

THREE FRACTION HIGH DOSE RATE BRACHYTHERAPY SCHEDULE FOR TREATMENT OF LOCALLY ADVANCED UTERINE CERVIX CANCER CENTER:

Clinical results, emphasis in dosimetric parameters and morbidity

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ABSTRACT •

PURPOSE: To evaluate a new fractionation scheme for patients with locally advanced uterine cervix cancer aimed at reducing costs of treatment in medical centers working beyond their capacity. Using a traditional multi-fractionation scheme in such centers delays the treatment sequence between external radiotherapy and brachytherapy.

Methods and Materials: 116 patients were treated with the four-field pelvic technique using megavoltage equipment (6-8MV linear accelerator or Co-60) 50 Gy dose with standard fractionation. They were further treated with brachytherapy using high dose rate equipment (Ir 192 with 10Ci of nominal activity Varisource). A three fractionation scheme was used (850cGy each prescribed to point A). Follow up period varied from 3 to 36 months.

Results: The evaluation considered local control, morbidity and three-year overall survival. Tumor free 3-year survival was 92% (Stage I), 71.8% (Stage II) and 49.8% (Stage III). The overall crude incidence of distant metastasis was 5% for stage I, 21.6% for stage II and 42.8% for stage III. Long term small bowel, rectal or bladder toxicity grade 1 and 2 was present in 68 % of the patients and grade 3, 7%. A sub analysis of rectal morbidity showed no difference when compared to results in literature.

Conclusion: This analysis showed no significant differences regarding the three year local control, disease free survival and late morbidity rates when comparing its overall results with those obtained with traditional fractionation schemes. Therefore we find this new scheme to be a feasible alternative to cover the needs of saturated medical centers increasing the number of patients treated during the average life span of the iridium source thus ultimately reducing the costs of treatment.

Key words: Cervical Cancer, Brachytherapy, High-dose rate.



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INTRODUCTION •

Radiation therapy treatment for locally advanced uterine cervix cancer is well established. Megavoltage external beam irradiation to the pelvis followed by intracavitary brachytherapy (ICBQT) either with low or high dose rate has proved to be the standard care for these patients (1-6). However there is a major concern about the potential for increased risk of late morbidity using high dose rate brachytherapy and also about the lack of consensus in what is the optimal fractionation (7). Thus the American Brachytherapy Society has recommended the brachytherapy fractionation number to be ranged from 4 to 8 (8). Nevertheless in many countries where there is a great incidence of this pathology, the cost of treatment increased proportionally to the number of fractions used individually and the design of an optimal treatment program depends on the requirements of each particular center. In the Oncology Hospital, National Medical Center at Mexico City, high dose rate brachytherapy with Iridium was initiated in 1996. Annually an average of 800 patients with this diagnostic are received leading to a potential of at least 3000 implants according to the recommendations of the optimal fractionation given by the ABS which is far beyond the capacity of this center's current facilities. This leads to the employment of a new treatment scheme using three weekly applications of high dose rate brachytherapy for an equivalent total dose to point A of 80 Gy combined with external radiation therapy. The present paper analyzes the results of the first 116 patients treated with this new fractionation putting a special emphasis on the relationship between dosimetric parameters and complications.

METHODS AND MATERIALS •

In June, 2000 we prospectively started a new scheme of treatment for advanced cervical cancer patients. Two hundred and twenty two patients were considered to receive high dose rate intracavitary brachytherapy during June 2000 and Octo-

ber 2001. One hundred sixteen of these patients received the new scheme of three fractions, each one of 850 cGy prescribed to point A. The rest of the patients were treated with different fractionation and are not included in this study.

Each patient was submitted to external beam radiotherapy to the whole pelvis with a 4 field "box" technique with anterior, posterior and two lateral opposed fields with classic limits. External radiation dose of 5000 cGy was delivered with megavoltage equipment using mainly 6-8 MV linear accelerator or Co-60 in the case of very slim patients. Radiation therapy was supplied with daily fractions of 2.0 Gy for 5 days a week. Neither parametrial boosts nor central shields were employed.

After external beam radiotherapy, three applications of high dose rate brachytherapy were performed once a week. The first application of ICBQT was done within the two weeks following the completion of external beam radiotherapy. The mean treatment time of the whole radiotherapy treatment (external beam plus ICBQT) was 61.8 days.

A high dose rate remote afterloading unit (VarioSource) was used with a source of Ir 192 with 10 Ci of nominal activity. The applicator system was composed by Fletcher-Suit applicators with intrauterine tandem and vaginal colpostats of different sizes according to the individual patients' anatomy. The dose was prescribed to point A. In the first ICBQT, dosimetric planning was performed in each patient by means of an orthogonal system. In the two other applications, the adequate applicator position was verified with fluoroscopy and when required, a second set of orthogonal films was taken to adjust the dosimetric plan. A total of 348 implants were performed. Dose of prescription was 850 cGy to point A except in 3 patients with disease stage IIB and dosimetric determination of rectal dose deemed high by the physician, in such cases the dose was reduced to 800 cGy to point A.

