Reduced radiation boost volume recommended but craniospinal axis dose remains unchanged for average-risk pediatric medulloblastoma

Children’s Oncology Group trial finds survival not compromised from smaller radiation volume to posterior fossa but upholds standard doses for craniospinal irradiation

BOSTON, September 25, 2016 -- In the largest trial conducted for average risk (A-R) medulloblastoma, survival rates following reduced radiation therapy (RT) boost volumes were comparable to standard treatment volumes for the primary tumor site but lower doses of craniospinal axis irradiation were associated with higher event rates and worse survival, according to research presented today at the 58th Annual Meeting of the American Society for Radiation Oncology (ASTRO). Findings from this phase III randomized trial indicate that physicians can adopt smaller boost volumes for posterior fossa RT but should maintain the standard RT dose for craniospinal irradiation (CSI).

The most common type of brain malignancy in children, medulloblastoma is an aggressive tumor that originates in the lower, rear area of the brain but has a propensity to spread to the upper brain and spine. As a result, the standard of care following surgical resection for these children has included systemic chemotherapy and irradiation to both the posterior fossa (i.e., the primary site) and the craniospinal axis. Complications of craniospinal irradiation, however, include considerable negative effects on patients’ neurocognitive abilities, endocrinologic function and hearing.

Researchers from the National Cancer Institute-supported Children’s Oncology Group conducted this phase III trial to assess outcomes from a reduced radiation boost volume to the posterior fossa among pediatric A-R medulloblastoma patients and a lower CSI dose specifically in younger children. While several single-institution trials have found limited posterior fossa boost to be comparable to whole posterior fossa boost, this is the first trial that was sufficiently powered to state
definitively that there is no survival difference between the two approaches.

Findings are based on data from 464 patients ages three to 21 with A-R medulloblastoma. Eligible patients had complete or near-complete resection of their primary tumors and no evidence of anaplasia or spread of the cancer beyond the posterior fossa. Patients were randomized to receive either a standard radiation boost volume to the posterior fossa (PFRT group, $n = 237$) or a reduced dose of involved field RT (IFRT group, $n = 227$). The 226 patients who were ages three to seven were also randomized to receive either a standard irradiation dose of 23.4 Gy to the craniospinal axis (SD-CSI group, $n = 110$) or a reduced dose of 18 Gy (LD-CSI group, $n = 116$). Following maximum surgery and within 31 days following resection, patients began six weeks of RT. After a one month break, patients began to receive alternating cycles of Cisplatin and Cytoxan-based chemotherapy.

Primary outcomes included the amount of time from study entry to disease progression, disease recurrence, death from any cause, or second malignant neoplasm. Researchers compared rates of overall survival (OS), event-free survival (EFS), local failure and distant failure by computing Hazard Ratios (HR) and performing intent to treat analysis.

With a median follow-up of more than six and a half years, reduction in the volume of RT boost to the posterior fossa did not compromise overall or event-free or survival in pediatric patients with A-R medulloblastoma. Overall survival at five years was $84.1 \pm 2.8$ percent for patients who received the reduced volume with IFRT and $85.2 \pm 2.6$ percent for patients who received the standard volume with PFRT. EFS at five years was $82.2 \pm 2.9$ percent for IFRT and $80.8 \pm 3.0$ percent for PFRT. Rates of local failure also did not vary significantly between treatment arms. Local failure at five years was $1.9 \pm 0.1$ percent for IFRT and $3.7 \pm 1.3$ percent for PFRT ($p = 0.178$).

“This trial -- the largest of its kind to date -- indicates that it is safe to adopt a limited posterior fossa boost for patients receiving radiation therapy for average risk medulloblastoma, and that these children can have similar positive outcomes with lower chances of radiation affecting surrounding brain tissue” said Jeff M. Michalski, MD, MBA, FASTRO, professor of radiation oncology at Washington University in St. Louis and lead author of the study. “Additional data are needed, however, to address the appropriate volume for patients with higher risk disease or those who have metastasis at the time of diagnosis.”

