this genomically heterogeneous disease.

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VISTA Blockade Immunotherapy in a MULTI-Modal Approach to Triple Negative Breast Cancer (TNBC) in MICE and IMPACT on Microbiome

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Purpose/Objective(s): The majority of patients with TNBC fail to derive benefit from PD-L1 blockade alone. Recent phase III trial results show that PD-L1 blockade increases survival when combined with chemotherapy, warranting exploration of more effective treatment combinations. One potential new agent is the V-domain Ig suppressor of T cell activation (VISTA), a negative checkpoint ligand that inhibits T cell activation via a mechanism that is non-redundant with PD-1. In this study, the highly metastatic 4T1 mouse model of TNBC is used to test the combination of focal tumor radiation (RT) with low dose cyclophosphamide (CYP), VISTA and anti-PD-1 therapy, and explore its impact on the microbiome (MB). **Materials/Methods:** Mice were inoculated with 4T1 cells (day 0) and randomly assigned to one of several treatment groups (6-10 per group). RT was 12 Gy x 2 on d13 and 14. Anti-VISTA was given 3x/wk starting d14; anti-PD-1 on d14, 17 and 20; and CYP on day 9. Mice were followed for tumor growth and survival or euthanized at day 21 or 32 to assess tumor-infiltrating lymphocytes/ T-cell responses or mets. MB samples were obtained at d8, 12, 13 and 15. **Results:** RT significantly delayed tumor growth (p<0.05) but did not impact mets. Anti-VISTA or anti-PD-1, alone or combined, did not reduce primary tumor growth or mets, but VISTA blockade was as effective as anti-PD-1 when combined with RT. No further improvement in met control was seen with RT+dual PD-1/VISTA blockade. Surprisingly, addition of CYP 4 days before RT led to further significant improvement in met control in RT+ dual PD-1/VISTA treated mice (30% met-free on d32 (p<0.001)), increased priming of tumor-specific CD8+ T cells, and increased tumor infiltration of CD8+ T cells (53.5% vs 14.0% in control vs 16.5% in RT+anti-VISTA vs 21.1% in RT+anti-PD1, p<0.05). Strikingly, the quadruple treatment group displayed the highest median survival (54.5d vs 34d in control vs 45.5d in RT+anti-PD1, p<0.01). The therapeutic effects of anti-VISTA were in part due to reduced intra-tumoral granulocytic MDSC. The impact of CYP and RT on the composition, diversity and abundance of the MB were analyzed for distinctive changes.

Conclusion: PD-1 blockade has shown remarkable benefits in a small subset of patients, prompting investigations to identify promising combinations such as the use of RT + anti-PD-1. Here we show that RT can also synergize with anti-VISTA in inducing systemic anti-tumor responses, providing the first evidence that RT sensitizes refractory tumors to VISTA blockade. Remarkably, treatment with anti-VISTA markedly improved the therapeutic effect of RT+PD-1 blockade, but only in the presence of low-dose CYP prior to RT. We are currently investigating the mechanisms of this very promising combination, particularly on the changes in gut MB. Overall, these results suggest that a multipronged approach may be necessary to enhance response to IT in TNBC.

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Presence of Giant Circulating Cancer-Associated Macrophage-like Cells after Definitive Chemoradiation Predicts for Progression in Locally Advanced Non-Small Cell Lung Cancer Patients

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Purpose/Objective(s): Circulating cancer-associated macrophage-like cells (CAMLs) are a recently described stromal cell found in the peripheral blood of cancer patients that have been shown to be associated with disease progression. Giant CAMLS ($\geq 50 \mu\text{m}$) observed at baseline, before initiation of treatment, were previously reported to be predictive of disease progression in non-small cell lung cancer (NSCLC). In this prospective analysis of patients with unresectable locally advanced NSCLC, we explored the utility of CAMLS in predicting progression based on blood samples collected before, during, and at the completion of definitive chemoradiation therapy (CRT).

