Original Article

Role of neoadjuvant chemotherapy and radiotherapy in locally advanced carcinoma of the cervix

Rajshree Dayanand Katke, Rewadkar Mahesh Shivhar[1], Priyanka Pagare[2]

Department of OBGY, Cama and Albless Hospitals, Grant Government Medical College, [1]Department of Radiotherapy, Cama and Albless Hospital, [2]Department of OBGY, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai, Maharashtra, India

ABSTRACT

Aim: To study the outcome and complications of neoadjuvent chemotherapy in locally advanced Carcinoma of Cervix in Indian patients. To study the outcome and complications of Radiotherapy in locally advanced Carcinoma of Cervix in Indian patients. **Materials and Methods:** It is a Prospective analytical study of 95 (n=95) patients registered in the Out-patient section (OPD) of Department of Radiation Therapy and Oncology and indoor patients in gynaec oncology ward in tertiary care institute with histopathologically proven carcinoma of cervix were included in the study. Study duration was from August 2012 to August 2014. Patients with Histologically confirmed cases of carcinoma of cervix with FIGO stage IIB to IVA who were suitable for chemoradiotherapy were included in the study. The baseline characteristics Age, Parity, Weight, Height, Body Surface Area, Socioeconomic Status, FIGO Staging, Histological Variety of Carcinoma Cervix, pre and post treatment ECOG score were noted. The median follow up period was 18 months. All patients were given 3 cycles of Neoadjuvent chemotherapy with each cycle 3 weeks apart, consisting of the drugs dose calculated according to body surface area, Injection Paclitaxel was given as intravenous infusion in a dose of 175 mg /m^2 on day 1 of chemotherapy cycle whereas Injection Cisplatin was given in a dose of 60 mg /m^2 intravenous infusion in two divided doses on day 1 and day 2 of neoadjuvent chemotherapy cycle. NACT was followed by concurrent chemoradiotherapy which included conventional fractionated radiotherapy (CFR) with weekly injection cisplatin 35mg/m^2, EBRT of total dose 50Gy (Gray) in 25 fractions, 200cGy (centigray) per fraction daily for 5 days a week and brachytherapy i.e. Intracavitary Radiation Therapy (ICRT) was given. **Results:** RECIST 1.0 criterion was used for assessment of the response to treatment. Out of 95 patients, 72 patients (75.78%) had complete response. Partial response was seen in 13 patients (13.68%). Stable disease was seen in 7 patients (7.3)%. 3 patients (3.15%) had progressive disease. Subjective response was evaluated after asking the patient about status of their presenting symptoms one month after completion of whole treatment. Out of 90 patients who had vaginal discharge, 80 patients (88.89%) got relief after complete treatment. Out of 65 patients who had vaginal bleeding, 59 patients (90.76%) were free of this symptom at the completion of treatment. Out of 36 patients who suffered with pelvic discomfort at the start of therapy, 16 patients (44.44%) got symptomatic improvement. During the course of treatment, 56 patients (58.94%) developed Nausea and Vomiting, 30 patients (31.57%) had diarrhoea, 10 patients (10.52%) had cystitis, 7 patients (7.36%) had proctitis, 9 patients (9.47%) developed peripheral neuropathy, 15 patients (15.78%) suffered fever and rash. Renal complications occurred in 7 patients (7.36%). Hematological side effects including anemia neutropenia and thrombocytopenia were noted in 25 patients (26.31%) Median follow-up period for patients was 18 months. Overall survival rate at 1 year after treatment was 74.73% whereas Disease free survival rate at 1 year after treatment was 69.47%. **Conclusions:** We conclude that, the study has demonstrated a good response rate to NACT followed by CRT in patients with locally advanced carcinoma of cervix with regard to tumour response, overall and disease free survival. The combination of paclitaxel with cisplatin for use in neoadjuvnant chemotherapy showed acceptable adverse effects.

Key words: Carcinoma cervix, chemotherapy, neoadjuvant chemotherapy, radiotherapy

Address for correspondence: Dr. Rajshree Dayanand Katke, Department of Obstetrics and Gynecology, Cama and Albless Hospital, Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai - 400 001, Maharashtra, India.
E-mail: drrajshrikatke@gmail.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.197888

Cite this article as: Katke RD, Shivhar RM, Pagare P. Role of neoadjuvant chemotherapy and radiotherapy in locally advanced carcinoma of the cervix. Clin Cancer Investig J 2016;5:365-8.

