

## ORIGINAL ARTICLE

# Clinical results of medium dose rate brachytherapy combined with external beam radiotherapy in the treatment of advanced cervical carcinoma

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## Summary

**Purpose:** To evaluate the overall and disease-free survival of patients with advanced cervical carcinoma (FIGO stages IIB-III B) treated with external beam radiotherapy (EBRT) and medium dose rate brachytherapy (MDR-BT) plus/minus surgery.

**Patients and methods:** One hundred and seven patients received preoperative RT (group A) and 154 were treated with definitive RT (group B); 73 patients in both groups also received cisplatin as radiosensitizer. EBRT delivered as preoperative reached a total dose of 44-46 Gy/pelvis, whereas the definitive RT reached a total dose of 62-64 Gy with standard fractionation. MDR-BT was performed with a LDR/MDR Cs-137 Selectron machine; 10 Gy/point A were delivered in the preoperative group A and 14 Gy/point A/1-2 fractions in group B. Cisplatin as radiosensitizer was

administered during EBRT at a dose of 20 mg/m<sup>2</sup>/day for 5 days with 21 days interval between cycles.

**Results:** With a median follow-up of 44.4 months (range 3.4-61.6) the overall survival at 3 years in group A was 92% vs. 68% for group B ( $p < 0.01$ ). According to FIGO stages 3-year overall survival was 88% in stage IIB, 79% in IIIA and 60% in IIIB ( $p < 0.01$ ). Three-year local control was 73.5% (192 patients). Thirty-three (13%) patients developed locoregional recurrences, and another 8 (3.07%) locoregional recurrences plus distant metastases.

**Conclusion:** The association of EBRT with MDR-BT represents an effective treatment in advanced cervical carcinoma. A significant difference in 3-year overall survival was found, favoring preoperative RT, with a very good rate of local control.

**Key words:** brachytherapy, cervical cancer, chemotherapy, medium dose rate, survival

## Introduction

Invasive cervical cancer is the second most common malignancy in women and accounts for nearly 500.000 cases and 250.000 deaths per year [1].

In Romania, cervical cancer represents a public health problem and constitutes 15% of the total cancer cases, ranking first among female genital cancers (ap-

proximately 67% of the cancers of the genital area), and constitutes the second cause of cancer death in females. Also Romania takes the first place among European countries concerning the incidence and mortality due to cervical cancer [2,3], with incidence and mortality rates of 22-24 and 14.04/100,000, respectively [4].

In Romania most cervical cancers are diagnosed late [5], with approximately 70% of the total number of cases being in advanced stages (FIGO IIB-IV).

Five-year survival in advanced cervical cancer is 30-50% in stage III and approximately 10% in stage IV [6].

Locoregional control remains a major problem in advanced cervical cancer; pelvic failures are approximately 40-50% in stage III, and locally controlled cases bear a substantial risk of developing distant dissemination [7].

From 1999 a therapeutic guide for cervical cancer has been elaborated at our Institution by introduc-

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ing concomitant chemoradiotherapy in the standard treatment for locally advanced cases [8].

Over the years, EBRT for cervical cancer has been well standardized and uniform, however the brachytherapy (BT) component still presents variations. The preloaded applicator using radium and Cs tubes has been replaced by remote controlled after-loading using miniaturized Cs sources.

We have been using BT with an LDR/MDR Selectron machine with Cs-137 pellets since 1995.

Experience with MDR-BT has been scarcely reported in the relevant literature so far [9].

## Patients and methods

During the period January 1, 2000 to December 31, 2001, 261 patients suffering from advanced locoregional cancer of the uterine cervix (FIGO stages IIB-III B) irradiated at the "Ion Chiricuta" Oncology Institute, Department of Brachytherapy, were included in this retrospective study.

The staging system adopted was the FIGO classification as modified by Fletcher [10,11]. The distribution of patients according to stage is shown in Table 1.

### Patients' allocation and EBRT

The cases were allocated in two groups: RT followed by surgery, and RT alone, with or without associated chemotherapy (cisplatin as radiosensitizer 20mg/m<sup>2</sup>/day for 5 days every 3 weeks).

