

BRACHYTHERAPY FOR STAGE IIIB SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX: SURVIVAL AND TOXICITY

ANTONIO CARLOS ZULIANI^{1*}, MAÉRCIO DE OLIVEIRA CUNHA¹, SÉRGIO C. B. ESTEVES², JÚLIO CÉSAR TEIXEIRA³,

Trabalho realizado na Seção de Radioterapia, Departamento de Tocoginecologia, Universidade Estadual de Campinas, Campinas, SP

SUMMARY

OBJECTIVE. To compare survival and toxicity of three different treatments for stage IIIB cervix cancer: low-dose-rate (LDR), high-dose-rate (HDR) brachytherapy and association of HDR and chemotherapy.

METHODS. Between 1985 and 2005, 230 patients with FIGO stage IIIB squamous cell carcinoma of the uterine cervix received 4-field pelvic teletherapy at doses between 40 and 50.4 Gy, with a different complementation in each group. The LDRB group, with 42 patients, received one or two insertions of LDR, with Cesium-137, in a total dose of 80 to 100Gy at point A. The HDR group, 155 patients received HDR in 4 weekly 7 Gy fractions and 9 Gy to 14.4 Gy applied to the involved parametria. The CHT group, 33 patients, were given the same treatment as the HDR group and received 5 or 6 weekly cycles of cisplatin, 40 mg per m².

RESULTS. The five-year progression-free survival (PFS) was 60% for the HDR group and 45% for the LDR group, and the two-year PFS for the CHT group was 65% (p = 0.02). The five-year Overall Survival (OS) was 65% for the HDR group and 49% for the LDR group. The two-year OS was 86% for the CHT group (p = 0.02). Rectum toxicity grade II was 7% for the LDR group, 4% for the HDR group and 7% for the CHT group that had one case of rectum toxicity grade IV.

CONCLUSION. Patients that received HDR had better OS and PFS. The Chemotherapy-HDR association showed no benefit when compared to HDR only. Toxicity rates showed no difference between the three groups.

KEY WORDS: Uterine cervical neoplasms. Radiotherapy. Brachytherapy. Cisplatin.

*Correspondência:

ADepartamento de Radioterapia, CAISM- Unicamp
Rua Alexander Fleming, nº 101 - Cidade Universitária Zeferino Vaz
Campinas, SP
CEP 13083-881
aczo.rt@gmail.com

INTRODUCTION

Carcinoma of the uterine cervix affects mainly women of low socioeconomic status and 80% of the cases occur in developing countries. Screening and vaccination are the best way to combat cervical cancer and the disease is prevented through tracking programs. However, incidence of advanced-stage tumors still remains very high in Brazil. Stage IIIB cervical cancer accounts for about 25% of cases diagnosed in our institution. In 2008, an estimated 21,560 of new cases of cervical cancer were diagnosed in Brazil¹. Lack of cervical cancer awareness among the population, late stage at diagnosis and lack of specialized treatment centers interfere with the probability of curing the disease.

According to the International Federation of Gynecology and Obstetrics (FIGO), at stage IIIB the carcinoma has extended to the pelvic wall, hydronephrosis or a nonfunctioning kidney are found². Brachytherapy plays an important role in managing patients with advanced-stage tumors, improving the four-year survival rate to 46% for stage IIIB disease, compared to only 19% for tumors treated with external beam radiation alone³. This form

of therapy allows high doses of radiation to be beamed directly at the tumor, while neighboring tissues receive lower radiation doses. Teletherapy using high-energy photon beams, in the past was only associated with low-dose-rate brachytherapy (LDR). Now it is also performed with high-dose-rate brachytherapy (HDR) and more recently, combined with chemotherapy^{4,5,6,7}.

Cervical cancer treatment for advanced-stage disease has undergone some changes in our institution since 1985. Accompanying changes in literature, we have made adjustments for the reality of our country. Until 1996, LDR was the brachytherapy used. With the introduction of high-dose-rate brachytherapy, in May 1996, treatment became an outpatient procedure available to many more patients⁸. Subsequently, our institution began to use chemotherapy plus concomitant radiotherapy to treat cervical cancer in 2003, supported by better results obtained from studies published in 1999 showing the benefits of combined therapy^{9,10,11}.

This study aims to compare survival and toxicity rates of LDR, HDR and HDR plus chemotherapy for stage IIIB cervix cancer. An important feature of this study is the reported toxicity of the HDR and cisplatin association.

1. Médicos Especialistas da Universidade Estadual de Campinas, Campinas, SP

2. PhD - Chefe seção de radioterapia da Universidade Estadual de Campinas, Campinas, SP

3. PhD - Médico do departamento de Tocoginecologia da Universidade Estadual de Campinas, Campinas, SP

METHODS

This is an historical comparison between treatment regimens.

