

Feasibility of Neoadjuvant Chemotherapy followed by Concomitant Chemoradiotherapy in Figo Stage IVA Cancer Cervix

Manashi Ghosh¹, Vinita Trivedi², Kaustub³, Brajesh Kumar⁴

ABSTRACT

Introduction: The conventional treatment of Carcinoma Cervix Stage IV A, has been a judicious combination of external beam radiotherapy and intracavitary brachytherapy, which offered an alternative to radical surgery for patients with tumors larger than 4 cm confined to cervix. Adjuvant and neoadjuvant chemotherapy, however, has been tested in cervical carcinoma for many years without success.

Material and Methods: Several trials with either adjuvant chemotherapy alone or sequential radiation and chemotherapy for high risk, surgically treated early stage patients have failed to show prolong survival. The objective of this study was to see feasibility in terms of local response, treatment related toxicities and pattern of relapse of neo-adjuvant chemotherapy (NACT) followed by concurrent chemoradiotherapy (CT+RT) with cisplatin and 5-Fluorouracil (5-FU) in FIGO stage IV A cancer cervix. Total 55 patients of Carcinoma Cervix Stage IVA were given 2-3 cycles of NACT with Cisplatin and 5-FU at 3 weekly intervals. In patient with complete response or partial response concurrent Radiotherapy was given.

Result: In this study neoadjuvant chemotherapy had significantly reduced local disease prior to definitive chemoradiotherapy. It decreased appearance and controlled distant metastasis. Concurrent chemoradiotherapy increases local control at the cost of increased toxicities. Though toxicities were increased but were managed easily.

Conclusion: Thus, neoadjuvant chemotherapy followed by concurrent chemoradiotherapy is a possible option for patients with FIGO Stage IVA (locally advanced) carcinoma cervix.

Keywords: Carcinoma Cervix; External beam Radiotherapy (EBRT); Neo Adjuvant Chemotherapy (NACT); Concurrent Chemoradiotherapy; Intra Cavitary Radiotherapy; Cisplatin and 5-Fluorouracil (5-FU).

highest incidence of cervical cancer is seen in females of Chennai. A belt of high incidence rates even higher than that in Chennai is seen in North Eastern districts of Tamil Nadu state including Pondicherry which had the highest minimal age adjusted incidence rates (MAAR) of 39.2/10000. If current trend continues by 2050 there will be over 1 million new cases annually worldwide.

High incidence and mortality in developing countries are due to-

- Lack of awareness of cervical cancer among population, health care provider and policy makers.
- The unavailability and poor quality of screening programs which fails to diagnose the precursor lesions and early stage disease.
- Limited access to health care services.
- Lack of functional referral system.

In India and other developing countries where most of the women are reluctant to be screened regularly, present with locally advanced stage (FIGO III and IV A) compared with developed countries where most women present with early stage disease.

Because of difference in disease spectrum of cancer cervix and associated problem for treatment and supportive measures, management of locally invasive cancer poses a formidable challenge to the oncologist. The conventional treatment has been a judicious combination of external beam radiotherapy and intracavitary brachytherapy for locally advanced disease (stage IIB, III, IVA) which offered an alternative to radical surgery for patients with tumors larger than 4 cm confined to cervix. According to International Federation of Gynecology and Obstetrics (FIGOs) Annual Report, the 5-year survival of patients with Stage IIIB and FIGO Stage IVA together has been 25%.⁵

In an endeavor to improve the outcome of the cancer cervix, a number of randomized controlled trials (RCTs) have

INTRODUCTION

The incidence of cervical cancer has declined in western world, but on global scale it is the second most common cancer in world. The estimated new cases of cervical cancer are about 5,00,000 per year globally and about 2,75,008 patients die annually.¹ In developing countries cervical carcinoma is the most prevalent female malignancy. Carcinoma cervix is the most frequent cause of death from cancer in women from developing world and most of these cases are locally advanced at diagnosis.² Higher incidence had been seen in Latin America and less frequent in Jewish and European women and Fiji Islanders.³

