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Original Article

Chemotherapy and Management of Locally Advanced Carcinoma Cervix

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ABSTRACT

Background & Objective: **the present study was undertaken to ascertain the incidence of early, advanced cancer cervix and its recurrence and role of chemotherapy in locally advanced cancer cervix.**

Material and Methods: **The present study was conducted in the Departments of Obstetrics & Gynaecology, Pathology and Radiotherapy and the specimens examined in the Department of Pathology of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India from July 2009 to July 2010. One hundred histologically confirmed carcinoma cervix cases were divided into two groups. I: Study group of cases receiving different types of chemotherapy and II: Control group comprised of cases on pre and postoperative radiotherapy and surgery. Patients were staged and locally advanced inoperable cases (Stage IB-IVA) were given different types of chemotherapy. Thereafter subjective and objective assessment was made according to World Health Organization (WHO) criteria of tumor response.**

Results: **Majority of cases (60.0%) presented in stage IIB of disease by International Federation of Gynecology and Obstetrics (FIGO) classification. Commonest symptom was postmenopausal vaginal bleeding, 70.0% cases. 68.0% & 56.0% cases showed complete response (CR) on chemotherapy and radiotherapy respectively. Stage IIB patients showed the best response with CR in 70.0% & partial response (PR) in 16.7% cases. Colposcopic evaluation on 12 -18 months follow up showed 08 to be disease free, with decrease in size of tumor.**

Conclusion: **Chemotherapy is an effective mode of therapy and can be considered as an adjunct to surgery or radiotherapy to improve the overall survival of cancer cervix patients.**

Key words: **Cervix Cancer, Chemotherapy**

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Introduction

Cervical cancer is the second most common malignancy in women worldwide, and it remains a leading cause of cancer-related death for women in developing countries (1). The incidence of invasive cervical cancer has declined steadily in the developed world over the past few decades; however, it continues to rise in many developing countries. The change in the epidemiological trend in the developed countries has been attributed to mass screening with Papanicolaou tests (2). Internationally, 500,000 new cases are diagnosed each year. Unlike the United States, where the annual incidence is 6.8 cases or less per 100,000 women, rates in parts of South America, Africa and Asia range as high as 52.8 cases per 100,000 women (3).

To stem the deaths due to cervical cancer, various modalities of treatment have arisen viz onco-surgery, radiation therapy and various schedules of chemotherapy like neoadjuvant, adjuvant, therapeutic and concurrent. The national cancer institute has recommended that concurrent or concomitant chemotherapy should be used in all cases of locally advanced or bulky tumors (4).

Attempts to define the role of chemotherapy in the management of carcinoma cervix continue to challenge gynecologists and medical oncologists. Keeping this view in mind, the present study was undertaken to ascertain the incidence of early, advanced cancer cervix and its recurrence and role of chemotherapy in locally advanced cancer cervix.

Material and Methods

The present study was conducted in the departments of Obstetrics & Gynaecology, Pathology and Radiotherapy and the specimens examined in the Department of Pathology of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India from July 2009 to July 2010. The study included 100 cases of histologically confirmed carcinoma cervix which were divided into two groups-**I:** Study group; which was subdivided into 3 subgroups depending upon the type of chemotherapy received – A: neoadjuvant, B: concurrent and C: surgery and concurrent chemotherapy. **II:** Control group, which was subdivided into two subgroups, A: Cases on radiotherapy alone, B: Cases with surgery and post operative radiotherapy.

After a detailed clinical history, thorough systemic and gynecological examination and routine investigations, patients were staged using the clinical staging system proposed by FIGO and locally advanced inoperable cases (stages IB-IVA) were eligible for first line treatment with chemotherapy.

Neoadjuvant chemotherapy regime composed Inj. Cisplatin 75 mg/ m^2 body surface area(BSA), in divided doses on day 1 and 2 with Inj. Methotrexate 25 mg/m^2 BSA on day 1. Two such cycles were given at an interval of three weeks. Concurrent chemotherapeutic regime comprised Inj. Cisplatin 50 mg IV infusion + Inj. 5-flurouracil 750 mg IV infusion x 6 cycles given weekly along with radiation therapy (50 Gy of Co-60 γ rays for 5 weeks).

