# STUDY OF CONCURRENT CISPLATIN AND EXTERNAL RADIOTHERAPY PRIOR TO RADICAL HYSTERECTOMY AND LYMPHADENECTOMY IN PATIENTS WITH STAGE IB-IIB CERVICAL CANCER

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**Abstract-** The purpose of this study was to describe the feasibility of a combined preoperative chemoradiation program Ib-IIa, bulky and suspicious IIb by radical surgery in patients with stage Ib-IIb cervical cancer. From September 1999 to April 2002, 30 patients with carcinoma of the cervix were treated with preoperative external beam radiotherapy of 45 Gy in 5 weeks. Patients received concurrent continuous infusion of cisplatin 50 mg/m$^2$ for one day in week during 5 weeks of radiation. Radical surgery was performed 4-6 weeks after completion of the preoperative treatment. Toxicity with chemoradiation was usually mild. Two patients developed vesicovaginal fistula, and four developed long-term hydronephrosis that needed ureteral stenting. Clinical response was observed in 100% of the patients (23.7% complete response). The analysis of the surgical specimens revealed complete pathological response in 43.3% of the cases and partial pathological response in 56.7%. The degree of pathological response was not predictable by the degree of clinical response. Thirty months disease-free survival and overall survival were 66.3% and 77.31%, respectively. Patients with complete and partial pathological response were not significantly different in terms of disease-free survival (p= 0.08) and overall survival (p= 0.3). Cisplatin in preoperative chemoradiation is effective and usually well-tolerated in bulky cervical cancer and parametrial invasion, inducing a high rate of clinical and pathological complete responses. When this therapy is followed by radical surgery, disease-free and overall survival rates are higher. The latter may be possible only through extensive surgical resection with a parallel increase in complication rates.

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**Key words:** Cervical cancer, chemoradiation, radical surgery

## INTRODUCTION

Cervical cancer is the most common gynecological malignancy, worldwide. In the early stages of disease, survival is influenced by multiple factors such as tumor size and lymph node metastasis, lymph-vascular involvement and histologic grade (1,2). The standard treatment of advanced cervical cancer is definitive radiotherapy (3). The incidence of local failure after definitive radiotherapy ranges from 25 to 60% (3). Concurrent chemoradiation offers certain theoretical advantages over sequential chemotherapy and radiation, because it avoids delay in starting definitive radiotherapy,

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decreases the time needed to induce cross-resistance, and offers the possibility of eradicating subclinical metastasis (4,5). At the clinical level, chemoradiation regimens are well-tolerated with acceptable toxicity (6,7). Cisplatin is a drug used in chemoradiation regimens that displays dual radio-sensitizing and cytotoxic properties (8,9). The use of surgery as adjuvant after preoperative radiation or chemoradiation is an unusual strategy in advanced cervical cancer. This approach has gained acceptance because of experience in the combined treatment of rectal and other malignancies during the past two decades (3). Some studies have shown excellent local control rates in the range of 75-85%, with 45-65% of the surgical specimens free of disease (10,11). In 1999 we initiated a program to treat patients with stage Ib-IIb cervical cancer using chemoradiation and adjuvant radical surgery. The results are presented in this report.

# MATERIALS AND METHODS

From September 1999 to April 2002, 30 patients with biopsy-proven carcinoma of cervix were treated under this protocol. Mean age at diagnosis was 52.1 years (range 28-75). Inclusion criteria included: stage Ib-IIb tumors, >4 cm and suspicious stage IIb tumors. Patients and tumor characteristics are presented in table 1.

Diagnostic workup included history, physical, and gynecological examination, complete blood count (CBC), liver and metabolic panel, blood urea nitrogen, creatinine, chest X-Ray, abdominal and pelvic contrast CT scan. Chemotherapy consisted of intravenous infusion of cisplatin 50 mg/m$^2$ one day a week, during 5 weeks of external beam radiotherapy (EBRT).