The cervical cancer load in India is about 1,25,000 each year and 79,000 women dies of disease in India alone.⁴ According to PBCR (Population Based Cancer Registries) of India

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aimed to explore the possibility of a survival benefit by incorporating chemotherapy agent as a concomitant agent with radiotherapy. Five randomized studies accruing almost 2000 patients demonstrated the superiority of the arm with Cisplatin based chemotherapy during pelvic radiation.⁶⁻¹⁰ The positive results of these RCTs prompted the National Cancer Institute (NCI) to issue an 'alert', urging clinicians to consider concomitant chemoradiotherapy as a standard of care for locally advanced cervical cancer. Additional evidence supporting these results has come from two additional phase III trials utilizing other radiosensitizers.^{11,12} These studies have confirmed that the benefits of chemoradiation are not limited to surgically staged patients and that the patients with more advanced FIGO Stage (IIIB) benefit the most.¹²

A subsequent systemic review and meta-analysis of data presented in publications suggested a large benefit of concomitant chemoradiotherapy in survival, progression free survival and local and distant control rates in locally advanced carcinoma cervix.¹³

Adjuvant and neoadjuvant chemotherapy, however, has been tested in cervical carcinoma for many years without success. Several adjuvant trials with either chemotherapy alone or sequential radiation and chemotherapy for high risk, surgically treated early stage patients have failed to prolong survival.

At least eight randomized phase III trials comparing radiation alone with neoadjuvant chemotherapy followed by definitive radiation in locally advanced cervical cancer show no advantage in terms of response and overall survival. There are, however, still potential therapeutic advantages to giving chemotherapy alongside local treatments that were standard for locally advanced disease. Neoadjuvant chemotherapy given prior to surgery may reduce tumor size and control micro metastasis. A number of randomized trials have explored the use of NACT as an adjunct to either radiotherapy or surgery in comparison with radiotherapy (RT) alone and cisplatin-based regimes have been favored because of impressive response rates. Most of these randomized trials have been relatively small and their results range from significant increase in survival¹⁴ to significant reduction in survival with NACT.¹⁵

Despite these results, in this study it had been tried, to improve results of neoadjuvant chemotherapy by incorporating concurrent chemotherapy with radiation in stage IVA cancer cervix uteri. Stage IVA is one in which disease is extended beyond cervix to adjacent structures like bladder, bowel. The bladder, bowel involvement must be proven by cystoscopic and procto-sigmoidoscopic examination and biopsy.

The objective of this study was to see feasibility in terms of local response, treatment related toxicities and pattern of relapse of neo-adjuvant chemotherapy (NACT) followed by concurrent chemoradiotherapy (CT+RT) with cisplatin in FIGO stage IV A cancer cervix.

MATERIAL AND METHODS

The study was carried on patients attending Department of Radiotherapy of Mahavir Cancer Sansthan, Patna. Total

fifty-five patients of carcinoma cervix stage IV A disease who fulfilled the inclusion criteria were evaluated for neoadjuvant chemotherapy followed by concomitant chemoradiotherapy. All were treated with curative intent, after taking detailed history and proper clinical examination, provisional diagnosis and staging was done. Patients were subjected to routine investigations and metastatic work up. Before starting treatment informed consent of the patient was taken, patient attendants were explained the nature of disease, kind of treatment intended and related toxicities.

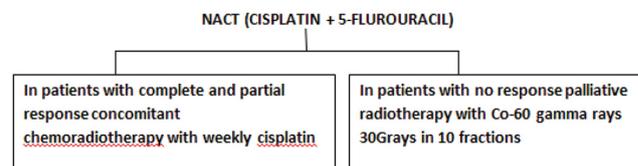
Staging

Patients were staged according to the system adopted by FIGO i.e International Federation of Gynecologist and Oncologist Staging for carcinoma of the cervix.¹⁶

ECOG Performance status

ECOG performance status scale was followed, patient with ECOG 0, 1, were not included in the study.¹⁷

Planned treatmentcourse



Neoadjuvant chemotherapy

All the patients were subjected to 2 cycles of combined Neoadjuvant chemotherapy with Cisplatin and 5Fluorouracil. Cisplatin – 60 - 75 mg/m² IV, infused over 1-2 hours, Day1. 5-FU – 1000 mg/m² IV over 72 hours of continuous infusion, Day 1-3.

