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ROLE OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CHEMORADIOTHERAPY IN LOCALLY ADVANCED CARCINOMA OF CERVIX: AN INSTITUTIONAL STUDY

Dr Mahesh Rewadkar Assistant Professor, Department of Radiotherapy, Cama and Albless Hospital Mumbai-400001.

Dr S. O. Kothari* Senior Resident, Department of Radiotherapy, Cama and Albless Hospital Mumbai-400001. *Corresponding Author

ABSTRACT

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). The definition of NACT in cervical cancer is the administration of chemotherapy for the purpose of reducing the cancer volume before the main treatment.

Methodology: Retrospective study conducted in a tertiary care centre from August 2012 to August 2017 including 95 patients of locally advanced Ca Cervix.

Results: Improvement in DFS and OS with Neoadjuvant chemotherapy noted.

Discussion: 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.

KEYWORDS : Neoadjuvant, Ca Cervix, TPF

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]. In cervical cancer, cancer develops in the tissues of the cervix, which is a part of the female reproductive system. The cervix connects the upper body of the uterus to the vagina. The endocervix (the upper part which is close to the uterus) is covered by glandular cells, and the ectocervix (the lower part which is close to the vagina) is covered by squamous cells. The transformation zone refers to the place where these two regions of the cervix 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 usually squamous cell carcinoma, and around 80-90% of cervical cancer cases (more than 90% in India) are of this type[3]. Cancer that develops in the endocervix is called adenocarcinoma. In addition, a small percentage of cervical cancer cases are mixed versions of the above two, and are called adeno-squamous carcinomas or mixed carcinomas. There are also some very rare types of cervical cancer, such as small cell carcinoma, neuroendocrine carcinoma[2] etc. 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 second most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012[5]. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. The screening coverage in Asian countries is low and varies from 50 percent in Singapore to 2.6-5 percent in India[6, 7]. Sankarnarayanan R et al8screened the population in the Osmanabad district in India using, visual inspection of the cervix with acetic acid (VIA) and concluded that, in a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervicalcancer[8,9]

RATIONALE OF NEOADJUVANT CHEMOTHERAPY

The definition of NACT in cervical cancer is the administration of chemotherapy for the purpose of reducing the cancer volume before the main treatment.[12]

In 1997, Sardi et al.[13]reported the first randomized trial to investigate the role of NACT in 205 stage 1B women with cervical squamous cell carcinoma. [13]The NACT regimen with 10-day intervals included 3 cycles composed of 50 mg/m2 cisplatin, 1 mg/m^2 vincristine, and 25 mg/m^2 bleomycin. NACT enabled radical hysterectomy for inoperable bulky cervix cancer and improved the rate of complete resectability.[(13,14)] NACT reduced the pelvic recurrence rate significantly and increased the survival rate while decreasing the rate of parametrial invasion Neoadjuvant Chemotherapy - Increasing Relevance in Cancer Management 88 and lymph node metastasis. An initial tumor size of less than 4.8-cm diameter showed a better response to NACT than a larger tumor size.[14]As the size of the tumor increases, the proportion of hypoxic cancer cells with decreased chemosensitivity increases. Therefore, the potential for complete resection decreases for large tumors. [15,16]NACT increased the sensitivity of tumor cells to radiation therapy and decreased the proportion of hypoxic cells. Moreover, chemotherapy can be more effectively delivered to tumor volume before blood vessel is destructed by surgery or radiation therapy.[17]However, an undesired delay in the main treatment and resistance to radiation therapy can occur after NACT. [18, 19]

There are, however, still potential therapeutic advantages to giving chemotherapy along with local treatments that were standard for locally advanced disease, prior to the widespread use of concomitant chemoradiotherapy. The rationales for the use of neoadjuvant chemotherapy (NACT) are multiple. Tumor-size reduction may facilitate subsequent local therapy, whether radiotherapy or surgery. This reduction can transform inoperable tumors into radically resectable ones[20] . Also, NACT has been suggested to increase radiosensitivity and decrease the hypoxic cell fraction. Moreover, NACT treats the micrometastatic disease, preventing a significant proportion of relapses. Prior to surgery, the blood supply to the tumor is uncompromised, allowing improved drug delivery and distribution by NACT. Finally, response to NACT has been identified as an important prognostic factor in several studies. In addition, by giving chemotherapy prior to radiotherapy, there may be a less likelihood of increased radiotherapy toxicity, as seen with the concurrent approach [21, 22].

Several approaches have been used to enhance the therapeutic effect of radiation therapy, one of which is use of cytotoxic drugs (chemotherapy) along with radiation therapy. Randomized clinical trials show improved local control and survival with the use of concurrent chemotherapy and radiation therapy for patients with locally advanced cancers. There are least two proposed reasons why chemoradiotherapy might be successful. The first is radiosensitization.

