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## **International trial confirms safety, effectiveness of high-dose brachytherapy plus pelvic radiation for cervical cancer**

*Multicenter trial in seven countries confirms optimal radiation dosing schedule for localized disease and outlines expected outcomes for treatment teams in resource-constrained settings*

SAN DIEGO, September 24, 2017 – Findings from a new multicenter, international clinical trial confirm the effectiveness of high-dose brachytherapy, or internal radiation therapy, for managing locally advanced cervical cancer. Tumor control was significantly better following four fractions of 7 Gray (Gy) each than following two, 9-Gy fractions of high-dose-rate (HDR) brachytherapy, but neither overall survival nor severe treatment-related side effects differed between the treatment groups. Findings from the International Atomic Energy Agency (IAEA) trial will be presented today at the [59th Annual Meeting](#) of the American Society for Radiation Oncology (ASTRO).

“Cervical cancer is the leading cause of cancer death among women in the developing world, and 80 percent of these patients live in lower- or middle-income countries, such as the ones in our trial. It is essential that we have data applicable to these real-world settings,” said May Abdel-Wahab, MD, PhD, FASTRO, a study co-author and director of the Division of Human Health at the International Atomic Energy Agency in Vienna, Austria.

“Our trial demonstrates that combining pelvic radiation therapy with four fractions of 7 Gy HDR brachytherapy is effective for locally advanced cervical cancer. In addition, it gives physicians data-supported guidance from a large, randomized study on what to expect in terms of outcomes if a regimen of two, 9-Gy fractions is used in resource-constrained settings.”

### **AMERICAN SOCIETY FOR RADIATION ONCOLOGY**

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The prospective, randomized multicenter trial tested two approaches to delivering HDR brachytherapy with or without chemotherapy for patients with intermediate-stage cervical cancer. All patients received 46 Gy of curative-intent pelvic external beam radiation therapy in 23 fractions. All patients also received HDR brachytherapy in one of two dosing schedules. Half of the patients received four applications of 7 Gy each (4x7 Gy), while the other half received two applications of 9 Gy each (2x9 Gy). Additionally, half of the patients in each brachytherapy group received chemotherapy (cisplatin 40 mg/m<sup>2</sup> in weeks 1-5), while the other half did not. The median follow-up for surviving patients was 48 months (range 1-84 months).

A total of 601 patients with intermediate-stage cervical cancer were enrolled between September 2005 and May 2010. Patients in this international trial represented seven countries, including Mumbai (257 cases), Peru (147), South Africa (76), Brazil (53), Pakistan (31), Morocco (19) and Macedonia (18). The average patient age was 49 years (range 26-71). All patients had either stage IIB (73.2%) or stage IIIB (26.8%) disease, and no patients had contraindications for radiation therapy or chemotherapy.

Overall survival at five years following treatment was 67.2 percent for all patients (95% CI = 62.7-71.2%). The survival rate was higher for women with stage IIB disease (71%) than for stage IIIB disease (58%) ( $p = 0.03$ ). Overall survival rates for patients who received pelvic radiation and 4x7 Gy HDR brachytherapy were 73.1 and 62.2 percent with and without chemotherapy, respectively. Among patients in the 2x9 Gy HDR brachytherapy group, rates were 65.1 and 68.3 percent with and without chemotherapy, respectively ( $p = 0.1$  between the four arms).

Among patients with stage IIB disease, neither brachytherapy dosing nor the addition of chemotherapy had a significant influence on the overall survival rate. Survival rates were estimated using the Kaplan-Meier method and compared between arms using the log-rank test.

Five-year rates of locoregional control, or tumor control in the site and surrounding area of the primary tumor, favored the 4x7 Gy brachytherapy approach, with or without the addition of systemic therapy ( $p = 0.0007$ ). Rates for patients who received pelvic radiation and 4x7 Gy brachytherapy were 88 and 89 percent with and without chemotherapy, respectively, compared to control rates on the 2x9 Gy brachytherapy arm of 78 and 75 percent with and without chemotherapy, respectively.

Severe treatment-related side effects did not differ significantly between treatment arms. Actuarial rates of grade 3 or higher genitourinary side effects for patients who received pelvic radiation and 4x7 Gy brachytherapy were 5.9 and 7.3 percent with and without chemotherapy, respectively; for the 2x9 Gy brachytherapy arm, they were 7.2 and 7.3 percent with and without chemotherapy, respectively. Actuarial

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rates of grade 3 or higher gastrointestinal side effects for patients who received pelvic radiation and 4x7 Gy brachytherapy were 6 and 5.3 percent with and without chemotherapy, respectively; for the 2x9 Gy brachytherapy arm, rates were 5.9 and 5.3 percent with and without chemotherapy, respectively.

There was a modest positive effect of cisplatin on toxicity in the 2x9 Gy brachytherapy arm only ( $p = 0.066$ ), but chemotherapy did not significantly influence overall survival, cancer-specific survival or tumor control in the cervix and surrounding region.

“The findings that chemotherapy did not significantly affect survival or tumor control in this setting seem to be different than the results of the meta-analysis from the [Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration](#), which found six percent differences in local control due to the effect of chemotherapy,” explained Dr. Abdel-Wahab. “However, it is important to note that our study was not powered to detect differences in local control that are less than 10 percent. In other words, the results of the two studies are not mutually exclusive.”

