
2016 ASTRO Annual Meeting

Late-breaking Abstracts

LBA-1

N107C/CEC.3: A Phase III Trial of Post-Operative Stereotactic Radiosurgery (SRS) Compared with Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease

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Purpose/Objective(s): WBRT is the standard of care to improve intracranial control following resection of brain metastasis. However, SRS to the surgical cavity is widely used in an attempt to reduce cognitive toxicity, despite the lack of high level comparative data substantiating efficacy in the post-op setting.

Materials/Methods: On this multi-institutional cooperative group trial patients with one to four brain metastases were randomized to either SRS or WBRT after resection of one lesion. The unresected metastases were treated with SRS in both study arms. The primary endpoints were cognitive deterioration free survival (CDFS) and overall survival. Cognitive deterioration was defined as decline >1 SD from baseline in any of the 6 cognitive tests. Major secondary endpoints included local control of the surgical bed, time to intracranial failure, and QOL.

Results: Between July 2011 and December 2015, 194 patients were enrolled with a median follow up of 15.6 months (range 0, 48.5 months). Baseline characteristics were well-balanced between study arms. The median age was 61, most had a single metastasis (77%), and lung was the most common primary tumor (59%). There was a shorter CDFS after WBRT vs. SRS to the surgical cavity (median 2.8 vs. 3.2 months, HR = 2.0, p<0.0001). Cognitive deterioration at 6 months was more frequent after WBRT vs. SRS (85.7% vs. 53.8%, p = 0.0006). At 6 months, there was more cognitive deterioration in the WBRT arm in immediate recall (47.9% vs. 17.3%, p<0.0001), delayed recall (62.5% vs. 27.5%, p<0.0001), and processing speed (37.5% vs. 17.3%, p=0.03). Overall intracranial tumor control at 6 and 12 months was 90.0% and 78.6% with WBRT vs. 74.0% and 54.7 % with SRS (p<0.0001). There was better QOL with SRS at 3 months including overall QOL (mean change from baseline -1.5 vs. -7.0; p= 0.03) and physical wellbeing (-6.4 vs. -20.2; p= 0.002). At 6 months, there was better QOL with SRS including brain-specific concerns (2.9 vs. -4.4; p= 0.045) and physical wellbeing (-3.2 vs. -15.1; p= 0.016).

Conclusion: Decline in cognitive function at 6 months was more frequent with WBRT. Despite worse intracranial control, better QOL was reported in the SRS arm. Overall survival and local control will be presented at the time of the meeting.

Results of COG ACNS0331: A Phase III Trial of Involved-Field Radiotherapy (IFRT) and Low Dose Craniospinal Irradiation (LD-CSI) with Chemotherapy in Average-Risk Medulloblastoma: A Report from the Children's Oncology Group

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Purpose/Objective(s): Conventional therapy for A-R medulloblastoma is standard dose CSI (SD-CSI) to 23.4Gy and posterior fossa radiotherapy (PFRT) to 54Gy with cisplatin/cyclophosphamide based chemotherapy. This trial tests whether a 5.4Gy reduction in the CSI dose (18Gy, LD-CSI) in patients 3-7y and a reduction in boost volume (IFRT) in patients 3-21y receiving chemotherapy results in non-inferior event free survival (EFS) or overall survival (OS).

Materials/Methods: 549 children with A-R medulloblastoma were enrolled, 464 were eligible and without excessive residual disease or anaplasia by central review, and were randomized to PFRT (237) or IFRT (227). Of those, 226 were 3-7y and randomized to SD-CSI (110) or LD-CSI (116). Time to Event is the primary endpoint, defined as time from study entry to disease progression, disease recurrence, death from any cause, or second malignant neoplasm. Each RT comparison is based on a one-sided 1- β confidence interval for the Hazard Ratio (HR). Analysis of CSI dose is stratified on the PF volume, and *vice versa*. Intent to treat analysis is used.