INTRODUCTION

Cancer refers to a class of diseases in which a cell or a group of cells divide and replicate uncontrollably, intrude into adjacent cells and tissues (invasion) and ultimately spread to other parts of the body than the location at which they arose (metastasis).[1] The transformation zone refers to the place where the two regions of the cervix – endocervix and ectocervix – meet.[2] There are several types of cervical cancer classified on the basis of where they develop in the cervix. Cancer that develops in the ectocervix is called squamous cell carcinoma, and around 80–90% of cervical cancer cases (more than 90% in India) are of this type.[3] Although cancer of the cervix can develop in women of all ages, it usually develops in women aged 35–55 years, with the peak age for incidence varying with populations.[4] For instance, it was found to be 30–40 years in the UK, and 35–39 years in Sweden. In India, the peak age for cervical cancer incidence is 45–54 years, which is similar to the rest of South.[3] Cervical cancer is the fourth most common cancer in women, and the seventh overall, with estimated 528,000 new cases in 2012.[5] Based on India studies performing human papillomavirus (HPV) detection tests in cervical samples, about 5.0% of women in the general population are estimated to harbor cervical HPV-16/18 infection at a given time, and 82.7% of invasive cervical cancers are attributed to HPVs 16 or 18.[3] In Indian women, age-adjusted incidence rates vary from 8.8 per 100,000 women population in urban areas to 22.5 per 100,000 women population in rural areas.[4] The introduction of Papanicolaou test led to significant reduction in mortality and morbidity. The screening coverage in Asian countries is low and varies from 50% in Singapore to 2.6–5% in India.[6,7] Sankaranarayanan *et al*.[8] screened the population in Osmanabad district in India using visual inspection of the cervix with acetic acid and concluded that in a low-resource setting, a single round of HPV testing was associated with a significant reduction in the number of advanced cervical cancers and deaths from cervical cancer.[8,9]

One of the motivations behind neoadjuvant chemotherapy (NACT) in the treatment of cervical cancer was to reduce tumor size to facilitate cure. Local control might also be improved with early control of micrometastases. Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of treatment depends on a careful balance between external beam radiotherapy (EBRT) and brachytherapy that optimizes the dose to tumor and normal tissues and the overall duration of treatment.[10]

Aims

- To study the effects and side effects of NACT in locally advanced carcinoma of the cervix in Indian patients
- To study the effects and side effects of radiotherapy in locally advanced carcinoma of the cervix in Indian patients.

PATIENTS AND METHODS

It is a prospective analytical study conducted from August 2012 to August 2014. Patients with histologically confirmed cases of carcinoma of the cervix with the International Federation of Gynecology and Obstetrics Stages IIB to IVA who were suitable for chemoradiotherapy (CRT) were included in this study. All patients were investigated with baseline complete blood count (CBC), kidney function test, X-ray chest posteroanterior (PA) view, and computed tomography (CT) scan of the abdomen-pelvis. Since vaginal bleeding and anemia are common in cervical carcinoma, hemoglobin ≥8 g %, total lymphocyte count 4000/mm^3, and platelet count ≥100,000 were considered as normal for enrolling patient in this study.

On CT scan, size of lesion, presence/absence of hydroureter and hydronephrosis, and any loss of fat planes with bladder, rectum, or both were noted. X-ray chest PA view of each patient was done just to rule out any metastasis. All patients were given three cycles of NACT with each cycle 3 weeks apart, consisting of the drugs dose calculated according to body surface area; injection paclitaxel was given as intravenous (IV) infusion in a dose of 175 mg/m^2 on day 1 of chemotherapy cycle whereas injection cisplatin was given in a dose of 60 mg/m^2 IV infusion in two divided doses on day 1 and day 2 of NACT cycle. Linear accelerator and iridium-192 were used as source of EBRT and brachytherapy, i.e., intracavitary radiation therapy (ICRT), respectively. EBRT was followed by ICRT within 15 days. During EBRT, all patients were on oral hematinic with multivitamin supplements and investigated weekly for CBC. All patients were treated with conventional fractionated radiotherapy with weekly injection cisplatin 35 mg/m^2 IV, where the EBRT of total dose 50 Gy in 25 fractions, 200 cGy per fraction daily for 5 days a week was given. Injection cisplatin 35 mg/m^2 IV over 1 h infusion was given weekly during EBRT course. ICRT to Point A where the total dose of 21 Gy was given in three fractions, single fraction of 700 cGy a week. Patients were evaluated monthly for the first 3 months after completion of treatment, 3 monthly for remaining 1st year, and 4 monthly during second. Since we have dedicated cancer wing in our hospital, our social workers either visit or escort the patients from their home or call the patients to hospital for follow-up. Hence, each patient was followed till the end of this study.

