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Scientific Paper

Feasibility study of conformal forward planned simultaneous integrated boost technique comparable to IMRT and VMAT in pelvic irradiation for locally advanced cervical cancer

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Abstract

Aim: To check the feasibility of simultaneous integrated boost (SIB) using a forward planned field in field (FIF) conformal technique for the treatment of carcinoma of the cervix IIIB and compare it dosimetrically with other advanced inverse planning techniques.

Methods: In our study 33 patients of carcinoma of the cervix IIIB were planned for SIB using conformal FIF technique and they were compared with retrospectively planned IMRT and VMAT techniques. SIB using conformal FIF was planned by two different methods.

Results: The results of our study indicate that forward planned Conformal SIB techniques are comparable with inverse planned techniques dosimetrically, in terms of conformity Index, Homogeneity Index, Maximum dose, etc. The ability of FIF SIB plans to produce dose contrast in differential dose accumulation was compared and analyzed and the results were encouraging. To treat an advanced/bulky disease like Carcinoma of the Cervix IIIB in centers with large patient load, utilizing advanced techniques such as IMRT and VMAT is both technically and practically difficult. Despite VMAT's shorter delivery time, the procedures involved are time-consuming.

Conclusion: Hence forward planned SIB techniques may be used to achieve similar dosimetric effects of IMRT and VMAT techniques without much compromise in plan quality and patient throughput for treating bulky carcinoma of the cervix IIIB cases. However, the clinical results need to be carefully compared and evaluated and reported.

Key words: forward planning; SIB; field in field; inverse planning; biological evaluation; carcinoma of the cervix.

Introduction

Management of locally advanced cervical cancer has changed from time to time. Pelvic radiation at conventional fractionation with weekly cisplatin chemotherapy and followed by brachytherapy is the standard of care. The quest for an increased cancer cure has made many investigators to evolve a better treatment plan. Simultaneous integrated boost (SIB) is an IMRT technique that allows the planning and irradiation of different targets at different dose levels in a single treatment session instead of using sequential treatment plans. The advantage of SIB is to deliver a higher dose to the tumour while reducing the overall treatment time (OTT) which may translate into an improvement in local control [1-3]. It has been reported that dose escalation in a bulky disease like carcinoma of the cervix IIIB helps in local control [4-5]. This study explores the feasibility of clinical implementation of SIB for FIGO stage IIIB advanced cervical cancer using Field in Field technique without using more developed and sophisticated techniques like IMRT and VMAT.

Materials and Methods

Treatment planning

Patients with IIIB disease according to the FIGO staging were included. 33 patients who were fit for chemo-radiation were included in the study. The median age of 46 years and the oldest being 63 years with the youngest at the age of 35. Ethical committee approval and informed consent from the patients were obtained. Patients were simulated in the supine position with arms over the chest. Planning CT scans were acquired with 2.5 mm slice thickness in GE Optima 580 wide bore CT. Three lead shots were placed at the level of symphysis pubis for localization and to help correct the translational and rotational errors. Skin markers were used. All

the patients taken for the study were treated on the same Clinac 2100 C/D (Varian Medical Systems, Palo Alto, USA) equipped with On-Board imager for daily setup verification.

Target delineation

The gross tumour volume of the cervix (Primary GTV) was defined as the visible macroscopic tumour based on all the available clinical and imaging data. The clinical target volume (CTV cervix) was defined as the Primary GTV, corpus uteri, bilateral parametrium, involved nodes and upper third of the vagina. In cases with vaginal involvement, the CTV cervix was extended 2 cm below the vaginal involvement. The planning target volume of the CTV cervix (PTV cervix) was obtained using a three-dimensional anisotropic expansion of 10, 7, and 7 mm in the antero-posterior, left-right, and cranio-caudal direction, respectively. The asymmetrical margin for PTV was based on the fact that that the cervical cancer movements are not uniform in all directions [6]. The elective lymph nodal areas included the common, internal and external iliac nodes, the obturator and pre-sacral region. Using a three-dimensional expansion of 2 mm and 7 mm around nodes, respectively, the CTV nodes and PTV nodes were created. PTV cervix and PTV nodes were merged with a safety margin of 7mm to produce Pelvic PTV [7].

The radiation treatment plan consists of whole pelvic radiotherapy to a total dose of 49.4 Gy in 26 fractions using conformal FIF technique with simultaneous boost of 54.6 Gy to the Primary GTV. All patients were then treated with HDR brachytherapy 6.5 Gy per fraction for 3 weekly fractions. Patients received weekly cisplatin during the external radiation. Treatment planning was carried out on Eclipse (V15.5) treatment planning system (TPS), (Varian Medical Systems, Palo Alto, USA). All the plans were calculated using AcurosXB dose calculation algorithm [8-12].