Results: With median follow-up of 6.6 years, there was a significant difference in EFS between patients with anaplasia or excess residual disease by central review compared to other eligible patients ($p=0.015$, one-sided log-rank test). The 5-year OS in PFRT and IFRT was $85.2\% \pm 2.6\%$ and $84.1\% \pm 2.8\%$, respectively. The 5-year EFS in PFRT and IFRT was $80.8\% \pm 3.0\%$ and $82.2\% \pm 2.9\%$, respectively. The 94% upper confidence limit of the HR was 1.3 and because this was lower than the prespecified limit of 1.6, IFRT was deemed to be non-inferior to PFRT. The 5-year OS in SD-CSI and LD-CSI was $85.9\% \pm 3.8\%$ and $78.1\% \pm 4.4\%$, respectively. The 5 year EFS in SD-CSI and LD-CSI was $82.6\% \pm 4.2\%$ and $72.1\% \pm 4.8\%$, respectively. The 80% upper confidence limit of the HR was 1.9 and because this was higher than the prespecified limit of 1.6, non-inferiority of LD-CSI to SD-CSI is not established. Local failure was $1.9\% \pm 0.1\%$ and $3.7\% \pm 1.3\%$ at 5 years for IFRT and PFRT, respectively ($p=0.178$). The majority of PF failures (29 of 45, 64%) were accompanied by neuraxis failure. None of the IFRT patients had an isolated posterior fossa failure outside the boost volume. Isolated distant failure was $12.8\% \pm 3.2\%$ and $8.2\% \pm 2.8\%$ at 5 years for LDCSI and SDCSI, respectively ($p=0.115$). Ten patients developed second malignancies.

Conclusion: For patients with A-R medulloblastoma, these data support decreasing radiation boost volume to the primary site. However, decreasing CSI dose to 18Gy may increase risk of recurrence and is not recommended. Pretreatment imaging review may avoid enrollment of inappropriate patients in these trials.

A Phase III, Randomized Double-Blind Study of Doxepin Rinse versus Magic Mouthwash versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Head and Neck Radiotherapy with or without Chemotherapy (Alliance A221304)

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Purpose/Objective(s): Oral mucositis (OM) is a major cause of morbidity during radiotherapy (RT) of the head and neck (H&N). “Magic Mouthwash,” a term encompassing a variety of lidocaine based rinses, is widely used for OM but no large randomized controlled trials (RCT’s) have shown it to be beneficial. In 2012, Doxepin oral rinse (DOX) was shown to reduce OM pain, compared to placebo, in a large RCT.

Materials/Methods: A multi-institution, randomized, double-blind, placebo-controlled, three arm phase III trial with optional continued active agent usage, was designed to assess the efficacy of DOX (25 mg in 5 ml water) or a diphenhydramine/lidocaine/antacid (DLA) preparation vs. a placebo rinse and spit for the treatment of RT-related OM and conducted through the Alliance for Clinical Trials in Oncology. Patients undergoing definitive H&N RT (> 45 Gy) with OM pain rated > 4 using a patient reported numerical analog pain questionnaire (scale 0 to 10) were eligible. Patients received a single blinded dose of DOX, DLA, or placebo. To assess OM related pain after the rinse, a pain questionnaire was given at intervals from baseline to 4 hours. The primary endpoint was total OM pain reduction as measured by the area under the curve (AUC) of the pain scale over 4 hours following the single dose of rinse. The baseline-adjusted AUC between two treatment arms was compared using the Wilcoxon rank-sum test. After study completion, patients were given the option to continue the study drug.

Results: 275 patients (228 eligible for the primary endpoint) were enrolled from 11/01/14 and 5/16/16. Baseline factors were evenly distributed. Analysis of the primary endpoint revealed differences in pain mean AUC reduction between DOX vs. Placebo (11.9 vs. 8.7, $p = 0.01$) and DLA vs. Placebo (11.7 vs. 8.7, $p = 0.004$). The repeated measures analysis showed that time, treatment arm, age and mucous membrane scores had statistically significant effects on pain scores. The DOX arm had less mouth pain at 30 minutes (2.9 vs. 3.8, $p = 0.03$) and 60 minutes (2.9 vs. 3.8, $p = 0.03$) compared to placebo. The DLA arm experienced less mouth pain at 5 minutes (3.5 vs. 4.4, $p = 0.01$), 15 minutes (2.9 vs. 4.0, $p = 0.003$) and 30 minutes (2.8 vs. 3.8, $p = 0.004$) as compared to placebo. The DOX arm reported more drowsiness at 30 minutes ($p = 0.03$) and 60 minutes ($p = 0.01$), and significantly more fatigue than patients on placebo ($p = 0.03$). There were no other adverse event differences between arms. Only 15% of patients on DOX used additional analgesics at 4 hours post oral rinse compared to 28% on the placebo arm ($p = 0.05$). There were no differences in additional analgesic usage between Placebo and DLA (19% vs. 28%, $p = 0.22$).

