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Efficacy of cisplatin based concurrent chemoradiation followed by intracavitary brachytherapy in locally advanced carcinoma cervix: Experience from Northern Pakistan

Abstract

Objectives: To determine the efficacy of cisplatin based concurrent chemoradiation followed by Intracavitary brachytherapy in locally advanced carcinoma cervix patients.

Study Design: Descriptive Case Series

Place and duration of study: Nuclear Medicine, Oncology, Radiotherapy Institute (NORI), Islamabad from December 2010-December 2011.

Methods: Patients were given external beam radiation dose of 50 GY with concomitant weekly cisplatin 40mg/m2 over period of 5 weeks. EBRT was followed by ICRT 04 fractions of 06 GY on weekly interval using HDR Ir192 source. After 06 weeks of completion of treatment response was assessed on MRI. Response rates were scored according to WHO guidelines.

Results: The response rate achieved in this study with concurrent chemoradiation was 72.2%. Twenty-two out of 52 (40.7%) patients showed complete response, 17 (31.5%) showed partial response, 08 (14.8%) patients had stable disease. Nineteen (59%) patients out of 32 showed complete response in stage II and I and 03 (13%) patients out of 22 showed complete response in stage III & IV.

Conclusion: Cisplatin based concurrent chemoradiotherapy is effective in the treatment of locally advanced carcinoma cervix in our setup. Treatment outcome was better in stage IB2 & II.

Keywords: Uterine cervical neoplasms; Brachytherapy; Cisplatin; Chemoradiotherapy; Treatment outcome

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Introduction

Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012.[1] 86% of all deaths due to cervical cancer are in developing, low- and middle-income countries. Its incidence and mortality in developed world has decreased substantially because of well-developed screening programs.[2] In Pakistan carcinoma cervix is less common as compared to other gynecological malignancies. According to our statistical record in NORI 40-65 patients present every year (25% of the total gynecological malignancies). It is second commonest to ovarian tumors among gynecological malignancies at NORI.[3]

The standard of care for locally advanced cervical cancer (FIGO IB2–IVA) is concurrent chemoradiation. The chemotherapy agents used are cisplatin, cisplatin combined with fluorouracil or hydroxyurea. Weekly cisplatin achieved the best responses, even when compared with the combination with fluorouracil. These results led the United States National Cancer Institute (NCI) to recommend platinum-based chemotherapy for the treatment of locally advanced cervical carcinoma. Intracavitary brachytherapy is the essential component of radical treatment for cervical cancer. Platinum Based chemoradiation is the standard regimen.[4,5]

This treatment approach is superior to radiotherapy alone in terms of local control, control of occult metastatic disease, disease free survival and overall survival with slight increase in gastrointestinal and hematological side effects. The total treatment duration should be less than 08 weeks.[6] Concurrent chemoradiotherapy significantly improves the survival for patients with stage IIB-IIIB cervical cancer compared to radiotherapy alone.[7] The use of concurrent chemotherapy has shown an absolute increase in survival rate of 12% and cisplatin is found to be the most effective drug. A study showed promising results with the complete response of 83% and partial response of 17% of patients.[8] Chemoradiation followed by brachytherapy is particularly effective in early stages and an overall disease free survival at 2 yrs and 5 yrs was 80.4% and 72.2% in stages Ib2-IIB.[9] Cisplatin based chemoradiation results in complete response rate of 91% and is a better compliant and tolerable compared to other treatments.[10] Complete and partial response rates of 82% and 18% were shown by another study for the same treatment.[11]

Uterine cervical cancer is the second most common cancer among gynecological cancers in females in Pakistan and most of the patients present in locally advanced stage due to inadequate screening facilities, lack of proper health care system and lack of education. There is very limited data regarding the effectiveness of this treatment in our country. The number of patients registered at our hospital with CA cervix is rising with time, and most of them present at locally advanced stage, chemoradiation followed by brachytherapy is being used at NORI for a couple of years but the results are not documented.

