A Randomized Trial of Chemotherapy Followed by Pelvic Radiation Therapy in Stage IIIB Carcinoma of the Cervix

By Luis Souhami, Roberto A. Gil, Sergio E. Allan, Paulo Cezar V. Canary, Carlos Manoel M. Araújo, Luiz Henrique J. Pinto, and Telma Ruth P. Silveira

Because of the poor results in stage III B carcinoma of the cervix with standard treatment using radiotherapy alone, we designed a randomized trial to determine whether administration of chemotherapy before pelvic irradiation would improve survival. Between May 1984 and August 1986, 107 patients with previously untreated squamous cell carcinoma were randomly assigned, after stratification by age (< 50 v > 50 years), extent of parametrial involvement (unilateral v bilateral), and lymphangiographic findings (negative v positive) to pelvic radiotherapy (RT; arm A) or three cycles of chemotherapy (CT; bleomycin, vincristine, mitomycin, and cisplatin [BOMP]), followed by the same radiotherapy regimen (CT + RT; arm B). The groups were balanced by age, performance status, extent of parametrial involvement, bulkiness of cervical disease, nodal involvement, and presence of hydronephrosis. Minimal follow-up is 34 months. A complete local response was observed in 32.5% of the patients in arm A and in 47% of the patients in arm B ($P = .19$). Overall 5-year survival rates were 39% for the RT arm and 23% for the CT + RT approach ($P = .02$). Toxicity was severe in arm B and included fatal pulmonary toxicity in four patients. Locoregional and distant failures were similar in both groups. We conclude that, despite a satisfactory response rate, neoadjuvant BOMP chemotherapy adversely affects survival in stage III B cervical cancer and is associated with unacceptable toxicity.

J Clin Oncol 9:970-977. © 1991 by American Society of Clinical Oncology.

ALTHOUGH much progress has been made in the early detection and control of carcinoma of the cervix since the introduction of the Papanicolau test, it is estimated that about 13,500 new cases of invasive cervical cancer will be diagnosed in 1990 in the United States with 6,000 patients dying from the disease.[1] The incidence is even more pronounced in developing countries where carcinoma of the cervix is the most frequently diagnosed malignancy in females,[2,3] with the majority of the patients presenting with advanced disease.[2,4]

While surgery and radiotherapy (RT) are equally effective in early-stage disease, radiation therapy has been the primary treatment modality for stage III disease, with 5-year survival rates between 30% to 45% being reported.[4-8] Attempts to improve these results, including the use of hypoxic cell sensitizers,[9] hyperbaric oxygen therapy,[10] and neutron therapy[11] have met with limited or no success.

The role of chemotherapy (CT), either as a single agent or in combination, has been extensively evaluated in advanced or recurrent disease.[12-17] Response rates ranging from 0% to 90% have been reported but are usually of short duration. Vogl et al[18] and Alberts et al[19] using a combination of bleomycin, vincristine, mitomycin, and cisplatin (BOMP) in patients with metastatic and/or recurrent disease reported high response rates (> 20% of the patients with a complete response [CR]) with acceptable toxicity. Because of the high remission rate, these authors felt this combination should be used as a front-line treatment for locally advanced cervical cancer.

The use of upfront CT as initial treatment before pelvic RT would be theoretically advantageous as the vascular supply to the tumor is not compromised, allowing a higher local tissue concentration of drugs, thereby improving the effectiveness of CT. To test this hypothesis, we began in 1984 at the Instituto Nacional de Câncer (Rio de Janeiro, Brazil) a prospective randomized trial comparing neoadjuvant BOMP CT followed by pelvic RT (CT + RT) versus pelvic RT alone in

From the Departments of Radiation Oncology, Medical Oncology and Epidemiology, Instituto Nacional de Câncer, Rio de Janeiro, Brazil.

Submitted July 30, 1990; accepted December 5, 1990.

Presented at the 72nd meeting of the American Radium Society, Scottsdale, Arizona, April 21-25, 1990.

Dr L. Souhami's present address is McGill University, Department of Radiation Oncology, Montreal, Canada.

Address reprint requests to Luis Souhami, MD, Montreal General Hospital, Department of Radiation Oncology, 1650 Cedar Ave, Montreal, Quebec, H3G 1A4 Canada.

0732-183X/91/0906-0009$3.00/0

patients with stage IIIB carcinoma of the cervix. Here we report the results of this study.

