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Original Article

NEOADJUVANT CONCURRENT CHEMORADIATION AND COMPLETION HYSTERECTOMY FOR STAGES IB2-III CERVICAL CANCER. PATHOLOGICAL RESPONSE AND SURVIVAL

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ABSTRACT

Aim of the Work: To assess the impact of neoadjuvant Cisplatin based chemoradiation followed by completion hysterectomy upon pathological response and survival in bulky cervical cancer.

Patients and Methods: 22 patients with bulky cervical cancer (stages IB2-III) included and followed up prospectively in this study between December 2003 and June 2006 using neoadjuvant chemoradiation of Cisplatin-Gemcetabine (weekly at 40mg/m² and 125mg/m², respectively, both for 6, concurrent to external beam radiation therapy 5040 cGy in 5 3/5 weeks with 180 cGy fraction) followed by completion hysterectomy three to six weeks later.

Results: The study included 22 patients. Overall, the mean age was 46.7 years (range 33-70), and almost 60% of the cases were stage IIB. Seventeen patients had undergone modified radical hysterectomy including pelvic lymph nodes dissection, five cases had undergone extrafascial hysterectomy and four cases were subjected to para-aortic lymph nodes dissection. Pathological responses were as follows: Pathological complete response (pCR) in twelve patients (54.5%), near complete (p-Near-CR) in four patients (18.2%) and partial response (pPR) in 6 patients (27.3%). After a median follow-up period of 24 months (range 10-30), seven patients experienced relapses in different sites, locoregional and distant, five of them were still alive and two died of the disease. 11 out of 12 cases that showed pCR were alive with no evidence of disease. Four out of 10 cases that showed residuals were alive with no evidence of disease while non of the patients (two) with extra uterine disease (positive para- aortic lymph nodes) at time of hysterectomy were alive.

Conclusion: In the curreny study, the combination of neoadjuvant concurrent chemoradiotherapy Gemcitabine-Cisplatin followed by completion hysterectomy seems to be active, well tolerated treatment regimen for locally advanced cervical cancer. It needs big number of patients to assure its benefits. Completion hysterectomy assures complete removal of any hidden tumor and presumably may improve local control and survival.

Key Words: Cervical, caner-neoadjuvant, chemoradiotherapy-local, control

INTRODUCTION

Survival of women with bulky cervical cancer has remained substantially unchanged during the last two decades. The long term out look is grim, with overall five-year survival rates of approximately 40% when conventional treatments are used.

Five randomized trials have demonstrated that survival with radiation therapy alone is lower than that with concomitant-cisplatin based chemoradiation[1,2]. Afterwards, a meta-analysis collaborated these findings confirming that chemoradiation offers an absolute survival benefit at five years of 12%[3]. Thus, Cisplatin based chemoradiation was largely accepted as the standard of care for cervical cancer patients whose treatment requires radiation therapy[4-6].

The aim of work was to report our experience with bulky cervical cancer cases that were treated with neoadjuvant concurrent chemoradiation and completion hysterectomy to evaluate the pathological response and survival.

PATIENTS AND METHODS

Patients aged less than 70 years with untreated, locally advanced (International Federation of Gynecology and Obstetrics [FIGO] stage IB2 to III) uterine cervix squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma were eligible.The inclusion criteria: Eastern Cooperative Oncology Group [ECOG] performance status greater than two, normal

hematological, hepatic and renal functions according to the following parameters: hemoglobin >9g/L, leukocyte count >4000/mm³ and platelets >100,000/mm³; total bilirubin and transaminases <1.5 times the high normal value and normal serum creatinine; normal ches X-ray. Abdominal and pelvic computed tomography or magnetic resonance imaging was also included in the staging work-up.

Treatment Plan:

Women with bulky stage IB2, II, and III cervical carcinoma were assigned to receive neoadjuvant chemoradiation of Cisplatin-Gemcetabine (weekly at 40mg/m² and 125mg/m², respectively, both for 6, concurrent to external beam radiation therapy 5040 cGy in 5 3/5weeks with 180cGy fractions) followed by completion hysterectomy. In all patients, completion hysterectomy (extra fascial, and modified radical) was performed three to six weeks after the neoadjuvant treatment.

