ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 8, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

# OUTCOME AND TOXICITY OF EXTENDED-FIELD INTENSITY MODULATED RADIOTHERAPY (EF-IMRT) IN LOCALLY ADVANCED CARCINOMA OF CERVIX – EXPERIENCE FROM TERTIARY CANCER CENTER

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*Received: 21 May 2024, Revised and Accepted: 05 July 2024*

**ABSTRACT**

**Objectives:** Whether to irradicate the para-aortic node prophylactically or not in locally advanced cervical carcinoma in the absence of para-aortic lymphadenopathy, the recommendation varies across guidelines. Extended field radiotherapy may improve overall survival (OS) by better local control of the para-aortic nodal region compared to pelvic RT alone, especially in patients unable to tolerate concurrent pelvic chemoradiotherapy.

**Methods:** This was a single institutional retrospective study carried out in the department of radiotherapy at NRSMCH, Kolkata. A total of 30 HPE-proven locally advanced cervical cancer patients treated with extended field intensity-modulated radiotherapy (IMRT) were selected for this retrospective study.

**Results:** Response assessment was done 12–16 weeks after completion of treatment and 26 patients (86%) had complete locoregional responses and four patients had the local disease (14%). The 2-year OS was 86%. The common toxicity was Grade I small bowel toxicity (diarrhea), skin reactions, and Grade I neutropenia, seen in 78%, 63%, and 58% of patients, respectively. Another acute toxicity was Grade I anemia seen in 35% of patients. The common late toxicity was Grade I lower GI (11%).

**Conclusions:** Extended Field-IMRT is a convenient, feasible, and effective treatment modality for target coverage and para-aortic nodal control with minimal toxicity.

**Keywords:** Locally advanced, Cervical cancer, Extended field radiotherapy.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i8.51519. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

## INTRODUCTION

Worldwide cervical carcinoma constitutes 3.1% (604127) of all new cancer cases and 3.4% (341831) of all cancer deaths.[1] In countries with low/medium human development index (HDI), the incidence and mortality age-standardized rate of carcinoma cervix are 18.8 and 12.4 per lakh population. The corresponding values in countries with very high/high HDI are 11.3 and 5.2, respectively [1]. In India, the majority of cervical cancer cases are diagnosed in locally advanced stages, and 5 years of disease-free survival (DFS) for Stage II, and III disease were 62% and 45%, respectively [2,3]. In locally advanced carcinoma cervix, concurrent chemoradiation is the standard of care [2,4,5]. In a study by Ramirez *et el*., even in patients with positive pelvic node and negative para-aortic lymphadenopathy in PET CT scan, up to 20–25% of patients had a micrometastatic disease in para-aortic node on Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer [6]. When these patients are treated with whole pelvic chemoradiotherapy (CRT) alone, up to 25% may get under treatment [6]. Whether to irradicate the para-aortic node prophylactically or not in locally advanced cervical carcinoma in the absence of para-aortic lymphadenopathy, the recommendation varies across guidelines. A Phase III trial (RTOG-90-01) compared pelvic concurrent chemoradiation (CRT) Vs prophylactic para-aortic radiotherapy extended field radiotherapy (EFRT) in locally advanced carcinoma cervix. Patients with Stage IB to IIB showed a statistically significant difference in DFS and overall survival (OS) in pelvic CRT arms compared to EFRT alone ($p<0.0001$). Patients with Stage III to IVA had better DFS ($p=0.05$) and a trend toward better OS ($p=0.07$) in the pelvic concurrent chemoradiotherapy arm [7]. However, NCCN guideline (version 1.2023) recommended that in patients with documented common iliac and para-aortic nodes, the volume of radiotherapy would be extended field pelvic and para-aortic field up to the level of renal vessels [5]. EFRT may improve OS by better local control of the para-aortic nodal region compared to pelvic RT alone, especially in patients unable to tolerate concurrent pelvic chemoradiotherapy [8]. External beam radiotherapy can be delivered by 3D-CRT or intensity-modulated radiotherapy (IMRT), and IMRT is more useful in situations such as para-aortic radiation and `-operative settings (post-hysterectomy adjuvant setting). The advantages of IMRT are good sparing of the small bowel, bone marrow, bladder, rectum, and femoral heads and potentially reducing both acute and late toxicity [8,9].

### Aims and objectives

The aim of the study was to present our experience with extended field pelvic and para-aortic IMRT in the treatment of locally advanced cervical carcinoma with common iliac lymphadenopathy, focusing on dosimetric parameters, toxicities, and treatment outcomes.