While reduced RT volume to the posterior fossa did not impact survival rates, a low dose of craniospinal irradiation was associated with lower rates of event-free and overall survival for the youngest pediatric patients. Overall survival at five years was $78.1 \pm 4.4$ percent for patients ages three to seven who received low dose irradiation therapy to the CSI versus $85.9 \pm 3.8$ percent for the standard CSI dose. EFS at five years was $72.1 \pm 4.8$ percent for the LD-CSI group, compared to $82.6 \pm 4.2$ percent for SD-CSI. Rates of
distant failure did not vary significantly between treatment groups. Isolated distant failure at five years was $12.8 \pm 3.2$ percent for LD-CSI and $8.2 \pm 2.8$ percent for SD-CSI ($p = 0.115$).

“Unfortunately, we were disappointed to find that a lower dose of irradiation therapy was associated with increased rate of failure in the younger children,” said Michalski. “Reducing the treatment by just three fractions from 23.4 Gy to 18 Gy was associated with a higher rate of events and diminished overall survival. Patients with average risk medulloblastoma should continue to receive a standard dose of 23.4 Gy to the craniospinal axis, unless they are enrolled in a clinical trial.”

The abstract, “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,” will be presented in detail during the clinical trials session at ASTRO’s 58th Annual Meeting at 3:15 p.m. Eastern time on Sunday, September 25, 2016. To speak with Dr. Michalski, please contact ASTRO’s media relations team on-site at the Boston Convention and Exhibition Center September 25 through 28, by phone at 703-286-1600 or by email at press@astro.org.

ATTRIBUTION TO THE AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING REQUESTED IN ALL COVERAGE.

Full study abstract available on the final page of this release.

ABOUT ASTRO’S ANNUAL MEETING
ASTRO’s 58th Annual Meeting, the nation’s premier scientific meeting in radiation oncology, will be held September 25-28, 2016, at the Boston Convention and Exhibition Center in Boston. The 2016 Annual Meeting is expected to attract more than 11,000 attendees from across the globe, including oncologists from all disciplines and members of the entire radiation oncology team. Led by ASTRO president David C. Beyer, MD, FASTRO, the 2016 meeting will feature keynote addresses from Kathleen Sebelius, former U.S. Secretary of Health and Human Services; Thomas James Lynch Jr., MD, Chair and CEO, Massachusetts General Physicians Organization; and Jason Ragogna, general manager, SMS and Safety Alliances, Corporate Safety, Security, and Compliance, Delta Air Lines, Inc. The Presidential Symposium, “Prostate Cancer: Defining Value and Delivering It,” highlights the meeting’s theme of “Enhancing Value, Improving Outcomes” and will feature recent practice-changing studies and current developments in value-based care for prostate cancer. ASTRO’s four-day scientific meeting will feature a record number of abstracts, including 368 oral presentations, 1,760 posters and 180 digital posters in more than 50 educational sessions and 20 scientific panels for 20 disease-site tracks. For more information about ASTRO’s 58th Annual Meeting, visit www.astro.org/AnnualMeeting. For press registration and news briefing information for ASTRO’s 58th Annual Meeting, visit www.astro.org/AMPress.

ABOUT ASTRO
ASTRO is the premier radiation oncology society in the world, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, the Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy.
standards, advancement of science and research, and advocacy. ASTRO publishes three medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.org); developed and maintains an extensive patient website, RT Answers (www.rtanswers.org); and created the Radiation Oncology Institute (www.roinstitute.org), a nonprofit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org.
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%± 2.6% and 84.1%± 2.8%, respectively. The 5-year EFS in PFRT and IFRT was 80.8%± 3.0% and 82.2%± 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% ± 3.8% and 78.1%± 4.4%, respectively. The 5 year EFS in SD-CSI and LD-CSI was 82.6% ± 4.2% and 72.1% ± 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%±0.1% and 3.7%±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%±3.2% and 8.2%±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.