Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 4, pp. 1077–1082, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.04.040

**CLINICAL INVESTIGATION** **Cervix**

# COMPARISON OF LATE TOXICITY BETWEEN CONTINUOUS LOW-DOSE-RATE AND PULSED-DOSE-RATE BRACHYTHERAPY IN CERVICAL CANCER PATIENTS

BARBARA BACHTIARY, M.D.,* AARON DEWITT,* MELANIA PINTILIE, M.SC.,† JOHN JEZIORANSKI, M.MATH.,* SANDI AHONEN, R.T.T.,* WILFRID LEVIN, M.D.,* LEE MANCHUL, M.D.,* IVAN YEUNG, PH.D.,* MICHAEL MILOSEVIC, M.D.,* AND ANTHONY FYLES, M.D.*

*Department of Radiation Oncology, Princess Margaret Hospital, Ontario Cancer Institute and University of Toronto, Toronto, Ontario, Canada; †Clinical Study Coordination and Biostatistics, Princess Margaret Hospital, Toronto, Ontario, Canada

**Purpose: To compare survival and severe late radiation toxicity between patients who received continuous low-dose-rate (LDR) brachytherapy (BT) and pulsed-dose-rate (PDR) BT for cervical cancer.**
**Methods and Materials: A retrospective review of cervical cancer patients who underwent primary radiotherapy with or without concurrent cisplatin was performed. Late Grade 3 or worse toxicities were assessed using the National Cancer Institute Common Toxicity Criteria. The study endpoints were overall and disease-free survival and the probability of severe late toxicity.**
**Results: A total of 109 patients (65.7%) received LDR BT and 57 (34.3%) received PDR BT. Seventy patients received concurrent chemotherapy with cisplatin. The 3-year overall survival and disease-free survival rate was 70% and 57% for the LDR group and 82% and 70% for the PDR group, respectively ($p = 0.25$ and $p = 0.19$). The 3-year probability rate for late Grade 3 or worse toxicity was 7.4% for LDR BT patients and 7.6% for PDR BT patients, respectively ($p = 0.69$) and 6.9% and 7.6%, respectively, for concurrent chemotherapy vs. none ($p = 0.69$).**
**Conclusion: No difference was found in severe late toxicity, overall survival, or disease-free survival between the LDR and PDR groups.** © 2005 Elsevier Inc.

**Cervical cancer, Radiotherapy, LDR brachytherapy, PDR brachytherapy, Toxicity.**

## INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and the most common cause of cancer-related death in women of developing countries (1). Standard management of advanced disease includes external-beam radiotherapy (RT), intracavitary brachytherapy (BT), and concurrent chemotherapy (2). In most centers worldwide, BT is given using continuous low-dose-rate (LDR) or high-dose-rate (HDR) BT, but pulsed-dose-rate (PDR) BT has been suggested as an alternative (3, 4). In PDR BT, the continuous LDR is replaced by a series of HDR pulses, typically taking a few minutes each hour and typically with the same overall dose and overall time as the corresponding LDR regimen (5).

When compared with LDR, PDR and HDR have a number of advantages. The dose distribution can be optimized to a greater extent by varying the source dwell times and locations and patient care is easier to plan between pulses or fractions.

Finally, from the radiobiologic point of view, multiple fractionation regimens such as PDR and HDR may produce a better therapeutic ratio between tumor control and late effects than LDR (6, 7). In HDR, the fraction size is technically restricted; however, in PDR, any fraction size and overall treatment time can be selected.

Although PDR BT has been increasingly used in the treatment of cervical cancer, to date only a few data are available on late toxicity and survival (8). No clinical data are available for PDR vs. LDR in cervical cancer patients.

The objective of this article was to compare overall and disease-free survival and the type and frequency of late toxicity in patients who underwent PDR BT vs. LDR BT for cervical cancer.

## METHODS AND MATERIALS

### *Patients*

A total of 308 patients were prospectively enrolled in a translational research program at the Princess Margaret Hospital (To-

Reprint requests to: Anthony Fyles, M.D., Department of Radiation Oncology, Princess Margaret Hospital, 610 University Ave., Toronto, ON M5G 2M9 Canada. Tel: (416) 946-6522; Fax: (416) 946-2111; E-mail: Anthony.Fyles@rmp.uhn.on.ca

Supported by the CIHR program for Excellence in Radiation Research for the 21st century.

