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# Pulsed-dose-rate vs. high-dose-rate intracavitary radiotherapy for locally advanced carcinoma of cervix: A prospective randomized study

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**ABSTRACT**

**PURPOSE:** To compare late radiation toxicities in patients with carcinoma of cervix treated with pulsed-dose-rate (PDR) vs. high-dose-rate (HDR) intracavitary radiotherapy (ICRT).

**METHODS AND MATERIALS:** Between July 2010 to April 2012, 37 patients with Stage IIB-IIIB (International Federation of Gynecology and Obstetrics 2009) squamous cell carcinoma of cervix were randomized to receive either HDR (7 Gy each in three fractions, repeated weekly) or PDR (70 cGy hourly pulses for 39 hours, total 27 Gy) ICRT after external beam radiotherapy. Late rectal and bladder toxicities were assessed using Radiation Therapy Oncology Group criteria, and vaginal toxicity was graded as per common terminology criteria for adverse events. Overall survival and disease-free survival were estimated using Kaplan−Meier method.

**RESULTS:** Nineteen patients received HDR and 18 received PDR ICRT with median followup 34 and 29 months, respectively. In HDR vs. PDR arm, late rectal toxicities grade ≥2 (16.7% vs. 21.1%, $p = 1.000$), grade ≥3 (10.5% vs. 0%, $p = 0.486$), late bladder toxicities grade ≥2 (10.5% vs. 0%, $p = 0.486$), and late vaginal toxicities grade ≥2 (15.8% vs. 5.6%, $p = 0.604$) were not statistically different. For HDR and PDR ICRT groups, 4-year disease-free survival was 67.1% vs. 71.8% ($p = 0.195$) and overall survival was 77% vs. 75% ($p = 0.322$), respectively.

**CONCLUSION:** In this small group of patients, there were fewer events in form of late radiation toxicities in PDR arm, although statistically not significant. Further studies are required to define role of PDR compared to HDR ICRT in cervical carcinoma. 

*Keywords:* Carcinoma cervix; Brachytherapy; High dose rate; Pulsed dose rate; Intracavitary radiotherapy

## Introduction

Worldwide, cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths (1). Most patients present in locally advanced (IB2-IVA) stages (2). For locally advanced carcinoma of cervix (LACC), concurrent chemoradiotherapy followed by intracavitary radiotherapy (ICRT) is the standard treatment (3). ICRT, which is a form of brachytherapy, is an integral part of radical treatment of cervical carcinoma. It offers highly conformal dose distribution with rapid dose fall off, resulting into better therapeutic ratio in comparison to even high-tech external beam irradiation techniques (4). Low dose rate (LDR), high dose rate (HDR), and pulsed dose rate (PDR) are various dose rate systems being used for ICRT around the world with varying experience and expertise. Although LDR has been used for treatment of cervical carcinoma for more than a century, currently, HDR is being preferred worldwide over LDR because of physical advantages (better dose optimization, radiation safety, and short treatment time). Radiobiologically, LDR is considered advantageous over HDR in terms of late tissue effects, although not reflected in randomized trials (5). PDR brachytherapy was developed in 1990s combining physical advantages of HDR and radiobiologic advantages of LDR

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brachytherapy. In PDR, instead of delivering the dose continuously as in LDR, a series of hourly HDR pulses, continuing few minutes each hour, is delivered. Typically, the overall dose and treatment time are same as corresponding LDR schedule. PDR compared to LDR has many distinct advantages such as isodose optimization, better therapeutic ratio attributed to multiple fractionation regimens, and better patient care as patient can be attended and required nursing care can be given during pulse off time (6). In high turnover centers, PDR may look disadvantageous from logistic point of view because of long treatment time. But its role can be justified if clinical results are better than HDR as radiobiologically expected. But there is no randomized study comparing PDR and HDR. PDR is generally presumed to be radiobiologically equivalent to LDR, and studies comparing HDR to LDR are perceived as HDR vs. LDR/PDR. As we have discussed, PDR is different from LDR in multiple aspects, so, this generalization is not justified.

