A Dosimetric study Comparing Outcome Advantages of Intensity Modulated Radiotherapy versus 3D-CRT versus Arc Therapy doses to Organs at Risk and Target in Gastric adenocarcinoma. Single Institution

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Abstract:

Background: Gastric adenocarcinoma worldwide is the 4th common cause of death. The corner stone in treatment is surgery followed by radiotherapy to improve survival and decrease local recurrence which ≥ 80%. Low radiation tolerance of liver and kidney can subsequently cause life threatening damage. Our goal is to investigate the optimal radiation technique offering best target coverage, preventing recurrence and preserving nearby sensitive risk organs.

Materials and Methods: This is a dosimetric study including 10 patients with gastric cancer referred to our hospital for adjuvant chemoradiotherapy after total or subtotal gastrectomy. Three-dimensional (3D-CRT) conformal radiotherapy, intensity-modulated therapy (IMRT), volumetric modulated arc therapy (VMAT) plans were created for each patient. For the 30 plans, comparative dosimetric analyses of target volume (Dmean, D95, D98, D2), Homogeneity (HI) and conformity (CI). Organs at risk (OAR) were compared by dose-volume histogram, Dmean, Dmax, V20,35, V45 for the three techniques.

Results: IMRT and VMAT were more homogeneous than 3D-CRT ($p<0.05$). However, the best conformal plans were yielded with VMAT ($p = 0.033$). IMRT and VMAT were significantly better protecting OARs than 3D-CRT. The lowest Dmax to the heart was obtained with VMAT with statistically different than IMRT and 3D-CRT($p=0.00$). The mean liver doses were not statistically different between the 3 techniques. However, liver V35 and V45 were significantly lower in IMRT ($p= 0.003$ and $p=0.006$, respectively) and VMAT ($p=0.002$ and $p=0.003$, respectively) than 3D-CRT. Both kidneys were better preserved with IMRT and VMAT. The adjacent left kidney was better spared with significant lower (Dmax, Dmean, V20, and V35) in IMRT and VMAT than 3D-CRT plans. Dmean and V35doses of spinal cord were significantly higher in 3D plans while the doses of other two techniques were lower.

Conclusions: In comparison to 3D-CRT both IMRT, VMAT is preferable techniques for conformity of target volume and preserving the left kidney and the heart. However, for better HI & CI regarding PTV coverage, and for less toxicity to OAR, VMAT is preferable and more advantageous than IMRT &3DRT in adjuvant gastric adenocarcinoma.

Key words: Gastric cancer, IMRT, VMAT,3DRT, CI, HI, Organs at risk (OAR)

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Introduction:

Gastric adenocarcinoma is the 4th most common cause of cancer death worldwide [1]. Every year, 6 out of every 10 people are diagnosed with stomach cancer. The cornerstone of treatment is surgery, which depends on the stage of the tumor and the lymph nodes involved. For most patients, surgery alone is not enough to improve survival, as local recurrence occurs in more than 80% of cases [2]. Since the 2001 SWOG/INT0116 trial, concurrent chemotherapy and radiation therapy (CRT) have become the standard of care [3]. The target and lymph nodes to be irradiated are extensive,

irregular, and close to radiosensitive organs such as the kidneys, heart, and liver, which have low radiation tolerance. Radiotherapy-induced liver and kidney failure can lead to life-threatening damage.

Therefore, different radiation therapy techniques in different studies have been applied, starting from three-dimensional radiation therapy (3DRT) to modern techniques, such as Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), and Tomotherapy aiming primarily to decrease doses to Organs At Risk (OAR) and overcome under-dosage to the target caused by protecting risk organs which may increase the risk of local recurrence in gastric cancer. All studies compared either 3DRT vs IMRT, or IMRT vs VMAT, and only few studies compared the three techniques in adjuvant setting.

Objectives:

Analyze the dosimetric parameters of three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT) for appropriate treatment planning techniques yielding the best tumor volume dose distribution and maximum organ preservation.