## METHODS

### Study design

This was a single institutional retrospective study carried out in the department of radiotherapy at NRS Medical College and Hospital, Kolkata. The inclusion criteria were (1) HPE-confirmed locally advanced cervical carcinoma with documented common iliac lymphadenopathy, (2) patients treated with EFRT, (3) of age >18 years; The exclusion criteria were (1) patients without HPE reports, and (2) patients with metastatic disease.

**Data collection**

From January 2019 to December 2020, according to inclusion and exclusions criteria, as mentioned earlier, a total of 30 HPE-proven locally advanced cancer patients treated with extended field IMRT were selected for this retrospective study. We focus mainly on data about demographic details, histology, clinical stage, treatment received, dosimetric details, treatment-related toxicities, and treatment outcomes. The confidentiality and anonymity of study subjects were assured.

*Planning CT scan*

All patients are immobilized in the supine position, hand above the head, on the all-in-one board. The patients ask to void urine and then drink 500 ml water and half an after that, planning a non-contrast and contrast-enhanced CT scan (CECT) with 3 mm slice thickness done in a CT simulator in our department. Target volume and organ at risk (OAR) delineation: Gross tumor volume is defined as all clinically and radiologically (CT scan, MRI, and PET-CT) visible tumors. The investigations used to detect pelvic and para-aortic nodal status were mainly CT scans, MRI, and/or PET-CT scans. Laparoscopic evaluation of the para-aortic node was not done in any of the patients due to logistic issues. Clinical target volume (CTV) was contoured on each axial CT slice and includes both pelvic, para-aortic nodal, and primary CTV. The nodal CTV (CTV3) isotropically expanded by 7 mm margins to create nodal planning target volume (PTV3) and a 1 cm margin was added to primary tumor CTV (CTV1; CTV2) to create PTV1 and PTV2. All three PTVs (PTV1, PTV2, and PTV3) were merged to create the final PTV. All the contouring was done according to the prevailing contouring guidelines [5,10]. The OAR: bi-lateral kidney, bladder, rectum, bowel bag, and bi-lateral femoral head were contoured as organs at risk.

*Radiotherapy treatment planning and treatment execution*

Five to nine field IMRT inverse plan generated and optimized using AAA algorithm and depicted in Figs. 1 and 2. After contouring and treatment planning, the treatment plan and digitally reconstructed radiograph (DRR) of the planned CT scan were transferred to the treatment console. During the treatment delivery, the patient's position, immobilization, and bladder protocol are repeated as previously described during the planning CT scan and portal images (PI) acquired before radiotherapy treatment delivery. Auto-matched, and manual image registration and fusion of bony landmarks in orthogonal PI with DRR of planning CT scan were done to evaluate the translational setup and fine-tuned manually if needed for the best possible matching by position bony landmarks for example vertebral body, bony pelvis, and sacrum. In the case of the CB-CT scan, we can see the bladder and rectal feeling and compare it to the planned CT scan. If translational set errors were ≥0.05 mm in any direction, then set-up error correction was made before treatment. Three-session intracavitary application (brachytherapy) was done with a dose of 7 Gy per session up to a total dose of 21 Gy.

*Toxicity assessment and follow-up*

All the patients were evaluated weekly during radiotherapy, every 3 months during the first 2 years, and 6 months thereafter. During the follow-up visit, a physical examination, CECT scan, and/or MRI of the abdomen and pelvis were performed as indicated to assess disease control. All toxicities (both acute and late) were assessed every week during radiotherapy and subsequent follow-up and recorded according to CTCAE Vs 4.03. Late toxicity is defined as toxicity that occurs 3 months after completion of radiotherapy. Statistical analysis: All the data collected were recorded on an Excel sheet and data were analyzed on SPSSVs22.

## RESULTS

Between January 2019 and December 2020, a total of 30 patients were radically treated with extended field IMRT. The most common histology was squamous cell carcinoma all the demographic and dosimetric details are shown in Tables 1 and 2, respectively. The radiotherapy treatment time ranged from 37 to 45 days, averaging 42 days. Eleven patients aged >65 years of age did not receive concurrent cisplatin. A total of 3–6 cycles of weekly cisplatin 40 mg/m$^2$ with a median of four cycles were given concurrently. Patients who developed Grade III toxicities during the course of radiotherapy (GI toxicity, skin reaction, neutropenia, deranged KFT, and patients' refusal) did not receive further concurrent cisplatin and thereafter received only radiotherapy.

