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News Release

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Contact: Liz Gardner
703-286-1600
liz.gardner@astro.org

Leah Kerkman Fogarty
703-839-7336
leah.fogarty@astro.org

Phase III trial confirms pelvic radiation as standard of care for high-risk, early-stage endometrial cancer

Brachytherapy-chemotherapy combination not superior to radiation alone for recurrence-free and overall survival; radiation alone demonstrated better pelvic control, fewer severe side effects

SAN DIEGO, September 25, 2017 – In a new phase III trial report from the National Clinical Trial Network group, NRG Oncology, recurrence-free and overall survival rates for women with stage I-II high-risk endometrial cancer were not superior following vaginal cuff brachytherapy plus chemotherapy when compared with pelvic radiation therapy. Risks of pelvic and para-aortic nodal recurrence and frequency of short-term side effects were greater for the brachytherapy-chemotherapy approach. High completion rates for each treatment arm suggest that both therapies are well-tolerated by patients. Findings will be presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO).

Clinical trials in the early 2000s (e.g., Gynecology Oncology Group (GOG)-99, PORTEC) found that external beam radiation therapy to the pelvis following surgery to remove early-stage endometrial cancer reduced tumor recurrence rates compared with post-surgical observation alone, which established adjuvant pelvic radiation as the standard treatment for stage I-II patients. In recent years, however, many physicians have begun treating early-stage patients at higher risk of recurrence with an alternative approach of vaginal cuff brachytherapy followed by chemotherapy. GOG-249 was designed to directly compare the two approaches.

"Our trial clearly demonstrates that adjuvant pelvic radiation should remain the standard of care for high-risk, early-stage endometrial cancer patients. It also suggests that the trend in our field of abandoning pelvic radiation in favor of chemotherapy-brachytherapy combinations for high-risk patients is premature

and not supported by clinical evidence," said Marcus Randall, MD, FASTRO, lead author of the study and a professor of radiation medicine at the University of Kentucky in Lexington. "The cohort of women with high-risk histologies did not demonstrate any benefit from the addition of chemotherapy, but they did experience worse nodal control rates and more short-term side effects."

GOG-249 was a phase III randomized trial designed to test whether adjuvant brachytherapy plus chemotherapy improved recurrence-free survival compared with the standard treatment of pelvic radiation for early-stage, high-risk endometrial cancer. Eligible patients included women with high-risk stage I-II histology, including stage II tumors, stage I-II serous or clear-cell carcinomas and stage I endometrioid tumors if the patient demonstrated clinic-pathologic features associated with a high risk of recurrence, based on criteria established in the GOG-33 trial and used in the GOG-99 trial.

Most patients (74%) had stage I disease and endometrioid histology (71% versus 15% serous and 5% clear-cell carcinomas). The median patient age was 63 years. All patients underwent hysterectomy prior to radiation or chemoradiation therapy.

One of two treatment arms was randomly assigned to patients: adjuvant external beam RT to the pelvis (PXRT) or vaginal cuff brachytherapy plus chemotherapy (VCB/C). The PXRT group (n = 301 patients) received a median radiation dose of 45 Gray (Gy) delivered over five weeks through standard four-field radiation or intensity-modulated radiation therapy (IMRT). Patients with serous, clear-cell or stage II tumors were eligible for a vaginal cuff brachytherapy boost, and 35 percent of the cohort received this additional therapy. The VCB/C group (n = 300 patients) received either high-dose rate (HDR) or low-dose rate (LDR) brachytherapy followed by three cycles of chemotherapy including paclitaxel (175 mg/m 2 – 3 hour) and carboplatin (AUC 6 – 21 days). Nearly all 601 patients accrued for the trial completed treatment (91% PXRT, 87% VCB/C).

There were no statistically significant increases in recurrence-free survival (RFS) or overall survival (OS) in the brachytherapy-chemotherapy arm. At a median follow-up of 53 months, 82 percent of patients were alive and recurrence free at three years for both the VCB/C and PXRT patient groups. Three-year OS rates were 91 percent for pelvic radiation and 88 percent for the brachytherapy-chemotherapy combination, but this difference was not statistically significant (p = 0.57). Survival distributions were estimated using the Kaplan-Meier method and compared using a log rank test.