### Group A (n=107)

EBRT was delivered with linear accelerator or <sup>60</sup>Cobalt, followed by boost BT. At the end of the 5 weeks of RT, with a dose of 44-46 Gy to the pelvis and 54-56 Gy to the cervix, the patients were reevaluated by the radiotherapist and a surgeon. Cases considered operable were re-examined 4-6 weeks after completing RT for surgical intervention (colpohysterectomy with bilateral adnexectomy and pelvic lymphadenectomy).

**Table 1.** Patient distribution according to stage and therapeutic groups

Stage	Group A	Group B	Total
	EBRT+MDR-BT+Surgery n (%)	EBRT+MDR-BT n (%)	
IIB	77 (82.8)	16 (17.2)	93 (35.63)
IIIA	28 (28.28)	71 (71.72)	99 (37.94)
IIIB	2 (2.9)	67 (97.1)	69 (26.43)
Total	107 (41)	154 (59)	261 (100)

For abbreviations see text

### Group B (n=154)

The inoperable cases or those with contraindications for surgical intervention, continued RT with reduction of the upper limit of the pelvic field at a dose of 50 Gy to the pelvis and continuation up to a total dose of 62-64 Gy/6-7 weeks to the pelvis and 72-78 Gy to the cervix. Patients with concomitant chemotherapy continued cisplatin during this period, arriving to a total of 3-4 cycles.

The distribution of patients according to stage and therapeutic groups is shown in Table 1.

### Brachytherapy

In the last two weeks of EBRT, BT was delivered to the cervix level, superior 1/3 of the vagina and internal 1/3 of the parametrial tissues, by Selectron LDR/MDR device, with 36 sources of Cs-137 and using the dosimetric Plato system.

The total dose delivered was 10 Gy prescribed to point A, according to the Manchester system in the case of operable patients, and 14 Gy prescribed to point A delivered in one or two fractions in the case of patients treated exclusively with RT.

The applicators included uterine probes of various lengths and angles from 0 to 45 degrees, at which the vaginal ovoids with 2 or 2.5 cm in diameter or the vaginal ring with various diameters and angles were fixed. Treatment was individualized, depending on the anatomy of each patient.

Uterovaginal ring applicator was used in 199 (77%) patients; 39 (15%) patients were treated with the Manchester type applicator, and 11 (4%) with colpostats without uterine probe due to difficulties of carrying out hysterometry; in 5 (2%) patients uterine applicator was used because of difficulties related to their anatomy; in 3 (1%) patients vaginal cylinder was used due to the impossibility of performing hysterometry; in 4 (1.5%) patients uterine applicator was used at which the vaginal cylinder was attached because of the tumor invasion of the vaginal wall.

### Response definitions

Response was evaluated after gynaecological examination performed by a gynecologist and a radiotherapist, along with imaging studies (ultrasonography or CT scan or both). Response criteria were as follows: complete response (CR): complete disappearance of the cervix tumor and its extension (vagina, parametrial tissues); partial response (PR):  $\geq 50\%$  decrease of the known lesion(s); stable disease (SD):  $< 50\%$  decrease or  $< 25\%$  increase of the known lesion(s); progressive dis-

ease (PD): increase >25% of the cervix tumor or the locoregional extension, or appearance of new lesion(s).

### Survival estimations

Overall survival was calculated from the date of starting treatment to the last patient's visit or death. Disease-free interval was calculated from the date of starting treatment to documented disease recurrence.

### Statistical methods

Survival curves were constructed using the Kaplan-Meier method. Comparison between survival curves was made with the log-rank test and a value of  $p < 0.05$  was considered statistically significant.

## Results

The age of the patients in both groups ranged between 20 and 79 years (median 48). Fifty patients were under 40 years and equal or above 40 years were 211 patients. The peak incidence was observed between 40-59 years (Figure 1).

In group A the median age was 45.9 years (range 23-71), while it was 50.9 years (range 28-76) in group B.

Two hundred and forty-five patients (93.87%) had epidermoid carcinoma, of which 99 (40.41%) were in group A, and 146 (59.59%) in group B. Other histologies are described in Table 2.