We conducted a prospective randomized study with the hypothesis that PDR ICRT would reduce late rectal and bladder toxicity compared with HDR ICRT. We also aimed to compare late vaginal toxicities between the two arms as secondary objectives.

## Methods and materials

### *Patient characteristics*

Between July 2010 to April 2012, 37 patients with histopathology proven International Federation of Gynecology and Obstetrics 2009 Stage IIB-IIIB squamous cell carcinoma of cervix were enrolled in this study. To be eligible, patients age had to be between 25 and 65 years, with a Karnofsky performance status ≥70, hemoglobin ≥10 gm/dL, total leukocyte count ≥4000/mm$^3$ to ≤11,000/mm$^3$, absolute neutrophil count ≥1500/mm$^3$, platelets ≥100,000/mm$^3$, blood urea 10−20 mg/dL, creatinine clearance >50 mL/min, and normal liver function tests. Patients with nonsquamous histology, para-aortic lymph node involvement, distant metastasis, metachronous/synchronous malignancy, and history of treatment for cancer and any comorbidity hampering radical treatment for cervical cancer were excluded. Informed written consent was obtained before enrollment into study. Institutional ethics committee approved this study.

Pretreatment workup included a medical history, complete physical and gynecologic examination, complete blood count, liver and kidney function tests, chest radiography, contrast-enhanced computed tomography of abdomen and pelvis. Only for those patients with clinical or radiologic suspicion of involvement in bladder and/or rectum, cystoscopy and sigmoidoscopy were performed. Patients were staged clinically on the basis of the pretreatment workup in a multidisciplinary clinic comprising a radiation oncologist, a medical oncologist, and a gynecologist. Patient's characteristics are summarized in Table 1.

### *Study design*

It was a nonblinded, prospective randomized trial. Thirty-seven eligible patients were randomized to one of two treatment arms: PDR or HDR by random computer generation number in a nonstratified manner. Patients in both the arms received external beam radiation therapy (EBRT) to pelvis to a total prescription dose of 50.4 Gy in 28 fractions over 5.5 weeks with concurrent cisplatin, administered intravenously once a week at a dose of 40 mg/m$^2$. After completion of EBRT, all patients received brachytherapy, starting within a week using either PDR or HDR ICRT. Flow diagram showing study outline is summarized in Fig. 1.

### *Radiotherapy planning*

For EBRT, simulation was done in supine position with patients immobilized using custom thermoplastic immobilization devices on a fluorosimulator (Oldelft Simulator, Nucletron). Conventional radiotherapy planning was done consisting of a four-field "box" arrangement using parallel opposed anteroposterior/posteroanterior and lateral fields without blocks or shielding. Bony landmarks and a cervical marker (radio-opaque marker placed in vagina at most distant portion of cervical growth) were used during fluorosimulation for design of field portals as follows: (*1*) superior border: L4-L5 intervertebral space, (*2*) lateral border: 1.5 cm lateral to border of true pelvis, (*3*) inferior border: 3 cm below the cervical marker, (*4*) anterior border: anterior symphysis pubis, and (*5*) posterior border: junction of S2/S3 or encompassing the entire sacral hollow depending on disease extent. All patients were treated on a linear accelerator, CL 2300 CD (Varian Medical System, Palo Alto, California, United States). Concurrent weekly chemotherapy (cisplatin 40 mg/m$^2$) was administered during the course of EBRT.

On completion of EBRT, patients received brachytherapy starting within 1 week. A standard Fletcher-Suit

Table 1
Patient characteristics in PDR ICRT and HDR ICRT arms

| Characteristic | PDR ICRT arm | HDR ICRT arm |
|---|---|---|
| No. of patients | 18 | 19 |
| Age, median (range) | 51 (35−65) | 45 (35−65) |
| FIGO stage (n) | | |
| IIB | 08 | 10 |
| IIIA | 00 | 01 |
| IIIB | 10 | 08 |
| KPS, median (range) | 90 (70−90) | 90 (70−90) |

FIGO = International Federation of Gynecology and Obstetrics; KPS = Karnofsky performance status; PDR ICRT = pulsed-dose-rate intracavitary radiotherapy; HDR ICRT = high-dose-rate intracavitary radiotherapy.