Materials/Methods: This 3 year prospective single blinded study assessed the role of CAMLS in determining clinical outcomes in patients undergoing definitive CRT for unresectable, locally advanced NSCLC (stage IIB n=7, stage IIIA n=22, stage IIIB n=11, and stage IIIC n=3). Patients were enrolled between December 2015 and January 2018. Median follow up after the completion of CRT was 14.9 months. CAMLS were collected by obtaining peripheral blood from patients at baseline before treatment (T0), during treatment (T1), and at the completion of treatment (T2). Blood was filtered using filtration and CAMLS quantified. CAML size $\leq 49 \mu\text{m}$ or $\geq 50 \mu\text{m}$ was quantified with the observer blinded to clinical information. Relapse free survival (RFS), progression free survival (PFS), and overall survival (OS) were analyzed at each time point.

Results: We evaluated 43 patients with unresectable locally advanced NSCLC and obtained a total of 172 samples. CAMLS were identified in 78% of samples (81% at T0, 86% at T1, and 74% at T2), averaging 2.28 CAMLS per 7.5 mL sample. Patients with giant CAMLS ($\geq 50 \mu\text{m}$) compared to those with smaller CAMLS ($\leq 49 \mu\text{m}$) at T0 or T1 exhibited no difference in RFS, PFS, or OS. Patients with detectable giant CAMLS at the completion of treatment (T2) demonstrated significantly worse RFS (HR=7.66, 95% CI 1.87-31.4, p=0.0047), PFS (HR=4.51, 95% CI 1.36-14.96, p=0.0139) and OS (HR=3.86 95% CI 1.02-14.59, p=0.0465). Median RFS, PFS, and OS for patients without giant CAMLS was not reached, while median RFS, PFS, and OS for patients with giant CAMLS was 7, 13, and 13 months, respectively.

Conclusion: Our data suggest that the presence of giant CAMLS at the completion of definitive chemoradiation for locally advanced NSCLC is predictive of disease progression and death. Continued prospective validation of CAMLS as a peripheral blood-based biomarker is needed to validate these findings. Accurate stratification of individual patients based on the presence of giant CAMLS may aid in more personalized therapeutic regimes, particularly in the era of adjuvant immunotherapy, while determining the role of CAMLS in the disease process may uncover new therapeutic modalities.

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The Low-Dose Bath Paradox: Do Spatial Irradiation Patterns Play a Role in the Incidence of Radiation Pneumonitis Following PSPT or IMRT?

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Purpose/Objective(s): Radiation pneumonitis (RP) is a common side effect of thoracic irradiation, whose incidence has been associated with several dose-volume histogram (DVH) predictors, including the lung volume receiving at least 20 Gy (V_{20}), the mean lung dose and V_5 [Pinnix *et al.* IJROBP 2015; 92(1):175]. Nonetheless, a randomized trial of IMRT vs passively scattered proton therapy (PSPT) for non-small cell lung cancer (NSCLC) [Liao *et al.* J Clin Oncol 2018; 36(18):1813] did not show any difference in RP incidence, despite PSPT significantly spared healthy lung tissues, with a p -value of the null hypothesis on V_5 of 10^{-10} . Following the recent findings on regional dose-sensitivity of the lungs [Palma *et al.* IJROBP 2016; 96(1):127], this study aims to explore whether the spatial location of dose delivery in PSPT and IMRT patients could account for the observed mismatch between DVH predictors and RP outcome in the trial.

Materials/Methods: We analyzed 178 patients prospectively treated with PSPT (64) or IMRT (114) for NSCLC to a prescribed dose of 66 or 74 Gy(RBE) in conventional daily fractionation with concurrent chemotherapy. 32 (28%) of IMRT patients and 23 (36%) of PSPT patients developed any CTCAE-grade RP, while 22 (19%) of IMRT patients and 18 (28%) of PSPT patients developed clinically symptomatic RP. A Voxel-Based Analysis (VBA) of local dose differences in healthy tissues was performed according to a non-parametric permutation test accounting for multiple comparisons and possible non-dosimetric confounding factors. From the obtained 3D significance maps, we derived the clusters of voxels that exhibit significant dose differences between groups.