The patients' median follow-up was 44.4 months (range 3.4-61.6). Overall survival and disease-free interval for both groups were calculated at 3 years.

The overall survival for the 2 groups at 3 years was 78% (Figure 2).

The overall survival was 92% for the combined treatment group (EBRT+MDR-BT+surgery), as compared to 68% for the definitive radiotherapy group (EBRT+MDR-BT) ( $p < 0.01$ ; Figure 3).

The overall survival in relation to tumor diameter

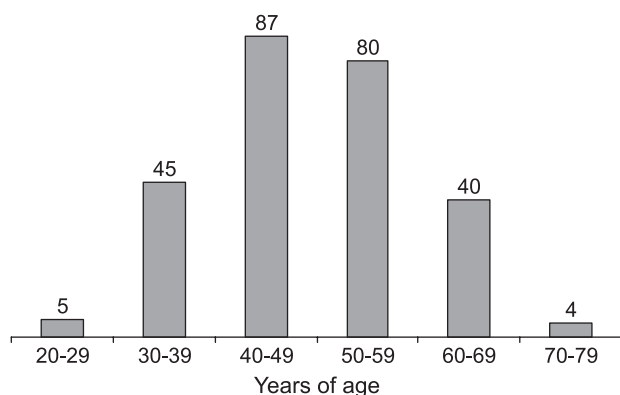


Figure 1. Patient distribution by age.

Table 2. Patient distribution according to histology

Histology	Group A Patients, n (%)	Group B Patients, n (%)	Total Patients, n (%)
Epidermoid carcinoma	99 (92.5)	146 (94.8)	245 (93.8)
Adenocarcinoma	6 (5.6)	4 (2.6)	10 (3.8)
Small cell carcinoma	1 (0.9)	2 (1.3)	3 (1.1)
Undifferentiated carcinoma	1 (0.9)	2 (1.3)	3 (1.1)

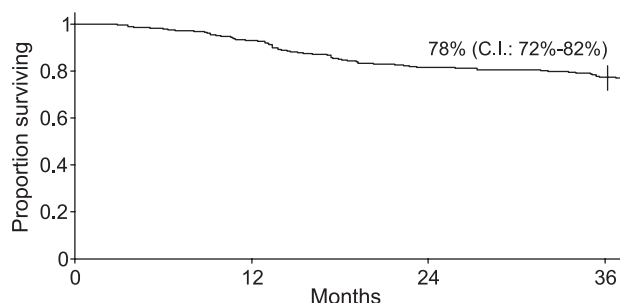


Figure 2. 3-year overall survival for the 2 groups. 95% CI: 95% confidence interval.

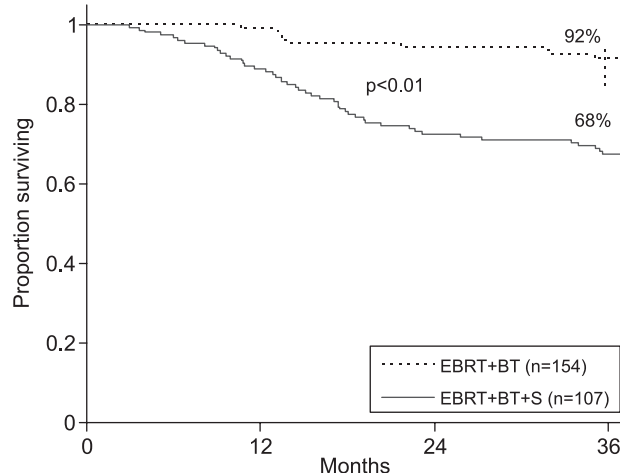
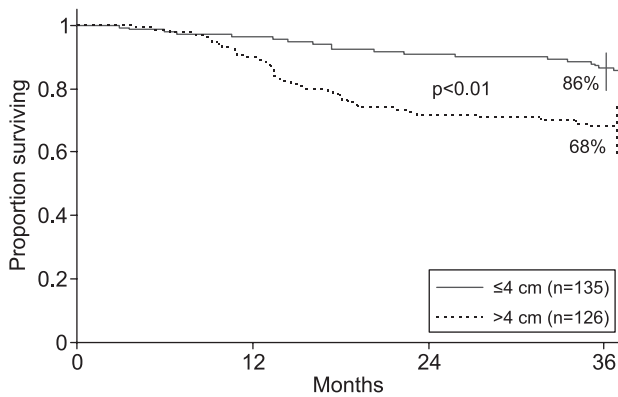


Figure 3. 3-year overall survival according to the therapeutic group.