Volume Treated:

Patients were simulated in the supine position using computerized tomography simulator. The upper border of the target volume was at the L4-5 interspace while the lower border was taken at the inferior border of the obturator foramen if there was no vaginal extension. However, in cases where there was vaginal involvement, the entire length of the vagina was included down to the introitus. The lateral borders were 2cm lateral to the pelvic brim. The lateral border anterior margin was placed at the pubic symphysis; the posterior margin was designed to cover at least 50% of the rectum in stage IB[2] while extended to the sacral hollow in patients with more advanced tumors.

All patients were treated by isocentric box technique treatment field.

Assessment of Pathological Response:

Pathological response was considered as complete (pCR) if there were no viable tumor cells in the surgical specimen (primary tumor and lymh nodes), near complete or microscopic response (p Near-CR) was considered with the presence of few foci of malignant cells up to 1millimeter in diameter and partial response (pPR) was considered if the residual tumor was larger than 1 millimeter.

Follow-Up:

Median follow-up period was 24 months (range 10-30). Follow-up included pelvic examination every three months after finishing the whole treatment plan. Radiological imaging including MRI study was performed if clinically indicated.

Data Management:

The primary end points were assessment of pathological responses, progression-free survival and survival. Progression-free survival was calculated from the date of entry into the study to the date of disease recurrence, death or the last follow-up visit. Survival was calculated from the date of entry into the study to the date of death or the last follow-up visit, as estimated by Kaplan Meier methods[7]. Recurrences were classified as local if they were detected in the pelvis or vagina and as distant if they were detected in extra pelvic sites.

RESULTS

Twenty two patients were enrolled in this study. Overall, the mean age was 46.7 (range 33-70 years) (Table1) and almost 60% were FIGO stage IIB (Figure1). All patients received neoadjuvant concurrent chemoradiation followed three to 6 weeks later by completion hysterectomy; five out of 22 cases had undergone extrafascial hysterectomy while seventeen cases had undergone modified radical hysterectomy; and four patients had para-aortic lymph nodes dissections because of concern of palpable disease. Type of surgery in relation to clinical stage is shown in table 2.

Table 1: Patients Characteristics (22 patients).

Characteristic	No.	%
Age (years)		
Mean	47.9	
Range	33-70	
Performance status (ECOG)		
0-1	20	91
2	2	9
Histologic Diagnosis		81.8
Squamous cell	18	13.6
Adenocarcinoma	3	4.5
Adeno-squamous	1	
Clinical stage (FIGO)		
IB2	3	13.6
IIA	2	9
IIB	13	59
IIIA	1	4.5
IIIB	3	13

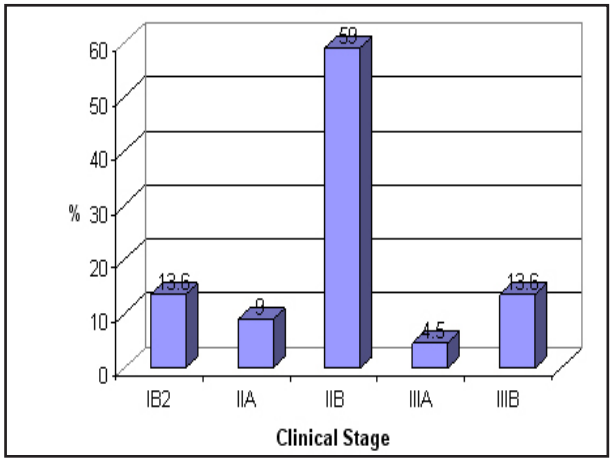


Fig. 1: Percentage of Clinical stage in the study group

Table 2: Type of surgery in relation to clinical stage (22 patients).