Conclusion: OM pain was significantly less following both DOX and DLA rinse vs. placebo. Both agents were well tolerated. This study confirms the findings of N09C6 that DOX is effective in reducing RT related OM pain compared to placebo. These results also provide the first multi-center RCT evidence that DLA is effective in reducing RT-related OM pain.

ClinicalTrials.gov: NCT02229539

Treatment with 6 Cycles of CVP or R-CVP after Involved Field Radiation Therapy (IFRT) Significantly Improves Progression-free Survival Compared to IFRT alone in Stage I-II Low Grade Follicular Lymphoma: Results of an International Randomized Trial

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Purpose/Objective(s): Involved field radiation therapy (IFRT) alone is potentially curative in stage I-II low-grade follicular lymphoma (FL) but relapse occurs in >50% of cases, predominantly outside RT fields. We hypothesized that systemic therapy given after IFRT would improve disease control, as assessed by progression-free survival (PFS).

Materials/Methods: This multicenter, randomized controlled trial enrolled patients (pts) from Australia, New Zealand and Canada. Eligible patients had stage I-II low-grade FL (grade 1,2 or 3a) after adequate staging, including CT scans and bone marrow aspirate and trephine. FDG-PET staging was permitted but not mandated. Pts were randomized to one of 2 arms; A: IFRT alone or B: IFRT followed by 6 cycles of cyclophosphamide 1000 mg/m² IV D1, vincristine 1.4 mg/m² D1 and prednisolone 50mg/m² D1-5 (CVP). A protocol amendment in 2006 added rituximab 375 mg/m² D1 to arm B (R-CVP). Randomization was stratified by center, stage, age (<60/≥60) and whether PET-staged.

Results: From Feb 2000 to July 2012, 150 patients were recruited: 75 per arm. In Arm B, 44 patients were allocated CVP and 31 R-CVP. At randomization 75% had stage I, median age was 57 years, 52% were male, 48% were PET staged and 8% had an extranodal site (ENS). Median potential follow-up time was 9.6 years (range, 3.1-15.8). Major protocol deviations occurred in 2%. PFS was significantly superior in Arm B, HR 0.57 (95% CI 0.34-0.95) p=0.033. Those Arm B patients randomized to R-CVP had markedly superior PFS compared with those randomized to IFRT alone after the trial amendment, HR 0.26 (95% CI 0.07-0.97) p=0.045. Other factors associated with superior PFS were ENS (p=0.02), fewer involved nodal regions (p=0.047) and PET staging (p=0.056). Fewer patients had transformation to high-grade lymphoma in Arm B (4 vs 10). Significantly more toxicity > grade 2 occurred in Arm B. Ten deaths were observed in Arm A vs 5 in Arm B but overall survival (OS) is not currently significantly different (p=0.4); 10 yr rates 95 vs 87%.

Conclusion: Systemic therapy with CVP or R-CVP after IFRT significantly improved PFS compared to IFRT alone. Longer follow-up is required to assess the effect of systemic therapy on OS. This trial may establish a new standard of care in early stage FL.

Extreme Hypofractionation vs. Conventionally Fractionated Radiotherapy for Intermediate Risk Prostate Cancer: Early Toxicity Results from the Scandinavian Randomized Phase III Trial “HYPO-RT-PC”

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Purpose/Objective(s): Prostate cancer is postulated to have high radiation-fractionation sensitivity which suggests a potential therapeutic benefit for hypofractionated (HF) radiotherapy (RT). Results from randomized studies investigating efficacy and side-effects of *moderately* hypofractionated (M-HF) schedules have recently been reported in the literature. Data from randomized trials with *extreme* hypofractionation (E-HF) are however hitherto lacking. We here report two-year toxicity results from the Scandinavian multicenter phase III trial (HYPO-RT-PC) comparing E-HF with conventional fractionation (CF).

