ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 07 | July - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TOLERANCE AND FEASIBILITY OF PROPHYLACTIC PARAAORTIC NODE IRRADIATION IN CARCINOMA CERVIX PATIENTS

Radiotherapy

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KEYWORDS

INTRODUCTION:

The role of prophylactic paraaortic node irradiation in carcinoma cervix patients in FIGO stage III C1 has gained importance in the recent past. After the role of concurrent chemoradiation in carcinoma cervix came into existence, the role of extended field irradiation lost its importance due to the toxicities involved in treating such a large field. Cervical cancer is the second commonest malignancy diagnosed among Indian women(1). Radical pelvic chemo-radiation followed by brachytherapy has produced 5 year overall survival rates, nodal and systemic control rates of 89, 87% and 77% respectively(2). Most of the patients had distant relapses or relapse at paraaortic region after chemoirradiation and involvement of pelvic lymph nodes at diagnosis was the strongest predictor of para aortic lymph node recurrences(3,4). With the evolution of newer techniques like rapidarc/ VMAT, the use of prophylactic paraaortic irradiation again came into existence(5,6). The purpose of this study is to look into the acute and late toxicities of patients receiving prophylactic paraaortic irradiation with pelvic RT in carcinoma cervix patients.

MATERIAL AND METHODS

This is a comparative prospective observational study conducted on patients of cervical cancer treated between August 2021- March 2022 in the department of radiotherapy and oncology, NRI medical college, Mangalagiri, Andhra Pradesh, India. Eligibility criteria into the study were biopsy confirmed FIGO (International federation of gynecology and obstetrics) (2018) stage IB2 – IVA cases of cervical cancer planned for definitive chemoirradiation, Karnofsky performance scale >70 [34], normal creatinine clearance (>80 ml/min). Uncontrolled medical co-morbidities, previous history of chemoradiation to the pelvis and postoperative status were exclusion criteria. Informed consent was taken from all patients. Institutional ethics committee approval was obtained for this study. Pretreatment workup included a pelvic examination followed by complete staging workup with complete haemogram, liver function tests, kidney function tests, chest X-ray, ECG, MRI abdomen and pelvis or CECT abdomen & Pelvis.

All patients of carcinoma cervix IIIC1 i.e., positive pelvic lymph nodes, positive common iliac lymphnodes and negative para aortic nodes received Extended field Radiotherapy(EFRT), EBRT dose of 45 Gy in 25 fractions over 5 weeks, at 1.8 Gy per fraction to pelvic and para-aortic regions, with a simultaneous integrated boost of 55 Gy-57.5 Gy in 25 fractions over 5 weeks at 2.25 – 2.30 Gy per fraction to the involved pelvic nodes. Rest of the diagnosed cases of carcinoma cervix from IB2 – IVA, planned for concurrent chemoirradiation received pelvic RT(PRT) OF 45 gy/ 25#. Concurrent chemotherapy was given to all patients with weekly injection Cisplatin at 40 mg/ m2. All patients were scheduled to receive IMRT and intracavitary brachytherapy (ICBT). IMRT was delivered with Rapidarc. The gross tumor volume (GTV) covered pelvic LNs. For patients other than IIIC1 treatment volume includes Pelvic RT(PRT), the clinical target volume (CTV) had an upper border at the level of aortic bifurcation and included the primary tumor, cervix, uterus, parametrium, upper part of the vagina and the pelvic lymph node region Intracavitary brachytherapy was given after completion of external radiotherapy to a dose of 7 Gy HDR (High-dose-rate) prescribed to highrisk CTV in four fractions 3- 4 days apart. The dose of HR CTV D90 should be 85Gy+/-10%.

Pelvic treatment volume delineation was in accordance with published guidelines(7,8). For delineation of the prophylactic para aortic nodal basin, great vessels were delineated as surrogates, and the space between the psoas muscles was included in accordance with guidelines given by Beriwal et al.(9). Bladder, rectum, sigmoid, femurs, kidneys and spinal cord were delineated as organs at risk (OAR)according to RTOG (Radiotherapy oncology group) guidelines, and all the potential space for bowel loops in the abdomen was delineated as bowel bag(10).

Thirty-four cases of newly diagnosed cervical cancer (IB2 – IIIC1) with multiple pelvic lymph node metastases confirmed by CT/MRI were collected from August 2021 to March 2022. The primary endpoint was toxicity evaluation and the secondary endpoints include DFS. IBM SPSS statistics software v26 was utilized for the statistical analyses. The short-term efficacy, recurrence rate, and adverse reactions were analyzed by Fisher's exact probability test. Data were presented as the percentage of total samples that were assigned in each group.

Table 1 Patient Characteristics

GROUP	Extended field group (n = 17)	Pelvic-field group (n=17)
Median age	46	53
Median KPS score	80	80
Tumor size		
<4 cm	2(11.76%)	3(17.65%)
>4 cm	15(88.24%)	14(82.35%)
Pathology		
Squamous cell carcinoma	16(94.12%)	16(94.12%)
Non squamous cell carcinoma	1(5.88%)	1(5.88%)
Clinical stage		
IB	1(5.88%)	0(0.00%)
IIA	1(5.88%)	1(5.88%)
IIB	8(47.06%)	10(58.82%)
IIIA	0(0.00%)	1(5.88%)
IIIB	6(35.29%)	5(29.41%)
IVA	1(5.88%)	0(0.00%)

RESULTS

After completion of the treatment, the patients were evaluated every 3 months for the first 2 years, and every 6 months thereafter. Acute toxicity associated with radiotherapy was assessed in accordance with the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAEv4)11 and was defined as toxicity occurring between the initiation of treatment and 90 days after completion. Acute toxicity was

assessed weekly during the course of radiotherapy, at the completion of RT and after 1 month; late effects were evaluated at each clinical visit. Adverse events for >90 days after the completion of treatment were graded in accordance with the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring system.