Patients and Methods:

Ten patients with histologically proven gastric adenocarcinoma who underwent total or subtotal gastrectomy followed by adjuvant chemo-radiotherapy were included in the study. After correcting their laboratory profiles, reviewing the surgical data, and performing postoperative CT with contrast, patients were transferred to start their adjuvant localized radiation therapy. The study was conducted at Kasr Al-Ainy, Cairo University, from October 2023 to May 2024 with universal funding. This study was approved by the research ethics committee of the Faculty of Medicine of Cairo University (acceptance date: September 20, 2023; number: N 97-2023).

Patient Positioning:

On the day of CT, all patients were asked to fast for at least two hours. The patients were aligned supine on a Wing-board with arms raised above the head to ensure immobilization. CT planning with a slice thickness of 2.5 mm was initially performed covering the lower chest, abdomen, and pelvis. The images were transferred to the Eclipse™ treatment planning system (V:8.6, Varian Associates, Palo Alto, CA, USA). All patients were planned to receive the curative postoperative dose of 45 Gy over 25 fractions over five weeks (1.8 Gy). Each patient had three plans for the different techniques: 3DRT, IMRT, and VMAT. A total of 30 plans were calculated.

Target Volumes and OAR Delineation

The target volumes and doses were defined according to ICRU Reports [4,5]. Clinical Target Volume (CTV): is defined as the anatomical, anastomotic, and microscopic site of the primary tumor, in addition to draining lymph nodes (perigastric, celiac, para-aortic, splenic, peripancreatic, and hepato-duodenal lymph nodes). All will be delineated as CTV. Planning Target Volume (PTV): is an additional margin of 5-10 mm added to the CTV to account for minimal setup and patient uncertainties. Organs At Risk (OAR): Includes the heart, liver, both kidneys, and the spinal cord.

The treatment was delivered using 6 MV photons on a linear accelerator Clinac 2100 (Varian, Palo Alto, USA). All plans were normalized so that at least 95% of the PTV received 100% of the desired dose.

Treatment Plan

- In 3D-RT planning, we used three fields: two parallel opposing wedged fields and one lateral field.
- For IMRT inverse planning: Seven fields with the gantry angled at 0°, 51°, 102°, 153°, 204°, 255°, and 306°.
- For VMAT: Two full arcs (one clockwise - CW - and one counterclockwise - CCW). All calculations were done with a grid size of 0.25 mm using the AAA Algorithm (Analytical Anisotropic Algorithm).
- Dose constraints accepted for the liver were that 70% of it should receive less than 30 Gy, with the mean dose (D-mean) being less than 25 Gy. For the kidneys, 70% of each kidney should receive less than 20 Gy, with a D-mean for each being less than 18 Gy. The spinal cord's maximum dose was less than 45 Gy [6]. The volume of the heart receiving 40 Gy is called V40 ≤ 80%, V45 ≤ 60%, with heart D-mean ≤ 40 Gy. For the lungs, D-max ≤ 50 Gy, D-mean ≤ 20 Gy, V20 ≤ 35% of the prescribed dose. These constraints provide better organ function without complications caused by irradiation of larger volumes or overdose.

Plan Evaluation

All three plans for each patient were evaluated based on the different volumes and doses delivered to the PTV and OAR by: Dose Volume Histogram (DVH), Conformity Index (CI), and Homogeneity Index (HI).

For the PTV, plan evaluation was done by analyzing:

- Different doses received by PTV, including Volume receiving 95%, 98%, 2%, of the prescribed dose (D95, D98, D2, respectively), and mean dose (D-mean).
- Dose Volume Histogram: A histogram comparing different volumes receiving different doses, in addition to comparing different plans to determine the best plan with proper coverage of PTV and least effect on OAR.
- Conformity Index (CI) & Homogeneity Index (HI):

CI is defined according to RTOG as:

$$CI = \frac{V\ 100\%\ \text{prescribed dose for PTV}}{\text{Volume PTV}}$$

Range 0–1, with 1 being highly conformal. A value < 1 indicates that the volume of the target is not adequately irradiated, while a value > 1 signifies that the irradiated volume is greater than the target volume.