**Table 1.** FIGO stage and histology

| **FIGO stage** | **n** | **%** |
|---|---|---|
| Ib1 | 1 | 3.3% |
| Ib2 | 12 | 40.0% |
| IIa | 7 | 22.3% |
| IIb | 10 | 33.4% |
| **Histology** | | |
| SCC | 29 | 96.6% |
| Adenocarcinoma | 1 | 3.4% |

The total chemotherapy was administered only when leukocyte counts were greater than 3000/mm$^2$, platelet counts greater than 75000/mm$^2$, and serum creatinine level below or equal to 1.5 mg/dl. EBRT was started simultaneously with chemotherapy. The radiation field included the whole pelvis in all patients. An AP/PA or four field technique was used to encompass the target volume with 15-MV cobalt unit. All fields were treated every day, 5 days a week, with 1.8-2.0 Gy daily fractionation up to 45-46 Gy total dose. Surgery was scheduled for 4-6 weeks after the end of chemoradiation course. Clinical response and resectability were evaluated by gynecologic examination. All patients were considered surgical candidates.

The surgical procedure was type III radical hysterectomy including pelvic node dissection and para-aortic node sampling.

The degree of pathologic response was verified in the surgical specimens and lymph nodes. Complete pathological response (path CR) was defined as tumor eradication higher than 95%; meaning either a tumor-free specimen or just a few microscopic scattered tumoral foci in the cervix (provided that the lymph nodes and surgical margins were negative). Any other histological response was scored as a partial pathological response (path PR). Patients were followed every 3 months. Patient evaluation included gynecological examination, CBC, vaginal cytology, abdomeinal and pelvic CT scan, chest X-ray and other studies as deemed necessary. Contingency tests were used to evaluate the association between the variables. An event was defined as relapse, evidence of disease progression or death. Survival figures were calculated according to Kaplan-Meier method, compared by log rank test and Breslow's statistical method (12,13) and estimated from the first day after surgery. Statistical analyses were performed with SPSS version 9.

# RESULTS

**Toxicity**

Mild to moderate nausea and vomiting were seen in 16 patients (Table 2). Intra-operative complications included one cases of significant bleeding. Post-operative complications included 2 cases of vesico-vaginal fistula.

**Table 2.** Chemoradiation WHO grade II toxicity

| | n | (%) |
|---|---|---|
| Nausea vomiting | 16 | 53.3% |
| Urinary infection | 1 | 3% |
| Diarrhea | 3 | 10% |
| Dermatitis | 1 | 3% |

**Table 3.** Postoperative and long term complications

| **Postoperative complications** | No |
|---|---|
| Fever (38° for at least 2 days) | 2 |
| Wound breakdown | 2 |
| Vesico-vaginal fistula | 2 |
| Mild post-operative ileus | 1 |
| ARF* | 1 |
| **Long-term complications** | |
| Long-term complication | 4 |
| Hydronephrosis | 4 |
| Leg edema | 1 |
| Rectal prolapse | 1 |

* Acute renal failure

Long-term toxicity included 4 cases of RTOG grade 3-4 hydronephritis (13.3%) due to ureteral stenosis which required secondary stenting. One patient presented with rectal prolapse and another patient with complete bowel obstruction one year after surgery that needed repair (Table 3).

## Response

Clinical response: All 30 patients were evaluated clinically 2 to 4 weeks before surgery. Seven patients (23.3%) showed complete clinical response, and 23 (76.7%) partial clinical response.

No statistically significant differences were found according to FIGO stage (Table 4).

Pathological response: Thirteen out of 30 surgical specimens had path CR (43.3%). Seventeen patients (56.7%) had a path PR. There was no statistically significant association between clinical and pathological responses (p= 0.190, table 4). Seven patients had positive lymph nodes in surgical specimens (23.3%). Eight patients had parametrial involvement (26.7%) and fourteen had residual tumor in the pathology report (46.6%).