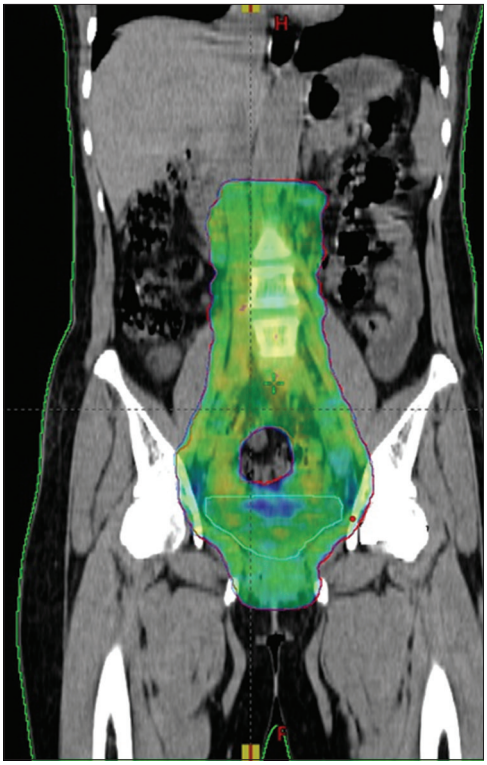

**Fig. 1: Pelvic and para-aortic Radiation, (dose in color wash)**

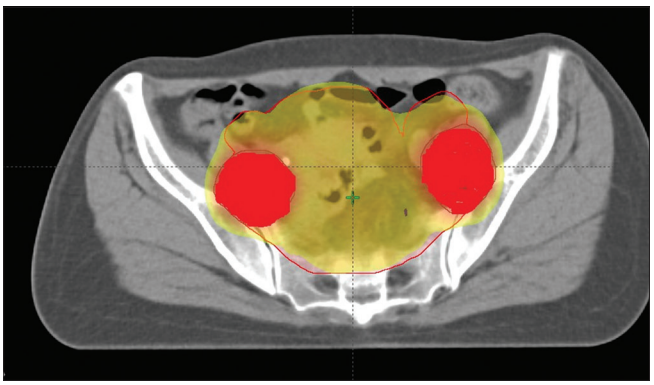

**Fig. 2: Nodal volume (red color) receiving 55 Gy The rest of the volume is 50 Gy (yellow color; dose in color wash)**

**Treatment outcome**

Response assessment was done 12–16 weeks after completion of treatment 26 patients (86%) had complete locoregional responses and four patients had local disease (14%). Pelvic exenteration of the residual or progressive disease could not be possible in anyone due to logistic issues and metronomic chemotherapy was given. The 2 years OS was 86%.

**Treatment-related adverse events**

The common toxicity was Grade I small bowel toxicity (diarrhea), skin reactions, and Grade I neutropenia, seen in 78%, 63%, and 58% of

patients, respectively. Another acute toxicity was Grade I anemia seen in 35% of patients. The common late toxicity was Grade I lower GI (11%). Chronic nephrotoxicity was not seen in our patients as all patients had a kidney function test within normal limits. All the toxicities are shown in Table 3.

## DISCUSSION

In this retrospective study, we have reported outcomes of prophylactic EFRT in patients with locally advanced pelvic node-positive carcinoma of the cervix. In our study, 90% of patients were in a locally advanced stage of squamous cell histology and 10 % of patients had adenocarcinoma.

In patients with a high risk of harboring occult micrometastatic disease in the para-aortic nodal region, as the standard whole pelvic radiotherapy field would not cover the para-aortic region, whole pelvic radiotherapy alone may be inadequate treatment in these patients. After treatment with the whole pelvic radiotherapy field, the common site of treatment failure is the para-aortic nodal region. Therefore, at least theoretically, EFRT to include the para-aortic lymph node region may improve outcomes compared to the use of the whole pelvic radiotherapy field. The median follow-up of our study was 24 months, and the median OS was 86%. One prospective study reported 3 years of OS and PFS of 83.6 and 73.4%, respectively with EF-IMRT [11]. Other studies reported also reported similar 5 years in OS and PFS [12].