HI is defined as:

$$HI = \frac{(D2\% - D98\%)}{Prescribed\ Dose}$$

An optimal HI value is zero; thus, the smaller the HI, the more homogeneous the dose distribution to PTV.

The evaluation of OAR (heart, spinal cord, kidneys, and liver) doses was done according to Quantitative Analysis of Normal Tissue Effects in Clinics (QUANTEC) parameters & EORTC-RTOG [7,8]. Different doses and volumes were evaluated as: D-min, D-max, D-mean, and volumes receiving different doses V20, V35, V45. Bowels were not delineated due to their variation during sessions.

Statistical Analysis:

The data were prepared using Microsoft Excel 2013. We compared doses to OARs, tumor dose coverage, CI, HI, and the minimum, mean, and maximum dose volumes of the target volume and OARs between the two dosimetric plans. Statistical analyses were performed using IBM SPSS version 22.0. A paired t-test was used to calculate differences within each planning technique. A p-value of <0.05 was considered to indicate a statistically significant difference.

Results:

Dosimetric Parameters of PTV:

The comparison of dosimetric parameters for PTV coverage, HI, and CI is shown in Table 1. The mean PTV volume was 989.8 ± 59.6 cc. For the Dmean of PTV, all techniques were comparable with no statistical significance between 3D-CRT, IMRT, and VMAT (45.34 ± 0.54, 45.13 ± 0.53, and 45.41 ± 0.38 Gy, respectively). IMRT and VMAT plans showed significantly higher coverage of D98, D95, and D2 compared to the 3D-CRT plan. VMAT significantly outperformed the other techniques regarding D2 coverage. (Figure 1) illustrates the planning evaluation for 3D-CRT, IMRT, and VMAT.

The homogeneity of the target volume (HI) was significantly better with IMRT and VMAT compared to 3D-CRT ($p = 0.007$ and $p = 0.002$, respectively). Additionally, CI was significantly higher for both VMAT (0.772) and IMRT (0.676) compared to 3D-CRT (0.495). VMAT provided superior CI compared to IMRT ($p = 0.033$).

Dosimetric Parameters of OARs:

Both kidneys were significantly better protected with IMRT and VMAT compared to 3D-CRT ($p = 0.005$ and $p = 0.018$, respectively). The Dmean, Dmax, V20, and V35 for the left kidney were more favorable with IMRT and VMAT plans ($p < 0.01$). VMAT plans provided significantly more protection to the left kidney than IMRT plans (Dmax, $p = 0.001$; Dmean, $p = 0.03$; V20, $p = 0.001$). IMRT plans offered better protection for the right kidney than VMAT and 3D-CRT, but the difference was not statistically significant.

The Dmax of the spinal cord was lower with VMAT compared to IMRT and 3D-CRT, (29.50 Gy, 31.93 Gy, and 35.44 Gy, respectively) but with no significant difference. For Dmean of the spinal cord, IMRT and VMAT had lower values (17.54 Gy and 14.09 Gy vs 21.81 Gy, respectively) with significant differences ($p = 0.037$ and $p = 0.019$, respectively). Additionally, IMRT and VMAT were associated with significant lower V35 for the spinal cord compared to 3D-CRT ($p=0.011$ and $p=0.020$, respectively) (Table 2).

The Dmean and V20 for the liver were comparable among the three techniques. However, V35 and V45 were significantly lower with both IMRT and VMAT ($p < 0.001$) (Table 2).