Distant Metastasis: There were two cases of distant metastasis: one to the lung, and one liver. There were no significant differences by stage (p= 1.00).

## Survival

After a median follow-up of 19.5 months (range: 9-30 months), overall survival was 66.6%. There were no statistically significant differences by stage (table 5). Thirty-month survival for path CR was 88.89% and for path PR, 62.2%, which was not statistically significant (Fig. 1).

Thirty-month disease-free survival was 66.3%. There were no statistical significant differences by stage (table 5). Disease-free survival for complete and partial pathological response were 88.8% and 48.27%, respectively (Breslow p=0.12) showing no statistically significant difference by pathologic responses (Fig. 2).

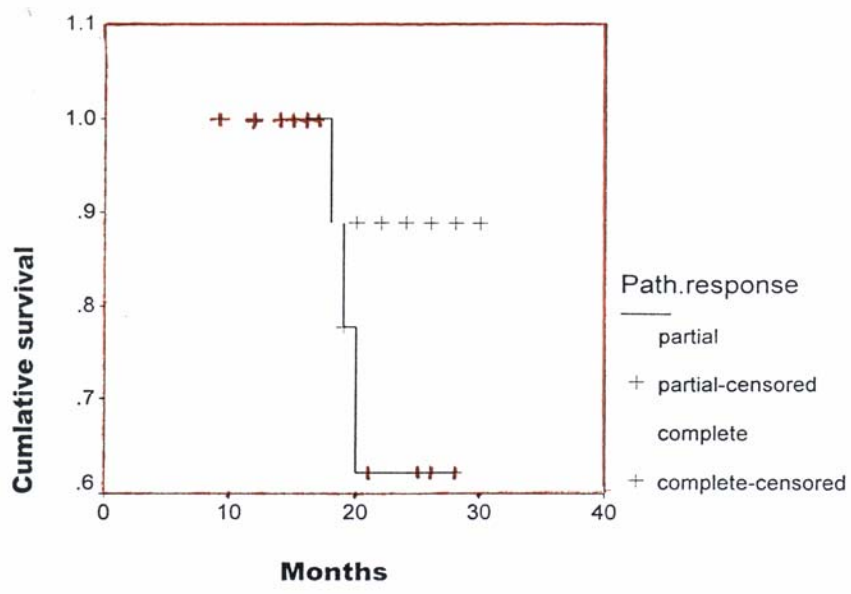


**Fig. 1.** Overall survival according to path response

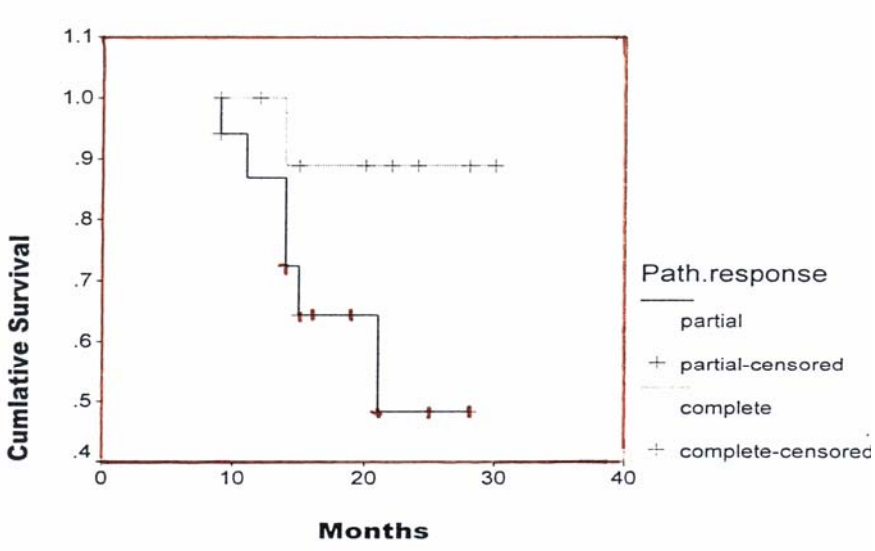


**Fig. 2.** Disease-free survival according to pathological response

**Table 4.** Clinical response stage cross-tabulation

| Clinical response | Stage | | | |
|---|---|---|---|---|
| | $Ib_1$ | $Ib_2$ | IIa | IIb |
| Complete clinical response | 1 (14.3%) | 3 (42.9%) | | 3 (42.9%) |
| Partial clinical response | | 9 (39.1%) | 7 (30.4%) | 7 (30.4%) |

p= 0.159

**Table 5.** Patients outcome according to FIGO stage

| Disease | $Ib_2$ | IIa | IIb | p value |
|---|---|---|---|---|
| Disease-free survival | 50 | 64.29 | 87.5 | NS* |
| Overall survival | 80 | 60 | 87.5 | NS* |

* NS= Nonsignificant

**Table 6.** Pathological response by clinical response

| Clinical response | Path CR | Path PR | p value |
|---|---|---|---|
| Complete | 5 | 2 | |
| Partial | 8 | 15 | 0.19 |

# DISCUSSION

Lack of local control is a major cause of treatment failure in patients with bulky or advanced carcinoma of the cervix. Several studies have confirmed that bulky cancer and extensive parametrial invasion are poor prognostic features (1-5). After a point dose of 85 Gy, pelvic failure rates of 25-37% in bulky (> 5 cm) stage Ib-IIa tumors, (14) and 35-50% for stages IIb-III are considered standard results (14). Bulky tumors have significantly hypoxic cell populations that are radioresistant (15,16). This mechanism has been implicated as a major cause of treatment failure. The radiation doses that would be needed to overcome the radiation resistance of hypoxic populations may exceed the normal tolerance of the surrounding healthy tissues. Surgical debulking could play a role in this scenario by eliminating