Physical Plan Evaluation

All the plans were extensively evaluated both qualitatively as well as quantitatively. Quantitative plan evaluation was based on cumulative dose volume histograms (DVHs) and different metrics and indices. The conformity index (CI) and homogeneity index (HI) for the Primary GTV were calculated for each plan using the radiation therapy oncology group (RTOG) definitions [13] according to

$$CI = \frac{V54.6}{Vboost} \quad \text{Eq. 1}$$

$$HI = \frac{D2\%}{54.6} \quad \text{Eq. 2}$$

where V54.6 is the volume of the prescription isodose (54.6 Gy) surface and Vboost is the total boost target volume; D2% is the dose (Gy) received by 2 % of the boost volume (maximum). For the Pelvic PTV, the quality of coverage (Q) and the heterogeneity index (hI) were calculated using definitions [14]:

$$Q = \frac{D98\%}{49.4} \quad \text{Eq. 3}$$

$$hI = \frac{D2\%}{D98\%} \quad \text{Eq. 4}$$

where D98% and D2% are the doses (Gy) received by 98 % (minimum) and 2% (maximum) of the Pelvic PTV, respectively. In addition to these, a dose contrast index parameter as explained in [15-16] was also calculated and analysed to assess the plan wise superiority in delivering differential dose distribution (SIB). A %DCI value closer to 100% indicates a better dose contrast. It is calculated as follows:

$$\%DCI = \frac{DCI}{iDCI} \times 100 \quad \text{Eq. 5}$$

where DCI is defined as the mean dose to the Primary GTV divided by the mean dose to the Pelvic PTV and iDCI is defined as the prescription dose to the Primary GTV divided by the prescription dose to the Pelvic PTV.

In addition to dose contrast index and other different quantitative indices for physical plan evaluation, we have also considered evaluating the plans as per the conformation number explained by van't Riet et al. [17] using the definition:

$$CN = \frac{TV_{RI}}{TV} X \frac{TV_{RI}}{V_{RI}} \quad \text{Eq. 6}$$

where CN is conformation number, TVRI is target volume covered by the reference isodose, TV is target volume, and VRI is a volume of the reference isodose. The first fraction in this equation defines the quality of the target coverage and the second fraction defines the healthy tissue volume receiving reference or higher than the reference dose of prescription. The CN ranges from 0 to 1, where 1 is the ideal value.

A dose-volume constraint of volume receiving 40 Gy ($V40_{Gy}$) should be lesser or equal to 40% volume and dose received by 195cc (D195cc) should be less than or equal to 40 Gy were honoured as per RTOG guidelines for femoral head and bowel bag respectively. The number of Monitor Units (MUs) per plan technique per se was assessed as IMRT technique requires larger MUs to deliver the same dose. To assess the volume of high dose spill in Pelvic PTV and assess the ability of the used technique to limit the high dose to Primary GTV volume, the volume of Pelvic PTV receiving 55 Gy ($V55_{Gy}$) was observed. The plan maximum dose (Max) in each technique was also observed for assessment.

Biological Plan Evaluation

All the plans were biologically evaluated based on the equivalent uniform dose (EUD) calculated from the integral DVHs of the respective plans using a free MATLAB based program [18]. EUD represents the uniform dose which leads to the same probability of local control as the actual non-uniform dose distribution. Also, Tumour Control Probability (TCP) was calculated using the same. The program requires certain input parameters namely the α/β value for the (carcinoma of the cervix) tumour cells and the Tumour Control Dose (TCD_{50}),

the dose that control half the tumours treated which is taken as 26.35 Gy [19] and a unitless parameter "a" taken as -13 [18]. The dose-response steepness index (γ_{50}) value taken as 2 for our calculations, is the change in TCP expected because of a 1% change in dose about the TCD_{50} [20].

Conformal SIB

With the conformal SIB technique, whole Pelvis and boost irradiation are combined in one treatment plan and are given simultaneously. The conformal FIF SIB (CRT_SIB) plans were generated using the traditional four-field box setup (AP, PA, and opposed Laterals) to deliver 1.9 Gy to the whole pelvic PTV (includes nodal involvement) and additionally reduced four fields, to deliver 2.1 Gy to Primary GTV with 6 MV X-rays, simultaneously. The MLC of pelvic four fields were fitted to the Pelvic PTV with 0.5 cm margin whereas MLC and jaws of the reduced fields were fitted to the Primary GTV with zero MLC margin as shown in **Figure 1** and **Figure 2** respectively.

Reduced fields weight was kept half that of the Pelvic fields' to begin. The first FIF was generated in the pelvic fields for the Pelvic PTV dose coverage (49.4 Gy) and secondly in the reduced fields for the Primary GTV dose coverage (54.6 Gy). Almost in all plans, two FIF subfields were generated per field, for both pelvic and primary GTV fields to meet the PTV planning objective of $V95\% \geq 95\%$. The FIF subfields were merged to ease and reduce the treatment execution time.