Weekly toxicity evaluation was done and the highest reported toxicity grade from the date of EBRT initiation to 6 weeks after treatment completion was recorded as worst acute toxicity. Rapidarc was well tolerated in all the patients with predominant occurrence of Grade 1 and 2 toxicities. Most of the patients had grade 2 enteritis as the predominant toxicity. Two patients in EFRT arm developed grade 3 diarrhoea. Both the patients were on anti retro viral therapy.. The occurrence of vomiting as a toxicity increased with increase in the volume of bowel bag receiving 45 Gy. Median volume of bowel bag receiving 45 gy in PRT is 0.32 cm^3(0.25 cm^3 – 0.42 cm^3) where as in EFRT the median V45 is 0.48 cm3(0.39 cm^3 – 0.56 cm^3). No increased acute toxicities were noted because of presence of SIB volumes. The median volume of PTV in the patient cohort was 2896 cc (range 2436–2987 cc) in the EFRT group. There were 10 patients (58.82%) with III-IV degree myelosuppression in the extended-field group and 3 patients (17.65%) in the pelvic-field group, and the difference was statistically significant (P=0.0324). However, there were no significant differences between the 2 groups in the occurrence of radiation enteritis and radiation cystitis.

Table 2: Patients developing grade 1 + 2 toxicities and grade 3 + 4 toxicities

Group	Myelosuppression		Radiation enteritis		Radiation cystitis	
	I + II	III + IV	I + II	III + IV	I + II	III + IV
Extended-field group (n=17)	7(41.18%)	10(58.28%)	16(94.11%)	3(17.64%)	17(100%)	0(0.00%)
Pelvic-field group (n=17)	14(82.35%)	3(17.65%)	13(76.47%)	1(5.88%)	17(100%)	0(0.00%)
P value (Fisher)	0.0324		0.4848		1	

Delayed toxicity and clinical response

The median follow up period was 16 months (range 6–24 months). Delayed toxicity predominantly manifested as grade1 pain abdomen which was seen in 52% (9/17) of the patients in EFRT group and 35%(6/17) in the PRT group and there was isolated delayed grade1 cystitis in the patient cohort 17 %(3/17) in both the groups. There was no > grade 2 delayed toxicity of any category in any group. At first follow up 3 patients had residual disease, 3 in the EFRT group and none in PRT group. Follow up MRI abdomen and pelvis at 6 months revealed persistent local disease in 3 patients and with bulky nodes has persistent pelvic nodal disease. Isolated PA nodal recurrences were not observed in any patient. No patient had local failure as their only site of recurrence.

DISCUSSION

In the past Extended field irradiation delivered using conventional 4 field technique resulted in grade 3 bowel toxicities in the range of 2–25% and grade 3 and above hematologic toxicities in the range of 20–80%(11–15). In the era of concurrent chemoirradiation and rapid arc, despite using a large field and no bone marrow constraints grade 3 toxicities were observed only in 58.82% of patients. Despite the use of a SIB to boost the involved pelvic lymph nodes, there wasn't any increase in acute toxicities attributable to the volume of high dose regions surrounding the SIB. This finding is consistent with those in the study by Gerstzen et al and Vargo et al where they used a similar dose to boost involved pelvic lymph nodes. They reported that SIB was well tolerated and did not report any increased toxicity due to SIB(16,17). Lee et al reviewed 206 cases of FIGO IB2-IVA cervical cancer patients (negative paraaortic lymph nodes) who received extended-field or pelvic-field IMRT. Among them, 20 patients (18.2%) in the pelvic-field group and 12 patients (12.5%) in extended-field group did not receive synchronous chemotherapy, and the remaining patients did receive synchronous chemotherapy. The 5-year survival rates of recurrence-free survival and OS in the pelvic-field and extended-field groups were 97.9% vs 87.6% (P=0.03) and 87.8% vs 74.5% (P=0.04), respectively. The results showed that prophylactic paraaortic radiotherapy improved the outcome of locally advanced cervical cancer(18). A study conducted by Wakatsuki M et al was a prospective single-arm multi-institutional trial in which 95 cases were locally advanced cervical cancer with pelvic lymph node metastasis and without paraaortic metastasis in East and Southeast Asian countries. The 2-year local control, progression-free survival, and OS rates for all patients were 96%, 78%, and 90%, respectively. Acute grade 3 leukopenia was observed in 20 patients (21%), and late grade 3 gastrointestinal toxicity was observed in 3%. The results showed that the delayed prophylactic paraaortic radiotherapy decreased the rate of distant metastases and improved PFS and OS rates, without increasing toxicity.(19)

The present study revealed that prophylactic paraaortic irradiation using rapid arc combined with chemotherapy to treat PALN metastasis can be used with more tolerable toxicities when compared with conventional pelvic radiation and chemotherapy. The main shortcoming of our study was the sample size. A larger sample size and longer median follow up would probably be better.

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