Point A was defined in compliance with the American Brachytherapy Society recommendations, as a point located from the intersection of the line connecting the mid dwell positions of the ovoids with the tandem, and moving superiorly along the tandem 2 cm and then 2 cm perpendicular to the tandem in the lateral direction.

Rectal and bladder dose were determined according to the ICRU Report 38 guidelines. Rectal reference dose was recorded in at least two points visualized on the lateral radiograph by instilling 20-30 ml of a diluted solution of barium contrast and some air into the rectum. Bladder reference dose was obtained in the point located on the surface of a Foley balloon filled with 7 cc of iodine radiographic contrast snagged into the trigone of the bladder. This point corresponds to the maximum dose on the surface of the balloon closest to the system.

Late rectal and bladder complications were analyzed as a function of rectal and bladder point dose and were graded according to the Toxicity criteria of the RTOG/EORTC late radiation morbidity scoring scheme.

Patients' follow-up was performed every 3 months and the follow-up time was recorded until the time of the present analysis.

The primary endpoints assessed were survival, pelvic control, relapse-free survival and distant metastases using the Kaplan-Meier method. The student T test and chi-square or Fisher's exact test were used to analyze the correlation of grade 3 or 4 complications with the dosimetric factors.

RESULTS

One hundred and sixteen patients were treated with a scheme of three fractions of high dose rate brachytherapy after external beam pelvic radiotherapy. The general characteristics of the patients are described in *Table 1*. Median age was 59.8 years (range of 19 through 89 years). Most of the

TABLE 1 •
General Characteristics of the Patients

Variable	Number
Age (median)	61.1 years range 34-83
Histology	
Squamous	97
Adenocarcinoma	11
Adenosquamous	8
Median dose to pelvis	49.76 Gy
Median dose with HDR brachytherapy	25.36Gy

TABLE 2 •
Frequency of Failure by Stage and Site of Failure

Site of failure	Local	Distant	Local & Distant	Total
Pelvis	11			11
Retro peritoneum		7*	3	10
Supraclavicular Node		2	1	3
Lung		3†		3
Bone		2	2	4
Abdomen		2		2
Percentage of failure				
Stage I and IIA	0%	5%		
Stage IIB	8.3%	21.6%		
Stage IIIB	28.5%	42.8%		

*Included one patient who presented also lung metastases and another with liver metastases; †included one patient with simultaneous brain metastases and one patient with simultaneous supraclavicular metastases.

TABLE 3 •
Dose to Rectal and Bladder points

Points of maximum dose	Minimal dose per fx	Maximal	Mean dose
Bladder	1199 cGy	1587 cGy	572.7 cGy
Total dose with three fractions	597 cGy	4761 cGy	1718 cGy
Rectum	307 cGy	1327 cGy	650.6 cGy
Total dose with three fractions	921 cGy	3981 cGy	1951 cGy

patients (83%) had epidermoide cell cancer and 70 % were staged as locally advanced cervical cancer (stage IIB 52.5% and stage IIIB 29.3%).

Minimal follow up was 3 months (the 2 patients that abandoned follow up) whereas maximum follow up was 36 months.

The actuarial tumor free 3-year survival rates were 92% for Stage I (which include 1 patient with stage IIA), 71.8% Stage II, and 49.8% Stage

III (which include 1 patient with stage IVA). At the time of the present study crude incidence of pelvic recurrence defined as disease recurring in true pelvis including central and parametrial failure was present in 0% of patients in stage I, 8.3% in stage II and 28.5% in stage III.

The overall crude incidence of distant metastasis was 5% for stage I, 21.6% for stage II and 42.8% for stage III. Six patients developed distant metastases and locoregional failure simultaneously. The main site of distant metastases was retroperitoneal (47%) followed by lung and osseous metastases (19% each respectively). Four patients had more than one site of distant metastases (Table 2).

No patient died during the treatment or one month after. However 4 patients (3.3%) suffered from grade 3 and 4 acute toxicity. One patient was submitted to laparotomy and hysterectomy 24 hrs after the last brachytherapy application due to uterine perforation. Six percent of the patients presented grade 1 and 2 rectal and bladder toxicity and were managed conservatively.

Long term small bowel, rectal or bladder toxicity grade 1 and 2 was present in 68% of the patients whereas grade 3 or worse morbidity was registered in 7%. Seven patients had severe rectum morbidity (one of which required laparotomy and colostomy permanently). The rest of the patients (5.1%) were treated conservatively with multiple blood transfusions. One patient developed severe bladder morbidity (hemorrhagic cystitis and required also blood transfusions in several occasions. The mean total dose delivered to the bladder and rectum with the three applications was 1718 cGy and 1951.53 cGy respectively (Table 3). The comparison of dose to the rectal point in patients with and without rectal morbidity showed no statistical significance (1945 cGy in patients without morbidity vs 1953 cGy in patients with grade 2 or greater rectal morbidity $p=NS$), No comparison was made between bladder dose and morbidity since only one patient developed severe morbidity.

