

Embargoed until 1:00 p.m. Pacific time, Sunday, September 24, 2017

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Long-term survival rates more than double previous estimates for locally advanced lung cancer

Phase III trial demonstrates 32 percent overall survival rate at five years following standard-dose treatment for stage III NSCLC; trial also finds no additional benefit from cetuximab

SAN DIEGO, September 25, 2017 — Long-term results of a phase III clinical trial indicate that survival rates for patients receiving chemoradiation for unresectable, locally advanced non-small cell lung cancer (NSCLC) may be more than twice as high as previous estimates. At five years following treatment with a standard dose of 60 Gray (Gy) radiation delivered in 30 fractions, the overall survival rate was 32 percent, setting a new benchmark of survival for patients with inoperable stage III NSCLC. The trial, RTOG 0617, also confirms that a standard dose of radiation therapy is preferable to a higher dose and that cetuximab offers no additional survival benefit for these patients. Findings will be presented today at the [59th Annual Meeting](#) of the American Society for Radiation Oncology (ASTRO) in San Diego.

Lung cancer claims the most cancer-specific deaths of any tumor type, both in the United States and worldwide. The American Cancer Society, using data from the National Cancer Institute, [estimates](#) five-year survival rates of five to 14 percent for patients who present with stage III NSCLC. RTOG 0617 was a phase III randomized trial that compared a standard radiation therapy dose of 60 Gy in 30 fractions with a higher dose of 74 Gy in 37 fractions for patients receiving concurrent chemotherapy with or without cetuximab for inoperable stage III lung cancer.

“Based on the two-year results [reported](#) in 2015, RTOG 0617 has already changed practice and established the standard radiation dose for patients receiving chemoradiation for stage III NSCLC,” said Jeffrey D. Bradley, MD, FASTRO, the principal investigator of the RTOG 0617 trial and a professor of

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radiation oncology and director of the S.L. King Center for Proton Therapy at the Washington University School of Medicine in St. Louis.

“When RTOG 0617 was initially reported, the results were surprising to most oncologists because the standard dose of 60 Gy was superior to the higher dose of 74 Gy in this setting. There have been numerous secondary analyses investigating the reasons for this result, and the data point toward greater radiation exposure to the heart in the high-dose arm being the main problem.

“The current report establishes an overall five-year survival standard for patients receiving standard-dose chemoradiation for stage III NSCLC that is substantially higher than previously estimated. This report also confirms that using a higher radiation dose is not beneficial and can lead to detrimental outcomes including lower survival rates and increase side effects.”

Patients enrolled in RTOG 0617 were randomized to one of two chemoradiation dose groups. Standard-dose treatment consisted of 60 Gy total radiation dose, and high-dose patients received 74 Gy total dose. Radiation was delivered in 2 Gy daily fractions through either intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy (3-D CRT). All patients received concurrent weekly chemotherapy with paclitaxel and carboplatin. Patients also were randomized to receive either cetuximab or a placebo. Full information on the trial design is available on the [RTOG website](#).

Across the 185 institutions in the United States and Canada that participated in RTOG 0617, a total of 544 patients with unresectable stage III NSCLC were accrued and 496 were eligible for analysis. The median patient age was 64 years (interquartile range [IQR] 57-70 years). Most patients were male (59%) and white (41%). The median follow-up for surviving patients was 5.1 years (IQR 4.6 – 6 years).

Survival rates at five years following chemoradiation were higher for patients in the standard-dose treatment arm than for those in the high-dose arm. Median overall survival (OS) following standard-dose treatment was 28.7 months (95% CI 24 - 38.4 months), compared with 20.3 months (95% CI 18-24 months) for the high-dose cohort (hazard ratio [HR] 1.35, $p = 0.004$). Five-year OS rates were 32.1 percent and 23 percent for the standard-dose and high-dose arms, respectively ($p = 0.004$).

Progression-free survival (PFS) rates at five years were 18.3 percent and 13 percent for the standard-dose and high-dose arms, respectively ($p = 0.055$). Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test and Cox proportional hazard models.

On multivariate analysis, differences in OS were driven by radiation dose (favoring the standard-dose regimen; $p = 0.03$), planning target volume ($p = 0.022$), the accrual volume of the treating institution ($p = 0.017$), presence of esophagitis/dysphagia ($p = 0.008$) and V5 heart dose/volume ($p = 0.005$).