Results: The VBA highlighted that:

1. significant dose differences between patients with and without RP are found in the lower part of the lungs and in the heart, independently from the RP severity threshold used for patients' grouping;
2. PSPT significantly reduced dose to healthy tissue in the medial-anterior and upper parts of the thorax;
3. the regions spared by PSPT and the clusters with doses significantly correlated to RP development are disjoint.

In particular, the mean dose differences between PSPT and IMRT in the clusters of voxel associated with the RP development are not significant ($p=0.39$ and $p=0.51$ for clusters derived for any CTCAE-grade RP and symptomatic RP, respectively).

Conclusion: The analyzed trial data provided a valuable opportunity to substantiate previously reported hypotheses on the prominent role of the lower parts of the lungs in the development of RP. Most importantly, the VBA of dose distribution associated to treatment modality showed that the tissues significantly spared by PSPT seemed not strongly sensitive for RP development. This could solve the seeming inconsistency between V_5 distribution and RP incidence in the studied trial. The relationship between RP and thoracic regional radio-sensitivity should be considered in clinical practice and in the design of future trials.

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Imaging-driven Biophysical Model for the Differentiation of Tumor Progression from Radiation Necrosis

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Purpose/Objective(s): This project validates the ability of a novel clinical imaging-driven biophysical model to predict the etiology of enhancing lesions following stereotactic radiosurgery (SRS) for brain metastasis (BM). These lesions present enormous clinical challenges as clinical symptoms and radiographic findings for radiation necrosis (RN) and tumor progression are often indistinguishable. We hypothesized that our model for differentiating RN from tumor progression could be validated in a large-scale retrospective cohort study.

Materials/Methods: A prospectively maintained database at our institution with 73 patients with 78 BM treated with SRS and histologically confirmed RN or tumor progression were retrospectively assessed using our biophysical model. Briefly, a reaction-diffusion logistic growth model mechanically coupled to the surrounding tissue was used to extract tumor cell proliferation rate and diffusion coefficients based on fitting areas of post-contrast *T1*-weighted MR enhancement observed during serial imaging time points. The model was then used to calculate mass effect due to the mechanical stress field incurred during lesion expansion. The Dice similarity coefficient was used to quantify the similarity of the model-estimated stress field with the edema front visualized in FLAIR imaging. These metrics for prediction of tumor progression versus RN were evaluated using a receiver operating characteristic curve and compared to standard radiographic morphometric analysis including the change in the longest dimension of the lesion, change in the volume of the lesion, and FLAIR/*T1* lesion quotient.

Results: Standard radiographic morphometric analysis of the serial post-contrast *T1*-weighted enhanced and FLAIR images reflected poor ability to differentiate between tumor progression and RN for the change in the longest dimension of the lesion (ROC AUC = 0.73, 95% CI: 0.61 – 0.85, $p = 0.0009$, 74% sensitivity and 63% specificity), change in lesion volume (ROC AUC 0.61, 95% CI: 0.47 – 0.75, $p = 0.1262$, 43% sensitivity and 64% specificity), and FLAIR/*T1* lesion quotient (ROC AUC = 0.55, 95% CI: 0.41 – 0.69, $p = 0.4723$, 77% sensitivity and 43% specificity). Conversely, parameters derived from our imaging-driven model were able to differentiate lesion etiology with excellent accuracy for tumor cell proliferation rate (ROC AUC = 0.86, 95% CI: 0.76 – 0.95, $p < 0.0001$, 74% sensitivity and 95% specificity) and Dice similarity coefficient associated with high model-estimated mechanical stresses (ROC AUC = 0.93, 95% CI: 0.86 – 0.99, $p < 0.0001$, 81% sensitivity and 95% specificity).

Conclusion: In patients with BM treated with SRS, our model demonstrated excellent accuracy for differentiating enhancing lesions and significantly outperforms standard radiographic assessment of image morphometric features.