Received Mar 3, 2005, and in revised form April 1, 2005. Accepted for publication April 4, 2005.

ronto, ON) and underwent RT for cervical cancer between January 1994 and December 2002. Of the 308 patients, 104 had previously undergone a hysterectomy and received adjuvant RT without BT and 204 underwent BT and were included in this study. All patients had histologically proven squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or clear cell carcinoma of the cervix. Twenty patients were part of an ongoing Phase II study evaluating the effect of concomitant celecoxib and were excluded. Patients with previous or concurrent malignancy ($n$ = 1), patients who were subsequently treated surgically ($n$ = 3), patients who had metastatic disease at presentation ($n$ = 2), and patients who had small-cell carcinoma ($n$ = 2) were excluded from this study. One patient was excluded because she was subsequently treated with cyclophosphamide for a second cancer. Nine patients were excluded because their charts were no longer available. No other exclusion criteria were otherwise applied. Analysis was based on the data of 166 patients. Stage and grade were determined according to the International Federation of Gynecology and Obstetrics criteria (9).

### Treatment

*External-beam RT.* The treatment policies have been previously described (10). In brief, external-beam RT (EBRT) was delivered to the pelvis or to the pelvis and para-aortic region (depending on the results of staging) using a planned dose of 4,500–5,000 cGy in 180–200 cGy daily fractions with 18–25 MV photons. A four-field box was used to treat the pelvis, and AP opposed fields were used for the para-aortic nodes. In 131 patients, a two half-value-layer posterior attenuator 3 cm wide at the midplane was used to reduce the rectal dose by approximately 20%.

*BT technique.* A single implantation of a linear intrauterine source without colpostats was performed under general anesthesia. Two orthogonal radiographs (AP and lateral) were obtained for dosimetry in all cases and validated for adequate source placement in relation to the sacral promontory and catheter balloon. A median dose of 4,000 cGy (range, 2,000–4,500) was prescribed 2 cm lateral to the midpoint of the sources (equivalent to Point A), depending on the original disease stage and response to EBRT using either LDR or PDR equipment. Seven patients had incomplete treatment and received <3,500 cGy BT.

Brachytherapy was started within 1–7 days after EBRT was finished. At Princess Margaret Hospital, two remote afterloaders for PDR BT and two for LDR BT are available. Between 1994 and 2000, two in-house LDR remote afterloaders (Calitron, Pune, India) were used. Since 2000, the Selectron (Nucletron, Veenendaal, The Netherlands) LDR remote afterloading system has been used. Both systems use 18 $^{137}$Ce sources, with an initial activity in the Calitron system of 15 mCi on average and in the

Table 1. Patient and tumor characteristics

| Attribute | Total ($n$ = 166) | LDR BT ($n$ = 109) | PDR BT ($n$ = 57) |
|---|---|---|---|
| Age (y) | | | |
| Median | 53 | 53 | 53 |
| Range | 23–84 | 23–84 | 23–77 |
| FIGO stage | | | |
| IB | 34 | 27 (24.8) | 7 (12.3) |
| IIA | 11 | 3 (2.8) | 8 (14.0) |
| IIB | 70 | 41 (37.6) | 29 (50.9) |
| IIIA + IIIB | 48 | 36 (33.0) | 12 (21.1) |
| Not stated | 3 | 2 (1.8) | 1 (1.8) |
| Tumor size (cm) | | | |
| Median | 5 | 5 | 5 |
| Range | 2–10 | 2–10 | 3–8 |
| Histologic type | | | |
| Squamous | 138 | 91 (83.5) | 47 (82.5) |
| Adenocarcinoma | 22 | 15 (13.8) | 7 (12.3) |
| Adenosquamous | 5 | 2 (1.8) | 3 (5.3) |
| Clear cell | 1 | 1 (0.9) | 0 (0) |
| Grade | | | |
| Well | 11 | 8 (7.3) | 3 (5.3) |
| Moderately | 100 | 63 (57.8) | 37 (64.9) |
| Poorly | 39 | 25 (22.9) | 14 (24.6) |
| Not stated | 16 | 13 (11.9) | 3 (5.3) |
| Pelvic nodes | | | |
| Negative | 78 | 50 (45.9) | 28 (49.1) |
| Positive | 54 | 32 (29.4) | 22 (38.6) |
| Equivocal | 34 | 27 (24.8) | 7 (12.3) |
| Initial hemoglobin (g/dL) | | | |
| Median | 12.45 | 12.4 | 12.8 |
| Range | 8.1–15.4 | 8.1–15.1 | 8.8–15.4 |
| Nadir hemoglobin (g/dL) | | | |
| Median | 11.4 | 11.5 | 11.3 |
| Range | 7.2–14.5 | 7.2–14.5 | 7.5–14.3 |

*Abbreviations:* LDR = low-dose-rate; BT = brachytherapy; PDR = pulsed-dose-rate; FIGO = International Federation of Gynecology and Obstetrics.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.