Cycle repeated after 21 days.

Every patient was counselled about the toxicities of chemotherapy. They were advised to take proper diet, lots of fluids throughout the treatment and extra fluid on the day of chemotherapy, take care of personal hygiene.

Next cycle was administered on 21st day after complete blood count, kidney function test, liver function test and serum electrolytes test. Evaluation of response was done after 2 weeks of 2nd cycle of chemotherapy¹⁸ by clinical examination, cystoscopy and proctosigmoidoscopy. Response evaluation was done as per WHO guidelines.

Concurrent chemoradiotherapy

After NACT, patients showing complete and partial response were subjected to radiotherapy with weekly cisplatin 40 mg/m² with radical intent. Patients with no response (NR) after NACT were subjected to palliative external beam radiotherapy (EBRT) with total dose of 30Gy in 10 fractions at the rate of 3Gy per fraction followed by chemotherapy. Radiotherapy was started on day 21 of 2nd cycle of NACT. Concurrent cisplatin 40mg/m² was started preferably from day1 of radiotherapy at weekly interval for 5weeks was given. Injection cisplatin in 4hours infusion was given before radiotherapy.

Radiation therapy

All patients received external beam radiotherapy (EBRT)

based on International commission on radiation units and measurements ICRU- 50.¹⁹ EBRT was given with Co-60 gamma ray stelecobalt machine using 4 MV photons. Total dose of 50 Gy in 25 fractions at the rate of 2 Gy per fraction in 5weeks was given to whole pelvis. Radiotherapy was given 5 days a week.

Intracavitary brachytherapy (ICRT)

After completion of concurrent chemoradiotherapy patients were subjected to ICRT as early as possible.²⁰ Intracavitary brachytherapy (ICRT) done with Microselectron-HDR, Iridium-192 sources following ICRU-38 recommendation²¹ with Fletcher Suit applicators. Three applications of 500cGy-700cGy each to point A (a reference point 2cm superior and 2cm lateral to the external OS) were done 1week apart. Rectum and bladder were pushed away

as far as possible from the ovoid's using vaginal gauge packing.

Monitoring of toxicities

Patients were monitored regarding gastrointestinal, skin, mucosal and other toxicities. All the patients were routinely monitored for hydration, nutrition and performance status. If needed supportive treatment with fluids, antiemetics, antibiotics, antacids, NSAIDs, filgrastim S.C injections and blood transfusion was given.

End point and evaluation of treatment

The response to NACT was evaluated clinically and by cystoscopy and proctosigmoidoscopy after second cycle of chemotherapy. At the end of chemoradiotherapy evaluation of response was done after six weeks according to WHO criteria.¹⁸

Post treatment assesment

On completion of therapy patients were assessed after 6weeks for locoregional control, distant metastasis and toxicities by physical and pelvic examination and whenever needed by abdominal USG, chest X-ray, cystoscopy and proctosigmoidoscopy. Subsequent assessments were done 12weekly for next 2years.

Toxicity scoring criteria

The acute and chronic toxicities to chemoradiation were assessed according to Radiation Therapy Oncology Group (RTOG) toxicity criteria.²² Toxicity to NACT was evaluated according to NCI CTCAE V 3.0 (CTCAE- Common Terminology Criteria of Adverse Events).²³