The cumulative incidence of pelvic or para-aortic nodal recurrence at five years among the VCB/C group (9.2%, 25 recurrences, 20 in the pelvis) was twice that of the pelvic radiation cohort (4.4%; 12 recurrences, 6 in the pelvis) (Hazard Ratio (HR) = 0.47, 95% CI 0.24-0.94). The cumulative incidence of vaginal

and distant tumor recurrences, however, did not differ significantly between the groups. The cumulative incidence of distant recurrence at five years was 18 percent for both groups.

Short-term side effects were more pronounced on the brachytherapy-chemotherapy arm, while long-term side effects were similar for both treatments. Grade 3 or higher adverse events were reported in 187 patients receiving VCB/C, compared with 32 patients in the PXRT group. Severe late effects, or side effects that occurred after treatment ended, were reported in 35 patients who received VCB/C and 37 who received PXRT. Side effects were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.

"Previous GOG trials confirmed that pelvic radiation is an effective, safe and tolerable option to manage early-stage endometrial cancer. The current trial confirms that this standard treatment is preferable to the experimental approach of vaginal cuff brachytherapy followed by chemotherapy, in terms of tumor control in the nodal regions and also in terms of acute toxicity. This finding holds true even for patients at a higher risk of recurrence," said Dr. Randall. "Researchers can focus now on determining the optimal radiation dosing and fractionation schedules for various patient sub-groups, as well as refining the techniques we use to deliver external beam therapy to the pelvis and continue to investigate therapies to decrease distant failures in this high-risk group."

The abstract, "A phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A Gynecology Oncology Group study," will be presented in detail during a news briefing and the Plenary Session at ASTRO's 59th Annual Meeting in San Diego (full details below). To schedule an interview with Dr. Randall and/or outside experts in gynecologic 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: Monday, September 25, 11:00 a.m. – 12:00 p.m. Pacific, San Diego Convention Center, room 24C, webcast: http://www.bit.do/astro17-2
- Scientific Session: Plenary, Monday, September 25, 2:15 – 3:45 p.m. Pacific time, San Diego Convention Center, Ballroom 20

Resources on Gynecologic Cancer and Radiation Therapy

- Digital brochure: Radiation Therapy for Gynecologic Cancers
- Videos: Radiation Therapy for Gynecologic Cancers (Spanish version), An Introduction to Radiation Therapy (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 LBA-1: A phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A Gynecology Oncology Group study

M. Randall[1], V. Filiaci[2], D. McMeekin[3], C. M. Yashar[4], R. Mannel[3], R. Salani[5], P. DiSilvestro[6], J. Burke[7], T. Rutherford[8], N. Spirtos[9], J. Cho[10], J. Kim[11,12], P. Anderson[13], W. Brewster[14], W. Small[15], M. Carney[16], C. Aghajanian[17], and D. S. Miller[18]; *[1]University of Kentucky, Lexington, KY, [2]NRG Oncology Statistics and Data Management Center, Buffalo, NY, [3]University of Oklahoma, Oklahoma City, OK, [4]University of California San Diego, San Diego, CA, [5]The Ohio State University, Columbus, OH, [6]Brown University, Providence, RI, [7]Memorial University, Savannah, GA, [8]Yale Gynecologic Oncology, New Haven, CT, [9]Women's Cancer Center of Nevada, Las Vegas, NV, [10]University of Hawaii, Honolulu, HI, [11]Seoul National University, Seoul, Korea, Republic of (South), [12]Korean Gynecologic Oncology Group, Seoul, Korea, Republic of (South), [13]Fox Chase Cancer Center, Philadelphia, PA, [14]University of North Carolina, Chapel Hill, NC, [15]Loyola University Medical Center, Maywood, IL, [16]University of Hawaii Cancer Center, Honolulu, HI, [17]Memorial Sloan Kettering Cancer Center, New York, NY, [18]University of Texas-Southwestern, Dallas, TX*

Purpose/Objective(s): To determine if vaginal cuff brachytherapy and chemotherapy (VCB/C) could increase recurrence-free survival (RFS) compared to pelvic external beam radiation therapy (PXRT). Secondary objectives included comparisons of overall survival (OS), patterns of failure, and frequency/severity of adverse events between the treatment arms.