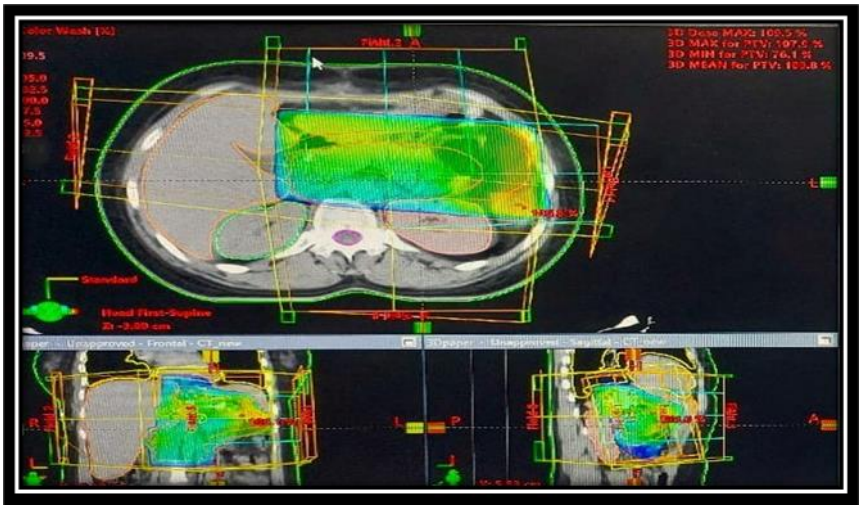
For the heart, VMAT achieved a significant lower Dmax compared to IMRT and 3D-CRT (22.91 Gy, 25.91 Gy, and 37.20 Gy, respectively; $p = 0.001$). VMAT and IMRT both showed significant improvement in V45 for the heart compared to 3D-CRT ($p = 0.0001$). The DVH parameters for 3D-CRT, IMRT, and VMAT are shown in (Figure 2).

Discussion:

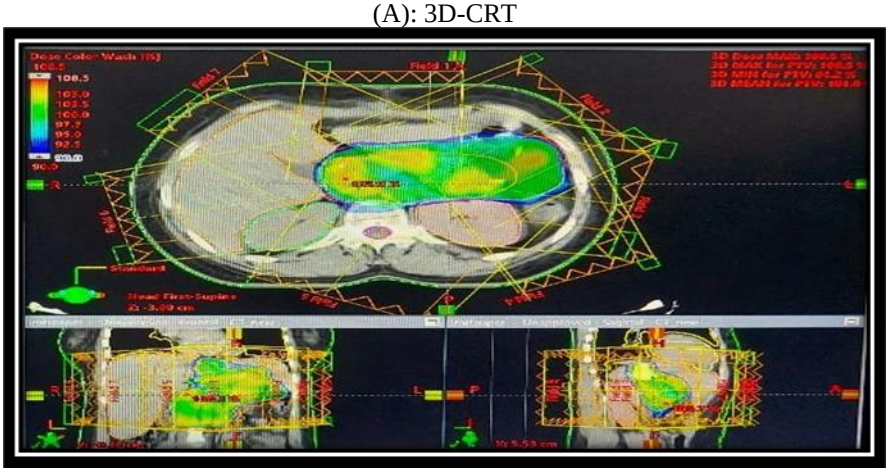
Gastric cancer often leads to local recurrence postoperatively, with standard adjuvant treatment aiming to decrease this risk through radiation therapy and chemotherapy. The post-operative volume to be irradiated is large, irregularly shaped, and close to radiosensitive organs such as the liver, kidneys, spinal cord, and heart. Few dosimetric studies have investigated the different radiation modalities in an attempt to reduce the radiation-associated toxicities after postoperative chemotherapy for gastric cancer with proper sparing surrounding organs at risk [9]

In the current study, we evaluated dosimetric parameters for 3D-CRT, IMRT, and VMAT techniques in postoperative gastric adenocarcinoma. Our findings indicated that both IMRT and VMAT offer better HI and CI compared to 3D-CRT, providing improved target coverage. This result aligns with studies by Pelin Altinok et al. and Zhang T et al. [10.11], although a study by Sadia Sharmin et al. (2023) compared 3DRTwith IMRT found that IMRT's uniformity was not statistically superior to 3D-CRT (HI: 1.02 ± 0.02 vs. 1.12 ± 0.14, $p = 0.08$) [12]. However, our study shows that VMAT has significantly better CI compared to IMRT and 3D-CRT, consistent with Gokcen Inan's research [13].