Type	n	%
CR	4	7.3
PR	41	74.5
NR	7	12.7
PD	3	5.5

Table-1: Response rate of neoadjuvant chemotherapy

Response	n	%
CR	26	57.8
PR	14	31.1
NR	5	11.1
PD	0	0

Table-2: Clinical response at the end of the treatment

Toxicities	n	%					
Leucopenia	35	63.6					
Anemia	4	7.3					
Thrombocytopenia	10	18.2					
Neutropenia	15	27.3					
Mucosal	28	50.9					
Diarrhea	42	76.4					
Nausea & Vomiting	32	58.2					
Neurological	6	10.9					
Hair Loss	18	32.7					
Renal	3	5.5					
Hepatic	0	0					
Fever	2	3.6					
Toxicity	Grade I	Grade II	Grade III	Grade IV			
Leucopenia	8(14.5%)	21(38.1%)	4(7.3%)	2(3.6%)			
Anemia	0	1(1.8%)	3(5.6%)	0			
Thrombocytopenia	0	4(7.3%)	6(10.9%)	0			
Neutropenia	8(14.5%)	4(7.3%)	3(5.6%)	0			
Mucosal	22(40%)	6(10.9%)	0	0			
Diarrhea	14(25.5%)	25(45.5%)	3(5.6%)	0			
Nausea & Vomiting	8(14.5%)	19(34.5%)	5(9.1%)	0			
Neurological	0	3(5.6%)	3(5.6%)	0			
Hair Loss	10(18.1%)	8(14.5%)	0	0			
Renal	2(3.6%)	1(1.8%)	0	0			
Hepatic	0	0	0	0			
Fever	0	1(1.8%)	1(1.8%)	0			

Table-3: Common toxicities criteria version 3 scored during NACT

Toxicity	Grade I	Grade II	Grade III	Grade IV	Grade V
Leucopenia	8(17.3%)	15(33.3%)	4(8.9%)	0	0
Anemia	6(13.3%)	3(6.7%)	3(6.7%)	0	0
Thrombocytopenia	6(13.3%)	4(8.9%)	5(11.1%)	0	0
Neutropenia	3(6.7%)	2(4.4%)	4(8.9%)	0	0
Diarrhea	10(22.2%)	12(26.7%)	11(24.4%)	2(4.4%)	0
Vomiting	9(20%)	14(31.1%)	5(11.1%)	0	0
Skin	12(26.7%)	13(28.9%)	7(15.6%)	0	0
Mucositis	10(22.2%)	12(26.7%)	8(17.8%)	0	0
Genitourinary	7(15.6%)	9(20%)	3(6.7%)	0	0
Neurological	4(8.9%)	5(11.1%)	2(4.4%)	0	0
Fever	10(22.2%)	5(11.1%)	3(6.7%)	0	0
Weight loss	14(31.1%)	7(15.6%)	7(15.6%)	0	0

Table-4: Common toxicities criteria version 3 scored during CRT

At risk	45	100%
Recurred	27	60%
Local failure	19	42.2%
Systemic failure	3	6.7%
Local and systemic failure	5	11.1%
Lost to follow up	1	2.2%
Death	2	4.4%
Disease free	15	33.3%

Table -5: Disease status at 12 months of follow up

Toxicity	Grade I	Grade II	Grade III	Grade IV	n	%
Skin	10 (23.8%)	4 (9.5%)	3 (7.1%)	0	17	40.5
S.C Tissue	8 (19.0%)	4 (9.5%)	2 (4.8%)	0	14	33.3
Mucous Membrane	7 (16.7%)	5 (11.9%)	2 (4.8%)	0	12	28.6
Small intestine/Large intestine	10 (23.8%)	5 (11.9%)	3 (7.1%)	0	18	42.9
Bladder	6 (14.3%)	3 (7.1%)	0	0	9	21.4

Table-6: Late toxicities

Disease Status	n	%
Alive without disease or recurrence	15	35.7
Alive with persistent or recurrent disease	23	59.8
Alive with metastatic disease	2	4.8
Death	2	4.8

Table-7: Disease status at the end of the study

STATISTICAL ANALYSIS

All the statistical analysis (Chi-squared tests) was done by using the software "Graph Pad Prism 5.0" at 95% significant level. The p value is considered significant when $p \leq 0.05$.

RESULTS

Most of the patients had partial response (74.5%) followed by complete response (7.3%). No response and progressive disease seen in 7.0% and 5.5% respectively (table-1). Overall response after chemoradiotherapy was 89% (CR- 58% and PR- 31%) and 11% patients had no response (table-2).