A correlation among the doses delivered to bladder and rectal points according to the ICRU-38 recommendations and long term toxicity revealed a lack of correspondence between the doses calculated for each one of the high dose rate brachytherapy applications to this points and the presence of long term toxicity greater than grade 2. Also a coefficient of Spearman correlation was done in patients with and without long term grade 3 or more rectal toxicity, and there was no statistical difference found in the maximal proximal punctual doses to the rectal point for those patients with severe morbidity, compared to those without rectal toxicity.

DISCUSSION •

According with multiple reports from several centers around the earth it has been considered that external beam radiation therapy and high dose rate intracavitary therapy, is as effective as external beam radiation therapy and low dose rate brachytherapy in terms of local control, survival and morbidity ratio for the treatment of patients with cervical cancer (1-6). However the main concern in regard with the high dose rate brachytherapy treatment has to do, with the optimal fractionation that must be employed and the literature analysis shows a lack of consensus regarding the optimal number of fractions and the dose fractionation (8). The American Brachytherapy Society recommendation for high dose rate brachytherapy is a schedule of 4-8 fractions once a week with doses ranging from 500 to 1000 cGy (7). In developing countries the incidence of cervical cancer is superior to that in developed countries (9), so the use of a large number fractionation increases the cost and saturates the facilities with a prolongation of the total length of the treatment affecting adversely the local control of the tumor (10). Therefore, based on the comparison of Rote (11) we modified the previous schedule of fractionation from 30 Gy administered in four weekly fractions, to a three schedule of 850cGy per fraction to point A administered once a week.

The present results prove that three fractions were safe and effective in the management of patients with locally advanced cervical cancer. The rate of three year local control (Fig. 1), disease free survival (Fig. 2) and late morbidity were similar to those reported employing a great number of fractions. The use of three weekly fractions allows us to include a great number of patients during the life span of the iridium source. However we acknowledge that the risk of rectal complications increases according to the dose prescribed in each intracavitary brachytherapy.

The ICRU report 38 recommends during the dosimetry the assessment of dose to a reference point in order to specify the absorbed dose to the bladder and rectum (12). For the latter, this point is described in the lateral projection of the applicators on an AP line drawn from the distal end of the uterine source or the middle of the ovoid sources. The dose estimated at this point correlates with the incidence of late rectal complications (13,14) although some authors have demonstrated a lack of significant correlation between the incidence of complications and dose rates to normal tissue reference points (15).

In our series the total rectal dose was not predictive of complication. The rate of G3-4 rectal morbidity in the 116 was 6.0% and the mean dose to the rectal reference point did not vary in patients either with or without rectal complications. Only one patient suffered bladder related late toxicity. The incidence of severe bladder complications in the present study is of 0.8 percent this patient with a stage IIB cervical cancer received a dose to the bladder reference point of 925 cGy and presented chronic bladder toxicity manifested with recurrent macroscopic hematuria requiring a blood transfusion. No further analysis of the correlation among the dose received to the bladder point was performed due to the small number of patients with severe late morbidity. Of course we acknowledge that the risk of bladder and rectal complications does depend upon the dose delivered to the rectum and bladder and

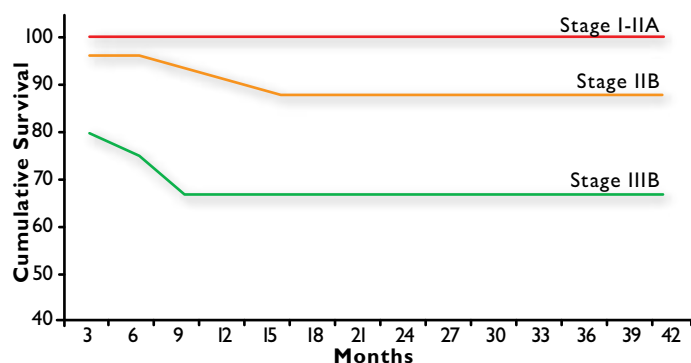


FIGURE 1 •
Three year local control

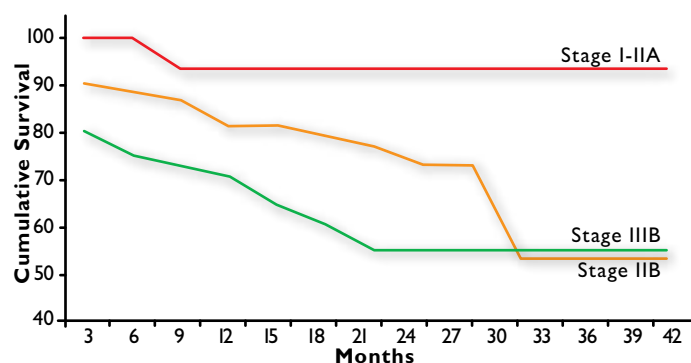


FIGURE 2 •
Three year disease free survival

every effort should be made in order to ensure a low complications risk by means of an adequate brachytherapy methodology (16-18).

The present study showed that a three brachytherapy schedule using a total dose of 2550cGy to point A is safe and effective in the management of patients with carcinoma of the cervix uterine. The rate of rectal morbidity G3 or greater is consistent with the data reported in the literature (1, 5, 8). We recommend such schedule of treatment for centers with a high demand of attention.

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