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Comparison between 3 Dimentional Conformal Radiotherapy, Sequential Intensity Modulated Radiotherapy and Simultaneous Integrated Boost Intensity Modulated Radiotherapy as a Boost for Pelvic Lymph Nodes for Patients with Cancer Cervix

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Authors' contributions

This work was carried out in collaboration between all authors. Author MM designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SAF, AA and SA managed the analyses of the study. Authors RAE and AO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The study aims to Compare 3 Dimentional Conformal Radiotherapy (3DCRT), sequential Intensity Modulated Radiotherapy (sIMRT), Simultaneous Integrated Boost-Intensity Modulated Radiotherapy (SIB-IMRT) for positive pelvic lymph nodes for patients with cancer cervix treated with concurrent chemo-radiotherapy.

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Materials and Methods: C-T simulation was done for 10 patients with cervix cancer who had pelvic nodes, the clinical target volume (CTV) included the upper vagina, parametria, uterus, cervix, presacral area, and draining lymph nodes. One cm was added to form the Planning Target Volume (PTV). The organ at risk (OAR) included the bladder, rectum, pelvic bones marrow (PBM). Nodal CTV was expanded 7 mm to form nodal PTV. 3DCRT, sIMRT and SIB-IMRT planes were done. Doses of 3DCRT and sIMRT plans were 50 Gy to pelvic PTV with a nodal boost of 16 Gy in a total of 33 fractions while SIB plan treating the targets to the same doses in 25 fractions (i.e., 2 Gy per fraction to the pelvic PTV and 2.4 Gy per fraction to the boost PTV).
Results: Comparable target volume coverage (V95%) was achieved with the 3 plans, maximum dose was significantly reduced using conformal plan for the boost plans with p= 0.01. Median dose for V45 of the rectum was the lowest with sIMRT (p= 0.015), the median dose for V50 of the bladder was the lowest in sIMRT plan (p= 0.007), the V10 of the bone marrow was low in the sIMRT plan (p= 0.015).
Conclusion: The sIMRT boost for pelvic lymph nodes produce the same coverage as 3DCRT and SIB-IMRT and spares significantly the OAR.

Keywords: SIB-IMRT; sIMRT; 3DCRT.

1. INTRODUCTION

Cervical cancer is responsible for about 2% of the cancer deaths in women in the United States, with less than 13,000 new cases of invasive disease and 3000 to 4000 deaths each year [1]. Invasive cervical cancer is the third most common malignant tumour in women (after breast and colorectal cancers) worldwide, and accounts for about 500,000 cases and 275,000 deaths per year [2].

For locally advanced disease, chemotherapy and radiotherapy have been the standard of care since the 1999 publication of a National Cancer Institute (NCI) alert based on the results of five Phase III randomised clinical trials [3-7].

Several acute and late genitourinary, gastrointestinal, and haematological toxicity may occur as a result of radiation including cystitis, enteritis, anaemia due to bone marrow suppression as an acute complications in addition to late complications of radiotherapy as intestinal obstruction, bladder fistula and contracture [8].

IMRT was associated with significantly less acute and chronic gastrointestinal toxicity [9].

In cancer cervix, there are many factors related to pelvic lymph node involvement including depth of stromal invasion and presence of lymphovascular space invasion with direct proportion relation between them [10].

Patients with lymph node involvement often receive additional external beam boost doses to the nodal volumes [11].

The use of sequential boost IMRT for treatment of extended fields (EF) for cancer cervix with para-aortic lymph nodes was studied at University of Pittsburgh Cancer Institute, the study confirmed that when the duodenal dose was kept within the prescribed limits, V55 below 15cm^3, patients who received EF-IMRT had very low rates of side effects and excellent regional control [12].

In another study, Sixty-one patients with cervical cancer (stage IBI-IVA) diagnosed from 2003 to 2012 with PET-avid pelvic nodes treated with extended field IMRT (45 Gy in 25 fractions with concomitant boost to involved nodes to a median of 55 Gy in 25 fractions) with concurrent cisplatin and brachytherapy were retrospectively analysed. Extended field IMRT was well tolerated and resulted in low regional recurrence in node-positive cervical cancer. The dose of 55 Gy in 25 fractions was effective in eradicating the disease in involved nodes, with acceptable late adverse events [13].