DISCUSSION

Total 55 patients were accrued in the study. The median age of the presentation was 53 years, majority of the patients

were in 51-60 years age group. In this study 69.1% of patients belonged to rural population and 30.9% of patients had come from urban area. Since over 70% of the Indian population resides in the rural areas, cancer of cervix still contributes the number one cancer in the either sex. In this study highest incidence of cervical carcinoma was present in patients with high parity, belonging to the low socio-economic strata. In this study most of the patients had performance status of ECOG 0 (40.0%) and ECOG 1(34.5%). In this study most common histological type was squamous cell carcinoma (89.1%) followed by adenocarcinoma (9.1%) and adenosquamous (1.8%). According to WHO classification²⁴ most common histological type is squamous cell carcinoma. Majority of the patients had poorly differentiated cancer followed by moderately differentiated and well differentiated cancer. Various meta-analysis has shown that poorly and moderately differentiated squamous cell cancer have poor prognosis than well differentiated cancer.²⁵

In this study all patients were given neoadjuvant chemotherapy (Cisplatin + 5-FU) with planned dose, except in 6 (10.9%) patients in whom dose modification was needed. Dose modification was done due to grade III diarrhea and grade IV leucopenia. The acute side effects were managed

conservatively.

In series of Sundfor et al²⁶ 4 patients out of 47 needed major dose reduction due to low creatinine clearance. 5 – FU infusion stopped after 3 days of infusion because of mucotoxicity and then ototoxicity. In this study the response rate after 2 cycles of NACT as follows CR- 4 (7.3%), PR- 41 (74.5%), NR-7 (12.7%), and PD- 3 (5.5%).

In series of Sundfor et al²⁶ the overall response rate after NACT was 72% (31/43), 2 patients had CR, 29 patients had PR and 12 patients had SD.

In series of Marth C et al²⁷ 15 patients with bulky FIGO Stage Ib or IIa carcinoma cervix received neoadjuvant chemotherapy before surgery for two three cycles. Complete response was seen in four patients, partial response in 10 patients, which represents 93% overall response rate. One patient had stable disease, none had progressive disease.

During NACT most disabling morbidities were grade III toxicities, only 2 patients had developed grade IV leucopenia. Grade III toxicities were leucopenia (63.6%), anemia (7.3%), vomiting (52.8%), diarrhea (76.4%) and neurological (10.9%).

In series of Sundfor et al²⁶ the dominating acute toxicity was mucositis. 8 patients experienced mucosal toxicity of grade III or IV. 7 patients had grade III diarrhea, 1 patient had grade III neurotoxicity. Other grade III toxicity were ototoxicity, hair loss and general. The reason for mucositis being the most common acute toxicity may be 5 days C.I of 5-FU 1000mg/m² whereas in our series 5-FU 1000mg/m² was given as 3 days c.i.

During chemoradiotherapy grade III toxicities were leucopenia (8.9%), anemia (6.7%), diarrhea (24.4%), vomiting (11.1%), skin (15.6%), genitourinary (6.7%), neurological (4.4%) and weight loss (15.9%). Two of the patients suffered grade IV diarrhea in last week of treatment and none had grade V (death) morbidities. All patients tolerated the treatment well with proper supportive care. All grade III and grade IV toxicities were managed conservatively in our hospital set up.

In series of Duenas et al²⁸ the toxicities during chemoradiation following NACT was mostly grade I and grade II skin (28%), upper GI (64%), lower GI (71%), genitourinary (21%). Grade III and grade IV toxicities were leucopenia in 21% and neutropenia in 7%.

In this study the incidence of grade III toxicities were higher because all of our patients were treated with Co-60 gamma rays whereas in series of Duenas et al they used linear accelerator in some patients.

In another series of Duenas et al²⁹ triple modality of neoadjuvant chemotherapy followed by radical hysterectomy and adjuvant radiation concurrent with cisplatin is found to be a highly active treatment or locally advanced cervical carcinoma with acceptable toxicity. With median follow up of 12 months late toxicities were recorded. Most of the patients had grade I and grade II toxicities. 3 (7.1%) had grade III skin toxicities, 2(4.8%) patients had grade III subcutaneous tissue toxicity, 3 (7.1%) patients had grade III mucosal toxicity and 3(7.1%) patients had grade III intestinal toxicity.