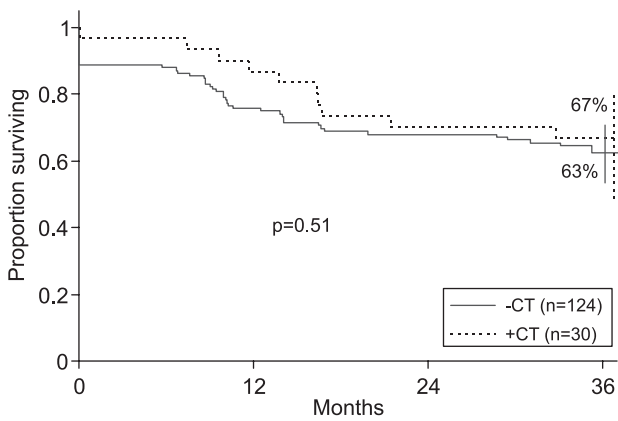
was 86% for tumors  $\leq 4$  cm as opposed to 68% for tumors  $> 4$  cm ( $p < 0.01$ ; Figure 4).

The disease-free interval in group B (EBRT+MDR-BT) was 67% in patients who received cisplatin, compared with 63% for those without chemotherapy ( $p = 0.51$ , possibly due to the small number of patients: 30 vs. 124 in whom chemotherapy was administered; Figure 5).

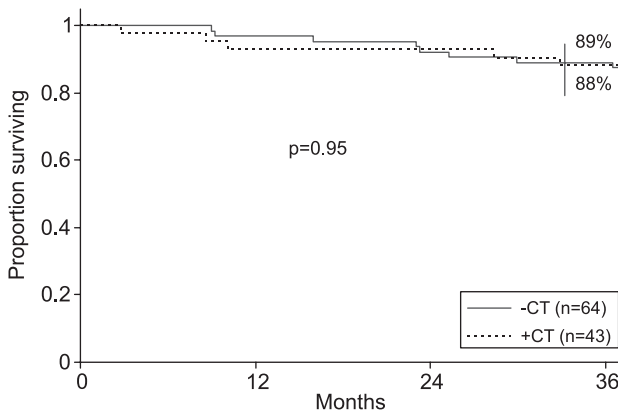
The disease-free interval in group A (EBRT+MDR-BT+Surgery) was 89% in patients without chemotherapy, compared with 88% for those with chemotherapy ( $p < 0.05$ ; Figure 6).



**Figure 4.** 3-year overall survival according to tumor diameter.



**Figure 5.** 3-year disease-free interval of patients treated exclusively with radiotherapy, with vs. without chemotherapy (CT).