The assessment of tumor response was done according to WHO criteria of tumor response i.e.,1) Subjective response which included symptomatic relief of pain, bleeding and improvement in general condition. 2) Objective response: graded into (a) Complete response (CR) $\rightarrow$ disappearance of all measurable disease (b) Partial response (PR) – decrease in tumor size equal to or greater than 50% of the product of the two maximal diameters (c) Stable disease (SD) $\rightarrow$ less than 50% regression of tumor and (d) Progressive disease (PD) $\rightarrow$ greater than 25% increase in size of tumor or appearance of new lesions.

The study was approved by Jawaharlal Nehru Medical College Hospital Ethics Committee.

Results

Majority of patients were in the fifth decade of life as 36 cases (36.0%); followed by 34 cases (34.0%) in the sixth decade, with mean age of patients being 51.5 years. Distribution of patients according to FIGO classification revealed majority of patients as 60.0% in FIGO stage IIB where the tumor extended beyond the cervix with parametrial involvement, followed by 20.0% patients in stage III B with tumor extension to pelvic sidewalls.

The present study showed the upward trend in cervical cancer with increasing parity. 36.0% of patients had parity of more than five, with higher incidence in rural patients (58.0%) than urban ones (42.0%). Majority of the patients, 60.0% were from lower socioeconomic status with a marital age of 18 years or less. Post-menopausal vaginal bleeding was the most common symptom in 70.0% cases; followed by vaginal discharge in 64.0%, pelvic pain in 58.0% and contact bleeding in 42.0% cases.

Squamous cell carcinoma was the major histological type in 90.0% cases, followed by adenosquamous in 6.0% and adenocarcinoma in 4.0% cases. Large cell keratinizing was the most common subtype of squamous malignancy, 48.0% cases.

Out of 50 patients on chemotherapy alone, 68.0% showed complete response (CR), whereas CR was noted in 56.0% patients receiving radiotherapy only (Table 1). Patients in stage IIB showed the best response after combination of chemo-irradiation, with CR in 70.0% and PR in 16.7% cases, followed by patients in stage IIA and stage IIIB who showed CR in 50.0% and 40.0% cases respectively (Table 2). On analysis of response according to histological type, 55.6% of patients with squamous cell carcinoma showed CR whereas PR was seen in 33.3% cases. CR was seen in 100% cases of adenocarcinoma whereas in patients of adenosqumous carcinoma 66.7% showed CR and 33.3% showed PR.

Table 1- Objective response (WHO Criteria) in study group and control group (n = 100)

Groups	No. of Patients	Complete Response N (%)	Partial Response N (%)	Stable Disease N (%)	Progressive Disease N (%)
Study Group					
a) Neoadjuvant CT + RT	32	20 (62.5)	8 (25.0)	-	4 (12.5)
b) Neoadjuvant CT + Surgery	4	4 (100)	-	-	-
c) Concurrent Chemo-irradiation	14	10 (71.4)	2 (14.3)	2 (14.3)	-
Total	**50**	**34 (68.0)**	**10 (20.0)**	**02(4.0)**	
Control Group					
a) RT alone	38	20 (52.6)	14 (36.8)	-	4 (10.5)
b) Surgery + RT	12	8 (66.7)	4 (33.3)	-	-
Total	**50**	**28 (56.0)**	**18 (36.0)**	**-**	**4(8.0)**

Table 2- Response to CT + RT according to Clinical Stage

FIGO stage	No. of Patients	Complete Response N (%)	Partial Response N (%)	Stable Disease N (%)	Progressive Disease N(%)
IIA	8	4 (50.0)	4 (50.0)	-	-
IIB	60	42 (70.0)	10 (16.7)	4 (6.7)	04 (6.7)
IIIA	-	-	-	-	-
IIIB	20	8 (40.0)	10 (50.0)	2 (10.0)	-
IVA	12	4 (33.3)	8 (66.7)	-	-
Total	**100**	**58**	**32**	**6**	**4**

The common cytological changes observed in Papanicolaou smears after chemo-radiotherapy, was nuclear enlargement in 87.0% cases, vacuolization of cytoplasm in 85.0% cases (Fig. 1), with multinucleation and polychromasia in 70.0% cases each. Wrinkling of nuclei and bizarre cells were seen in 59.0% and 43.0% cases respectively.