This study is designed to determine the response in our patients so that a protocol is designed in future with acceptable morbidity and better tolerance.

Objective

The objective of the study was to determine the efficacy of cisplatin based concurrent chemoradiation followed by Intracavitary brachytherapy in locally advanced CA cervix patients in terms of complete response and partial response.

Material and methods

This study is a descriptive case series. It was carried out in Oncology department of NORI Islamabad. Study was completed in one year. Total Fifty-four patients were recruited in the study according to our selection criteria. Consecutive sampling (Non-probability sampling technique was employed). Patients with Karnofsky PS >70%, Stage IB2-IVA based on clinical examination, EUA and MRI Pelvis showing growth in the cervix staged according to FIGO guidelines, histopathologically proven Squamous cell Carcinoma Cervix were included in the study. Patients with uncontrolled hypertension and diabetes, coexisting second malignancy, those who have taken any other anticancer treatment except for BCC and SCC and patients with abnormal RFTs and LFTs were excluded from the study. The study was approved by the hospital Ethical Review Committee. Informed consent was taken from every patient fulfilling the inclusion criteria. Premenopausal patients were explained regarding ovarian ablation and infertility following treatment.

Patients included in the study were those registered at the outpatient department of Oncology at NORI Hospital. They were evaluated in detail through History, Physical examination, and Investigations including hematology, Biochemistry, CT scan and MRI pelvis. Each patient was discussed in Multidisciplinary meetings (MDM) consisting of Oncology Department NORI hospital and Gynecology, Radiology and Pathology department of Pakistan Institute of Medical Sciences Islamabad.

EBRT was administered to the whole pelvis using Linear accelerator machine over period of 5 weeks up to total dose of 50GY in 25 fractions with 25mg/m^2 weekly Cisplatin.6MV, 10MV or 15MV energies were used. Chemotherapy was administered one hour before radiation treatment. Four-field BOX or AP/PA technique was used according to the energy selected. The superior border of the field was at the level of intervertebral disc between L4 and L5. The lateral border was 1.5cm lateral to the bony pelvic wall. The Inferior border was at the level of inferior margin of obturator foramen, or up to the level of introitus if vagina were involved. EBRT was followed by ICRT O4 fractions each of 6 GY on weekly interval starting within 01 week on completion of EBRT. It was administered by using Fletcher suit applicators using HDR Ir 192 source. Rectum and urinary bladder was pushed away from the ovoids as far as possible using vaginal gauze packing. Patients were examined every week during treatment.

Cisplatin 40 mg/m2 was administered for 6weeks on the first day of every radiotherapy week.ECOG status and biochemical profile was assessed, prior to each chemotherapy cycle. Full blood counts and clinical assessments were performed weekly throughout the treatment.

Response was assessed at 6 weeks with MRI Pelvis. Complete response was defined as disappearance of all known disease at 6 weeks. Partial response is defined as more than or equal to 50% reduction in the known disease. Stable disease was labeled if it didn't meet the criteria of complete response, partial response or progressive disease. More than or equal to 25% increase in the known disease was defined as progressive disease. Overall response was the sum of partial and complete responses.

Data analysis

All data was entered and analyzed using SSPS version 19. Categorical variables (Symptoms at presentation, tumor grade, disease stage, response to therapy) were analyzed for frequency and percentage distribution. Quantitative data like age was analyzed for Mean±SD.

Results

A total of 54 patients with histopathological diagnosis of SCC of cervix were enrolled in the study. One Patient lost to follow up and one patient died of myocardial infarction.

Demographics

Mean age of the patients was 52 years ± 09 with a range from 28 to 80 years. 35 (64%) patients were postmenopausal. Clinicopathological features are shown in Table 1.