Materials/Methods: The HYPO-RT-PC non-inferiority trial accrued 1200 intermediate risk prostate cancer patients (T1c-T3a, PSA ≤ 20 with one or two of the following risk factors; T3a or Gleason ≥ 7 or PSA > 10) from July 2005 to Nov. 2015. Patients were randomized with a 1:1 allocation ratio to either CF, 39x2.0 Gy=78 Gy over 8 weeks, or to E-HF, 7x6.1 Gy=42.7 Gy over 2.5 weeks (RT every other weekday). No androgen deprivation therapy was allowed. The two treatment schedules were designed to be equieffective for late normal tissue complication probability ($\alpha/\beta=3$ Gy). Image guided RT based on fiducial markers was delivered to the prostate only (CTV) with a 7 mm isotropic CTV-PTV margin. The main OAR constraint was $V_{90\%} \leq 15\%$ for rectum. A majority of the patients (80%) were treated with 3DCRT and the remaining with VMAT. Physician's evaluation of side-effects was performed according to a modified RTOG scale. Patient Reported Outcome Measurement (PROM) was performed with the PCSS questionnaire using a VAS scale to evaluate urinary and bowel symptoms as well as sexual function.

Results: Median follow-up time from randomization for the entire patient population is 4.2 years. 866 eligible patients had until May 2016 reached the two-year follow-up. There were no significant differences in the prevalence of physician reported grade 2+ toxicity at two years between E-HF and CF for urinary (5.4% vs. 4.6%, $p=0.59$) and bowel (2.2% vs. 3.7%, $p=0.20$) toxicity. The corresponding figures for acute toxicity at end of RT was 27.6% vs. 22.8% ($p=0.11$) and 9.4% vs. 5.3% ($p=0.023$), respectively. Impotence at two years was 34% in both arms compared to 16% at baseline. PROM data revealed no significant differences in any of the individual items/questions at two years. A small, but significant worse urinary function was observed in the the E-HF arm compared to CF in 4/14 symptoms at one year. At end of RT, bowel function had significantly worse PROM scores in the E-HF arm in 7/10 items but no significant differences at 3 and 6 months. Sexual function was similar in both arms. **Conclusion:** E-HF resulted in a low incidence of side-effects with no significant differences compared to CF at the two-year follow-up.

Continued Benefit to Rectal Separation for Prostate RT: Final Results of a Phase III Trial

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Purpose/Objective(s): SpaceOAR, an FDA approved hydrogel (Hy) to create rectal-prostate space was evaluated in a single blind Phase III trial of image guided intensity modulated prostate RT (IG-IMRT, Mariados et al, IJROBP 2015). Men (n=222) were randomized 2:1 to hydrogel (markers + Hy) or control (Ct, markers only) receiving 79.2/1.8 Gy to prostate ± SV with the primary end-point reported at 15 months. We now report final results with last follow-up (FU) 4/7/16.

Materials/Methods: Late (>90 days) CTCAE v 4.0 toxicity was evaluated by chi-squared test. For quality of life (QOL) the Expanded Prostate Cancer Index Composite (EPIC) was collected at baseline and serially. Mean changes from baseline in EPIC domains were tested by repeated measures models with contrasts to compare treatments at each time. Proportions of men with minimally detectable changes (MDC) in each domain were tested using repeated measures logistic models with pre-specified thresholds.

Results: There was no difference in FU (median Ct 37.0 mo (range 26-46) vs Hy 37.1 (32-47) p>0.1) or response to EPIC at last FU (Ct 60% vs Hy 65%, p>0.1). The incidence of grade 1+ (Ct 9.2% vs Hy 2.0% p=0.028) or 2+ (Ct 5.7% vs Hy 0% p=0.012) rectal toxicity continued to favor Hy. Grade 1+ urinary incontinence also favored the Hy group (Ct 19.6% vs Hy 4.3% p=0.003); with no difference in grade 2+ urinary toxicity (p=0.7). At last FU the decline in EPIC bowel summary was greater in Ct (-5.3) vs Hy (+0.48, p<0.05). The 5.5 point difference in bowel QOL between arms met threshold for a clinically detectable change (4-6 pts). Moreover from 6 months onward bowel QOL consistently favored Hy (p=0.002); with largest differences in stool frequency and urgency. At last FU Ct men had a greater decline in urinary QOL (-3.3) vs Hy (+0.6, p<0.05), but a difference was not observed at other time points (p=0.13). No difference in sexual or vitality/hormonal QOL was noted between arms (p>0.5). At last FU more men had a detectable (MDC) decline in bowel QOL for Ct vs Hy (40.9% vs. 14.0%, OR: 3.6 [95%CI:1.6-8.0] p=0.002) as well as for urinary QOL (29.6% vs 16.5%, OR: 2.4 [1.1-5.6] p=0.04). Further, at 36 mo Ct men were more likely to see large declines (twice MCD) in bowel (20.5% vs 5.4%, OR:3.9 [1.3-11.9] p=0.02) and urinary QOL (22.7% vs. 7.7%, OR: 3.3 [1.2-9.1] p=0.02). Bowel declines were more likely in those treated to prostate + SV, but the relative benefit of hydrogel spacer did not vary by inclusion of SV (p>0.5). Increasing volume of rectum in 5 Gy increments (V50-V85) all favored Hy and correlated with declines in bowel QOL (all p<0.01). There was no difference in response to RT with no biochemical failures to date and median PSA at last FU of 0.5 ng/ml in each arm (p=0.28).

