**Radiobiological Analysis of Outcomes Using External Beam Radiotherapy Plus High Dose-Rate Brachytherapy (4x7 Gy or 2x9 Gy) for Cervical Cancer in a Multi-Institution Trial**

J. Hendry,1 G.W. Jones,2 U.M. Mahantshetty,3 G. Sarria,4 N.W. da Motta,5 E. Fidarova,6 M. Abdel-Wahab,7 R.R. Prasad,6 A. Polo,8 114 and E. Zubizarreta6;

*1Macclesfield, United Kingdom, 2Trillium Health Partners, Mississauga, ON, Canada, 3Tata Memorial Hospital, Mumbai, India, 4Radioncologia - AUNA, Lima, Peru, 5HSR/iSCMPA, Porto Alegre, Brazil, 6International Atomic Energy Agency, Vienna, Austria, 7International Atomic Energy Agency, Vienna A-1400, Austria, 8IAEA, Vienna, Austria*

**Purpose/Objective(s):** To compare locoregional (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, multicenter 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 = 28.3Gy3 (EQD2 = 77 Gy). For arms B and D, BED10 and BED3 were 89.4 Gy10 (EQD2 = 74.5 Gy) and 115.8 Gy3 (EQD2= 69.4 Gy).

**Results:** Between September 2005 and May 2010, 601 patients were randomized. By center, 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 yr (26 - 71). Four hundred and forty patients had stage IIB cases, and 161 had stage IIIB (P= .7 across arms). Overall 5-yr survival was 71% for IIB patients and 58% for IIIB patients (P= .03). The 5-yr survival for all women, combined, was 67.2% (95% CI 62.7-71.2%). By treatment arm, 5-yr 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 center and stage, there was no statistical difference in overall survival by study arm (P= .1). For the 440 stage IIB patients, there was no statistical difference in survival with 4 HDR versus 2 HDR, and no difference with or without CT. Five-year 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= .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= .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 compared to 2 fractions of 9 Gy. No statistically significant differences in OS or AE were found between arms.