Between 1985 and 2005, two hundred and thirty (230) patients suffering from FIGO stage IIB squamous cell (epidermoid) carcinoma of the uterine cervix were treated in our institution, with three different techniques¹. All were included in this report, none had involvement of the lower third of the vagina, and their treatment results were retrospectively evaluated. All patients received 4-field pelvic teletherapy, at doses ranging between 40 and 50.4 Gy, with a different complementation in each group.

The LDR group, with 42 patients, mean age 54.3 years, treated between 1986 and 1996, received one or two insertions of LDR, with Cesium-137, reaching a total dose of 80 to 100Gy at point A and were followed for 5 years.

The HDR group, 155 patients, mean age 56.5 years, treated between 1996 and 2003 with HDR in 4 weekly 7-Gy fractions to point A, using the ICRU 38 criteria for evaluation of the organs at risk. They had dose complementation ranging from 9 Gy to 14.4 Gy applied to the involved parametria, and were also followed for 5 years.

The CHT group, 33 patients, mean age 54.8 years, treated between 2003 and 2005 with the same treatment given to the HDR group, received 5 or 6 weekly cycles of 40 mg of cisplatin per square meter of body surface area. These patients had a mean 2 year follow-up.

This study was reviewed and approved by the Research Ethics Committee of the institution.

Follow-up and statistical analysis

After treatment, patients were reassessed every four months during the first two years, every six months until the fifth year, and annually thereafter, on the basis of clinical examination, cervical cytology, imaging and laboratory tests. They were followed-up for five years, and loss to follow-up was 6% (14 patients). Treatment toxicity was graded according to criteria of the Radiation Therapy Oncology Group (RTOG)¹². Overall survival (OS) was measured from onset of therapy to the date of death or most recent follow-up, progression free survival (PFS) was the period from time of biopsy to date of first documented evidence of disease-progression.

The Kaplan-Meier method was used to generate survival curves for comparison of treatment results. A log-rank test was used to analyze results. Patients without recurrent disease were excluded at their last follow-up visit or death. For all statistical tests, $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 11.01 for Windows). Leadtoolsq 1991-2000 LEAD Technologies Inc.

RESULTS

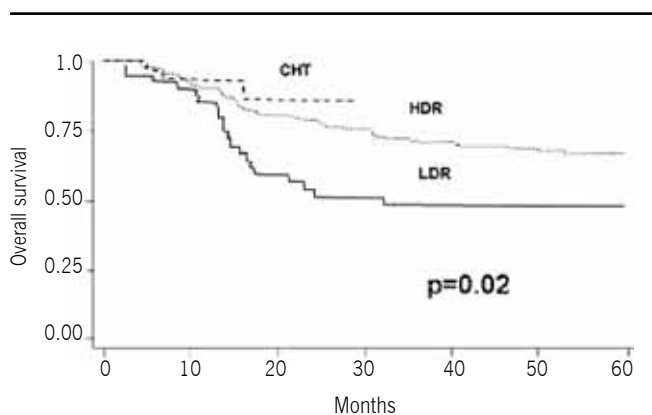
Progression free survival (PFS) was higher for groups that underwent HDR. The five-year PFS was 60% (95% CI, 51.2-68%) for the HDR group and 62% (95% CI, 36.7-79.5%) in two-year for the CHT group, compared to a five-year PFS of 45% (95% CI, 28.9-59.4%) in the LDR group receiving low-dose-rate-brachytherapy ($p = 0.02$). There was no difference between the HDR and CHT groups (Figure 1). The same pattern was observed for overall survival (OS). The five-year OS was

65% (95% CI, 52.2-73%) for the HDR group and the two-year OS was 86% (95% CI, 71.5-95.5%) for the CHT group, when compared to 49% (95% CI, 32.3-63.2%) for the LDR group ($p = 0.02$). No difference was observed in survival rates between HDR and CHT groups in the period studied (Figure 2).

Rectum toxicity grade II occurred in 3 patients (7%) in the LDR group, 6 patients (4%) in the HDR group and 3 patients (7%) in the CHT group. In the study only one case of grade IV rectal toxicity was described in the CHT group.

DISCUSSION

The current study used a time-series design to evaluate therapeutic response. Women receiving HDR showed improved rates of local control and overall survival, when compared to those receiving LDR. In our institution, patients treated with LDR had been treated many years before, possibly explaining the difference between HDR and LDR treatment. In the past, there was a longer delay in cancer diagnosis than nowadays and tumor volume was probably greater. Using an outpatient procedure such as HDR decreased treatment time and improved



Overall survival, by treatment group, calculated by Kaplan-Meier method. HDR = high dose rate brachytherapy; LDR = low dose rate brachytherapy; CHT = chemotherapy + HDR.

therapeutic response.

Cervical carcinoma has been treated with HDR in our institution since 1996. HDR proved to be as clinically effective as LDR in the management of cervical cancer. In rates of survival, relapse and complications, no statistically significant differences have been found between both treatment methods^{2,3,4,14,15,16,17}.