Conclusion: The benefit of SpaceOAR in reducing rectal dose, toxicity, and QOL changes following IG-IMRT for prostate cancer were maintained or increased with longer follow-up

providing strong evidence for the benefit of hydrogel spacer in this setting. Analysis of bladder dosimetry is on-going and will be presented.

Low-Risk Meningioma: Initial Outcomes from NRG Oncology/RTOG 0539

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Purpose/Objective(s): Summarize the initial analysis of patients with low-risk meningioma enrolled on NRG Oncology/RTOG-0539.

Materials/Methods: This phase II trial allocated meningioma patients to 1 of 3 prognostic groups and management strategies according to WHO grade, recurrence status, and resection extent. Low-risk (Group 1) patients had either a gross totally (Simpson grade I-III) or subtotally resected (Simpson IV or V) newly diagnosed WHO 2007 grade I meningioma, and were observed after surgery. The primary endpoint was 3yPFS, compared to a pre-defined historical control estimate of 90%. AEs were scored using NCI CTCv3.

Results: Group 1 accrued 65 patients, at a rate faster than projected. Two were ineligible (1 registered to the wrong group, and 1 without required submissions for central pathology review). Among the remaining 63, 51 were female (81.0%). Gross total resection (GTR) was reported in 58 (92.1%): Simpson I in 38 (65.5%), II in 15 (25.9%), III in 4 (6.9%), and 1 GTR (1.7%) with unreported Simpson grade. Sufficient data for central confirmation of resection extent was available in 46 GTR patients, and GTR confirmed in 36 (78.3%). Subtotal resection (STR) was described in 5 patients (7.9%), all Simpson grade IV, all 5 centrally confirmed. 3 and 5y overall survival (OS)/PFS were 98.4/91.8% and 98.4/86.1%. 3 and 5y rates of local failure (LF) were 6.5 and 12.5%. By 5 years, 7 patients had progressed, 5/58 (8.6%) after locally reported GTR, and 2/5 (40%) after locally reported STR. No treatment-related grade 4 or 5 AEs were reported. 1 patient had a grade 3 AE (infection), 4 had grade 2 events (1 neurologic, 1 pulmonary, 1 pain, and 1 GI), and 5 grade 1 (3 neurologic, 1 constitutional, and 1 visual). For additional comparison, intermediate-risk meningioma patients (Group 2: new WHO II with GTR or recurrent WHO I of any resection extent) treated on this same protocol with external beam RT (54Gy/30) experienced 3/5y PFS 91.8/83.7%, 3/5y LF 4.1/14.3%, and had AEs limited to grade 1 or 2, with no grade 3 event.

Conclusion: This is the first clinical outcomes report for low-risk meningioma from a cooperative group trial. Patients with low-risk meningioma treated with surgery alone modestly exceeded outcome expectations based on historical controls at 3y (3yPFS 91.8%), but not at 5y (5yPFS 86.1%). 5yLF was 12.5%. Intermediate-risk patients treated in a separate group of the same protocol with RT had similar outcomes, 5yPFS 83.7% and 5yLF 14.3%. Both groups had comparably low rates of AEs. These results support surgery followed by observation for patients with newly diagnosed WHO grade I meningioma following GTR, but raise questions for this practice following STR (40% crude 5y local failure), a subcohort that could potentially benefit from adjuvant RT. Further follow-up and analyses are required before robust recommendations can be made.

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Final Analysis of a Randomized Phase III Trial of Accelerated versus Conventional Fractionation Radiotherapy for Glottic Cancer of T1-2N0M0 (JCOG0701)

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Purpose/Objective(s): Japan Clinical Oncology Group (JCOG) 0701 (UMIN-CTR: UMIN000000819) is a randomized controlled trial to confirm the non-inferiority of accelerated fractionation with 2.4 Gy/fraction (Ax) to standard fractionation with 2 Gy/fraction (Sf) for glottic cancer (GC) in terms of progression-free survival.