The study aims to compare between three different techniques of radiotherapy which are 3DCRT, Sequential IMRT (sIMRT), simultaneous integrated boost IMRT (SIB-IMRT) regarding target coverage for the pelvic nodal boost as well as dose to the organs at risk.

2. MATERIALS AND METHODS

A dosimetric study including ten patients with cervix cancer who had pelvic lymph nodes where CT simulation was done for them, where the intravenous contrast with full bladder and empty rectum were used for all patients, using GE-CT simulator with a slice thickness of 2.5 mm.

The clinical target volume (CTV) included the upper one-half of the vagina, both parametria, all uterus, uterine cervix, presacral area, and draining lymph nodes (lower common, internal, and external iliac lymph nodes).

The Planning Target Volume (PTV) was formed by adding a margin of 1 cm was added around the CTV. The organ at risk (OAR) included the bladder, rectum, pelvic bones marrow (PBM) including the lumbosacral BM (LSBM), iliac BM (IBM), and pubis.

In this study, boost volumes consisting of the positive regional lymph nodes, was done by the expansion of the nodal CTV by a 7 mm margin to form nodal PTV.

For each case three treatment planes were done, first with 3-dimensional conformal planning (3DCRT), second with sequential IMRT (sIMRT) and the third with simultaneous integrated boost (SIB-IMRT) with a comparison between the plans regarding PTV coverage and dose to organs at risk.

MONACO (5.1.10) was used to generate all treatment plans. Inverse-planned IMRT calculations were done with photon beams of 6 MV.

All patients received a dose of 50Gy in 25 fractions of 2Gy to the pelvic PTV. Boost doses were 16Gy. Such that the 3DCRT and sIMRT plans were generated to treat the pelvic PTV to 50Gy with a nodal boost to 16 Gy in a total of 33 fractions was compared to an SIB plan treating the targets to the same doses in 25 fractions (i.e., 2Gy per fraction to the pelvic PTV and 2.4Gy per fraction to the boost PTV).

2.1 Statistical Method

Data were analysed using SPSS win statistical package version 22. Numerical data were summarised as medians and ranges. Comparison between more than two groups for numerical variables was done by using the non-parametric Friedman test. Probability (p-value) equal or less than 0.05 was considered to be significant.

3. RESULTS

The dosimetric comparison was done between sequential IMRT (sIMRT), simultaneously integrated boost (SIB-IMRT) and 3 dimension conformal radiotherapy (3DCRT) to pelvic primary and nodal target volume (ptv 50) and boost target volume (ptv 16) for 10 patients with carcinoma of the cervix.

Plans were optimised to achieve at least 95% coverage of the PTV with 95% of the prescribed dose while minimising the volume that received more than 110% of the prescribed dose and maximally sparing the OAR, including small bowel, bladder, rectum, and bone marrow.

Parameters collected for each plan are listed in Table 1.

The coverage of dose distribution in the treatment groups was nearly the same in all plans with little dose heterogeneity (Fig. 1).

Comparable pelvic target volume coverage and boost target volume (V95%) was achieved with conformal, sIMRT and SIB-IMRT plans, while maximum dose was significantly reduced using conformal plan for the boost plans with p= 0.01.

Regarding dose to the organs at risk, the dose to the rectum, bladder and bone marrow was the least at the sIMRT plan in compared to other 2 plans whereas the small bowel dose was less in the SIB plans than the other 2 plans.

For a dose to both femori, it was lower at the sIMRT and SIB-IMRT plans than the 3DCRTH.

Dosimetric parameters collected for each volume are listed in Tables 1 and 2.

4. DISCUSSION

For patients with FIGO stages IB, IIB, and IIIB cervical cancer, the incidences of pelvic lymph node involvement are approximately 15%, 30%, and 50%, respectively [14,15].

Large numbers of patients with disease relapse have a nodal failure. This may be due to insufficient dose delivery to the suspected positive nodal metastasis [16].