Table 1 Clinicopathological features

Age range 28-80 years	
Mean age+/- SD 52 +/- 9 years	
Menopausal status	
Post Menopausal	35 (65%)
Pre Menopausal	19 (35%)
Clinical presentation	
Per Vaginal Bleeding	30 (55.6%)
Vaginal Discharge	20 (37%)
Urinary Complaints	02 (3.7%)
Post Coital Bleeding	2 (3.7%)
Grade	
Well differentiated	16 (29.6%)
Moderately differentiated	33 (61%)
Poorly differentiated	05 (09%)
Stage	
IB2	8 (14.8%)
IIA2	6 (11%)
II B	18 (33.3%)
III	14(25.9%)
IVA	08(14.8%)

Complete response and partial response were 40.7% and 31.5%, while overall response rate seen in the study population was 72% (Table 2).

Table 2 Response rates

Complete response	22 (40.7%)
Partial response	17 (31.5%)
Stable disease	08 (14.8%)
Progressive disease	5 (9.3%)

Nineteen (59%) patients out of 32 showed complete response in stage 1 & 2. Three (13%) patients out of 22 showed complete responses in stage 3 and 4 (Table 3 & Figure 1).

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Table 3 Response according to stage

Response	Stage IB2	Stage IIB	Stage IIA2	III	IVA	Total
Complete response	6	10	3	2	1	22
Partial response	1	6	3	5	2	17
Stable disease	0	2	0	4	2	8
Progressive disease	0	0	0	2	3	5
Total	7	18	6	13	8	52

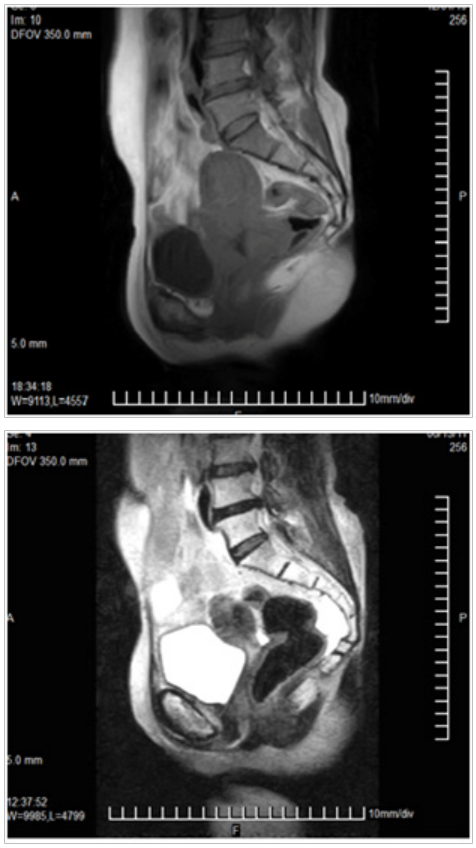

Figure 1 N=57; Epidemiological distribution of the pathological fractures, traumatic fractures, and nonunion.

Discussion

Cervical cancer is the second most common cancer in women among gynecological malignancies worldwide. Its incidence is decreasing in developed countries due to the incorporation of screening programs in the health care system; however in developing countries where the screening facilities are not available its incidence is still very high.[12] In Pakistan its incidence is comparatively low as compared to other Asian countries, particularly India and was similar to the Western Asian Muslim countries.[13] In our hospital it is the second most common gynecological malignancy.[14] Most of the patients with carcinoma cervix present in locally advanced stage.[15]

Radiotherapy is the main stay of treatment for locally advanced cervical cancer. Results of radiotherapy treatment alone are poor so many methods have been tried to improve the radio-responsiveness of the tumor. For improving the results of treatment in advanced stage disease, chemotherapeutic agents also have been used for last 2-3 decades. It has been used as neo adjuvant, concurrent chemo radiation and adjuvant. But only concurrent chemo radiation with cisplatin alone or in combination with other agents like 5 fluorouracil have recently been proven to give better response rates, disease free survival and overall survival in carcinoma cervix.[16] In February 1999, the US National Cancer Institute (NCI) issued an alert that chemo radiation should be considered for all patients with cervical cancer based on five randomized trials. The five randomized trials of cervical cancer involved different stages of the cervical cancer and a combination of treatment, but they shared a common result, all studies found that a concomitant treatment with cisplatin containing schedules (cisplatin, cisplatin and 5FU, cisplatin, 5FU and HU) and radiation therapy led to a better outcome than radiation therapy alone or in combinations with treatments that did not include cisplatin. This remarkable consistency offers compelling reason to consider cisplatin therapy in combination with radiation therapy as a new standard of care for patients with bulky stage IB disease, stage IIB through IVA and high risk cervical cancer cases.[17]