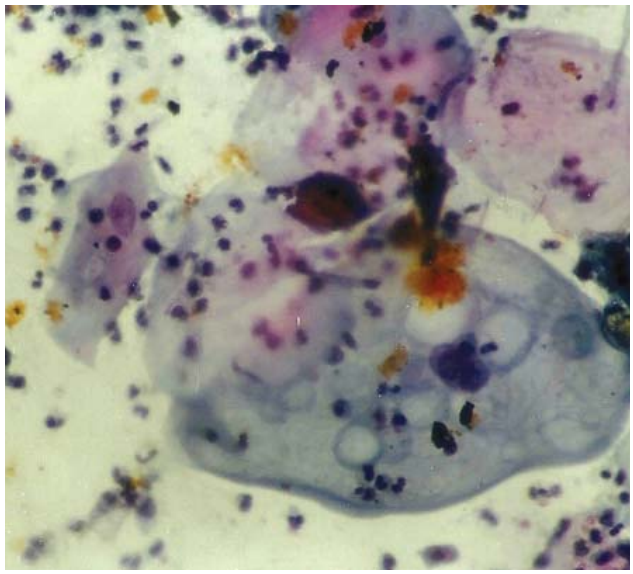

Fig. 1- Acute Radiation Change: Cells showing cytoplasmic vacuolation. Pap ×500

Complete response in well-differentiated carcinoma was noted in 61.9% cases and PR in 28.6% cases, whereas in moderately differentiated carcinoma, 58.3% showed CR and 37.5% showed PR while in poorly differentiated carcinoma, only 20.0% showed CR and a high percentage of cases (20.0%) presented with progressive disease (PD). Out of the 22 patients with tumor size < 3 cm, residual tumor size was < 0.5 cm in 20 cases and 0.5-2 cm of size in two cases. Out of 12 patients with initial tumor size of > 5 cm, residual tumor size was < 0.5 cm in 2 patients and 0.5 – 2 cm in 10 patients.

Out of 50 patients, 24 had following up period of 6 –12 months. Out of them, 20 were disease free and 4 had local recurrence. Among the 24 patients with follow up of 12-24 months, 10 were disease free, 4 had progressive disease and 8 had local recurrence and two had both local and distant metastasis. Both the patients on □24 months of follow up period died of the disease.

Colposcopic evaluation of patients were done before and after administration of chemotherapy and also on follow up visits which revealed decrease in size of tumor with therapy. Regression of distinctive malignancy feature, gradual disappearance of peripheral lesions and centripetal re-epithelialization of the cervix were sequentially registered. (Fig. 2a & 2b).

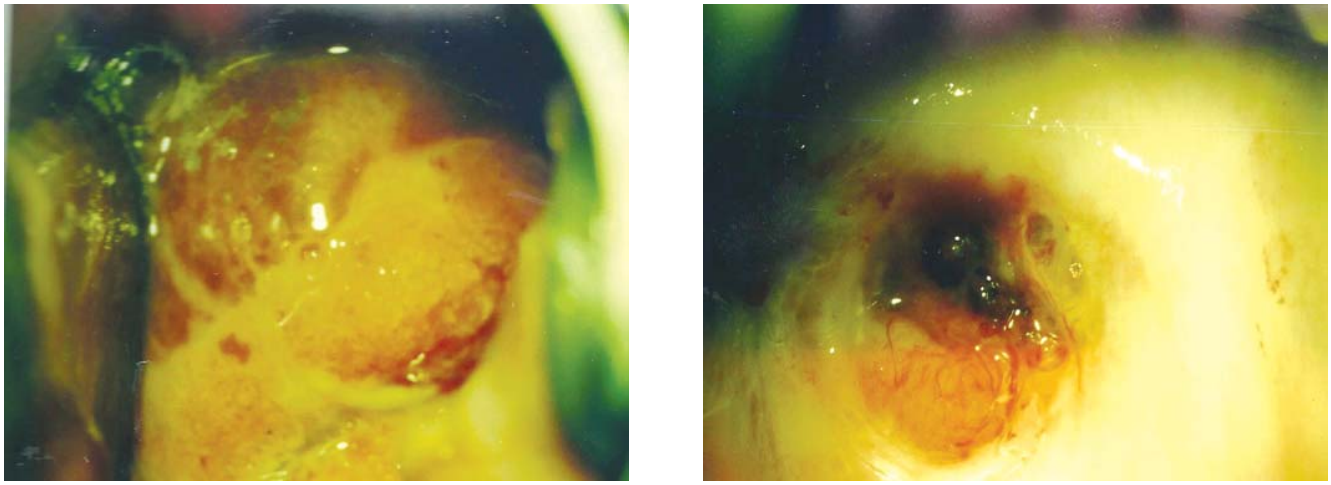

Fig. 2- (a): Colposcopic view of large polypoidal growth on cervix. **(b):** Cervix of same patient with no growth after neoadjuvant chemotherapy

Discussion

Early stage cervical cancer is usually curable with either surgery or radiotherapy, but locally advanced cancers have high number of treatment failure (5), and attempts to define the role of chemotherapy in the management of carcinoma cervix continue to challenge gynecologists and medical oncologists. Keeping this perspective in mind, the present study was undertaken to evaluate the role of chemotherapy in the management of locally advanced carcinoma cervix.