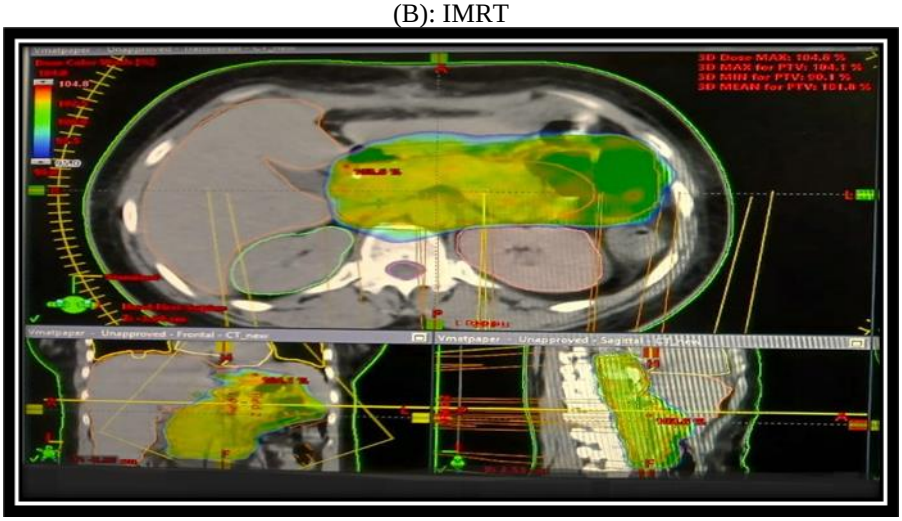
Another recent dosimetric study conducted by Makhtar I et al., 2022 [14], compared radiotherapy treatment plans using double-arc VMAT, IMRT versus 3DCRT techniques. The authors concluded that, the VMAT plans significantly provides higher mean CI (0.89 ± 0.03), than the IMRT (0.87 ± 0.02) and 3D-CRT (0.88 ± 0.03, $p=0.012$) techniques; $p < 0.05$. Our findings corroborate these results, showing superior CI with VMAT.