In this study, 3DCRT vs sIMRT vs SIB-IMRT were compared for dose delivery positive pelvic lymph nodes regarding target volume coverage and dose to the organs at risk as a trial to improve the therapeutic outcome of nodal positive cervical cancer.

In this study, regarding target volume, dose distribution was the same for all plans, where

coverage of the pelvic target volume and nodal boost target volume (v95%) was achieved for sIMRT and SIB-IMRT while maximum dose was significantly reduced using conformal plan for the boost plans with p= 0.01.

This is consistent with the fact demonstrated by Feng et al. [17], where target volume coverage was comparable in both SIB and sIMRT, however, Dogan et al. [18] recorded better conformity and heterogeneity with the use of SIB than sIMRT

The main concern when using dose escalation is the elevated number of acute serious adverse events.

Several dosimetric studies have evaluated the advantages of IMRT for cervical cancer in terms of dose reduction delivered to the organs at risk.

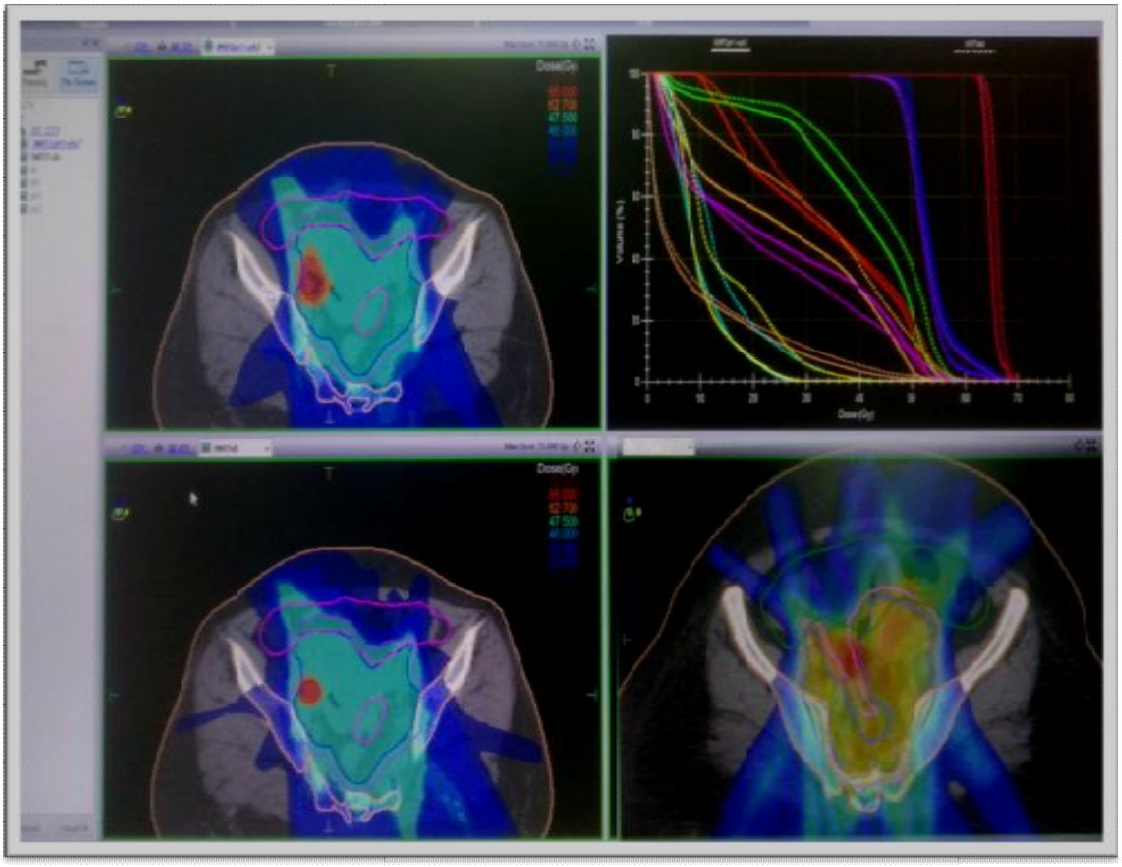

Fig. 1. Colour Wash and DVH for SIB-IMRT Plan, sIMRT and 3DCRT

Table 1. Physical doses to target volumes for both sIMRT, SIB-IMRT and 3DCRTH plans