The mean age of patients was 51.5 years in our study, which is comparable to the mean age of 52.2 years as reported by Zhao *et al.* (6). Majority of our patients, 60.0% belonged to FIGO stage IIB, followed by 20.0% patients in stage IIIB disease. Quite similarly Gonzalez *et al.* (7), in their study on 67 patients found majority of patients i.e., 23 in stage IIB followed by 10 patients in stage IIIB disease.

Our study revealed high parity to be associated with increased incidence of cancer, quite similar to Zhao *et al.* (6), who found parity as an independent risk factor for cervical cancer. A preponderance of cancerous patients (58.0%) with a rural background as compared to 42.0% urban population was noted by us. This disparity could be due to a high rural Indian population with low socio-economic status and factors like early age of marriage, high parity, and deficiency of micronutrients. A high incidence of the disease is noted in women of low socioeconomic status with human papilloma virus infection, who tend to marry at a young age(8). Most common presenting symptom was post menopausal bleeding in 70.0% cases, followed by vaginal discharge in 64.0% cases, a finding cogent with Zhao *et al.* (6).

Our study showed squamous cell carcinoma as the most common invasive cancer of the cervix, 90.0% cases followed by 6.0% cases of adenosquamous and 4.0% of adenocarcinoma, a finding concordant to Gonzalez *et al*. (7).

Out of 50 patients who received chemotherapy, 44 responded well with complete response in 68.0% and partial response in 20.0% cases. Thus, the overall response rate was 88.0%. In 36 patients receiving neoadjuvant chemotherapy, followed by surgery or radiotherapy; 66.7% showed CR and 22.2% showed PR. Four patients (11.1%) showed progressive disease while on chemotherapy. Gonzalez *et al.* (7) in their study on 61 patients with neoadjuvant chemotherapy showed 6 (9.8%) with complete and 55 (90.2%) with partial response. Out of 14 patients receiving concurrent chemo-irradiation, 71.4% showed CR while 14.3% showed PR. Only two patients showed minimal response. Thus results of concurrent chemo-irradiation was better as compared to neoadjuvant chemotherapy, but Duenas *et al.* (9) have reported 97.0% and 87.0%

ccomplete response rates after treatment with neoadjuvant chemotherapy and chemo-irradiation respectively. Concurrent use of cisplatin and 5-fluorouracil acts as a radiosensitizer and enhances the response of radiotherapy. In the control group receiving radiotherapy, 56.0% of patients showed CR, 36.0% showed PR and 8.0% showed progressive disease along with enhanced side effects and morbidity during radiotherapy as compared to study group.

Complete response was seen in 70.0% of stage IIB patients, followed by 50.0% in stage IIA, 40.0% in IIIB and markedly less with stage IVA disease. Kumar *et al.* (5) in their study of neoadjuvant chemotherapy in locally advanced cancer cervix found higher overall response rate of 88.0% in stage IIB disease, followed by 78.0% in stage IIA and 74.0% in stage IIIB disease.

Our study showed that 61.9% of well-differentiated carcinoma with CR and 28.6% with PR. Panici *et al.* (10) however, found an overall response rate of 100% in patients with well-differentiated carcinoma, 84.0%, and 67.0% with moderately and poorly differentiated malignancy respectively.

Tumor volume is one of the important prognostic factors. With increasing size of tumor, prognosis becomes poor; and response to therapy is directly related to the initial tumor size, a relationship found in our study. Panici *et al.* (11) also found that tumor size was significantly correlated with subsequent response to chemotherapy. They stated that complete or partial responses were 93.0% when tumor size was ≤ 5 cm but the percentage decreased to 68.0% when the tumor was bigger than 5 cm. Colposcopy played an important role in follow up of our patients. It helped in detecting residual disease or recurrence of disease after completion of therapy.

Conclusion

Chemotherapy is an effective mode of therapy with acceptable side effects like, hematologic toxicity and hence can be considered as an adjunct to available modalities of treatment like surgery or radiotherapy, to improve the overall survival of patients of cancer cervix.

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