Materials/Methods: Eligibility criteria included GC of T1-2N0M0, histopathologically proven squamous cell carcinoma, aged 20–80, PS of 0–1. Patients (pts) were treated with 66/70 Gy within 45/47 days for T1/T2 in Sf, and with 60/64.8 Gy within 33/37 days in Ax. The primary endpoint was the proportion of 3-year progression-free survival (PFS). Secondary endpoints included overall survival (OS), larynx progression-free survival (LPFS), proportions of treatment completion, and adverse events. The planned sample size was 360 pts with one-sided alpha of 5%, power of 80%, 3-year PFS of 80% in Sf and 85% in Ax, and a non-inferiority margin of 5%. Planned interim analyses were conducted twice using 0.5% of alpha in each to maintain the study-wise significance level at one-sided 5% and adjust for multiplicity, leaving 4.5% of alpha for the primary analysis.

Results: Between 2007 and 2013, 370 pts were randomized to Sf and Ax with 184 and 186 pts, including 356 males/14 females and 341/29 pts with PS 0/1. Median age was 68 (range, 35–80). In Sf, 137/46 pts had T1/T2, while 140/46 had T1/T2 in Ax. One pt enrolled in Sf with T1 was subsequently found to have T3. The median follow-up period of all randomized pts was 4.8 years (range, 0.1–8.3). In the last follow-up, 51/282 pts were alive with/without disease and 37 died. Among Sf/Ax, 5/8 pts died of disease, 10/11 of other causes, and 0/3 of unknown reasons. Three-year PFS were 79.9% in Sf and 81.7% in Ax. The non-inferiority of Ax was not confirmed with a difference of 1.8% (91% CI; -5.1–8.8%, $p=0.047$ [>0.045]). In ad hoc analyses, the cumulative incidences of local failure at 3 years in Sf/Ax were 15.9%/10.3%, those of regional or distant failure were 1.1%/3.3%, and those of death were 0.5%/3.3%. No significant differences were

observed in 3-year OS (98.4% vs. 93.5%) or LPFS (82.4% vs. 84.8%) between Sf and Ax. Proportions of treatment completion within the prespecified period were 95.1%/98.4% for Sf/Ax. Grade 3 acute toxicities (within 90 days) in Sf/Ax were as follows: skin in 10.2%/3.8%, any types of mucositis in 5.1%/6.0%, and any acute toxicities in 12.4%/10.9%. As for late toxicities (after 90 days), 1.1%/0.5% of grade 3 and 1.1%/0% of grade 4 developed in Sf/Ax. Grade 3–4 early or late toxicities were 13.2%/10.9% in Sf/Ax.

Conclusion: Sf remains the standard treatment for early GC because the 3-year PFS in Ax was slightly low and the non-inferiority of Ax was not confirmed. The similar efficacy and toxicities of Ax to Sf as well as its practical convenience indicate that Ax has potential as a treatment option for early GC.

A Multicenter Phase II Study of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

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Purpose/Objective(s): To evaluate the toxicity and treatment outcomes of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC).

Materials/Methods: A total of 73 patients with unresectable HCC showing an incomplete response after 1-5 sessions of transarterial chemoembolization were enrolled in a phase II clinical trial of SBRT from 6 institutions between January 2012 and April 2015. SBRT was delivered with a total dose of 45-60 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. Survival outcomes were analyzed with the Kaplan-Meier method. This trial is registered with ClinicalTrials.gov, number NCT01850667.

Results: Sixty-seven patients were evaluable with a median follow-up of 19 months (range, 2-42 months). Local control rate at 2 years and 3 years were 94.0% (95% confidence interval [CI], 76.1%-98.6%) and 89.0% (95% CI, 67.8%-96.6%), respectively. Overall survival rate at 2 years and 3 years were 83.5% (95% CI, 68.5%-91.7%) and 75.1% (95% CI, 50.9%-88.6%), respectively. Progression-free survival rate at 2 years and 3 years were 47.2% (95% CI, 32.8%-60.4%) and 37.2% (95% CI, 21.1%-53.3%), respectively. Intrahepatic failure-free survival rate at 2 years and 3 years were 51.1% (95% CI, 36.8%-63.8%) and 41.3% (95% CI, 24.9%-57.0%), respectively. Extrahepatic failure-free survival rate at 2 years and 3 years were 96.7% (95% CI, 87.3%-99.2%) and 87.0% (95% CI, 52.8%-97.0%), respectively. Severe treatment-related toxicities were reported in 2 patients (3.2%). One patient developed non-classic RILD at 4 months. Long-term toxicity of grade 3 esophageal ulcer with stenosis was reported in 1 patient at 6 months.