Type of Surgery	Clinical Stage (FIGO)	No. (%)
Extra-fascial Hyster-ectomy	IB2, IIA	5 (22.7)
Modified Radical Hysterectomy	IIB, III	17 (77.3)
Para-aortic Lymph nodes	IIB**, III***	4 (18.2)
Dissections		

Pathological response rates were as follows: Pathological complete response (pCR) in 12 cases (54.5%), near-complete (p-Near-CR) in 4 cases (18.2%) and partial (pPR) in 6 cases (27.3%). Two cases showed isolated para-aortic lymph nodes metastases; three cases showed residuals in the cervix as well as pelvic lymph nodes; one case showed residuals in the cervix as well as in the para-aortic lymph nodes and four cases showed residuals in the pelvic lymph nodes. Overall pathological response in relation to the clinical stage is shown in tables 3 and 4, figures 2 and 3.

Table 3: Overall pathological response in relation to clinical stage (22 patients).

Clinical stage (FIGO)	Pathological response		
	CR	Near - CR	PR
IB 2	2	1	-
II A	2	-	-
II B	7	2	4
III A	-	-	1
III B	1	1	1
Total (%)	12 (54.5)	4 (18.2)	6 (27.3)

Table 4: Overall outcome among twenty-two patients in relation to pathological response.

	Complete response (n = 12)	Residual disease (n = 10)
Relapse	1	4 (2 Near + 2 Partial)
No evidence of disease	11	4 (2 Near + 2 Partial)
Died	-	2 (Partial)

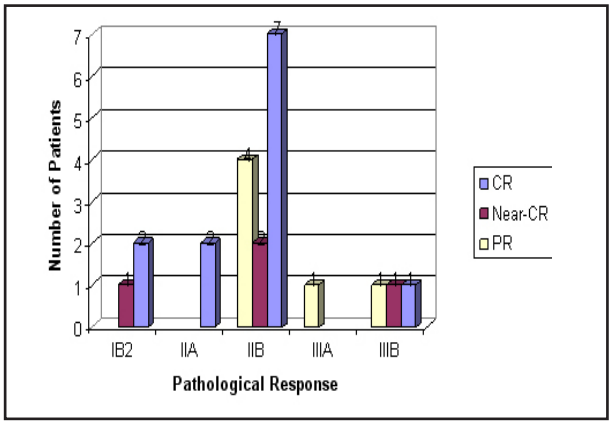


Fig. 2: Pathological response in relation to clinical stages

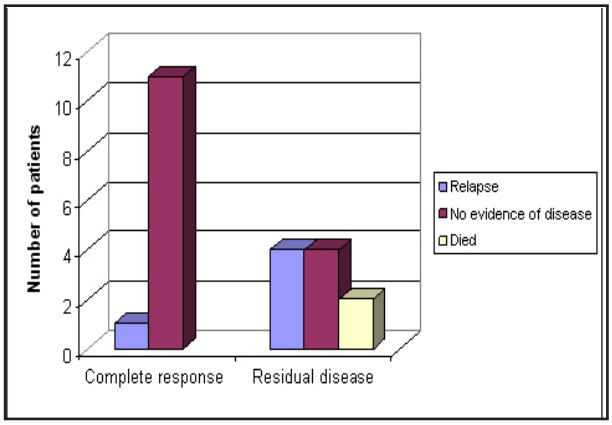
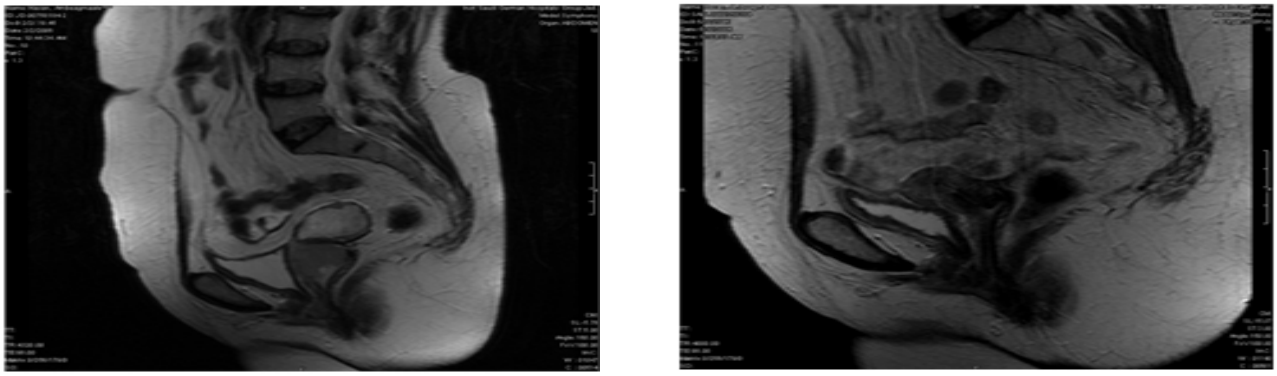