MATERIALS AND METHODS

Patient Entry Criteria and Evaluation

Between April 1984 and August 1986, 107 previously untreated patients with stage III B carcinoma of the cervix were entered on the study. Eligibility criteria consisted of a histopathologic diagnosis of squamous cell carcinoma, age younger than 70 years with no past history of malignancy, the lower third of the vagina free of disease, and a performance status greater than 50% in the Karnofsky scale. Patients also needed to have adequate medullary reserve (WBC $\geq$ 4,000/μL, platelet count $\geq$ 100,000/μL) and normal renal (BUN < 8.9 mmol/L, creatinine < 130 μmol/L, creatinine clearance > 1.17 mL/s) and liver (alkaline phosphatase < 110 U/L, bilirubin < 21 μmol/L) function. Staging evaluation included a complete medical history and physical examination, cystoscopy, chest x-ray, bipedal lymphangiogram, intravenous (IV) pyelogram, complete blood counts, and biochemistries. Computed tomographic scans were not routinely performed. Clinical assessment of tumor extension was performed by two investigators, and a pretreatment gynecologic examination under anesthesia was not required. The International Federation of Gynecology and Obstetrics staging criteria were used in this study. Patients with lymphangiographic findings of pelvic or paraaortic nodal disease were not excluded. No patient underwent lymph node biopsy to confirm the radiologic findings. The trial was performed after approval by local institutional ethics committee. All patients gave written consent before entry into the trial.

Fifty-two patients were randomized to the CT + RT arm and 55 to the RT arm. Of these, 16 were excluded from this analysis. In the CT + RT group, 11 refused further therapy, including pelvic RT, after only one cycle of CT, and two others were found to have abnormal renal function after randomization and before commencement of treatment. Three in the RT arm refused further treatment after only a few fractions of irradiation were delivered. Thus, there were 39 assessable patients in the CT + RT arm and 52 in the RT arm. The groups were balanced for age, extension of parametrial disease, lymph node involvement, hemoglobin level, bulkiness of the cervical disease, and the presence of hydronephrosis. Patient characteristics are outlined in Table 1.

Table 1. Patient Characteristics

Characteristic	Treatment Group: RT No. (%)	Treatment Group: CT + RT No. (%)	P
Total no. of patients studied	52	39	
Age (years)			
< 50	29 (56)	20 (51)	
> 50	23 (44)	19 (49)	
Median	49	50	
Range	26-69	24-69	
Parametrial disease			
Unilateral	28 (54)	24 (61.5)	.40
Bilateral	24 (46)	15 (39.5)	
Lymph nodal involvement	32 (61.5)	24 (61.5)	.97
Pelvic	32 (61.5)	24 (61.5)	
Paraaortic	17 (33.5)	13 (33)	
Hemoglobin level			
< 120 g/L	23 (44)	17 (43.5)	.95
> 120 g/L	29 (56)	22 (56.5)	
Barrel cervix	10 (19)	8 (20.5)	.98
Hydronephrosis	4 (7.5)	3 (7.5)	.95

Treatment Regimens

Radiation therapy was delivered using an 18 MeV photon linear accelerator. The radiation therapy was administered using an isocentric technique via a pair of parallel opposed anterior and posterior ports. The superior limit of the radiation field was the L5-S1 junction, the lower limit was the caudal pole of obturator foramen, and the lateral boundaries were 1.5 cm beyond the lymph nodes as demonstrated on lymphangiography. A tumor dose of 50 Gy, in 2 Gy daily fractions, 5 days per week, was prescribed at midplane. Both fields were treated on each day of treatment. Paraaortic radiation was not given, even for the patients with positive paraaortic nodes on lymphangiography. Following external-beam irradiation, a single low-dose rate intracavitary application was performed. A dose of 40 Gy was routinely prescribed to point A, which was located 2 cm superior to the cervical os (applicator flange) and 2 cm lateral to the central axis of the uterus. This RT regimen was used for both groups.

Chemotherapy consisted of bleomycin 15 U intramuscularly (IM) every 12 hours from days 1 to 4 (total dose, 120 U), vincristine 1 mg/m^2 IV on day 1, mitomycin 10 mg/m^2 IV on day 1, and cisplatin 50 mg/m^2 IV on day 1, given on an outpatient basis every 3 weeks for three cycles. RT was started 3 to 4 weeks after completion of the third cycle. Cisplatin was protected from light and given in 500 mL of normal saline over 1 hour to all patients. Hydration consisted of 1L of normal saline infused IV over 3 hours before cisplatin administration. Postcisplatin hydration consisted of 1.5 L of 5% dextrose in water in 0.5 normal saline given over 3 hours. Mannitol 200 mg was administered IV beginning 15 minutes before the cisplatin infusion. Potassium chloride at 20 mEq/L and magnesium sulfate were added as needed. Dexamethasone and metoclopramide were used as antiemetics.