According to Arai et al., the five-year overall survival rate for women with epidermoid carcinoma of the uterine cervix treated with HDR was 88.1% for stage IB, 76.9% for stage II, 67% for stage IIB, 52.2% for stage IIIB, 24.1% for stage IVA and 13.3% for stage IVB of the disease¹. Ferrigno found poorer results for stage III disease treated with HDR, regarding overall and progression free survival. According to the authors, the reason for these results may be the low doses used in HDR¹⁸.

Grades III and IV complication rates for all three treatment groups were equivalent to those found in literature.

In a study by Peiteret et al., acute major complications,

requiring hospitalization were observed in 5.5% of women receiving HDR for cervical cancer. The 30-day mortality rate was 1.6%. Some identified risk factors, including advanced patient age and a low Karnofsky performance status, increased the chance of acute events occurring due to treatment¹⁵. Another study described late complications requiring treatment in about 11% of women undergoing HDRB. The most commonly affected site, was the rectum followed by the urinary bladder³.

Patients who suffered from stage IIIB squamous cell carcinoma of the uterine cervix who were treated with HDRB had a better disease-free survival rate than those treated with the previously employed LDR therapy. While the HDR and CHT groups showed better results than the LDR group, all response rates are consistent with the literature. Since the LDR group had been treated many years before, we believe that these patients may have received a late diagnosis with worse clinical support, and thus worse results. Combined modality therapy (chemotherapy and radiation therapy) was performed in a small group of patients with only a short follow-up. Until now, the rates of overall survival and progression free survival have not shown any significant improvement in these patients.

Attempts to combine radiation therapy with chemotherapy originated many years ago¹⁹. Several papers have demonstrated that neoadjuvant chemotherapy was of no benefit for patients^{20,21}.

In 1999, the North American National Cancer Institute called attention to publications of phase III studies, showing that patients treated with radiotherapy plus concomitant platinum-based chemotherapy obtained greater benefits²². While these studies described differences regarding stage of disease, dose of radiation, use of HDR or LDR, all benefited from the combined treatment. Other studies have questioned this association, demonstrating that combined treatment failed to provide any benefits for patients with advanced-stage tumors. However, patients with early-stage cancer have benefited from concomitant treatment after surgery,^{23,24} although more recent trials did not confirm these data²⁵.

In this study, patients that received HDR had better OS and PFS. The chemotherapy-HD association showed no benefit when compared to HDR only, and toxicity rates showed no difference between the three groups. Randomized controlled trials are necessary to confirm these data²⁶, but the association of chemotherapy and HDR seems to be an acceptable treatment in these cases²⁷.

Conflict of interest: none

RESUMO

BRAQUITERAPIA PARA CARCINOMA EPIDERMÓIDE DO COLO DO ÚTERO ESTÁDIO IIIB: SOBREVIDA E TOXICIDADE

OBJETIVO. Comparar três diferentes tratamentos para câncer de colo do útero, estágio IIIB: braquiterapia de baixa taxa de dose (LDR), alta taxa de dose (HDR) e associação entre HDR e quimioterapia, quanto à sobrevida e toxicidade.

MÉTODOS. Entre 1985 e 2005, 230 pacientes com carcinoma epidermoide de colo do útero estágio IIIB receberam teleterapia pélvica em quatro campos, doses entre 40 e 50.4 Gy, e três complementações diferentes. Grupo LDR, com 42 pacientes, recebeu uma ou duas inserções de LDR, com Césio-137, na dose

total de 80 a 100Gy no ponto A. Grupo HDR, 155 pacientes, com HDR em quatro frações semanais de 7 Gy, e 9 Gy a 14.4 Gy nos paramétrios acometidos. Grupo CHT, 33 pacientes, tratadas da mesma forma que o grupo HDR, mais cinco ou seis ciclos semanais de cisplatina, 40 mg por m².

RESULTADOS. A sobrevida livre de progressão em cinco anos (PFS) foi 60% no grupo HDR e 45% no grupo LDR, e a PFS em dois anos para o grupo CHT foi 65% ($p = 0.02$). A sobrevida global em cinco anos (OS) foi 65% para o grupo HDR e 49% para o grupo LDR. A OS em dois anos foi 86% para o grupo CHT ($p = 0.02$). Toxicidade retal grau II foi 7% no grupo LDR, 4% no grupo HDR e 7% no grupo CHT, que teve um caso de toxicidade retal grau IV.

CONCLUSÃO. Pacientes que receberam HDR tiveram melhores índices de sobrevida. A associação quimioterapia-HDR não mostrou benefício quando comparada com apenas HDR. Os índices de toxicidade não foram diferentes. [Rev Assoc Med Bras 2010; 56(1): 37-40]

UNITERMOS: Neoplasias do colo do útero. Radioterapia. Braquiterapia. Quimioterapia.

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