Conformal Hybrid

The Conformal Hybrid (CRT_Hybrid) treatment plan was created by copying the sequentially planned pelvis and boost beams into an integrated treatment plan. The Four field conformal plans were created for Pelvic PTV and Primary GTV separately using 6 MV X-rays. Pelvic PTV plan of daily dose 1.9 Gy and reduced field boost plan for Primary GTV of daily dose 0.2 Gy each for 26 fractions are created. New FIF subfields were created for each of the four fields in the Pelvic PTV plan and MLCs are conformed to the Primary GTV with zero margin fit facilitating better control to limit the unintended excessive dose to the area outside the boost (Primary GTV), keeping the jaws' parameters unchanged as of the respective Pelvic PTV four fields. In Eclipse TPS it is possible to merge the FIFs to the parent field provided the jaw settings of the parent field and the FIF are same. In CRT_SIB we conform the jaws and MLCs to the respective PTVs (4 fields conforming to the Pelvic PTV and 4 fields to the Primary GTV) whereas in CRT_Hybrid, only the MLC is conformed to Primary GTV whereas jaws are kept similar to that of the fields conforming to Pelvic PTV (Figure 3 and figure 4 shows the jaw settings with MLCs alone conforming to respective targets). This enables to merge the FIF of particular gantry angle and effectively reduce the number of parent fields to be mode up to 4 in the CRT_Hybrid plan. During treatment execution, RTTs need not mode up each FIF if they're merged to the parent field which reduces the treatment execution time. MUs calculated for the reduced fields in the separate plan for Primary GTV to deliver 0.2 Gy of daily dose are copied to these FIF subfields conforming to the Primary GTV. **Figure 3** and **Figure 4** show the field arrangements of the four fields for Pelvic PTV and Primary GTV respectively representing the jaw settings and MLC conformations.

Intensity Modulated Radiotherapy (IMRT)

Equally distributed (0°, 72°, 144°, 216°, 288°) five field coplanar IMRT SIB plans were generated retrospectively for all patients with simultaneous dose accumulation of 1.9 Gy daily dose to Pelvic PTV and 2.1 Gy daily dose to Primary GTV using 6MV X rays with a constant dose rate of 500MU/min. As the CTV includes partial volumes of rectum and bladder due to the disease bulk, during optimization rectal and bladder dose objectives of $V40_{Gy} \leq 30\%$ and $V40_{Gy} \leq 3\,5\%$ respectively for PTV subtracted volumes were given only third priority. The volume of rectum and bladder included into PTV were subtracted from the respective OARs and optimal structures were created and dose-volume constraints were given for them during optimization. In the optimization window, the PTV subtracted volumes were given third-order priority whereas prime priority was given for PTVs and second priority to the small bowel. PTV coverage was not compromised as a result of overlap with the rectal and bladder volumes. The femoral head dose-volume constraint of $V40_{Gy} \leq 40\%$ was considered in the optimization. PTVs dose volume objectives of Pelvic PTV $D95\% \geq 47$Gy and Primary GTV $D95\% \geq 52$Gy were given top priorities.

Volumetric Modulated Arc Therapy (VMAT)

Double arc VMAT plans using 6MV X rays with a maximum dose rate of 600 MU/min were also generated retrospectively for all 33 patients with same dose-volume optimization objectives for PTVs and OARs as of the IMRT plans with routine complementing collimator rotation in each arc to reduce the tongue and groove effect. The VMAT plan consists of one clockwise and the other anti-clockwise rotation arcs. The Photon Optimizer (PO) optimization algorithm was used for optimization and AcurosXB algorithm was used for dose calculation with a dose resolution grid of 2.5 mm in Eclipse V15.5 TPS.

Statistical analysis

Comparison and analyses of all the four planning techniques were performed by a repeated measures one-way ANOVA (with the Greenhouse-Geisser correction and Tukey's multiple comparisons test) or the Friedman test (with Dunn's multiple comparisons test) using GraphPad Prism version 6.04 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com) and the statistics were tabulated descriptively as mean ± standard deviation (SD) in **Table 1**. Statistically significant differences were assumed for a significance level of $p < 0.05$.