Conclusion: This is the first multicenter phase II study for SBRT in HCC. This treatment regimen is feasible and effective as evidenced by the high rates of tumor control, overall survival, and acceptable treatment-related toxicity. These results warrant confirmation in a randomized trial.

NRG Oncology/RTOG 1014: 3 Year Efficacy Report From a Phase II Study of Repeat Breast Preserving Surgery and 3D Conformal Partial Breast Re-Irradiation (PBrI) for In-Breast Recurrence

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Purpose/Objective(s): RTOG 1014 is a prospective phase II trial of 3D-conformal external beam PBrI following repeat lumpectomy for in-breast recurrence following previous whole breast irradiation (WBI). The primary endpoint was to evaluate skin, breast, and chest wall adverse events occurring within 1 year from treatment and has been previously reported. Initial efficacy data and treatment-related adverse events (AE) > 1 year are reported.

Materials/Methods: Eligibility criteria included in-breast recurrence occurring >1 year (yr) following WBI for initial lesion and confirmed to be <3cm, unifocal and resected with negative margins. Axilla was documented to be pathologic N0 or N1 without extracapsular extension. PBrI was targeted to surgical cavity + 1.5 cm for clinical target volume and an additional 1 cm expansion. Prescription dose of 45 Gy was delivered 1.5Gy BID for 30 treatments with 3-dimensional conformal radiotherapy (3DCRT). Secondary objectives include late adverse events (AEs) (> 1 yr from the end of PBrI), as graded by CTCAE version 4.0, and efficacy endpoints. In-breast recurrence (IBR) and freedom from mastectomy (MF) were estimated using the cumulative incidence method. Distant metastasis-free survival (DMFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method.

Results: Between 2010 and 2013, 65 pts were accrued and 58 eligible, completed treatment and evaluable for efficacy. Median age is 67.5 yo. 23 pts were DCIS and 35 invasive; 20 ≤1cm, 14 >1 to ≤2cm and 1 >2cm. All pts were node negative. Systemic therapy was delivered in 51.7%. Estrogen receptor is positive in 75.9%, Progesterone receptor positive in 56.9% and Her2 positive in 17%. Median follow-up is 3.64 yrs. There have been 4 patients (6.9%) with reported late grade 3 treatment-related AEs; no grade ≥4 AEs. There have been 2 patients who had an IBR for a 3-yr estimate of 3.7%; 4 patients had an ipsilateral mastectomy for a second breast conservation 3-yr estimate of 94.8%. Both DMFS and OS had a 3-yr estimate of 94.8%. Of the 2 IBRs, 1 was located within and 1 outside the treatment field. There were 4 ipsilateral mastectomies; 2 for IBR and 1 for toxicity. There was 1 bilateral mastectomy for contralateral disease.

Conclusion: Initial treatment outcome for partial breast re-irradiation with 3DCRT following second lumpectomy for patients experiencing in-breast failures after WBI demonstrates a successful second breast conservation and high local control. This adds to the growing data supporting this treatment approach as an alternative to mastectomy.

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The *KRAS*-variant is a Biomarker of Cetuximab Response and Altered Immunity in Head and Neck Cancer: NRG Oncology/RTOG 0522

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Purpose/Objective(s): There is a great need to find biomarkers of response to radiation and cetuximab in locally advanced head and neck squamous cell carcinoma (HNSCC), as well as biomarkers predicting altered immunity, enabling personalized treatment. To evaluate if the *KRAS*-variant, a germ-line mutation in a microRNA-binding site in *KRAS*, is a predictive biomarker of cetuximab response and altered immunity in the setting of radiation and cisplatin treatment in HNSCC.