Fig. 3: Overall outcome among 22 patients in relation to pathological response

Figures 4, 5 and 6 showed MRI comparative studies for three cases before and after neoadjuvant concurrent chemoradiation.

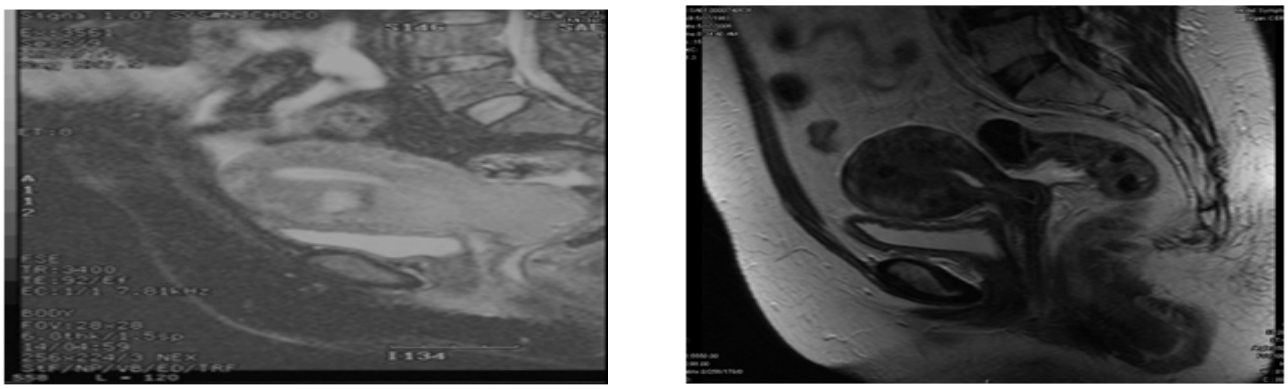
Treatment Related Morbidity:

A total of 132 cycles of Cisplatin-Gemcetabine were given to the whole study group. Acute toxicity was evaluated in all patients according to Radiation Therapy



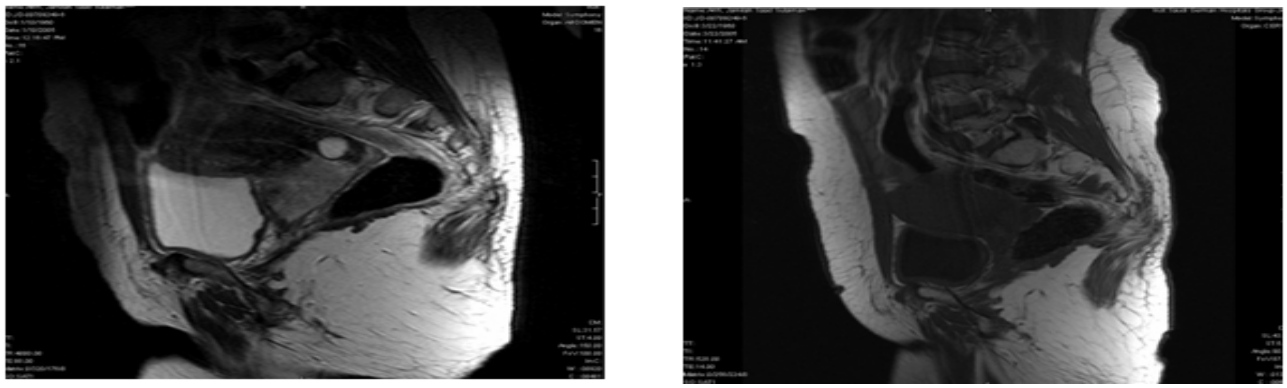
(a) (b)

Fig. 4 a and b: Sagital T2 M.R.I.showed bulky cervical tumor mass involving mostly the full thickness of cervix in a stage IIIA cervical cancer before treatment (a) and follow-up comparative study after concurrent chemoradiation showed complete radiological response where the cervix appeared of normal size with no identification of the previosly described cervical tumor mass (b).