RESULTS

Of 95 patients who were reassessed 1 month after completed neoadjuvant chemotherapy (NACT) and concurrent CRT according to response evaluation criteria in solid tumors (RECIST 1.0) criteria for tumor response

assessment, 72 patients (75.78%) had complete response, 13 patients (13.68%) had partial response, 7 patients (7.3%) had stable disease whereas 3 patients (3.15%) suffered progressive disease [Figure 1 and Table 1].

Of 95 patients, 2 patients (2.1%) were asymptomatic (Eastern Cooperative Oncology Group [ECOG] Grade 0) [Table 2], 39 patients (41.05%) were symptomatic but completely ambulatory (ECOG Grade 1), 44 patients (46.31%) were symptomatic, <50% in bed during the day (ECOG Grade 2), and 10 patients (10.52%) were symptomatic, >50% in bed, but not bedbound (Eastern Cooperative Oncology Group [ECOG] Grade 3), after complete treatment.

Of 95 patients, 56 patients (58.94%) developed nausea and vomiting, 30 patients (31.57%) developed diarrhea, 10 patients (10.52%) had cystitis, 7 patients (7.36%) had proctitis, 15 patients (15.78%) had fever and rash, 9 patients (9.47%) had peripheral neuropathy, and 7 patients (7.36%) suffered renal complications. Twenty-five patients (26.31%) had hematological adverse effects which included anemia, neutropenia, and thrombocytopenia [Table 2].

Of 95 patients, 71 patients (74.73%) survived 1 year after completed treatment whereas 24 patients (25.26%) succumbed to death either due to disease progression or other reasons [Figure 2].

Of 95 patients, 66 patients (69.47%) were disease free 1 year after completed treatment whereas 29 patients (30.52%) were still suffering with disease or succumbed to death due to disease [Figure 3].

Table 1: Response rate of patients after NACT with CRT

Response	Number of patients (*n*=95)	Percentage
Complete response	72	75.78
Partial response	13	13.68
Stable disease	7	7.3
Progressive disease	3	3.15

Table 2: Complications of patients post treatment

Complications	No. of patients	Percentage
Nausea and vomiting	56	58.94
Diarrhea	30	31.57
Cystitis	10	10.52
Proctitis	7	7.36
Fever and rash	15	15.78
Peripheral neuropathy	9	9.47
Renal complications	7	7.36
Hematological adverse effects which included anemia, neutropenia, and thrombocytopenia	25	26.31