In addition to providing guidance for clinical teams treating women with cervical cancer, the study also demonstrates the feasibility of conducting global clinical trials, including trials in lower- and middle-income countries where resources for research tend to be more restricted.

The abstract, “Analysis of outcomes using external beam radiotherapy plus high dose rate brachytherapy (4x7 Gy or 2x9 Gy) for cervix cancer in a multi-institution trial,” 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. Abdel-Wahab 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](mailto: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: Plenary, Monday, September 25, 2:15 – 3:45 p.m. Pacific time, San Diego Convention Center, Ballroom 20

**Resources on Gynecologic Cancers 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](http://www.redjournal.org)), *Practical Radiation Oncology* ([www.practicalradonc.org](http://www.practicalradonc.org)) and *Advances in Radiation Oncology* ([www.advancesradonc.org](http://www.advancesradonc.org)); developed and maintains an extensive patient website, *RT Answers* ([www.rtanswers.org](http://www.rtanswers.org)); and created the Radiation Oncology Institute ([www.roinstitute.org](http://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](http://www.astro.org) and follow us on our [blog](#), [Facebook](#) and [Twitter](#).

**Abstract LBA-2: Analysis of outcomes using external beam radiotherapy plus high dose rate brachytherapy (4x7 Gy or 2x9 Gy) for cervix cancer in a multi-institution trial**

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**Purpose/Objective(s):** Compare loco-regional (LR) control and adverse effects (AE) of external beam radiotherapy (EBRT) in combination with 2 different fractionation schedules of HDR brachytherapy (HDRBT) with or without chemotherapy (CT) in cervical cancer.

**Materials/Methods:** A prospective, randomized, multi-center international trial of the IAEA tested four combinations of HDRBT and CT in cervical cancer. Eligible patients were women with stages IIB and IIIB cervical carcinoma being treated with curative intent and with no contraindications for EBRT, HDRBT and CT. All patients were to receive EBRT, 46 Gy in 23 fractions to the pelvis. Prescribed HDRBT dose in arm A, was 4 applications of 7 Gy each to point 'A' while in arm B it was 2 applications of 9 Gy. Arms C and D were similar to arms A and B but with cisplatin (40mg/m2) in weeks 1 through 5. LR tumor-control, overall survival and acute/late AE were compared between arms. Using a/b values of 10 Gy for tumor control and 3 Gy for late-AE, biological effective doses (BED) and equivalent doses (EQD2) were calculated for each arm. Arms A and C had BED10=102.8Gy10 (EQD2= 85.7 Gy) and BED3=128.3Gy3 (EQD2 = 77Gy). For arms B and D, BED10 and BED3 were 89.4 Gy10 (EQD2= 74.5 Gy) and 115.8 Gy3 (EQD2= 69.4Gy).

**Results:** Between Sep 2005 and May 2010, 601 patients were randomized. By centre, there were 257 cases from Mumbai, 147 cases from Peru, 76 from South Africa, 53 from Brazil, 31 from Pakistan, 19 from Morocco and 18 from Macedonia. Average age was 48.7 y (26 - 71). Four hundred and forty patients had stage IIB cases, and 161 had stage IIIB (p=0.7 across arms). Overall 5-y survival was 71% for IIB patients and 58% for IIIB patients (p=0.03). The 5-y survival for all women, combined, was 67.2% (95% CI 62.7-71.2%). By treatment arm, 5-y overall survival was: 62.2% in A, 68.3% in B, 73.1% in C, and 65.1% in D. By log-rank test, stratified by centre and stage, there was no statistical difference in overall survival by study arm (p=0.1). For the 440 stage IIB patients there was no statistical difference in survival with 4 HDR vs. 2 HDR, and no difference with or without CT. 5-y tumor control and adverse effects are reported in table 1. Tumor control was lower in arms B and D compared to arms A and C (p=0.0007). No statistically significant difference in AE was found. The only effect of cisplatin was an increased-AE trend in the 2x9 Gy arm-B (p=0.066).

**Conclusion:** A dose-effect relationship was found for tumor control in our study. Local control was significantly superior for the arms including 4 fractions of 7 Gy HDRBT as compared to 2 fractions of 9 Gy. No statistically significant differences in OS or AE were found between arms.

Study arm	5-yr tumor control (+) %, 95% CI	Genitourinary		Gastrointestinal	
		G3-5 toxicity (*)	fistula	G3-5 toxicity (*)	fistula
Arm A: EBRT 46 Gy + HDRBT (4x7 Gy)	88 (81-92) %	7.3%	0%	4%	1.3%
Arm B: EBRT 46 Gy + HDRBT (2x9 Gy)	78 (71-84) %	6.7%	0.6%	4%	1.3%
Arm C: (Arm A + CDDP)	89 (82-94) %	5.3%	0.6%	6%	0%
Arm D: (Arm B + CDDP)	75 (67-82) %	7.2%	0%	5.9%	0%

+p=0.0007; \*excluding fistula

**Author Disclosure:** G.W. Jones: None. J. Hendry: None. U.M. Mahantshetty: None. G. Sarria: None. N.W. da Motta: None. E. Fidarova: None. M. Abdel-Wahab: Member; United Nations ute agency task force steering committee educational and expert panel; ACR & Florida Radiological Society (FRS). R.R. Prasad: None. A. Polo: None. E. Zubizarreta: None.