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Acute Toxicity Patterns in Adaptive High Precision Radiotherapy for Head and Neck Cancer - a Randomised Controlled Trial

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Purpose/Objective(s): Adaptive Radiation therapy (ART) aims to take into account the changes in target volume and organs at risk during the course of fractionated radiation therapy & this has possible advantage in terms of improved local control, reduced toxicities and improved the

QOL. This study aims to assess the clinical impact of ART in terms of toxicities in primary SCC of HNC undergoing radical/adjuvant concurrent chemo-radiotherapy treatment.

Materials/Methods: The study enrolled 100 patients of histopathologically proven primary head-and-neck cancer and were randomized into ART and non-ART arms. Target/OAR delineation was done after CT simulation following rigid immobilization. All patients were started treatment with VMAT & image guidance. After treatment start, the patients were re-simulated using CT imaging again at 3rd, 5th and 7th week. Predefined adaptive re-contouring workflow using deformable image registration was applied to generate adaptive plan. For patients in ART Arm, the new plan was executed for the remaining fractions. In Non ART Arm treatment was continued as per the original plan. All the patients were observed for total volume of Parotid glands at week 1, 3, 5 and 7. RTOG Criteria was used for documenting acute reactions in form of acute xerostomia, mucositis and dysphagia in both arms at week 3, 5 and 7. Median follow-up was 6mo.

Results: The percentage volume change in parotid glands was observed to be 6.25%, 16.37% and 28.39% in adaptive arm and 11.53%, 23.54% and 32.56% at 3-5 and 7 weeks (P-value 0.009 and 0.0123rd and 5th wk respectively). On clinical examination Grade 2 Xerostomia at 3, 5 and 7 wk was seen in 10%, 36% and 70% patients in adaptive arm whereas in 16%, 46% and 88% in non-adaptive arm (P-value 0.006 at 7th wk). The significant difference in mucosal reactions between both arms was observed throughout the course of study in favour of adaptive arm. None of the patients in adaptive arm had Grade 3 mucosal reactions as compared to 26% in non adaptive arm. The difference in mucosal reaction was most significant at 7th week of treatment (p value 0.004). At week 3 and 5, patients having grade 2 or higher reactions were 14% and 46% in adaptive arm as compared to 26% and 70% in non-adaptive arm. (p values 0.029, 0.023). Dryness of mouth has a significant impact on swallowing. In our study we observed grade 2 or higher dysphagia to be 6%, 38% and 80% in adaptive arm whereas 2%, 48% and 84% in non-adaptive arm at 3, 5 and 7 weeks. Though absolute number of patients having adverse dysphagia reaction was lower in adaptive arm, this difference was not statistically significant (p value 0.15, 0.59, 0.09)

Conclusion: Volume changes in parotid glands and gross tumour is observed throughout the course of radiation treatment and ART can aid in better sparing of parotid glands with an advantage over non-ART in terms of reduced acute toxicity reactions. Present study is first RCT reported in literature where an attempt is made to correlate dosimetric and toxicity criteria.

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Effective Volume of Parotid Glands for Assessing Radiation Injury during Radiation Therapy for Head and Neck Cancer

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Purpose/Objective(s): It has been shown that the reduction of the physical volume of the parotid glands (PGs) during radiation therapy (RT) for head and neck cancer (HNC), although associated with radiation damage, could not be used to predict the xerostomia. The purpose of this work is to propose an effective volume (EV), by excluding the fat from the physical volume (PV), to improve the prediction for radiation injury of PGs in RT for HNC.

Materials/Methods: Diagnostic-quality CT data acquired daily during CT-guided RT using a CT-on-rails and the xerostomia data for 21 HNC patients were analyzed. For each selected daily CT, the PGs, submandibular glands (SMGs), and subcutaneous fat were contoured. The Hounsfield Units (HU) and volumes of these contours were used to calculate the EV of PGs with two assumptions: (1) the HU of acini cells in PGs can be substituted with that of SMGs, and (2) the HU of adipose cells can be substituted with that of the subcutaneous fat. The correlation between PV or EV with mouth dryness were analyzed using Pearson correlation tests. The significances were inspected using paired two-tailed t-test.