radioresistant populations remaining after chemoradiation. A recent study has compared patients with a partial pathological response to those with a complete pathological response. The latter have better local control (p= 0.004), disease-free survival (p= 0.002), overall survival (p= 0.038), and distant metastases- free survival (p= 0.002) (3). But in this study, after a median follow-up of 19.5 months (range: 9-30 months), overall survival was 66.6%; 30 months survival for complete and partial pathological responders was 88.89% and 62.22%, respectively. Thirty months disease-free survival was 66.3%. Disease-free survival for complete and partial pathological response were 88.89% and 58.27%, respectively. In the present study, the correlation between clinical and pathological response is highly

significant but in this study there was no statistically significant association between clinical and pathological response (p= 6.19) (Table 4). Seven patients had positive lymph nodes (23.3%) and 8 had parametrial involvement (26.7%) in pathology reports.

For those patients achieving a complete clinical response, intracavitary brachytherapy rather than radical surgery seems to be the preferable option to complete the initial external beam dose. Intracavitary brachytherapy had a relatively low complication rate compared to that seen with radical surgery (3). In patients unsuitable for intracavitary brachytherapy, interstitial brachytherapy or less radical surgery are acceptable alternatives. Intracavitary brachythrapy is unlikely to control extensive tumors that do not regress after chemoradiation, because part of the gross tumor volume may lie outside the high-dose region. The present study indicates that the use of radical adjuvant surgery after chemoradiation is feasible but it is associated with significant postoperative and long-term toxicity. The long-term results in 1986 patients with cervical carcinoma treated in the United States, in 1973, and 1983 indicate a major complication rate of 8-12%, half of whom required surgical intervention (17).

In the present series, 6 of 30 patients (20%) developed severe complications. The combined use of surgery and radiotherapy is associated with a complication rate higher than radiotherapy alone (18,19). A recent randomized study (20) had also shown a higher complication rate in patients treated with the combined modality compared to that seen in patients treated with surgery alone.

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