Materials/Methods: A randomized phase III trial was performed in endometrial cancer patients meeting eligibility criteria. All patients were required to undergo hysterectomy. Eligible patients had stage I endometrioid histology with GOG 99-based high intermediate risk criteria (based on age, tumor grade, depth of invasion, and presence of lymphovascular space invasion), stage II, or stage I-II serous (S) or clear cell (CC) tumors. Central pathology review was performed. Patients assigned to PXRT were treated with standard 4-field or Intensity-Modulated Radiation Therapy (IMRT) techniques to a mean dose of 45 Gy over 5 weeks. Additional VCB was optional for patients with S/CC tumors or stage II disease. Patients assigned to VCB/C received HDR or LDR brachytherapy followed by paclitaxel 175 mg/m2 (3 hour) + carboplatin AUC 6 q 21 days for a total of 3 cycles.

Results: A total of 601 pts were accrued; PXRT was assigned to 301 (18 did not receive study treatment) and VCB/C to 300 (9 did not receive study treatment). The median age was 63 years, 74% had stage I disease, and 89% underwent lymphadenectomy. Histology included 71% with endometrioid type, 15% S, and 5% CC. Nearly all pts completed the prescribed therapy (91% PXRT, 87% VCB/C). In the PXRT arm, IMRT was used in 36%, and vaginal cuff brachytherapy boost was added in approximately 35%. Acute toxicity was more common and more severe with VCB/C. Grade 3 or higher adverse events were reported in 32 patients on the PXRT arm versus 187 patients on the VCB/C arm. Grade 3 or higher late effects were seen in 37 and 35 patients on the PXRT and VCB/C arms, respectively. With a median follow-up of 53 months, the 36 month RFS was 82% for both PXRT and VCB/C. The 36 month OS was 91% vs 88% for PXRT and VCB/C, respectively. No significant differences were noted between the two arms in terms of vaginal or distant failure. However, pelvic or para-aortic nodal recurrences were significantly more common in the VCB/C arm (25 vs 12), largely driven by the difference in pelvic nodal failure (20 vs 6 patients). There was no statistically significant treatment effect heterogeneity with respect to RFS among clinical-pathologic variables evaluated.

Conclusion: This study did not demonstrate a superiority of VCB/C to PXRT in women with HR endometrial cancer. Acute and late toxicity and pelvic and para-aortic nodal failure were more frequent in the VCB/C arm.

Both arms appeared to be well tolerated with high completion rates. PXRT remains an effective, well-tolerated, and acceptable adjuvant treatment in patients with high risk, early-stage endometrial carcinoma.

Author Disclosures: M. Randall: Uterine Corpus Com; GOG/NRG. V. Filiaci: Research Grant; National Cancer Institute. Service Agreement for conducting research; GOG Foundation, Inc. participates in the executive committee; NRG Oncology Statistics and Data Management Center. D. McMeekin: None. C.M. Yashar: Employee; Abreos Biosciences. Partner; Kaiser Permanente. Advisory Board; Cianna Medical, MicroChips. Travel Expenses; MicroChips. Chair the committee for hospital credentialing; University of California San Diego; American College of Radiation Oncology, University of California San Diego. Chair meetings for review educational programs. R. Mannel: help lead organization; GOG Foundation. Group Chair; NRG. R. Salani: None. P. DiSilvestro: None. J. Burke: None. T. Rutherford: None. N. Spirtos: None. J. Cho: None. J. Kim: None. P. Anderson: None. W. Brewster: None. W. Small: Research Grant; Carl Zeiss. Speaker's Bureau; Carl Zeiss. Advisory Board; Varian. Travel Expenses; Carl Zeiss. Board Member; Loyola University Health System. ACR Leadership; ACR. Research; NRG Oncology, RTOG. M. Carney: None. C. Aghajanian: Honoraria; Clovis. Steering Committee Member; Mateon. D.S. Miller: Research Grant; Genentech, Merrimack, Novartis. Advisory Board; Genentech. Chair; NRG Oncology.