Cisplatin (cis-diamminedichloroplatinum II), which is the prototype drug, has been acknowledged to be a potent radiosensitizer for many years[23] and is used in this study. A second proposed reason to combine radiation and chemotherapy is to realize the benefit of improved local control of radiation along with the systemic effect of chemotherapy; a concept called spatial additivity[24]. An example of both radiosensitization and spatial additivity is provided by the use of chemoradiation for locally advanced cervical cancer in which both local and systemic relapse are decreased by combined therapy[25].

When cisplatin and irradiation are used concomitantly, substantial enhancement of cancer cell killing is observed. Coughlin and Richmond[26] and Douple[27]suggested two mechanisms for radiation enhancement by platinum: (a) in hypoxic or oxygenated cells, free radicals with altered binding of platinum to DNA are formed at the time of irradiation; and (b) interaction inhibits repair of sublethal damage.

Materials and Methods

Patients with Histologically confirmed cases of carcinoma of cervix with FIGO stage IIB to IVA who were suitable for chemoradiotherapy registered in the Department of Radiation Therapy and Oncology in tertiary care institute with histopathologically proven carcinoma of cervix were included in the study. From August 2012 to August 2017.

- 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 as intravenous infusion with dose 80mg/m2 in divided doses on day1 & day 2 of the neoadjuvent chemotherapy cycle along with Inj 5FU to doses of 1000mg/m^2/day on day 1 through day 4 (TPF regimen)
- Varian Trilogy, Theratron 780E Cobalt-60 EBRT machine and Ir^{192} (Iridium-192) were used as source of External Beam Radiation Therapy (EBRT) and brachytherapy i.e. Intracavitary Radiation Therapy (ICRT), respectively. EBRT was followed by ICRT within 15 days.
- All patients were treated with conventional fractionated radiotherapy (CFR) with weekly injection Carboplatin to AUC 2 dose weekly concurrently with the EBRT of total dose 50 Gray in 25 fractions, 2Gy/Fraction/day for 5 days a week was given. ICRT to Point A where, the total dose of 21Gy was given in 3 fractions, single fraction of 7Gy a week.

All patients were treated with standard pelvic portals with 3 Dimentional Conformal Radiotherapy (3DCRT) or box field technique and all fields were treated in same sitting. ICRT with central tandem and two ovoids. During treatment all patients were evaluated for the treatment complications, especially patients with chemotherapy induced nausea and vomiting was identified. Patients were admitted to ward for treatment if not responding to OPD based treatment.

RESULTS

This was a retrospective study conducted in the Department of Radiation Therapy and Oncology in tertiary care institute. Baselines characteristics were noted and after 3 cycles of Neoadjuvent Chemotherapy followed by concurrent chemo radiotherapy response were assessed as symptomatic improvement ECOG grading and tumour response by RECIST 1.1 criteria.

TABLE 1: DISTRIBUTION OF PATIENTS ACCORDING TO AGE.

AGE GROUP [YEARS]	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
<30	03	3.15
31-40	28	29.47
41-50	17	17.89
51-60	36	37.89
>60	11	11.57

Out of 95 patients, 3 (3.15%) were less than 30 years of age, 28(29.47%) were in the age group of 31 to 40 years, 17(17.89%) were in the age group of 41 to 50 years, 36 (37.89%) were in the age group of 51 to 56 years and 11(11.57%) were greater than 60 years old.

TABLE 2: DISTRIBUTION OF PATIENTS ACCORDING TO HISTOPATHOLOGY.

CELL TYPE	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
ADENOCARCINOMA	9	9.47
ADENOSQUAMOUS	2	2.10
SQUAMOUS	89	93.68

Out of 95 patients, 89 patients (93.68%) were histologically proven cases of Squamous cell carcinoma of cervix, 9 patients (9.47%) adenocarcinoma of cervix and 2 patients (2.10%) had adenosquamous histopathology on cervical biopsy report.

Table 3: Distribution of patients according to FIGO STAGING.

FIGO STAGING	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
IIB	50	52.63
IIIA	13	13.68
IIIB	24	25.26
IVA	8	8.42

Out of 95 patients, 50 (52.63 %) patients had FIGO stage IIB, 13 (13.68%) patients had FIGO Stage IIIA carcinoma of cervix, and 24 patients (25.26%) had FIGO stage IIIB whereas 8% patients (8.42 %) had FIGO stage 1VA

Table 4: Distribution of patients according to early treatment complications.

EARLY TREATMENT COMPLICATION	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
NAUSEA VOMITING	56	58.94
DIARRHOEA	30	31.57
CYSTITIS	10	10.52
PROCTITIS	7	7.36
PERIPHERAL NEUROPATHY	9	9.47
FEVER AND RASH	15	15.78
RENAL COMPLICATIONS	7	7.36
HEMATOLOGICAL	25	26.31

Out of 95 patients , 56 patients (58.94%) developed nausea ,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 , 7 patients (7.36%) suffered renal complications.