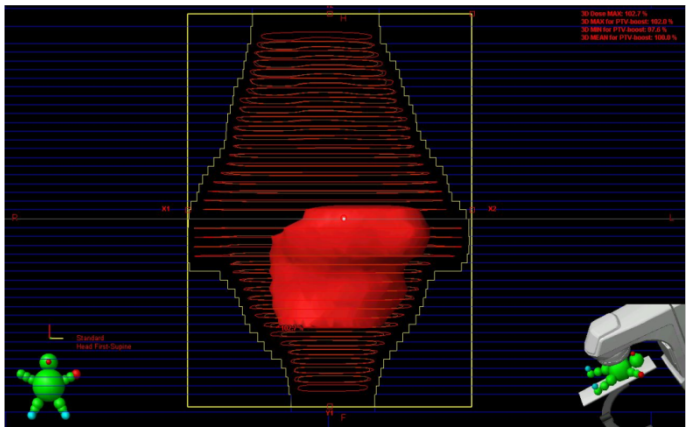

Figure 1. MLC & JAW setting for Pelvic PTV in CRT_SIB.

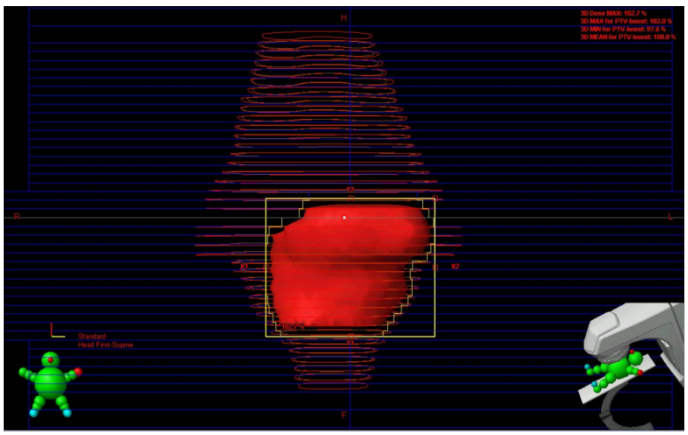

Figure 2. MLC & JAW setting for Primary GTV in CRT_SIB.

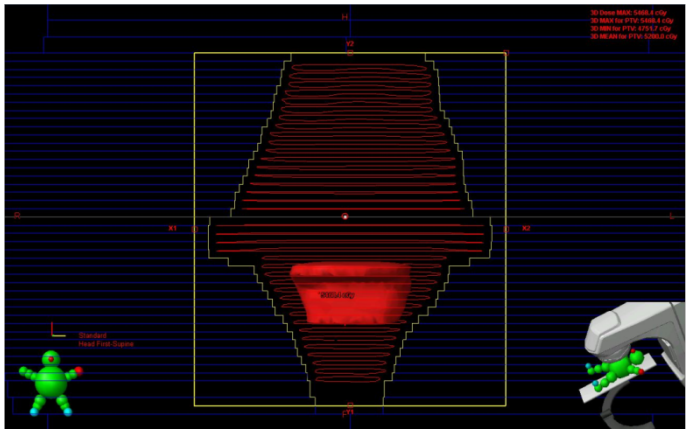

Figure 3. MLC & JAW setting for Pelvic PTV in CRT_Hybrid.

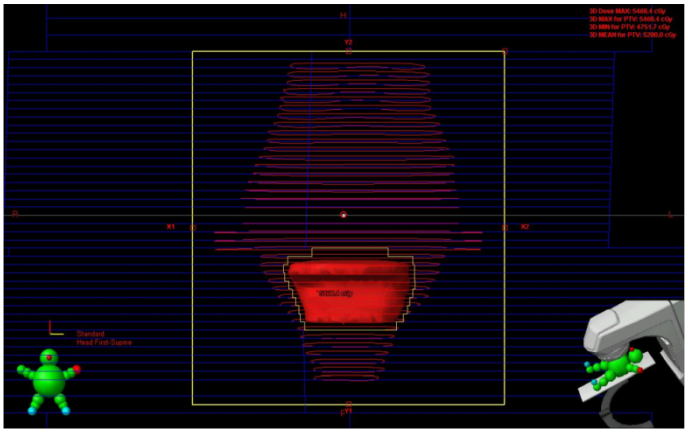

Figure 4. MLC & JAW setting for Primary GTV in CRT_Hybrid.

Table 1. The targets coverage and biological parameters and treatment efficiency multi-comparison analysis for all studied techniques (mean ± sd). Friedman test of significance ($p < 0.05$) was used in these cases; otherwise, repeated measures ANOVA significance test was used.