Six months after activation of the study, after nine patients had been treated with CT, the bleomycin dose was reduced to 15 U IM every 12 hours from day 1 to day 3 (total dose, 90 U), and after the first year, cisplatin administration was changed from day 1 to day 4. Except for one patient, all others received three cycles of CT and were able to tolerate full protocol doses of vincristine, mitomycin, and cisplatin. The third bleomycin cycle was either withheld or the bleomycin dose was reduced in 15% of the patients, mainly because of severe skin hyperpigmentation.

Response Criteria

The local response to treatment was evaluated at the time of the intracavitary therapy by a pelvic examination under

Table 2. Morbidity Grading System

Grade	Symptoms
1	Minor symptoms requiring no treatment
2	Symptoms responding to simple outpatient management Life-style (performance status) not affected
3	Distressing symptoms altering patients life-style; hospitalization for diagnosis or minor surgical intervention may be required
4	Major surgical intervention or prolonged hospitalization required
5	Fatal complication

Reprinted with permission from International Journal of Radiation, Oncology, Biology, Physics 13, M.V. Pilepich, J.M. Krall, W.T. Sause, et al: Correlation of Radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate. Analysis of RTOG Study 75-06. 1987, Pergamon Press. [20]

anesthesia. Patients in the combined modality group were also assessed for local response at the completion of CT and before the start of RT. However, this assessment was not done under anesthesia. A CR was defined as the complete resolution of all measurable disease and symptoms, a partial response (PR) was defined as a 50% or more decrease in the sum of the products of perpendicular diameters of measurable disease, and stable disease (SD) was defined as less than a 50% decrease in the sum of the products of perpendicular diameters of the measurable lesions. Following completion of irradiation, patients were assessed every 2 to 3 months for the first 2 years and every 6 months thereafter. Disease status was evaluated by pelvic examination and by appropriate radiologic and laboratory investigations. Pelvic failure was defined as disease recurring in the true pelvis including central and parametrial failure. Distant disease was defined as disease occuring outside the pelvis, including paraaortic lymph nodes. Only supportive palliative treatment was given to relapsing patients, and CT was not used as a salvage treatment for the patients in the RT-only arm.

End Points

All patients were observed to determine the efficiency of the combined therapy by comparing overall survival, rate of local control, incidence of distant metastases, and toxicity between treatment regimens. During RT, patients were assessed weekly and were questioned about the presence of treatment-related symptoms. Toxicity of CT was assessed before each course. Blood counts were performed weekly and the lowest granulocyte and platelet counts recorded. Although not a requirement of the study, attempts were made to keep the hemoglobin level $\geq$ 120 g/L during pelvic irradiation. Late complications were graded as per the morbidity grading system suggested by Pilepich et al,[20] which takes into consideration the impact of the complication on the patient performance and/or life-style and the required treatment for such complications (Table 2).

Statistical Analysis

Patients were randomly allocated to the two treatment arms by drawing cards in sealed envelopes. Patients were stratified by age ($<$ 50 years v $>$ 50 years), extensiveness of parametrial involvement (unilateral v bilateral), and lymphangiogram nodal findings (negative v positive). We planned to accrue 60 patients into each treatment arm, which would produce a power of 80% and detect an improvement of 25% in survival with the combined modality treatment at the $\alpha = 0.05$ level (two-sided test). The study was closed earlier because an interim analysis showed that, apart from increased serious toxicity, survival was significantly worse in the combined approach group, and we did not feel that a positive result could be obtained with a larger sample. Survival was calculated by the Kaplan-Meier method[21] and was measured from day 1 of therapy until last follow-up or death. Actuarial survival curves were compared by the log-rank method. Comparisons of variables between groups were based on the χ^2 test.

RESULTS

No patient was lost to follow-up. The median follow-up time for the RT arm is 51 months (range, 34 to 67) and is 44 months (range, 35 to 65) for the CT + RT.