Patterns of tumor recurrence, either in the same location or region as the initial tumor or further away, also favored the standard-dose regimen, although differences between the treatment arms did not reach statistical significance. Failure rates for the standard-dose and high-dose arms, respectively, were as follows: local failure in 38.2 percent versus 45.7 percent ($p = 0.068$); regional failure in 35.7 percent versus 38.4 percent ($p = 0.5$); and distant failure in 52.3 percent versus 57.6 percent ($p = 0.3$). Failure rates were estimated using the cumulative incidence method and evaluated through Fine-Gray models.

Treatment-related side effects were more pronounced with the high-dose regimen. There were three treatment-related deaths in the standard-dose arm, compared with nine in the high-dose arm. Rates of treatment-related grade 3 or higher toxicity for the standard-dose and high-dose arms, respectively, were as follows: dysphagia in 3.2 percent versus 12.1 percent ($p < 0.0001$); esophagitis in 5.0 percent versus 17.4 percent ($p < 0.0001$); and severe pulmonary events in 20.6 percent versus 19.3 percent ($p > 0.05$).

Cetuximab (delivered as a 400-milligram dose on day one, then 250-milligram doses weekly thereafter) did not confer a benefit for overall survival at five years. Median OS for patients who received cetuximab was 24 months (95% CI 20.4 - 30 months), compared with 24 months (95% CI 20.5 - 28.8 months) for those who did not (HR 1.0, $p = 0.048$). Moreover, there was no benefit of cetuximab for patients with epidermal growth factor receptor (EGFR) H-scores above 200, counter to earlier findings from the trial.

The abstract, "Long-term results of RTOG 0617; a randomized phase III comparison of standard dose versus high dose conformal chemoradiotherapy +/- cetuximab for stage III NSCLC," will be presented in detail during a news briefing and an oral abstract session at ASTRO's 59th Annual Meeting in San Diego (full details below). To schedule an interview with Dr. Bradley and/or outside experts in lung cancer, contact ASTRO's media relations team on-site at the San Diego Convention Center, September 24 through 27, by phone at 703-286-1600 or by email at press@astro.org.

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

This news release contains additional and/or updated information from the study author(s). Full original abstract and author disclosures available on the final page of this release.

Study Presentation Details

- News Briefing: Sunday, September 24, 1:00 – 2:00 p.m. Pacific time, San Diego Convention Center, room 24C, webcast: <http://www.bit.do/astro17-1>
- Scientific Session: Tuesday, September 26, 4:45 – 6:15 p.m. Pacific time, San Diego Convention Center, room 7A/B

Resources on Lung Cancer and Radiation Therapy

- Videos: [Radiation Therapy for Lung Cancer \(Spanish version\)](#), [An Introduction to Radiation Therapy \(Spanish version\)](#)
- Digital brochure: [Radiation Therapy for Lung Cancer \(Spanish version\)](#)
- Additional [brochures, videos and information](#) on radiation therapy from ASTRO's patient site, [RTAnswers.org](#)
- ASTRO's [clinical practice statements and guidelines](#)

ABOUT ASTRO'S ANNUAL MEETING

ASTRO's 59th Annual Meeting, the world's largest scientific meeting in radiation oncology, will be held September 24-27, 2017, at the San Diego Convention Center. The 2017 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. More than 2,800 abstracts sharing results from clinical trials and other research studies will be presented in conjunction with educational sessions and keynote addresses that underscore the meeting's theme, "The Healing Art and Science of Radiation Oncology." Led by ASTRO President Brian Kavanagh, MD, MPH, FASTRO, the 2017 meeting will feature keynote addresses from Richard D. Zane, MD, FAAEM, Chief Innovation Officer for the University of Colorado Health System; Lucy Kalanithi, MD, FACP, widow of Paul Kalanithi, MD, the best-selling author of "When Breath Becomes Air," with Heather Wakelee, MD, Paul's oncologist; and Vinay K. Prasad, MD, MPH, an assistant professor of medicine at the Oregon Health & Science University. During the four-day meeting, more than 200 exhibitors will demonstrate cutting-edge technology and medical device innovations for radiation oncology. Visit us online for more information about [ASTRO's 59th Annual Meeting](#) or [press opportunities at the meeting](#).

ABOUT ASTRO

The American Society for Radiation Oncology (ASTRO) is the world's largest radiation oncology society, 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. 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 and follow us on our [blog](#), [Facebook](#) and [Twitter](#).