(a) (b)

Fig. 5 a and b : Sagittal MRI comparative studies before (a) and after (b) concurrent chemoradiation showed complete radiologial response with no evidence of cervical tumor.



(a) (b)

Fig. 6 a and b: Sagittal MRIcomparative studies before (a) and after (b) neoadjuvant concurrent chemoradiation which showed complete disappeaance of cervical mass&unremarkable study of pelvis.

Oncology Group (RTOG) Criteria[8]. Grade 3 toxicity was not common, however treatment plan was well tolerated and no treatment related death was encountered (Table5).

Table 5: Treatment Related Morbidity (22 patients).

TOXICITY	GRADE	
	III	IV
ACUTE (RTOG)	No. (%)	No. (%)
Hematologic		
Neutropenia	2 (9)	-
Thrombocytopenia	1 (4.5)	-
Anemia	1 (4.5)	-
Gastrointestinal		
Nausea-vomiting	1 (4.5)	-
Diarrhea-tenesmus	3 (13.6)	-
Cutaneous	2 (9)	-
Cardiovascular	1(4.5)	-
Wound infection (WHO)	2 (9)	-
Urinary*	2 (9)	-
LATE (RTOG)		
Small bowel	1(4.5)	-
Dyspareunia	3 (13.6)	-

*Postoperative complication in the form of urinary fistulae

The grade three acute toxic reactions included neutropenia (9%), vomiting (9%), diarrhea (13.6%). One patient experienced transient cardiac arrhythmia, two patients developed post-operative infections. Two patients developed post-operative urinary fistula, one treated conservatively and the other patient requires exploration and re-implantation of the ureter into the bladder. Dyspareunia as a result of vaginal stenosis was encountered in two patients.

Survival Results

Fifteen patients are alive with no evidence of disease, five patients are alive with disease and two patients died of the disease (Table 4).

Eleven out of twelve cases (91.6%), who showed pCR are alive with no evidence of disease. 4/10 (40%) cases who showed residuals (pNear-CR, pPR): Are alive with no evidence of disease and non of the two cases with extra uterine disease (Positive Para-aortic lymph nodes metastases) at time of hysterectomy are alive.

Five patients are alive with disease; one case experienced local recurrence, another case developed para-spinal mass proved to be metastatic; a third case developed para-aortic lymph node metastases and pulmonary metastases were detected in two cases.

The pathological response was significantly affecting the relapse, since only 1/12 (8.3%) patient with pCR relapsed, compared with 6/10 (60%) patients with residual tumor in the pathological specimen, either pNear-CR or pPR (P=0.0001) (Figure 7). Overall survival was 12/12 (100%) in patients with pCR compared to 80% (8/10) for patients with either pNear -CR or pPR (P=0.0001) (Figure 8).

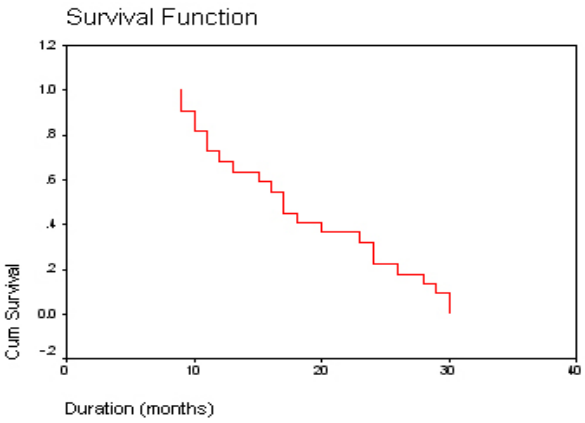


Fig. 7: Disease free survival among the 22 cases.