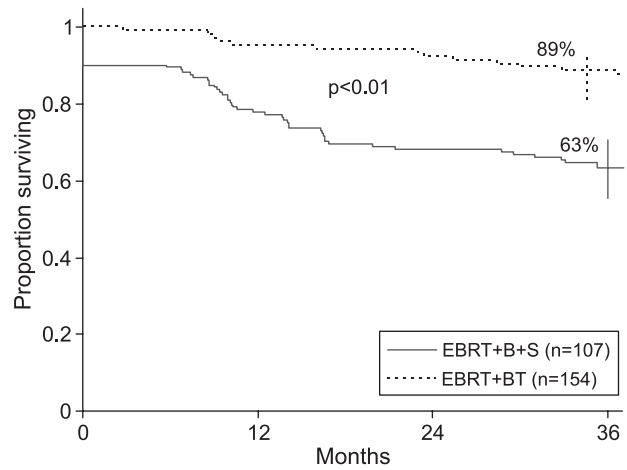


**Figure 6.** 3-year disease-free interval of patients treated with EBRT+BT+surgery, with vs. without chemotherapy (CT).

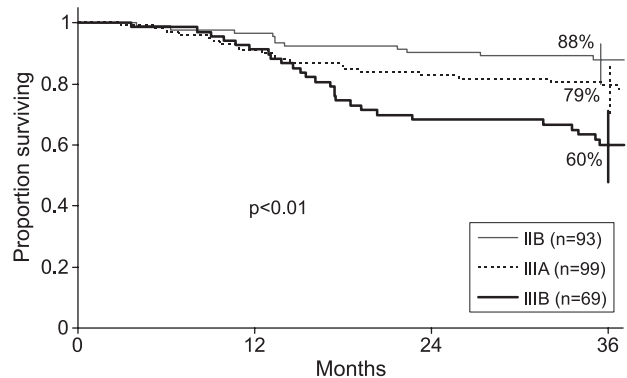
The disease-free interval was superior in group A patients (89%) in comparison with group B patients (63%) ( $p<0.01$ ; Figure 7).

Overall survival depending on stage for all patients was 88%, 79% and 60% for stages IIB, IIIA and IIIB, respectively ( $p<0.01$ ; Figure 8).

Overall survival in group A, depending on stage (IIB-IIIB) was 93% and 92%, respectively. Because



**Figure 7.** 3-year disease-free interval for groups A and B.



**Figure 8.** 3-year overall survival according to stage.

only 2 group A patients were in stage IIIB they were analyzed together with stage IIIA patients.

Overall survival depending on tumor dimension was 97% for tumors  $\leq 4$  cm vs. 85% for tumors  $> 4$  cm ( $p=0.15$ ).

Overall survival in relation to the dose delivered through BT was 98% for total dose (TD)=10 Gy/point A vs. 86% for TD=14 Gy ( $p=0.04$ ).

Concerning group B overall survival in relation to stage (IIB, IIIA and IIIB) was 75%, 72% and 60%, respectively.

Overall survival in relation to the dimension of the tumor was 78% for tumors  $\leq 4$  cm vs. 58% for tumors  $> 4$  cm ( $p=0.02$ ).

Overall survival depending on the dose delivered through MDR-BT was 65% for TD=14 Gy to point A and 60% for TD=10 Gy ( $p=0.37$ ).

Overall survival in groups A and B in relation to the administration or not of cisplatin was not possible to analyze due to the small number of patients to whom chemotherapy was administered.

In conclusion, the overall survival in group A was 92% vs. 68% in group B ( $p<0.01$ ).

At the end of the study (2004), 69 (26%) therapeutic failures had been registered: 13 (18.9%) in group A and 56 (81.1%) in group B. Local control was achieved in 73.5% (192 of 261) cases.

There were 33 (12.68%) pelvic relapses after a median disease-free interval of 14 months (mean 17.5, range 6-44.6), 8 (3.07%) pelvic relapses plus distant metastases and 13 (5%) cases with distant metastases alone. In 15 (5.75%) cases the disease progressed despite treatment.

Metastases were distributed as follows: 12 nodal (7 pelvic plus paraaortic lymph nodes, 3 pelvic lymph nodes, 1 inguinal nodes and 1 supraclavicular nodes), 5 pulmonary, 3 bony and 2 cerebral. A case of second primary tumor with pancreatic localization was registered.

Local control was obtained in 73.5% of the cases (192 of 261 patients). The operable stage IIB patients had the best local control as compared to stages IIIA and IIIB.

## Discussion

Cervical cancer represents a model for multidisciplinary approach. The goal of its treatment is obtaining a better local disease control (through a higher RT dose escalation) and maintaining a low rate of complications [12,13].

The optimal dose is obtained by combining external pelvic RT with intracavitary BT [14].

Various irradiation techniques seem to yield similar results. Hunter and colleagues compared 2 methods of irradiation: in the first one BT predominated, and in the second EBRT, the total dose being identical. Survival at 5 years was 38.6% and 40.3%, respectively, with comparable rates of pelvic relapses and major complications [15].