Abstract 227: Long-term results of RTOG 0617; a randomized phase III comparison of standard dose versus high dose conformal chemoradiotherapy +/- cetuximab for stage III NSCLC

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Purpose/Objective(s): RTOG 0617 had two primary objectives; to compare standard-dose (SD)(60 Gy) versus high-dose (HD)(74 Gy) chemoradiation therapy and to determine the efficacy of the EGFR antibody cetuximab for stage III NSCLC. Mature 5-year follow up data are reported.

Materials/Methods: This phase III randomized trial used a 2x2 factorial design with radiation dose as one factor and cetuximab as the other factor, with a primary endpoint of overall survival. Overall and progression-free survival rates were estimated using the Kaplan-Meier method and the survival rates compared using the log-rank test. Two-sided p values are shown. Cox proportional hazards models were used to evaluate the impact of treatment and other factors on overall and progression-free survival. Local, regional, and distant failure rates were estimated using the cumulative incidence method, and Fine-Gray models were used to evaluate the impact of treatment and other factors on these rates

Results: 544 patients were accrued and 496 were eligible for analysis. Median follow up for surviving patients is 5.1 years with an interquartile range of 4.6-6 years. Patient, tumor, and treatment characteristics are described in the primary manuscript. With respect to RT randomization, there were 3 Grade 5 adverse events in the SD arm and 9 in the HD arm (one additional since primary report with GI bleed). Treatment-related grade 3+ dysphagia and esophagitis occurred in 3.2% and 5.0% in the SD arm versus 12.1% and 17.4% in the HD arm, respectively (p<0.0001). There remains no statistical difference in overall pulmonary toxicity, with Grade 3+ events occurring in 20.6% and 19.3%, respectively. Median overall survival is 28.7mo vs 20.3mo (p=0.0072) for SD vs HD arms, respectively. 5-year OS and PFS rates are 32.1% vs 23% (p=0.004) and 18.3% vs 13% (p=0.055), respectively, favoring the SD arm. Factors impacting OS on multivariable analysis were radiation dose favoring SD, tumor location, institution accrual volume, esophagitis/dysphagia, PTV, and heart V5. Local, regional and distant failure patterns are 38.2% vs 45.7% (p=0.068), 35.7% vs 38.4% (p=0.5), and 52.3% vs 57.6% (p=0.3). The use of cetuximab confers no benefit. The prior signal of cetuximab benefit in patients with higher H-scores is no longer apparent.

Conclusion: 60 Gy with concurrent chemotherapy should remain the standard of care, with an OS rate amongst the highest reported in the literature for stage III NSCLC. Cetuximab, an antibody to EGFR, had no effect on OS.

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Support: This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP), U24CA180803 (IROC) from the National Cancer Institute (NCI) and Eli Lilly

Author Disclosures: J.D. Bradley: Research Grant; ViewRay, Inc., Mevion Medical Systems. Travel Expenses; Mevion Medical Systems. Organize NRG Oncology research agenda on lung cancer; American College of Radiology. Organize oral board examinations; American Board of Radiology. C. Hu: None. R.U. Komaki: None. G. Masters: None. G.R. Blumenschein: Research Grant; Bristol Meyers Squibb, Bayer, Novartis, XCoverly, AstraZeneca, GlaxoSmithKline, AbbVie. Bristol Meyers Squibb, Bayer, Celgene, Clovis, AbbVie, Ariad, AstraZeneca, Merck. S.E. Schild: Research Grant; Alliance. Travel Expenses; Alliance. J.A. Bogart: Partner; Upstate University Radiation Oncology. Travel Expenses; Alliance Clinical Trials. Chair, radiation oncology committee; Alliance. K.M. Forster: Help design clinical trials; CZ Biomed. A. Magliocco: None. V.S. Kavadi: Partner; Texas Oncology. Medical Director; US Oncology; US Oncology. S. Narayan: None. P. Iyengar: None. C.G. Robinson: Research Grant; Varian Medical Systems, Elekta. Speaker's Bureau; Varian Medical Systems, DFINE. Advisory Board; Radialogica. Travel Expenses; Varian Medical Systems, DFINE. Stock Options; Radialogica. R. Wynn: None. C.D. Koprowski: None. M.R. Olson: None. J. Meng: None. W.J. Curran: ASCO. H. Choy: Research Grant; Celgene. Advisory Board; Bayer, EMD.