	n=33	CRT_SIB	CRT_Hybrid	IMRT	RA
Primary GTV	CI	0.99 ± 0.01^{a}	1.00 ± 0.01^{b}	$0.99 \pm 0.01^{c,a}$	$0.99 \pm 0.01^{a,b}$
	HI	1.04 ± 0.01^{a}	1.04 ± 0.02^{b}	1.07 ± 0.01^{c}	1.07 ± 0.01^{c}
	EUD G (Gy)	56.17 ± 0.72^{a}	58.40 ± 2.23^{b},	$56.96 \pm 2.50^{c,a,b}$	$59.10 \pm 1.25^{b,c}$
	TCP G (%)	99.77 ± 0.02^{a}	$99.82 \pm 0.07^{b,a}$	$99.77 \pm 0.10^{c,a,b}$	99.84 ± 0.03^{b}
	CN G	0.51 ± 0.15^{a}	0.64 ± 0.39^{a}	0.96 ± 0.05^{b}	1.04 ± 0.08^{c}
	D2% (Gy)	56.82 ± 0.71^{a}	57.14 ± 0.71^{a}	58.42 ± 0.45^{b}	$58.86 \pm 0.63^{c,b}$
Pelvic PTV	Q	1.01 ± 0.02^{a}	$1.01 \pm 0.01^{b,a}$	0.99 ± 0.01^{c}	$1.00 \pm .01^{c}$
	hI	1.12 ± 0.02^{a}	1.12 ± 0.02^{a}	1.11 ± 0.02^{a}	1.12 ± 0.01^{a}
	EUD P (Gy)	46.28 ± 0.82^{a}	52.93 ± 1.54^{b}	$46.37 \pm 0.43^{c,a}$	47.21 ± 0.81
	TCP P (%)	98.90 ± 0.15^{a}	99.61 ± 0.11^{b}	$98.92 \pm 0.08^{c,a}$	99.06 ± 0.12
	$V55_{Gy}$ (%)	8.47 ± 4.45^{a}	14.58 ± 11.49^{b}	1.79 ± 1.77^{c}	3.43 ± 2.73^{c}
	CN P	0.58 ± 0.07^{a}	0.62 ± 0.11^{a}	0.76 ± 0.09^{b}	$0.77 \pm 0.11^{c,b}$
	D2% (Gy)	56.17 ± 0.54^{a}	56.37 ± 0.71^{a}	54.60 ± 1.40^{b}	$55.49 \pm 0.52^{c,b}$
	MU	354.2 ± 36.86^{a}	266.1 ± 25.31^{b}	965.2 ± 68.01^{c}	418.9 ± 49.94
	Max (Gy)	56.96 ± 1.21^{a}	$57.34 \pm 0.89^{b,a}$	58.99 ± 0.49^{c}	60.01 ± 0.65
	%DCI (%)	96.28 ± 1.32^{a}	$96.93 \pm 1.72^{a,b}$	98.59 ± 1.04^{c}	98.55 ± 0.48^{c}
Bowel Bag	D195cc (Gy)	33.7 ± 2.57^{a}	$33.01 \pm 2.34^{a,b}$	34.65 ± 3.13^{c}	35.26 ± 4.17
Femoral Head	$V40_{Gy}$ (%)	$7.99 \pm 5.60^{a,b,c}$	8.25 ± 6.17^{b}	4.42 ± 3.71^{c}	5.51 ± 3.42^{c}

*a,b,c Values having the same superscript in the same horizontal line are not significantly different. CI, conformity index as defined by **Equation 1**; HI, homogeneity index as defined by **Equation 2**; Q is the quality of coverage as defined by **Equation 3**; *hI*, heterogeneity index as defined by **Equation 4**; *%DCI*, percentage dose contrast index as defined by **Equation 5**; EUD, Equivalent Uniform Dose for Pelvic PTV (P) and Primary GTV (G); TCP, Tumour Control Probability of Pelvic PTV (P) and Primary PTV (G); $V55_{Gy}$, volume receiving 55Gy; CN, Conformation Number for Pelvic PTV (P) and Primary GTV (G); Max, Plan maximum dose; MU, Monitor Units; D195cc, dose received by 195cc; $V40_{Gy}$, volume receiving 40Gy; n, sample size.

Results

The plans were compared and analysed based on various dosimetric parameters. For all our IMRT and VMAT plans we used only 6 MV X-rays whereas for CRT techniques we used 15 MV X-rays also for patients having Antero-Posterior diameter more than 25 cm. **Table 1** shows the physical and biological evaluation parameters of the two targets and the plans for the studied techniques. The detailed description of ANOVA repeated measures analyses show that (mean ± sd) 354.2 ± 36.86, 266.1 ± 25.31, 965.2 ± 68.01 and 418.9 ± 49.94 MUs were used for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively. The maximum numbers of MUs used were 441 MU, 343 MU, 1057 MU and 658 MUs for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively.

Conformity Index

As per **Equation 1** calculations, a maximum CI of 1.00 was observed irrespective of techniques. With a CI range of (mean ± sd) 1.00 ± 0.01, 1.00 ± 0.01, 0.99 ± 0.01 and 1.00 ± 0.01 for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively.