25 patients (26.31%) had hematological adverse effects which included anaemia, neutropenia, and thrombocytopenia

Table 5: Overall Survival status at the end of 5 year after treatment.

Status at the end of 1 year	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
Survived	71	74.73
Dead	24	25.26

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

Table 6: Disease free Survival at the end of 5 year after treatment.

Status at the end of 1 year	NUMBER OF PATIENTS (N= 95)	PERCENTAGE %
Without disease	66	69.47
With disease	29	30.52

Out 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.

DISCUSSION

Cervical cancer is one of the most common gynecological malignancies in India. It is more common in rural population and lower socioeconomic group.

Conventional fractionation delivers 180 to 200 cGy per fraction five days a week. This fractionation scheme was developed because it offers highest probability of tumor control with tolerable acute reactions and acceptable delayed effects. In an attempt to improve the therapeutic ratio, the concept of Neoadjuvent Chemotherapy has evolved.

NACT represents a promising alternative to surgery or radiotherapy as initial treatment of locally advanced cervical cancer. The impact on survival of this relatively new approach is still a matter of discussion, and different treatment strategies may be considered. Some authors have observed that NACT followed by radiation has yielded neither higher response rates nor longer survival28 possibly due to the development of selective resistance to radiation after chemotherapy. Some authors have reported that NACT followed by surgery may improve survival in locally advanced cervical cancer as compared to radical surgery[29] According to some authors, only patients in complete or optimal partial response (minimal foci of microscopic tumor in the removed uterus) can benefit significantly in terms of disease-free survival.

Some studies have shown that the response to NACT may serve as an important prognostic factor, guiding the direction of subsequent therapy[30].Whether the response to NACT simply identifies a subset of patients who are destined to far better than non-responders has been questioned. However, as a group, those receiving NACT have in some studies demonstrated improved progression-free and overall survival.

In the study conducted by **M McCormack et al**. Complete or partial response rate was 85% (95% CI: 71–94) post-CRT. The median follow-up was 39.1 months.

Overall and progression-free survivals at 3 years were 67% and 68%, respectively.

Singh R B et al. evaluated role of dose dense Paclitaxel and cisplatin based neo-adjuvant chemotherapy (NACT) prior to standard concurrent chemo-radiation and found that 23patients out of 24 (95.83%) achieved Complete Response (CCRT) in locally advanced cervical cancer. **L. Souhami et al. (1991)** noted a response rate of 72 % (47% complete and 25% partial response) in the patients who received Neoadjuvent Chemotherapy (BOMP) followed by Radiotherapy .Overall five year survival rate was 23% and toxicity was more than patients group who received radiotherapy alone . **Park et al (2009)** noted a response rate of 91% (39.5% showed a complete response, 51.2% had a partial response to cisplatin-Paclitaxel, making the overall response rate 90.7% They assessed the response clinically and radiological 10 days post treatment in women with FIGO Ib2-IIb treated with 3 cycles of 10-day cisplatin and Paclitaxel prior to surgery. **Tabata et al. 2003** noted a 72% response following Neoadjuvent chemotherapy (BOMP) and Radiotherapy .5 year survival rate was found 43% Similarly, **Mori et al (2008)** reported a response rate of 87% in 30 patients with FIGO stage Ib2-IVa treated with 6 weeks of Carboplatin and Paclitaxel prior to surgery. **Duen as-Gonzalez et al (2003)** reported response rates of 95% in 43 patients with FIGO Ib2- IIIb disease treated with 3 cycles of 3-weekly Carboplatin and Paclitaxel chemotherapy prior to radical hysterectomy and CRT. In that study, response was assessed clinically and the planned dose of chemotherapy by washigher.

The observed Tumour response rate in this study after NACT one month after completed treatment i.e. NACT followed by concurrent chemo radiotherapy was 89.46% (75.78 % Complete response 13.68 % partial response), overall and disease free survival were 74.73% and 69.47% respectively In the present study, 58.94% patients developed Nausea and Vomiting, 31.57% patients had diarrhea, 10.52% patients had cystitis, 7.36% patients had proctitis, 9.47% patients developed peripheral neuropathy, and 15.78% patients suffered fever and rash. Renal complications occurred in 7.36% patients. Hematological side effects including anemia neutropenia and thrombocytopenia were noted in 26.31% patients. In the study conducted by **M McCormack et al.** Grade3/ 4toxicities were20% during NACT (11%haematological, 9%non- haematological) and 52% during CRT (hematological: 41%, non-hematological: 22%).

CONCLUSION

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, Cisplatin and 5FU for use in neoadjuvant chemotherapy showed acceptable adverse effects.