(A): 3D-CRT

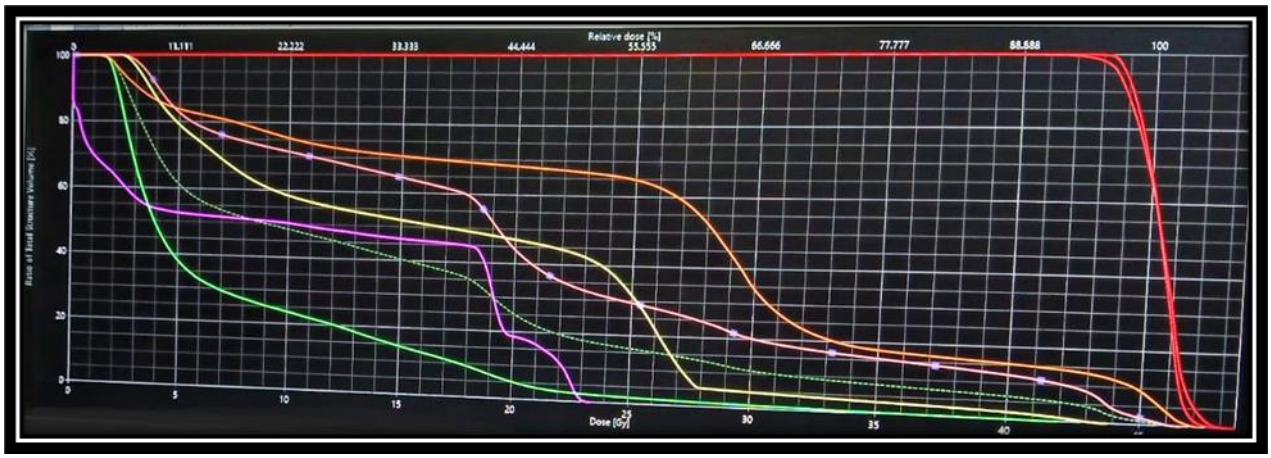


(B): IMRT

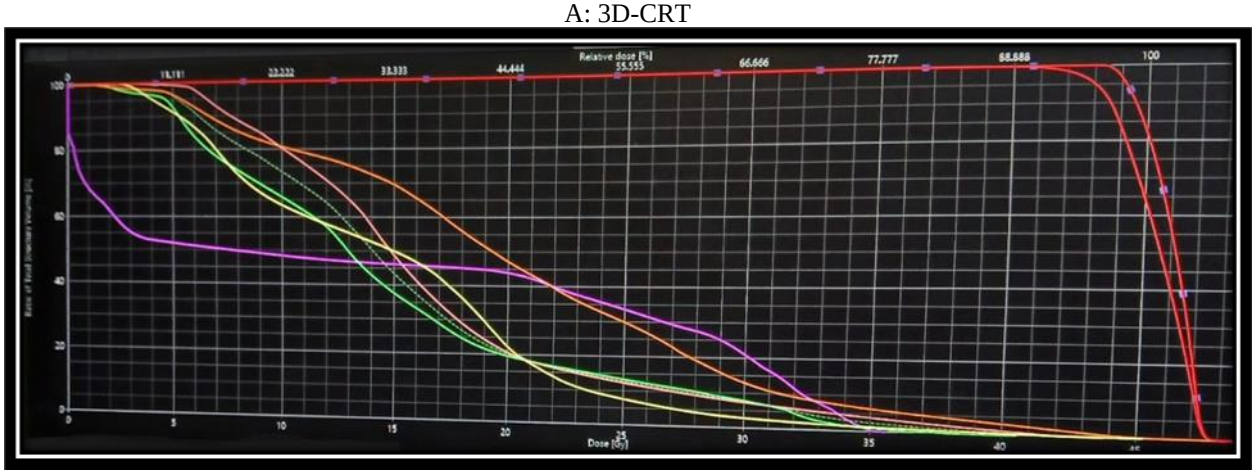


(C): VMAT

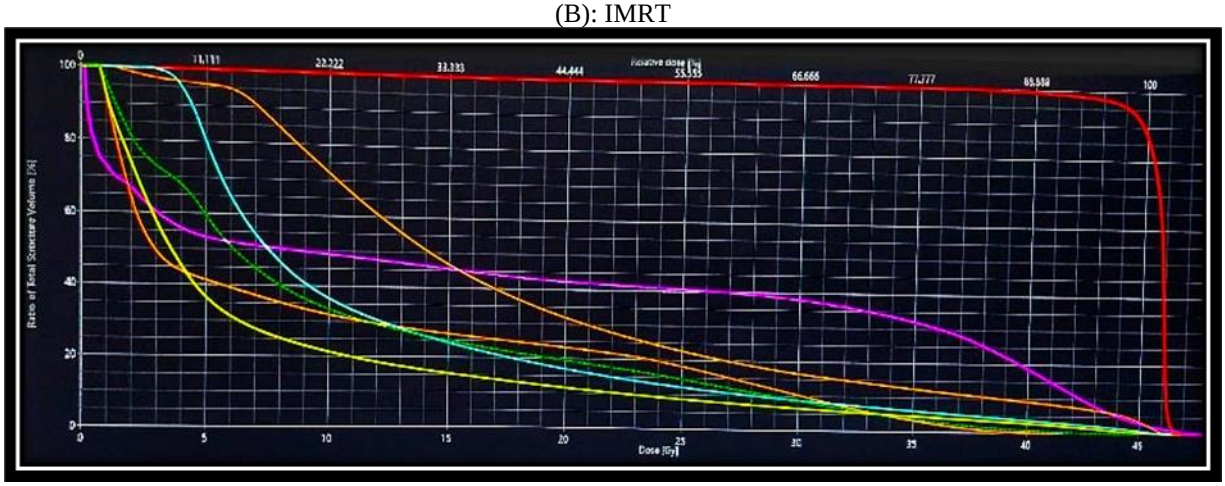
Figure (1): Isodose distribution of the same patient A: 3D-Conformal plan, B: IMRT plan, C: VMAT plan.