Table 3 shows the response rate for the two regimens. The CR rate was 32.5% and 47% ($P = .19$) for the RT and CT + RT, respectively. Seven patients were not included in response assessment in the combined modality group: four patients who died of CT complications, two who died of metastatic disease, all of them before commencement of RT, and one other patient whose pelvic disease progressed during CT and who received palliative irradiation only because of poor general condition. The CR rate after three cycles of BOMP CT was 25.5%.

Evaluation of tumor response by pelvic examination following therapy for advanced cervical cancer is a subjective and imprecise method of assessment. At the end of therapy, or even after several months posttreatment, it is difficult to be certain whether some of the pelvic findings are due to residual tumor or postirradiation fibrosis, allowing misinterpretation of tumor responses. In Table 4, we show the number of patients still alive in spite of their disease being classified as PR at the end of

Table 3. Comparison of Response Rates by Treatment Regimen

	RT		After CT		CT + RT*	
	No.	%	No.	%	No.	%
CR	17/52	32.5	10/39	25.5	15/32	47
PR	14/52	27	14/39	36	8/32	25
SD	16/52	31	9/39	23	8/32	25
Progressive disease	5/52	9.5	6/39	15.5	1/32	3

*Seven patients did not start RT.

Table 4. Response to Therapy and Number of Patients Alive at a Minimum Follow-Up of 3 Years by Treatment Regimens

	RT		CT + RT	
	No.	%	No.	%
CR	10/17	59	6/15	40
PR	8/14	57	3/8	37.5
SD	2/16	13	0/8	0
Progressive disease	0/5	0	0/1	0

treatment. For the partial responders, 57% in the RT arm and 37.5% in the CT + RT are alive with no evidence of disease progression at a minimum follow-up time of 3 years. These numbers are similar to those patients who were felt to have obtained a CR: only 59% (10 of 17) and 40% (six of 15) are still alive in the RT and CT + RT groups, respectively.

As of December 1989, 31 of the 52 patients in the RT group and 30 of 39 in the CT + RT had died. The overall 5-year actuarial survival for the two groups is shown in Fig 1. It was 39% and 23% for patients randomized to RT and CT + RT, respectively (P = .02 by the log-rank test). Median survivals were 25 months in the RT arm and 10.5 months in the CT + RT. The 5-year survival rates for the complete responders were 57% and 36% for the RT and CT + RT groups, respectively. Table 5 shows the sites of disease failure. Pelvic disease remains the major site of failure, with at least 50% of the patients failing within the irradiated volume. It was equally distributed between the treatment arms (RT, 54%; CT + RT, 50%). There was also no difference in the incidence of distant disease between RT and CT + RT (20% *v* 18.5%).

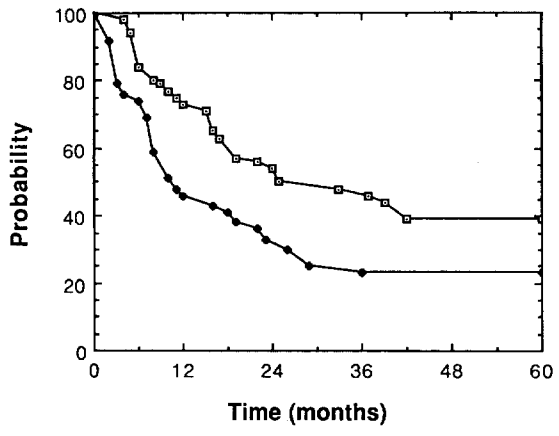

Fig 1. Overall survival rates. (□) RT, (◆) CT + RT; P = .02.

Table 5. Sites of Failure

	RT*		CT + RT†	
	No.	%	No.	%
Pelvis only	20	40	15	39.5
Pelvis + distant	7	14	4	10.5
Distant only	3	6	3	8

*Two patients not assessable.
†One patient not assessable.

Toxicity

Acute toxicity was pronounced in the combined treatment arm (Table 6). About two thirds of patients experienced moderate to severe nausea/vomiting. Skin hyperpigmentation was observed in half of the treated patients, being of severe degree in one third. Leukopenia and thrombocytopenia were not a problem, with only 7.5% of the patients experiencing a leucocyte nadir of less than 1,000/μL. Of greater concern was the bleomycin-related pulmonary toxicity. Five patients (13%) developed such a complication, and four died as a direct result. After two bleomycin-related lung deaths (two of nine treated patients), the bleomycin dose was reduced from 30 U daily for 4 days to 30 U daily for 3 days. In spite of this, two further patients experienced a similar complication (two of 18 treated patients). The cisplatin treatment day was then changed from day 1 to day 4 but yet another patient developed the same problem (one of 12 treated patients). At this time, an interim analysis that was performed disclosed a survival advantage for the RT group, and it was then decided to close the study. A more detailed description of the pulmonary toxicity has been the subject of another report.[22] Diarrhea was the main complication of pelvic irradiation, seen in eight patients (15.5%) on RT and 11 (34%) on CT + RT.