The mean age of presentation in this study was 52 years and most of the patients were postmenopausal. Most common symptom of presentation was vaginal bleeding (56%). However the patients presenting in IVA stage had urinary complaints as well. These results were similar to the study conducted by Kundu et al.[18] Most of the tumors were moderately differentiated. Most common stage of presentation was IIB. These results are consistent with the previous studies showing that the cervical cancer is twice as common in postmenopausal women as the premenopausal women.[19] Cervical cancer is seen as the most frequent malignant cause of postmenopausal bleeding.[20] As most of the patients are elderly belonging to lower socioeconomic status and living in rural areas, this becomes the main reason of delayed presentation of patients with cervical cancer. Most of the patients presenting in stage III and IV.[21,22] Tumor grade and stage are the predictors for the response to the treatment proved by many studies.[23–25] These findings are consistent with the results of the current study.

In our study 41% of patients showed complete response. 31% patients showed partial response. The overall response rate was 87%. Nineteen patients showed complete response in stage II, and I but only three patients showed complete response in stage III and IVA. These results are consistent with many previous studies showing complete and partial response rates of 86% and 18% respectively.[26] Another study showed complete pathological response rates of 55%.[27] The complete response rates are higher in stages IB2 and IIA than stage III and IV. Many old studies confirm that the response rates decrease as the stage progresses. A study showed the response rate of 62% in stage II decreasing to 57% in stage III. The overall response rates are found to be quite acceptable in this study however long term follow up is required to assess if this response turns into survival benefit.

Conclusion

Cisplatin based concurrent chemoradiation is effective in the treatment of locally advanced carcinoma cervix in our setup. Treatment outcome was better in stage IB2 & II.

Limitations and recommendations

The overall response rates are found to be quite acceptable in this study however long term follow up is required to assess if this response turns into survival benefit.

Acknowledgments

None.

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Conflicts of interest

The author declares no conflicts of interest.