The late toxicities in series of Duenas et al were grade II proctitis in two patients and grade III proctitis in two (28%) of patients. In this study 80.0% of the patients completed NACT in time. 4.5% patients completed NACT with 1 week delay due to grade III leucopenia and diarrhea. Delay of 2 weeks was seen in 5.5% patients due to grade IV diarrhea and grade III vomiting.

Chemoradiotherapy was started on stipulated time in 29/45(64.4%) patients, 9(20.0%) patients had delay of 1 week and 7(15.6%) patients had delay of 2 week. Delay in starting treatment was due to grade III and IV toxicities and some had unknown reasons.

ICRT had been started as early as possible after chemoradiotherapy. About 26(61.9%) patients had completed ICRT without any delay. 11(26.2%) patients had delay of 1 week and 5(11.9%) had delay of 2 weeks. Delay in starting treatment was due to grade IV diarrhea and vaginal mucositis.

Majority of the patients had completed chemoradiotherapy in scheduled time with 5 cycles of cisplatin 40mg/m²/week. 12 patients had 1-2 days delay and 8 patients had delay of 3-4 days. ICRT had been done within stipulated time in 57.1% of patients, 30.9% patients had delay of 1-2 days, 7.2% patients had delay of 3-4 days and 4.8% patients had delay of >5 days.

Reasons for prolongation of chemoradiotherapy and intracavitary brachytherapy were acute morbidities, technical reasons and holidays. At median follow up of 12 months, majority of patients had grade I and grade II toxicities, nobody had grade IV toxicities. 7.19% patients had grade III skin toxicities, other grade III toxicities were subcutaneous tissue (4.8%), mucous membrane (4.8%), small and large intestine (7.1%) related.

Majority of the patients (68.99%) were given total dose of 71 Gy at point A, 77.8% patients were given 65-69 Gy, 6.7% patients were given 60-64 Gy. 2(4.4%) patients did not go for ICRT as they developed vesicovaginal fistula after external beam radiotherapy. Later at median follow up of 12 months two patients with local failure developed vesicovaginal fistula.

At the end of the study out of 42 patients, 15 were alive without disease recurrence, 23 patients were alive with recurrent disease, 2 patients were alive with metastatic disease and 2 patients (4.8%) were dead.

In this study neoadjuvant chemotherapy had significantly reduced local disease prior to definitive chemoradiotherapy. It decreased appearance and controlled distant metastasis. Concurrent chemoradiotherapy increases local control at the cost of increased toxicities. Though toxicities were increased but were manageable at our hospital setup.

Thus, neoadjuvant chemotherapy followed by concurrent chemoradiotherapy is a possible option for patients with FIGO Stage IVA (locally advanced) carcinoma cervix.

CONCLUSION

A prospective non randomized study for feasibility, response and toxicities of “Neoadjuvant Chemotherapy Followed

by Chemoradiotherapy In FIGO Stage IV A Carcinoma Cervix" was taken in the department of radiation oncology, Mahavir Cancer Sansthan, Patna. Follow up period ranged from 6 months to 18 months, with median follow up of 12 months. Total 55 patients who fulfilled the eligibility criteria were enrolled for study. Age range of study population was 30-70 years with median age of 53 years. The patients with complete response and partial response (45/50) had undergone chemoradiotherapy and patients with no response and progressive disease undergone palliative radiotherapy. In this study NACT had significantly reduced local disease prior to definite chemoradiotherapy, decreased incidence of VVF and distant metastasis. Chemoradiotherapy increase local control at the cost of increased toxicities. Though the toxicities increased but were manageable at our hospital setup.

Thus, NACT followed by concomitant chemoradiotherapy is a possible option for patients with stage IV A carcinoma cervix. A randomized phase III trial is required to establish the value of NACT followed by concomitant chemoradiation versus chemoradiation. As this modality of NACT followed by chemoradiotherapy has already demonstrated encouraging results in head and neck cancer³⁰, esophageal cancer³¹ and lung cancer.³²

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