Table 6. Treatment-Related Acute Toxicity

	RT		After CT		CT + RT*	
	No.	%	No.	%	No.	%
Nausea/vomiting	3	6	32	82	4	12.5
Diarrhea	8	15.5	5	13	11	34
Skin hyperpigmentation			19	49		
Neuritis			3	7.5		
Leukopenia (< 1,000/μL)			3	7.5		
Mucositis			4	10		
Thrombocytopenia (< 100,000/μL)					2	6
Pulmonary			5	13		

*Seven patients did not start RT.

Late complications are shown in Table 7 and consisted of proctitis, cystitis, fistula, and vaginal stenosis. Grade ≥ 3 proctitis was seen more frequently on CT + RT. One patient in the RT group who had grade 3 cystitis, characterized by frequent hematuria, presented to the emergency room 19 months following completion of pelvic RT with gross hematuria with clots. During catheterization, her bladder was perforated. This patient developed a fulminant septicemia, and despite intensive surgical and medical treatments died soon after admission to the hospital. Postmortem study showed no evidence of cervical cancer.

DISCUSSION

This study was designed with the objective of answering the question of whether neoadjuvant BOMP chemotherapy is effective in stage III B carcinoma of the cervix. Vogl et al[18] treated 16 patients with advanced local and/or metastatic cancer of the uterine cervix. Except for two patients, all others had received previous treatment (CT in two, pelvic RT in 11, and major surgery in three). Of 13 assessable patients, 10 achieved PRs, with three other patients (23%) obtaining a CR. All responding patients experienced major symptomatic improvement. Alberts et al[19] studied the use of BOMP chemotherapy in 14 previously treated patients with advanced (stage IVB) and/or recurrent disease and reported a 29% CR rate. Treatments were well tolerated, and some long-term remissions were observed. Because of the high CR rate and low toxicity, both groups felt that this combination should be used as a front-line treatment of advanced carcinoma of the cervix.

The rationale for the use of neoadjuvant CT[23] is that (1) the blood supply to the tumor is not compromised by previous radiotherapy or surgery allowing for better drug distribution into the tumor, (2) patients' tolerance to CT may be enhanced as performance status and marrow reserve are unaltered by previous treatment, (3) decreasing the bulkiness of the primary disease would improve the effectiveness of the local RT, (4) there is the possibility of eradication of subclinical metastases, and (5) theoretically a tumor may be more chemosensitive before surgery or RT. These reasons together with the initial promising results with BOMP prompted us to start our randomized study.

Table 7. Treatment-Related Late Toxicity

	RT				CT + RT			
	Any		≥ Grade 3		Any		≥ Grade 3	
	No.	%	No.	%	No.	%	No.	%
Proctitis	7	14	3	6	10	25.5	8	20.5
Cystitis			1	2	1	2.5		
Fistula	3	6	3	6				
Vaginal stenosis	4	8	3	6	3	7.5	2	5

NOTE. Patients could have more than one complication.

Although 25.5% of the patients achieved a CR following three cycles of BOMP and 47% of the CT + RT group obtained a CR at the end of RT, the 5-year overall survival was significantly inferior in the CT + RT group than in the control arm (39% *v* 21%, $P = .02$). The reason for this surprising and disturbing finding is not entirely clear. It cannot be accounted for by patient selection as both groups were well balanced for the well-known prognostic factors in stage III carcinoma of the cervix.[4,24-27] More importantly, all patients in the CT + RT arm completed pelvic RT, as defined by the protocol guidelines, and therefore, inadequate irradiation dosage cannot explain the poorer results. Furthermore, even if we exclude the patients who experienced treatment-related death, the survival in the BOMP group remains significantly inferior (39% *v* 25%).