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References

1. WHO. World Cancer Report 2014. World Health Organization, Chapter 5.12, pp. 630.
2. Arbyn M, Castellsagué X, de Sanjosé S, et al. Worldwide burden of cervical cancer. *Ann Oncol.* 2011;22(12):2675–2686
3. Humera M. The role of brachytherapy in cancer cervix:Experience at Nuclear Medicine, Oncology, Radiotherapy Institute (NORI). Presented at International Conference on Advances in Radiation Oncology ICARO. 2009.
4. Centina L, Arias A, Candelaria M, et al. Brachytherapy versus radical hysterectomy after external beam chemoradiation:a non–randomized matched comparison in 1B2–IIB cervical cancer patients. *World J Surg Oncol.* 2009;7:19.
5. Kundu S, Basu S, Acharya S, et al. Chemoradiation in locally advanced cervical cancer, a randomized trial. *Indian J Med Pediatr Oncol.* 2008;29(4):12–18.
6. Haie–Meder C, Morice P, Castiglione M. Cervical cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow–up. *Ann of Oncol.* 2008;19:ii17–ii18.
7. Zeng SY, Li Ly, Shu KY, et al. Concurrent chemoradiotherapy versus radiotherapy in advanced cervical carcinoma. *Ai Zheng.* 2008;27(9):942–946.
8. Cetina L, Rivera L, Hinojosa J, et al. Routine management of locally advanced cervical cancer with concurrent radiation and cisplatin, five year results. *BMC Women's Health.* 2006;6:3.
9. Huguet F, Cojocariu OM, Levy P, et al. Preoperative concurrent radiation therapy and chemotherapy for bulky stage IB2, IIA, and IIB carcinoma of the uterine cervix with proximal parametrialinvasion. *Int J Radiat Oncol Biol Phys.* 2008;72(5):1508–1515.
10. Kim YS, Shin SS, Nam JH, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high–dose rate brachytherapy for locally advanced cervical cancer. Gynecol Oncol. 2008;108(1):195–200.
11. Negi RR, Gupta M, Kumar M, et al. Concurrent chemoradiation in locally advanced carcinoma cervix patients. *J Can Res Ther.* 2010;6(2):159–166
12. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60(5):277–300.
13. Jamal S, Moghal S, Mamoon N, et al. The pattern of malignant tumors:Tumour registry data analysis, AFIP, Rawalpindi, Pakistan (1992–2001). *J Pak Med Assoc.* 2006;56(8):359–362.
14. Humera M. The role of brachytherapy in cancer cervix:Experience at Nuclear Medicine, Oncology, Radiotherapy Institute (NORI). Presented at International Conference on Advances in Radiation Oncology ICARO. 2009.
15. Ryu SY, Lee WM, Kim K, et al. Randomized clinical trial of weekly vs. triweekly cisplatin–basedchemotherapy concurrent with radiotherapy in the treatment of locally advancedcervical cancer. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e577–e581.
16. Negi RR, Gupta M, Kumar M, et al. Concurrent chemoradiation in locally advanced carcinoma cervix patients. *J Can Res Ther.* 2010;6(2):159–166.
17. Al Mansour Z, Verschraegen C. Locally advanced cervical cancer:what is thestandard of care? *Curr Opin Oncol.* 2010;22(5):503–512.
18. Kundu S, Basu S, Acharya S, et al. Chemoradiation in locally advanced cervical cancer, a randomized trial. *Indian Journal of Medical & Paediatric Oncology.* 2008;29(4):12–18.
19. Epstein E, Jamei B, Lindqvist PG. High risk of cervical pathology among women with postmenopausal bleeding and endometrium <or=4.4 mm:long–term follow–upresults. *Acta Obstet Gynecol Scand.* 2006;85(11):1368–1374.
20. Anorlu RI, Orakwue CO, Oyeneyin L, et al. Late presentation of patientswith cervical cancer to a tertiary hospital in Lagos:what is responsible? *Eur J Gynaecol Oncol.* 2004;25(6):729–732.
21. Ibrahim A, Rasch V, Pukkala E, et al. Predictors of cervical cancer being at an advanced stage at diagnosis in Sudan. *Int J Womens Health.* 2011;3:385–389.
22. Coker AL, Du XL, Fang S, et al. Socioeconomic status and cervical cancer survival among older women:findings from the SEER–Medicare linked datacohorts. *Gynecol Oncol.* 2006;102(2):278–284.
23. Macdonald OK, Chen J, Dodson M, et al. Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. *Am J Clin Oncol.* 2009;32(4):411–416.
24. Atahan IL, Onal C, Ozyar E, et al. Long–term outcome and prognostic factors in patients with cervical carcinoma:a retrospective study. *Int J Gynecol Cancer.* 2007;17(4):833–842.
25. Lim A, Sia S. Outcomes of Chemoradiotherapy in Cervical Cancer–The Western Australian Experience. *Int J Radiat Oncol Biol Phys.* 2012;82(4):1431–1438.
26. Negi RR, Gupta M, Kumar M, et al. Concurrent chemoradiation in locally advanced carcinoma cervix patients. *J Can Res Ther.* 2010;6(2):159–166.
27. Dueñas González A, Cetina Perez L, Lopez Graniel C, et al. Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plusgemcitabine in cervical cancer: a randomized Phase II study. *Int J Radiat Oncol Biol Phys.* 2005;61(3):817–823.