Materials/Methods: Advanced HNSCC patients with known HPV status from two clinical trials were included. The NRG Oncology RTOG 0522 is a Phase III trial of cisplatin plus radiation +/- cetuximab. The UCLA CCRO-022 study is a Phase II trial of two cycles of induction paclitaxel and carboplatin followed by radiation and paclitaxel for HPV+ locally advanced HNSCC. Germline DNA was tested for the *KRAS*-variant in a CLIA-certified laboratory. In RTOG 0522, correlation between the *KRAS*-variant, p16 positivity, outcome, and TGF- β 1 levels was evaluated. In CCRO-022, broad immune phenotyping of *KRAS*-variant positive versus negative patients was performed. Hazard ratios (HR) were estimated by Cox model. Correlation of *KRAS*-variant status with cetuximab response, p16 status, immunophenotyping and plasma TGF- β 1 levels.

Results: Of 891 RTOG 0522 patients eligible for protocol analyses 413 had biological samples for *KRAS*-variant testing, and 376 had plasma for TGF- β 1 measurements. Seventy patients (16.9%) had the *KRAS*-variant. Overall, cetuximab improved both progression-free survival (PFS) for the first year (HR 0.31, p=0.04) and overall survival (OS) in years 1-2 (HR 0.19, p=0.03) for *KRAS*-variant patients. There was a significant interaction of the *KRAS*-variant with p16 status and treatment. *KRAS*-variant/p16-positive patients treated without cetuximab had worse PFS (HR 2.59, p=0.07) and OS (HR 2.48) than non-variant/p16-positive patients, with cetuximab improving OS for *KRAS*-variant/p16-positive patients compared to no cetuximab (HR 0.21). *KRAS*-variant patients in RTOG 0522 had significantly elevated TGF- β 1 plasma levels (p=0.03). In the 26 patients from CCRO-022, *KRAS*-variant patients had altered immune phenotypes.

Conclusion: *KRAS*-variant HNSCC patients significantly benefit from the addition of cetuximab to radiation and cisplatin, and demonstrate baseline immunosuppression. Cetuximab may help these patients by overcoming TGF- β induced suppression of antitumor immunity.

Shaping the Immune Landscape in Irradiated Breast Cancer Patients with Systemic TGF- β Blockade

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Purpose/Objective(s): This is a multi-institution pilot study targeting TGF β in metastatic breast cancer with the aim to counteract immune suppression and improve radiotherapeutic responses. Hypofractionated radiation was delivered to selected tumor metastasis in the rationale of creating personalized antigenic reservoirs to vaccinate each patient in vivo with her own, relevant tumor antigens and allow T cells to reach their full potential by blocking TGF β .

Materials/Methods: 22 patients with advanced disease underwent a 15-week treatment course with 5 cycles of either 1mg or 10mg TGF β neutralizing antibody, interspersed by 2 cycles of 3x 7.5Gy metastatic irradiation. Peripheral blood mononuclear cells (PBMCs) were isolated from each patient following serial blood draws and broadly immunophenotyped into common lymphoid and myeloid subsets according to flow cytometric profiles of 21 surface antigens. PBMC's tetramer/dextramer binding allowed for enumeration of tumor-specific T cells recognizing survivin, JARID1B, Mucin 1 or Her-2/neu. The balance of L-Tryptophan and Kynurenine in the circulation was determined by liquid chromatography/tandem mass spectrometry.

Results: Comparisons were made between the groups receiving 1 and 10mg. Most patients in the 10mg arm responded with an early expansion in CD4 Tregs while mMDSCs declined (ratio Tregs/mMDSC rising in 10mg vs 1mg, $p=0.026$) indicating that regulatory immune networks had shifted their balance away from myeloid towards lymphoid suppressors. The ability to boost the central memory CD8 T cell compartment with potentially long-lived recall responses also required the more potent dose of anti-TGF β antibody (relative increase at 2 weeks 10mg vs 1mg, $p=0.027$). The approach largely failed to generate de novo T cell responses against tumor antigens in the 11 HLA-A2+ patients that were tested although pre-existing survivin-specific T cells in 2 of 3 patients were boosted. CART analysis allowed accurate survival classification based on 2-week changes in CD8/mMDSC ratios (ROC AUC 0.824). An overall survival benefit of about 10 months was seen in the high dose antibody arm (median OS 64.1 weeks versus 20 weeks, $p=0.015$ log rank test).

Conclusion: Inhibiting TGF β in the context of radiation tumor damage may create a favorable systemic immune landscape limiting myeloid suppression while driving T cell memory but without great benefit for most patients with advanced breast cancer.