Homogeneity Index (HI)

Irrespective of the treatment technique the homogeneity indices were acceptable for the Primary GTV and were calculated according to **Equation 2**. As per the results reported in **Table 1**, CRT techniques were better in homogeneity compared to their inverse planning counterparts IMRT and VMAT techniques. The Maximum HI in each technique observed were 1.08, 1.07, 1.09 and 1.09. There exists statistical significance among techniques except between the IMRT and VMAT techniques. The HI range (mean ± sd) were 1.04 ± 0.01, 1.05 ± 0.01, 1.07 ± 0.01 and 1.08 ± 0.01 for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively.

Quality of Coverage (Q)

The quality of coverage for the Pelvic PTV was assessed based on **Equation 3** and the results were clinically acceptable as all our clinical plans were approved for treatment satisfying the $V95 \geq 95$ objective. All the techniques were comparable in terms of dose coverage quality. The coverage quality index range (mean ± sd) of 1.02 ± 0.01, 1.01 ± 0.01, 1.00 ± 0.01 and 1.00 ± 0.01 for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively were observed.

Heterogeneity Index (*hI*)

The dose heterogeneity in Pelvic PTV was calculated according to **Equation 4** and found to be clinically acceptable with the maximum *hI* index of 1.16, 1.16, 1.14 and 1.14 with the mean *hI* index range being 1.12 ± 0.02, 1.13 ± 0.01, 1.11 ± 0.03 and 1.12 ± 0.01 for CRT_SIB, CRT_Hybrid, IMRT and VMAT techniques respectively.

%Dose Contrast Index (*%DCI*)

The percentage dose contrast index assesses the ability of the planning technique to deliver differential doses to boost and elective volumes simultaneously. In our study the inverse planned IMRT and VMAT techniques show better %DCI calculated as per **Equation 5** compared to both conformal forward planned FIF SIB techniques explained. **Table 1** shows the mean of percentage dose contrast index range as 96.28 ± 1.32, 96.93 ± 1.72, 98.59 ± 1.04 and 98.55 ± 0.48 for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively.

Maximum Dose

The maximum dose is observed to be higher in inverse planned techniques (IMRT and VMAT) compared to the forward planned ones (CRT techniques). In that, CRT_SIB technique resulted in lower plan maximum dose compared to the CRT_Hybrid techniques. **Table 1** shows, the mean maximum dose range as 56.96 ± 1.21Gy, 57.34 ± 0.89Gy, 58.99 ± 0.49Gy and 60.01 ± 0.65Gy for CRT_SIB, CRT_Hybrid, IMRT, and VMAT techniques respectively.

D2% doses

In addition to the plan max dose which is a "point" dose, a more fair assessment of maximum doses would be the D2% doses in respective target volumes relative to the respective volumes' prescription doses. We observed a mean D2% dose of 56.82 ± 0.71 Gy, 57.14 ± 0.71 Gy, 58.42 ± 0.45 Gy and 58.86 ± 0.63 Gy for Primary GTV volume in CRT_SIB, CRT_Hybrid, IMRT and VMAT techniques respectively which is well within the planning objective of keeping max dose within 110% of the prescription dose of Primary GTV.

Conformation Number (CN)

In addition to the conformity indices calculated earlier, we wanted to calculate the conformity using the more legible method proposed by van't Riet et al. as per **Equation 6** and the results were 0.58 ± 0.07, 0.62 ± 0.11, 0.76 ± 0.09 and 0.77 ± 0.11 for Pelvic PTV target volume in CRT_SIB, CRT_Hybrid, IMRT and VMAT techniques respectively whereas the conformation number for Primary GTV volume were 0.51 ± 0.15, 0.64 ± 0.39, 0.96 ± 0.05, 1.04 ± 0.08 for CRT_SIB, CRT_Hybrid, IMRT and VMAT techniques respectively.

$V55_{Gy}$ in Pelvic PTV

To assess the extent of the spill of Primary GTV's prescription dose in the Pelvic PTV we observed the volume of Pelvic PTV receiving 55 Gy. In our study, the ratio of volumes of Pelvic PTV to Boost PTV (mean ± sd) ranged as 6.24 ± 3.06 in the study population. Also, we observed from these data that the extent of high dose spill in Pelvic PTV volume is not dependent on the ratio of target volumes rather the complexity

in the shape and position of the Primary GTV. The mean percentage volume range of Pelvic PTV that receives 55 Gy were 8.47 ± 4.45%, 14.58 ± 11.49%, 1.79 ± 1.77% and 3.43 ± 2.73% for CRT_SIB, CRT_Hybrid, IMRT, and VMAT plans respectively. The results show the obvious dose sculpting superiority of the inverse planning techniques (IMRT and VMAT) over the CRT techniques. An acceptable level of excessive coverage of Primary GTV dose was observed in the CRT techniques with the CRT_SIB technique significantly taking advantage over CRT_Hybrid in conforming the 54.6 Gy dose spill to Pelvic PTV as shown in **Figure 5** and **Figure 6** respectively.