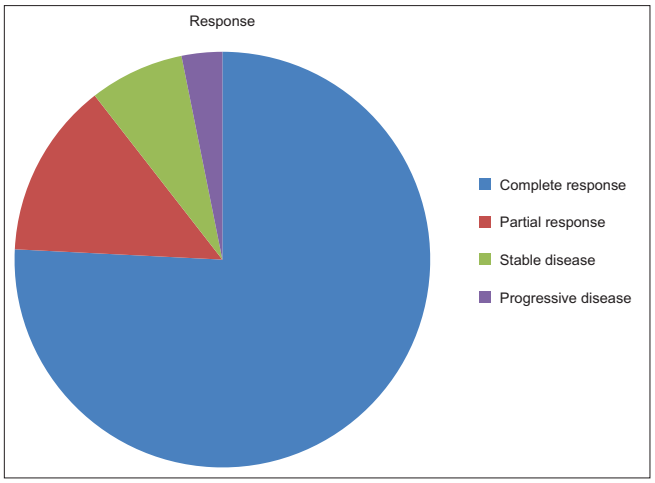

Figure 1: Response rate of patients after NACT with CRT

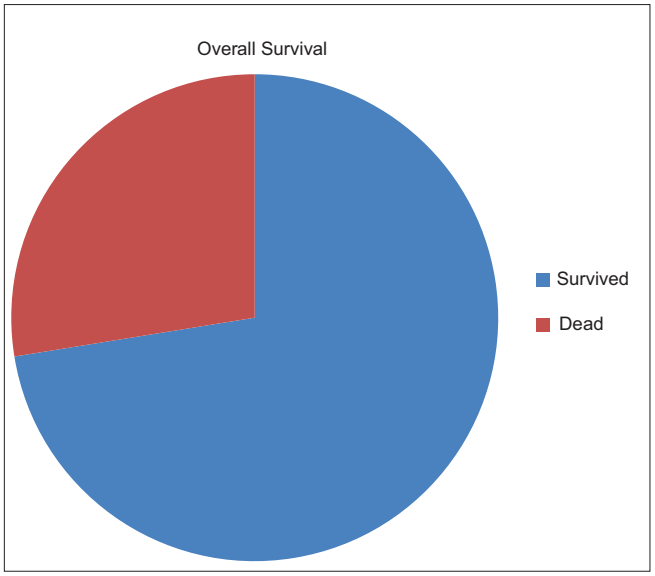

Figure 2: Overall survival of patients after treatment

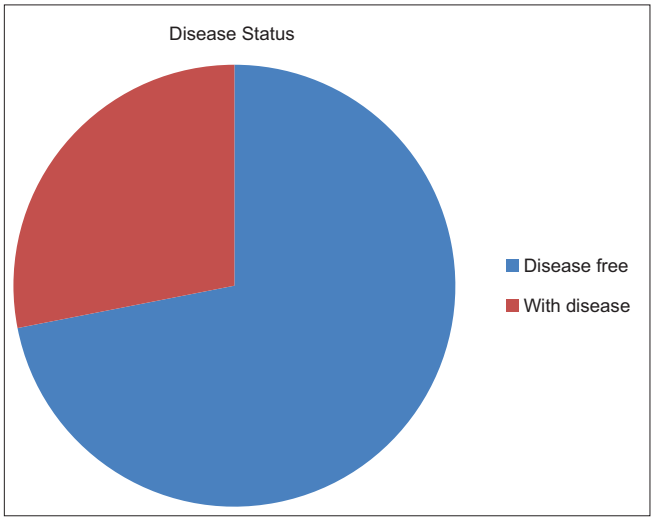

Figure 3: Disease status of patients after treatment

CONCLUSION

We conclude that the study has demonstrated a good response rate to NACT followed by CRT in patients with locally advanced carcinoma of the cervix with regard to tumor response, overall and disease-free survival.

The combination of paclitaxel with cisplatin for use in NACT showed acceptable adverse effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. National Cancer Institute: PDQ® Cervical Cancer Treatment. Bethesda, MD: National Cancer Institute. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessional. [Last modified on 2014 Dec 04].
2. American Cancer Society. "Detailed Guide: Cervical Cancer" ACS Website. Available from: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_what_is_cervical_cancer_8.asp. [Last accessed on 2009 Nov 18].
3. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, *et al*. ICO Information Centre on HPV and Cancer (HPV) Information Centre). Human Papillomavirus and Related Diseases in India. Summary Report 2014-1218.
4. Zeller JL, Lynm C, Glass RM. "Carcinoma of the cervix", JAMA patient page. JAMA 2007;298:2336.
5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al*. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://www.globocan.iarc.fr. [Last accessed on 2014 Dec 18].
6. Othman NH, Rebolj M. Challenges to cervical screening in a developing country: The case of Malaysia. Asian Pac J Cancer Prev 2009;10:747-52.
7. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: Low average levels and large inequalities. PLoS Med 2008;5:e132.
8. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, *et al.* HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385-94.
9. Sankaranarayanan R, Wesley RS. A Practice Manual on Visual Screening for Cervical Neoplasia. Vol. 41. Lyon: IARC Press; 2003. p. 1-45.
10. Eifel PJ, Berek JS, Markman MA. Cancer of the cervix, vagina, and vulva. In: DeVita VT Jr, Lawrence TS, Rosenberg SA. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2011, p. 1311-44.