Recently, Withers et al[28] have shown that clonogen repopulation in squamous cell carcinoma of the head and neck region accelerates after about 4 ± 1 weeks after initiation of radiotherapy. Since repopulation by surviving tumor clonogens is not a specific response to RT but rather results from killing of tumor cells, these authors have suggested that CT, which is effective in killing cells, could also lead to an accelerated regrowth of surviving clonogens, lessening the effect of subsequent RT. This may explain why in spite of a satisfactory rate of response following neoadjuvant CT, there was no improvement in local tumor control, and survival was adversely affected.

Similarly, in squamous cell carcinoma of the head and neck, upfront CT has produced impressive response rates, but again, this has not led to an improvement in survival rates over those achieved with RT alone.[29-31] Some randomized studies have, in fact, showed worse survival with

the use of neoadjuvant CT.[32,33] The most likely explanation for the poorer results in these neoadjuvant trials is the enhancement of accelerated tumor cell proliferation during treatment. Withers et al[28] have suggested that the accelerated repopulation late in the treatment involves only a small number of surviving cells, and rapid repopulation would not be detectable as a change in volume of the total tumor mass. Thus, a PR or even a CR could therefore be of questionable value in determining therapeutic effectiveness, as tumor masses would be still regressing while the subclinical clonogenic cell repopulation is accelerating. The mechanisms by which this increased cell proliferation occurs are not entirely clear, although, as suggested by Tannock,[34] it may result from improved nutrition of surviving cells following shrinkage of the tumor due to previous therapy.

Another possible explanatory mechanism for our poorer results with the combined treatment modality may be the development of cross-resistance between radiation and certain antineoplastic agents. The mechanisms responsible for such cross-resistance remain to be determined, but recent studies have shown significant similarity between the cytotoxicity of irradiation and alkylating agents and that tumor cells may develop mechanisms of resistance capable of decreasing the cytotoxic effects of some antineoplastic drugs as well as radiation.[35]

The choice of end point in assessing the therapeutic benefit of a new treatment modality in advanced carcinoma of the cervix has to be determined carefully. It is now clear that response rate is a poor end point. It is a subjective evaluation that frequently depends on the ability of the investigator to differentiate between residual local disease or treatment-induced parametrial fibrosis. In this study, 27% of the patients (14 of 52) in the RT group were called partial responders at the end of irradiation. Of these, 57% remain alive with no evidence of disease progression. Similarly, in the combined treatment group, 37.5% of the partial responders are still alive and well. Recently, comparisons between computed tomography and magnetic resonance imaging have suggested that the latter might become an important method in evaluating response to treatment.[36] Transvaginal parametrial needle biopsy has been used to detect postirradiation recurrent cancer of the cervix[37] and may also play an important role in defining treatment response. However, until such procedures prove to be definitive and precise, the use of response to therapy as a predictor of outcome should be abandoned as an end point in phase III trials.

The lung toxicity experienced by patients in the CT + RT group is unacceptable. In this study, the incidence of pulmonary toxicity was 13% (five of 39), with four patients dying from this complication.[22] None of the patients who experienced drug-induced pulmonary toxicity had any of the well-known risk factors for development of bleomycin lung toxicity.[38-39] Recently, Chambers et al[40] also reported a high incidence of pulmonary toxicity in patients receiving BOMP CT for gynecologic squamous cell carcinoma. These authors treated 23 patients (20 cervical cancer, two vulvar, one ovarian) and observed the development of pulmonary toxicity in eight patients (34.5%), with five of them dying a respiratory death while free of disease. As in our study, they could not correlate the incidence of lung toxicity with any of the standard risk factors. Two other studies[41-42] reported a 14% incidence of pulmonary toxicity with one fatal drug-related event occurring in each.

At present, there is no evidence to support the use of upfront CT before pelvic irradiation in stage III B cervical cancer. In fact, this approach might be detrimental, as demonstrated in the present study. The high toxicity rate of BOMP CT, in the dose and schedule used in this study, makes this combination unacceptable for routine use. The use of concomitant CT (usually fluorouracil and/or cisplatin) and RT has shown promising therapeutic results in a variety of tumors[43-45] and may prove useful in circumventing the problem of accelerated regrowth of surviving clonogens. The role of concurrent radiosensitizing CT has yet to be established in advanced carcinoma of the cervix, but this approach deserves further exploitation. The effectiveness of this approach will be evaluated in the near future by a prospective and randomized phase III trial sponsored by the National Cancer Institute of Canada.