The therapeutic protocol used at our Institution for locoregionally advanced cervical cancer is based on EBRT+BT with or without concomitant radiosensitizing chemotherapy with cisplatin, and reevaluation of patients at a dose of 44-46 Gy; cases with favorable response undergo operation 4-6 weeks after completion of irradiation; inoperable cases continue the same initial therapeutic protocol up to a total dose of 64 Gy.

Oncology centers in Europe, especially those in France [16] and Italy [17], advocates of the French school [16], as well as those from Asia [18], treat locoregionally advanced cervical cancer (in the case of good postirradiation response) with radiosurgical combination: the main objective in performing surgery after RT is to remove potential residual tumor and to achieve an accurate surgical staging. For those patients US investi-

gators [19] suggest exclusive treatment with RT in combination with chemotherapy, considering the higher complication rates in patients treated by surgery.

Currently there is no prospective randomized study comparing the results of the two therapeutic approaches (exclusive irradiation and radiosurgical combination).

Our study is a retrospective one with numerous boundaries, with all the inherent difficulties of such an approach. Different treatment philosophies exist concerning the routine delivery or not of radiosensitizing chemotherapy. With increasing number of patients and their follow up for relatively extended periods of time, interesting conclusions can be drawn concerning the multidisciplinary therapeutic approach of cervical cancer, MDR-BT and the establishment of a most effective regime of fractionation.

The prognostic value of the disease stage was confirmed in a study on 307 patients at the "I. Chiricuta" Oncology Institute during the period 1994-1996, the survival being 88% in stage IIB, and 59% in stage IIIB [20].

For patients in stage IIB treated exclusively by irradiation the 5-year survival was 60-65% [21]. In an analysis of the pattern of care study reported by Coia et al. [22] on 157 stage IIB patients the 4-year survival ranged between 54-67%; for stage IIIB it was 25-48%.

In our study, stage-dependent survival was 88% for stage IIB, 79% for stage IIIA and 60% for stage IIIB ( $p < 0.01$ ; Figure 8).

The overall survival according to the two different therapeutic approaches was in favor of the operated patients (92 vs. 68%,  $p < 0.01$ ).

Several authors have reported 3-year overall survival 50-75% in stage IIIB patients treated exclusively with EBRT and BT [23-26].

In a study from "I. Chiricuta" Oncology Institute tumor volume has proved a significant prognostic factor, and for the advanced locoregional IIB-IIIB stages the 5-year survival was 78% for tumors  $< 3$  cm as opposed to 64% for the ones  $> 3$  cm [20].

In the present study, the overall survival was higher in patients with tumors  $\leq 4$  cm (86%) vs. 68% for tumors  $> 4$  cm, the difference being statistically significant.

Although in TNM staging system the tumor volume is not mentioned as a prognostic factor, in the present paper the negative influence of the tumor volume on survival has proved real for the entire group of patients.

The results of the metaanalysis published by Green and colleagues in 2001 are convincing as far as the concomitant radiochemotherapy in cervical cancer is concerned [27]. The authors revised 19 randomized

trials with concomitant radiochemotherapy published during the period 1981-2000, in which 4580 patients were included. The conclusion was that the anticancer agent most frequently used was cisplatin and the most beneficial effect was noticed in stages I and II ( $p < 0.009$ ). The concomitant radiochemotherapy has determined an absolute benefit in the disease-free survival (16%,  $p < 0.0001$ ) and overall survival (12%,  $p < 0.0001$ ) vs. radiotherapy alone. The benefit obtained was related to both the reduction of local failure ( $p < 0.0001$ ) and the risk of death (being reduced by 29%) in the group treated with concomitant radiochemotherapy.

In our study analysis of survival depending on the administration or not of radiosensitizing chemotherapy was not carried out due to the small number of patients receiving cisplatin.

Our results, concerning local control and survival, have identified the clinical stage as the main prognostic factor, the operable cases having a disease-free interval of 88% and a 3-year survival of 92% vs. 63% and 68%, respectively, for the inoperable cases.

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