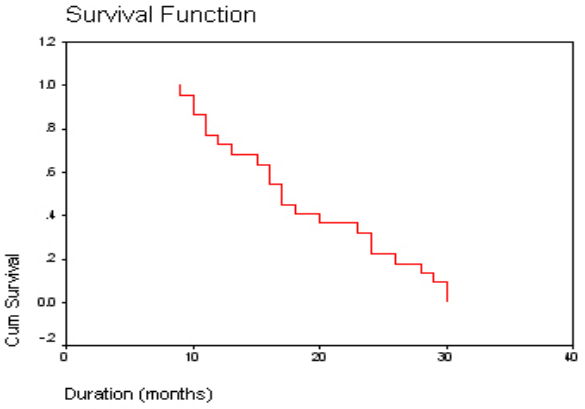


Fig. 8: Overall survival among the 22 cases.

DISCUSSION

Currently, Cisplatin-based chemoradiation is the standard of care for locally advanced cervical carcinoma[7]. This combined treatment has of proven efficacy even in patients treated outside of clinical trial[8]. Nevertheless, the five-year survival of locally advanced cervical cancer patients is around 79% hence other therapeutic approaches must be tested in order to further improve prognosis.

Several prospective phase II trials of preoperative chemoradiation with Cisplatin and five Fluorouracil have been performed. Resbeut et al. reported a complete pathological response rate of 40% in 40 patients staged

from IB to IVA[9]. With newer regimens of chemotherapy incorporating drugs such as Gemcetabine[10,11], Vinorelbine[12], Paclitaxel[13,14] or Irinotecan[15],complete pathological response rates are higher may lead potentially to better survival rates. In this sense, we have reported in our study that complete pathological response when adding Gemcetabine to Cisplatin as powerful radiosensitizer was 54.5% which indicates a higher complete pathological response than reported with cisplatin alone (47.5%) by Duenas et al.[16] With 100% as survival rate only one out of the twelve sample pathological responded experienced relapse, and this is matched with that figures reported by Candelariz et al.[17], where they concluded PCR (58.5%) with Cisplatin-Gemcetabine concurrent with radiotherapy. Also, Manay et al. registered complete, near-complete (as microscopic residual) and reported no local failures among the 13 patients with complete response suggesting that complete responders have the most favorable prognosis[18].

Resbeut et al.[19] made no distinction between complete and microscopic (near-complete). Responses, instead they reported only complete or partial pathological response, nor integrated pathological response to their survival analysis, however only one of the 16 patients with complete response had local recurrence suggesting its association with good prognosis. Jurado et al. defined complete pathological response as tumor eradication higher than 95% and found a 9-year local control rate of 93% versus 70% (p =0.038) for complete and partial responders, respectively[20]. Finally, the advantage of the completion hysterectomy is to assure complete removal of any hidden tumor. 40% (4/10) of patients in this study with residual disease in the cervical specimen at the time of hysterectomy are alive with no evidence of disease. Presumably, these patients may have had relatively worse survival without adjuvant hysterectomy.

The patients with disease outside of the pelvis at the time of surgery, as expected, did not benefit from surgery. The differentiation between patients with pelvic disease and extra pelvic disease thus becomes imperative. Laparoscopy to explore the abdomen which, includes the para-aortic nodes, before the initiation of radiation therapy or the time of hysterectomy. If macroscopic disease is found outside the pelvis with laparoscopy, a decision could be made to stop the procedure and save the patient the morbidity that is associated with hysterectomy.

CONCLUSION

The combination of neoadjuvant concurrent chemoradiotherapy Gemcetabine-Cisplatin followed by completion hysterectomy seems to be active, well tolerated treatment regimen for locally advanced cervical cancer. The combination of cisplatin-gemcitabine seems to be superior to cisplatin alone in terms of pathological response rate.

The results of this study would help to demonstrate whether this combination is also superior in terms of survival, however larger numbers of patients need to be included.

Total hysterectomy assures complete removal of any hidden tumor and presumably may improve local control rate and survival.

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