ACKNOWLEDGMENT

The authors thank Dr Carolyn R. Freeman for her critical review and helpful suggestions and Anna Foglietta for her expert preparation of this manuscript.

REFERENCES

1. Silverberg E, Boring CC, Squires TS: Cancer Stat 1990. CA 40:9-26, 1990

2. Vera R: Reflections on the management of cancer of the cervix in developing countries. Int J Radiat Oncol Biol Phys 8:953-955, 1982

3. Brumini R: Câncer Brasil. Dados histopatológicos. Campanha Nacional de Combate ao Câncer, Ministério da Saúde, 1982

4. Souhami L, Melo JAC, Gonzalo Pareja V: The treatment of stage III carcinoma of the uterine cervix with telecobalt irradiation. Gynecol Oncol 28:262-267, 1987

5. Montana GS, Fowler WC, Varia MA, et al: Carcinoma of the cervix, stage III. Results of radiation therapy. Cancer 57:148-154, 1986

6. Ulmer HU, Frischbier HJ: Treatment of advanced cancer of the cervix uteri with external irradiation alone. Int J Radiat Oncol Biol Phys 9:809-812, 1983

7. Perez CA, Kuske RR, Camel HM, et al: Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 14:613-621, 1988

8. Marcial VA: Carcinoma of the cervix. Present status and future. Cancer 39:945-958, 1977

9. Leibel S, Bauer M, Wasserman T, et al: Radiotherapy with or without misonidazole for patients with stage IIIB or stage IVA squamous cell carcinoma of the uterine cervix: Preliminary report of a Radiation Therapy Oncology Group randomized trial. Int J Radiat Oncol Biol Phys 13:541-549, 1987

10. Brady LW, Plenk HP, Hanley JA, et al: Hyperbaric oxygen therapy for carcinoma of the cervix—Stages IIB, IIIA, IIIB and IVA: Results of a randomized study by the Radiation Therapy Oncology Group. Int J Radial Oncol Biol Phys 7:991-998, 1981

11. Maor MH, Gillespie BW, Peters LJ, et al: Neutron therapy in cervical cancer: Results of a phase III RTOG study. Int J Radiat Oncol Biol Phys 14:885-891, 1988

12. Thigpen T, Shingleton H, Homesley H, et al: Cisplatinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: A phase II study of the Gynecologic Oncology Group. Cancer 48:899-903, 1981

13. Wallace HJ, Hreshehyshyn MM, Wilbanks GD, et al: Comparison of the therapeutic effects of Adriamycin alone versus Adriamycin plus vincristine versus Adriamycin plus cyclophosphamide in the treatment of advanced carcinoma of the cervix. Cancer Treat Rep 62:1435-1441, 1978

14. Omura GA, Velez-Garcia E, Birch R: Phase II randomized study of doxorubicin, vincristine, and 5-FU versus cyclophosphamide in advanced squamous cell carcinoma of the cervix. Cancer Treat Rep 65:901-903, 1981

15. Forney JP, Morrow CP, DiSaia PJ, et al: Seven-drug polychemotherapy in the treatment of advanced and recurrent squamous carcinoma of the female tract. Am J Obstet Gynecol 123:748-752, 1975

16. Bonomi P, Blessing JA, Stehman FB, et al: Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 3:1079-1085, 1985

17. Brenner DE: Combination chemotherapy of advanced cervix cancer, in Surwitt EA, Alberts DS (eds): Cervix Cancer. Boston, MA, Martinus Nijhoff, 1987, pp 137-160

18. Vogl SE, Moukhtar M, Calanog A, et al: Chemotherapy for advanced cervical cancer with bleomycin, vincristine, mitomycin C, and cis-diammine dichloroplatinum (II) (BOMP). Cancer Treat Rep 64:1005-1007, 1980

19. Alberts DS, Martimbeau PW, Surwit EA, et al: Mytomycin-C, bleomycin, vincristine, and cis-platinum in the treatment of advanced, recurrent squamous cell carcinoma of the cervix. Cancer Clin Trials 4:313-316, 1981

20. Pilepich MV, Krall JM, Sause WT, et al: Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate. Analysis of RTOG study 75-06. Int J Radiat Oncol Biol Phys 13:351-357, 1987

21. Kaplan EL, Meier P: Non-parametric estimations from incomplete observations. J Am Stat Assoc 53:457-480, 1953

22. Rabinowits M, Souhami L, Gil RA, et al: Increased pulmonary toxicity with bleomycin and cisplatin chemotherapy combinations. Am J Clin Oncol (CTC) 13:132-138, 1990