Bowel bag and Femoral head

Table 1 shows that in all the techniques we compared the dose–volume constraints for bowel bag and femoral head were met within limits as per RTOG guidelines.

EUD & TCP Plan Evaluation

EUD calculated from the integral DVH data using a MATLAB program resulted in a data of mean EUD range of 46.28 ± 0.82 Gy, 52.93 ± 1.54 Gy, 46.37 ± 0.43 Gy and 47.21 ± 0.81 Gy for the Pelvic PTV in CRT_SIB, CRT_Hybrid, IMRT, and VMAT plans respectively, whereas the EUD range for Primary GTV in the techniques compared were 56.17 ± 0.72 Gy, 58.40 ± 2.23 Gy, 56.96 ± 2.50 Gy and 59.10 ± 1.25 Gy for CRT_SIB, CRT_Hybrid, IMRT and VMAT plans respectively.

Table 1 shows the mean range of Pelvic PTV target's TCP calculated for all the plans in each technique as 98.90 ± 0.15%, 99.61 ± 0.11%, 98.92 ± 0.08% and 99.06 ± 0.12%. All planning techniques resulted in a minimum percentage of 98.61, 99.31, 98.76 and 98.92 TCP for the Pelvic PTV in CRT_SIB, CRT_Hybrid, IMRT, and VMAT plans respectively. Also, the minimum TCP percentage for Primary GTV was calculated as 99.76, 99.61, 99.52 and 99.81 whereas the mean TCP ranged from 99.77 ± 0.02%, 99.82 ± 0.07%, 99.77 ± 0.10% and 99.84 ± 0.03% for CRT_SIB, CRT_Hybrid, IMRT, and VMAT plans respectively.

Discussion

There are several factors that contribute to translating to good local control and complement overall treatment outcome. From studying the patterns of failure in locally advanced cervical cancer, only a small fraction of patients develop distant metastasis, and one can attribute poor local control as a major factor for failure among such patients. This has left us with a quest to explore treatment strategies to improve local control for such patients.

In cervical cancer, an extension of overall treatment time has a negative effect on local control and survival [21-25]. The reason for this may be due to accelerated repopulation of tumour cells during fractionated radiotherapy [26-27]. Hence a

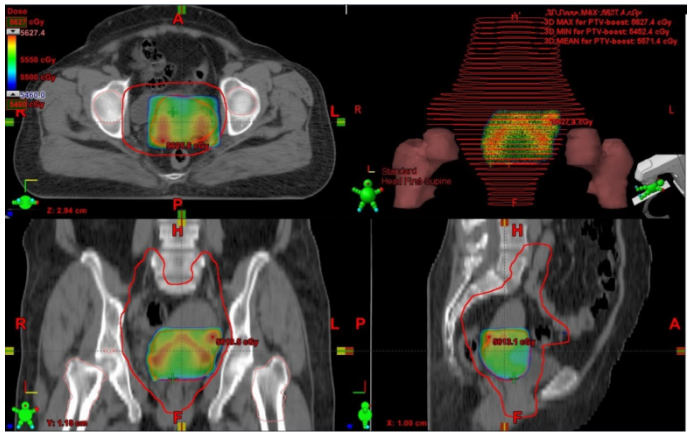

Figure 5. 54.6 Gy coverage in CRT_SIB.

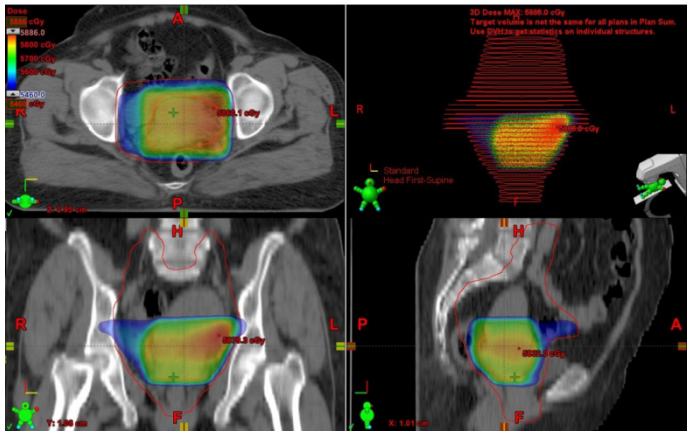

Figure 6. 54.6 Gy coverage in CRT_Hybrid.