**Table 1: Patient's demographic profile (n=30)**

| Variables | Percentage (%) |
|---|---|
| Median age (years) | 56.5 |
| FIGO stage | |
| IIIC1 | 30 |
| ECOG | |
| 0 | 17 |
| 1 | 12 |
| 2 | 1 |
| Histology | |
| SCC | 27 |
| Adenocarcinoma | 3 |

**Table 2: Dosimetry values (n-30)**

| Target/OAR | Mean Dose (D mean) |
|---|---|
| PTV_50 | 49.68 Gy |
| PTV_55 | 54.02 Gy |
| Bladder | |
| Dmax (Gy) | 52.94 |
| V45 (%) | 27.09 |
| Rectum | |
| Dmax (Gy) | 53.05 |
| V45 | 38.89 |
| Kidney_ RT | 12.19 |
| Kidney_ LT | 12.07 |
| Femoral Head_RT (Dmax, Gy) | 49.71 |
| Femoral Head_ LT (Dmax, Gy) | 48.81 |
| Small bowel (V45 in CC) | 296.31 |

**Table 3: Toxicities – acute and late (n=30)**

| SITE | GRADE | at 14 days | at 28 days | at 35 days |
|---|---|---|---|---|
| Skin | I | 27 | 16 | 14 |
| | II | 3 | 14 | 12 |
| | III | 0 | 0 | 4 |
| Small bowel (Diarrhea | I | 28 | 23 | 20 |
| | II | 2 | 7 | 8 |
| | III | 0 | 0 | 2 |
| Anemia | I | 13 | 12 | 7 |
| | II | 7 | 7 | 12 |
| | III | 0 | 1 | 1 |
| Neutropenia | I | 0 | 28 | 25 |
| | II | 0 | 1 | 4 |
| | III | 0 | 1 | 1 |

In our study, the common toxicity was Grade I small bowel toxicity (diarrhea), skin reactions, and Grade I neutropenia, seen in 78%, 63%, and 58% of patients, respectively. Only 26% of patients need to be hospitalized and the rest of the patients were treated conservatively. All the complications resolved with time in most of the patients and Grade 1 late lower GI toxicity in 6% of patients persisted up to 7 months. Vargo *et al* reported no late upper GI, hematologic, genitourinary toxicity (GU) toxicity; only 4% had Grade 4 lower GI toxicity [11]. In another study by Liang *et al*., acute Grade 3 or more hematological, GU, and GI toxicity were 58%, 3%, and 6%, respectively [12] The small bowel volume receiving radiotherapy dose >35 Gy was the significant predictor of acute toxicity during radiotherapy [13]. Another study by Chopra *et al*. reported that the predicted late Grade ≥3 bowel toxicity is the volume of the small bowel and large bowel receiving 15 Gy and should be 275 cc and 250 cc, respectively to reduce Grade ≥3 late toxicity <5% [14]. In our study, radiotherapy planning CT scan and execution of radiotherapy done in a full bladder in all patients, this factor may be one reason for low gastrointestinal toxicity in our patients. In a post-operative setting where the gut may be stuck in the pelvis and due to post-operative fibrosis gut may be less mobile so there is a chance of more GI toxicity in the case of post-operative adjuvant radiotherapy. As none of the patients underwent any surgical intervention before radiotherapy, this may also be a factor for less gastrointestinal toxicity [15,16].

The relative position of the bilateral kidney concerning the retroperitoneal nodal PTV is an important deterministic factor for how much volume of the kidney gets irradiated. Another factor is beam orientation, that is, co-planner versus non-co-planner beam orientations. The non-co-planner beams that avoid the incident beam directly over the kidney reduce low exposure to the same [17] and would be useful in patients with co-existing kidney dysfunction and very long life expectancy. In our study, the Dmean of the bilateral kidney was 12 Gy and none of the patients developed post-radiotherapy kidney dysfunction. During the execution of a non-co-planner IMRT plan, more setup accuracy experienced technologists, and more time are needed. Thus, unlike non-co-planner extended field-IMRT, the co-planner EF-MRT plan will be easily executed, decrease the workload and patient waiting time in the radiotherapy department, that is, co-planner EF-MRT IMRT plan is more convenient than non-co-planner EF Intensity-IMRT) [15].

### Limitations

We acknowledge that our study also has some limitations which are single-arm, retrospective design, and small sample size.

## CONCLUSIONS

EF-IMRT delivered tumoricidal dose to the target volume while sparing surrounding normal tissue, thus has a distinct dosimetric advantage over 3D-CRT. EF-IMRT is a convenient, feasible, and effective treatment modality in terms of target coverage and para-aortic nodal control with minimal toxicities.

## ACKNOWLEDGMENT

We likewise acknowledge the contributions of the Government West Bengal for supplying all treatment including planning CT scans free of cost and for their work by all medical physicists of our radiotherapy department.

## AUTHORS' CONTRIBUTIONS

AB, AM-Conceptualization, methodology, data collection, data interpretation, statistical analysis, and reviewing of the final manuscript; DB, DM, SA-Conceptualization, methodology, data interpretation, statistical analysis, and reviewing the final manuscript.

**CONFLICTS OF INTEREST**

Nil.

**SOURCE OF SUPPORT**

Nil.

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