	Conformal		sIMRT		SIB-IMRT		P value
	Mean	**STD**	**Mean**	**STD**	**Mean**	**STD**	
Pelvic PTV							
V95%	(96.4) %	(2.1)	(100) %	(0.0)	(99.9) %	(0.05)	(0.37)
Vmin	(60.2) Gy	(3.8)	(61.3) Gy	(1.7)	(62.2) Gy	(1.3)	(0.31)
Vmax	(66.9) Gy	(0.05)	(73.8) Gy	(4.08)	(71.2) Gy	(3.1)	(0.04)
Vmean	(65.2) GY	(1.1)	(66.8) Gy	(1.6)	(67.4) Gy	(2.07)	(0.24)
Boost PTV							
V95%	(94) %	(0.7)	(96.8) %	(0.8)	(95.6) %	(0.8)	(0.06)
V_{min}	(37.7) Gy	(0.8)	(35.2) Gy	(3.1)	(35.2) Gy	(3.2)	(0.20)
V_{max}	(55.8) Gy	(6.2)	(74.0) Gy	(4.5)	(71.4) Gy	(3.1)	(0.01)
V_{mean}	(49.7) Gy	(0.8)	(53.6) Gy	(1.1)	(52.2) Gy	(0.8)	(0.01)

Table 2. Physical doses to OAR for both sIMRT, SIB-IMRT and 3DCRTH plans

Characteristics	Conformal Median (range)	SIB-IMRT Median (range)	sIMRT Median (range)	p value
Rectum V45	79 (77-80) Gy	50 (38-55) Gy	43(18 -50) Gy	0.015
Bladder V50	34 (30-36) Gy	26 (20-32) Gy	17 (12-21) Gy	0.007
Bone marrow V10	96 (96-97) Gy	89 (83- 90) Gy	85 (68-89) Gy	0.015
Small bowel V45	376 (317-621) Gy	112 (107 -146) Gy	159(125-195) Gy	0.007
Right femur V50	0.4 (0 -1.5) Gy	0 (0-0) Gy	0 (0-0) Gy	0.050
Left femur V50	2.4 (0.2-3) Gy	0(0-0.04) Gy	0 (0- 0.01) Gy	0.009

Chan et al. [19] and Kavanagh et al. [20] demonstrated better protection of small bowel, rectum and bladder with IMRT over 4-Field and 3D conformal EBRT.

In this comparative dosimetric study, the small intestine bowel was better saved in the SIB – IMRT technique in compared to the other 2 techniques.

This is in accordance with the report of Poorvu et al. [21] who did not find any correlation between duodenal or other gastrointestinal toxicities and dose when nodal boosts of up to 65Gy were delivered.

Also, Feng et al. [17] recorded the small bowel doses to 2 cc and 0.1 cc were lower in the SIB-IMRT plans for almost all patients, including those with para-aortic boost volumes.

In contrast, Verma et al. [22] focused on duodenal data from patients treated with extended field SIB-IMRT and found that the rate of duodenal injury is associated with V55 and significantly increases as V55 exceeds 15 cm^3.

In the present study, the v45 of the rectum, v50 of the bladder, v10 of bone marrow and v50 of both femori more spared with the sIMRT plan than that of the 3DCRT and SIB-IMRT plans.

This is consistent with the study of Feng et al. [17], demonstrated that there were comparable results for dose to organs at risk between sIMRT and SIB-IMRT.

It was also verified by Vargo et al. [13] which also demonstrated adequate control of nodal disease and comparable toxicities to OAR when treated to 55 Gy in 25 fractions.

5. CONCLUSION

The present study showed that the use of sequential IMRT as a boost for pelvic lymph nodes in cases with cancer cervix spares organs at risk including bladder, rectum, bone marrow and femoral head much better than the simultaneous integrated boost IMRT and 3DCRT, but regarding small bowel volume, it is better spared by SIB-IMRT.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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