reduction in the overall treatment time (OTT) can improve local control. OTT has been stated as one of the most important prognostic factors and the pelvic failure rate is approximately 1% per day of extension of treatment time beyond 30 days [28]. Therefore simultaneous integrated boost technique was considered. Simultaneous integrated boost (SIB) is an IMRT technique that allows the planning and irradiation of different targets at different dose levels in a single treatment session instead of using sequential treatment plans. It is used to increase the dose to the boost volume while keeping the dose to the elective volume at a lower level. This technique was initially used in head and neck cancers and prostate cancer as early as 2000 and has been in use in cervical cancer since 2009 [29-31]. Reducing the OTT limits the effect of accelerated tumour repopulation. Dosimetrically some studies have shown that SIB-IMRT has advantages over sequential IMRT in dose escalation. These studies state that in SIB IMRT the dose distribution is even more conformal resulting in better coverage of the boost volume while sparing non-target tissues [32-34]. The role of IMRT to simultaneously boost the primary is unquestionable when small volumes are considered and where more organs at risk are around the target. But in an advanced pelvic malignancy where the target volume is large and where completely avoiding the bladder base or the recto-sigmoid septum are not recommended, 3D CRT may be attempted. This

study reveals the feasibility of clinical implementation of SIB using conformal Field in Field technique [35], without extending the treatment regimen and inverse planning techniques.

Our study results clearly indicate that our conformal SIB plans are comparable with IMRT and VMAT techniques in dosimetric aspects of the target volumes for SIB techniques in advanced Ca. Cervix IIIB diseases. The conformity index is better for IMRT and VMAT techniques which are obvious because of the dose sculpting capabilities of them but the conformal SIB techniques exhibit clinically acceptable levels. The conformation number also exhibits similar results of statistically significant superiority of intensity-modulated techniques. The number of MUs used to deliver the prescribed dose Show comparable values among all the plan techniques except the IMRT requiring exceptionally higher MUs. Both the conformal SIB planning techniques use lesser MUs compared to the advanced IMRT and VMAT techniques with a statistical significance which is desirable. In terms of maximum dose and D2% doses, conformal SIB techniques take an edge over the IMRT and VMAT techniques which is acceptable for the known reasons of intensity modulation. The dose heterogeneity indices calculated for the Pelvic PTV shows higher but clinically acceptable levels of heterogeneity as we measured the Pelvic PTV volume with zero margin subtraction of the Primary GTV structure. This was correlated with no statistical significance among any of the studied techniques. A technique wise comparative analysis of differential dose accumulation capability *(%DCI*) was done among the techniques studied and the inverse planned techniques were found superior due to obvious reasons of intensity modulations. The volume of Pelvic PTV receiving marginally higher than the Primary GTV's prescription dose (54.6 Gy) is a matter of concern in conformal planning techniques because of the known inability of dose sculpting. Our results show that CRT_SIB technique restricts this 55 Gy dose spill into Pelvic PTV better than the CRT_Hybrid planning technique. This may be due to the difference in the jaw settings between CRT_SIB and CRT_Hybrid regarding the Primary GTV fields. As the Primary GTV fields' jaws were matched with the setting of Pelvic PTV fields' jaws to facilitate field merge, the MLC interleaf leakage might have made the management of spill of extra dose to the Pelvic PTV difficult in CRT_Hybrid plans and hence this result. Although the 55 Gy volume in Pelvic PTV is higher in CRT_Hybrid, it is clinically acceptable after qualitative analyses of the section by section dose distribution and at the discretion of the concerned treating radiation oncologist. The homogeneity indices for all planning techniques studied were comparable and clinically acceptable. The biological evaluation of the plans also revealed that Pelvic PTV EUD range was the highest among all other techniques studied here compared to the CRT_Hybrid technique as the volume receiving boost PTV dose was statistically significant. This was the same in case of Primary GTV EUD range with an exception of RA technique having the highest EUD range which is correlated to the plan maximum dose. The range of maximum dose was found to be highest for RA technique with 60.01 ± 0.65 Gy. The TCP calculated for all techniques were comparable in absolute values but exhibited statistical significance over analysis except the CRT_SIB Vs IMRT in Pelvic PTV. Similarly for Primary GTV TCP, CRT_SIB Vs RA alone was not significant. However, despite the statistical significance, the absolute differences were quite small, and the clinical benefit of such small improvements is uncertain.

Conclusion

From our study, we infer that both conformal FIF SIB techniques can be used at centres with a high patient load to treat Carcinoma of the Cervix patients with bulky disease. The 3D-conformal SIB technique has results equal to that of a SIB-IMRT technique but does not involve the complexity (software and hardware requirements of planning and delivery) and time involved with treatment planning and delivery using IMRT and VMAT thereby improving patient satisfaction and clinical throughput. CRT_Hybrid requires relatively lesser time to generate a clinically acceptable plan but CRT_SIB gives better control over high dose spill. A long term study shall be performed to analyse the clinical outcomes of these techniques for a better understanding and reporting.

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