Results: On average, the fat initially accounted for 25.9% ± 15.4% of the PV of PG and raised to 30.2% ± 15.4% after RT (p=0.004). The change of EV (7.0±3.2 cm³) was significantly smaller than PV (9.1±4.6 cm³) (p=0.001) and was more correlated to the xerostomia grade than the change

of PV. By replacing PV with EV, the Pearson correlation coefficients between the absolute volume change and the xerostomia grade increased from 0.52 ($p=0.016$) to 0.72 ($p=0.0002$) and 0.40 ($p=0.07$) to 0.51 ($p=0.018$) for the relative volume change. The correlation between the absolute volume change and the relative volume change becomes more linear with a linear correlation coefficient increased from 0.56 to 0.72. In contrast to PV, EV led to clear clustering of the moderate xerostomia cases (grade 1 and 2) in a spread region along the linear fit of these cases (from 0 to 9.4 cm^3 , 70%) in the figure where the relative volume reduction was plotted with respect to the absolute volume reduction. For the studied cohort, this effective volume-based model has a sensitivity of 88% and a specificity of 100% for filtering the severe xerostomia cases (grade 2 and above).

Conclusion: By excluding the fat, we estimated an effective volume of parotid glands that significantly improves the correlation between the PG volume reduction and xerostomia grade during radiation therapy for head and neck cancer, allowing to predict the severity of radiation-induced mouth dryness more accurate and sooner.

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Habitat Evolution Imaging Biomarkers to Assess Early Response and Predict Treatment Outcomes in Oropharyngeal Cancer

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Purpose/Objective(s): The incidence of oropharyngeal cancer (OPC) has been rapidly increasing in recent years. There is an unmet need for reliable prognostic biomarkers in OPC. This work aims to develop an imaging signature to assess early response and predict outcomes of OPC based on serial FDG-PET and CT imaging analysis.

Materials/Methods: We propose a novel spatiotemporal habitat evolution-based method to analyze the complex response patterns. First, we used a robust two-stage clustering approach to partition the primary tumor and involved lymph nodes into spatially distinct subregions (i.e., habitats) based on the local image intensity and entropy maps. Second, we proposed 27 quantitative image features to characterize the serial volumetric change of the habitats and peritumor/nodal parenchyma at both regional and single-voxel levels between baseline and mid-treatment imaging. We then evaluated the reproducibility of the proposed features with respect to multiple delineations and image registration and removed redundant features with linear correlation above 0.95. Given the remaining features, we developed an imaging signature to predict progression-free survival (PFS) by fitting an L1-regularized Cox regression model in a training cohort of 81 patients treated with concurrent radiation and chemotherapy. Finally, we tested the imaging signature in an independent validation cohort of 81 patients with similar clinical features and treatment.

Results: We identified 3 phenotypically distinct subregions based on PET and CT imaging, which were metabolically active and heterogeneous (habitat 1), enhancing and heterogeneous (habitat 2), metabolically inactive and homogeneous (habitat 3). All 3 habitats showed high concordance across the two cohorts with in-group proportion ranging from 0.97 to 0.99. After removing redundant and less stable features (intra-class coefficient < 0.75), 21 features remained. The final Cox model consisted of 3 habitat evolution-based image features. This imaging signature predicted 2-year PFS with a reasonably good accuracy, AUC: 0.74, 95% CI: 0.69-0.78 (training) and 0.70, 95% CI: 0.65-0.74 (validation), and significantly outperformed traditional imaging response metrics such as tumor volume, SUV_{max} and MTV (AUC: 0.52-0.58). When tested in the validation cohort, the imaging signature stratified patients into high vs low-risk groups with distinct 2-year PFS (64% vs 90%; $P = 0.003$). On multivariable analysis, the imaging signature was independently associated with PFS (hazard ratio: 5.2, 95% CI: 1.6-17.5, $P = 0.008$) adjusting for clinical and pathologic factors including stage, HPV status, and smoking history.

Conclusion: The proposed habitat evolution-based imaging signature allows reliable assessment of early response and accurate prediction of outcomes in OPC. If validated, it can help identify patients who may benefit from de-intensification therapy or adjuvant immunotherapy.

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