23. Alberts DS, Aristizabal S, Surwit EA, et al: Primary chemotherapy for high-risk recurrence cervix cancer, in Surwitt EA, Alberts DS (eds): Cervix Cancer. Boston, MA, Martinus Nijhoff. 1987, pp 161-183

24. Souhami L, Melo JAC: Fatores prognósticos no carcinoma do colo de útero, estádio III. Rev Bras Cancerol 32:13-17, 1986

25. Benstead K, Cowic VJ, Blair V, et al: Stage III carcinoma of the cervix. The importance of increasing age and extent of parametrial infiltration. Radiother Oncol 5:271-276, 1986

26. Bush RS, Jenkin RDT, Allt WEC, et al: Definitive evidence for hypoxic cells influencing cure in cancer therapy. Br J Cancer. 37:302-306, 1978 (suppl)

27. Bush RS: Malignancies of the Ovary, Uterus and Cervix. London, England, Edward Arnold, 1979, p 171

28. Withers HR, Taylor JMF, Maciejewski B: The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27:131-146, 1988

29. Souhami L, Rabinowits M: Combined treatment in carcinoma of the nasopharynx. Laryngoscope 98:881-883, 1988

30. Tannock I, Payne D, Cummings B, et al: Sequential chemotherapy and radiation for nasopharyngeal cancer: Absence of long-term benefit despite a high rate of tumor response to chemotherapy. J Clin Oncol 5:629-634, 1987

31. Tannock IF, Browman G: Lack of evidence for a role of chemotherapy in the routine management of locally advanced head and neck cancer. J Clin Oncol 4:1121-1126, 1986

32. Kun LE, Toohill RJ, Holoye PY, et al: A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 12:173-178, 1986

33. Martin M, Mazeron JJ, Brun B, et al: Neo-adjuvant polychemotherapy of head and neck cancer: Results of a randomized study. Proc Am Soc Clin Oncol 7:152, 1988 (abstr)

34. Tannock IF: Combined modality treatment with radio-

therapy and chemotherapy. Radiother Oncol 16:83-101, 1989

35. Ozols RF, Masuda H, Hamilton TC: Keynote address: Mechanisms of cross-resistance between radiation and neoplastic drugs. NCI monogr 6:159-165, 1988

36. Kim SH, Choi BI, Lee HP, et al: Uterine cervical carcinoma: Comparison of CT and MR findings. Radiology 175:45-51, 1990

37. Lopez MJ, Kraybill WG, Fuchs GJ, et al: Trasvaginal parametrial needle biopsy for detection of post irradiation recurrent cancer of the cervix. Cancer 61:275-278, 1988

38. Comis RL: Bleomycin pulmonary toxicity, in Carter SK, Crooke ST, Umezawa H (eds): Bleomycin: Current Status and Developments. San Diego, CA, Academic, 1978, pp 279-291

39. Ginsberg SJ, Comis RL: The pulmonary toxicity of antineoplastic agents. Semin Oncol 9:34-51, 1982

40. Chambers SK, Flynn SD, Del Prete SA, et al: Bleomycin, vincristine, mitomycin C, and cis-platinum in gynecologic squamous cell carcinomas: A high incidence of pulmonary toxicity. Gynecol Oncol 32:303-309, 1989

41. Belinson JL, Stewart JA, Richards AL, et al: Bleomycin, vincristine, mitomycin-C, and cisplatin in the management of gynecological squamous cell carcinomas. Gynecol Oncol 20:387-393, 1985

42. Giannone L, Brenner DE, Jones III HW, et al: Combination chemotherapy for patients with advanced carcinoma of the cervix: Trial of mitomycin-C, vincristine, bleomycin and cisplatin. Gynecol Oncol 26:178-182, 1987

43. Al-Sarraf M, Pakaj TF, Cooper JS, et al: Chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma: A Radiation Therapy Oncology Group study. J Clin Oncol 8:1342-1351, 1990

44. Cummings BJ, Keane TJ, Thomas GM, et al: Results and toxicity of the treatment of anal carcinoma by radiation therapy or radiation therapy and chemotherapy. Cancer 54:2062-2068, 1988

45. Shipley WU, Prout GR, Einstein AB, et al: Treatment of invasive bladder cancer by cisplatin and radiation in patients unsuited for surgery. JAMA 258:931-935, 1987