A: 3D-CRT



(B): IMRT



(C): VMAT

Figure (2): DVH of the same patient, A: 3D-CRT, B: IMRT, C: VMAT

Heart (Yellow), Liver (Orange), Left Kidney (Cimon). Right Kidney (Light green), Mean for Both Kidneys (Doted dark green), Spinal Cord (Purple), PTV, CTV (Red)

Table (1): The dosimetric Parameters planning of target volumes (PTV)

Parameter	Mean			P- VALUE		
	3D-CRT	IMRT	VMAT	3D-CRT vs IMRT	3D-CRT vs VMAT	IMRT vs VMAT
Dmean (Gy)	45.34±0.54	45.13 ±0.53	45.41 ± 0.38	0.001	0.020	0.164
D98 (Gy)	41.62	42.16	42.69	0.041	0.001	0.299
D95 (Gy)	42.80	43.06	43.53	0.052	0.000	0.064
D2 (Gy)	47.93	47.03	46.48	0.488	0.010	0.112
HI	0.132	0.058	0.045	0.007	0.002	0.134
CI	0.495	0.676	0.772	0.010	0.000	0.033

Table (2): The dosimetric Parameters of organs at risk

OAR	Mean			P-VALUE		
	3D-CRT	IMRT	VMAT	3D-CRT vs IMRT	3D-CRT vs VMAT	IMRT vs VMAT
Left kidney:						
Dmax/Gy	44.46	42.77	40.58	0.001	0.000	0.000
Dmean/Gy	21.65	13.62	12.23	0.002	0.001	0.035
V20	54.50%	20.02%	16.27%	0.015	0.009	0.000
V35	27.41%	5.05%	4.98%	0.014	0.013	0.895
V45	2.24 %	0.11%	0.55%	0.196	0.105	0.380
Rt kidney:						
Dmax /Gy	40.39	35.21	34.07	0.069	0.028	0.239
Dmean/Gy	11.01	10.68	11.73	0.795	0.764	0.500
V20	17.55%	13.86%	14.62%	0.342	0.351	0.566
V35	11.43%	1.53%	2.2%	0.066	0.293	0.096
V45	1.50%	0%	0.03%	0.357	0.350	0.213
Dmean Both kidneys:	17.41	11.85	11.83	0.005	0.018	0.980
Liver:						
Dmax/Gy	45.41	44.89	44.79	0.294	0.053	0.104
Dmean/Gy	20.60	20.87	20.44	0.881	0.927	0.620
V20	44.59%	44.89%	44.54%	0.294	0.540	0.104
V35	25.19%	11.06%	10.32%	0.003	0.002	0.965
V45	7.88%	2.59%	2.89%	0.006	0.003	0.620
Heart:						
Dmax/Gy	37.20	25.91	22.47	0.001	0.000	0.000
Dmean/Gy	7.4	5.25	6.14	0.070	0.595	0.232
V20	11.97%	6.24%	7.37%	0.069	0.148	0.518
V35	4.15%	1.17%	1.28%	0.170	0.184	0.776
V45	1.54%	0.12%	0.10%	0.000	0.000	0.893
Spinal Cord:						
Dmax/Gy	35.44	31.93	29.50	0.25	0.120	0.250
Dmean/Gy	21.81	17.54	14.09	0.037	0.019	0.114
V20	49.98%	57.97%	48.40%	0.104	0.977	0.234
V35	38.88%	1.41%	3.19%	0.011	0.020	0.350

Abbreviations: 3DCRT: 3D conformal radiation therapy; IMRT: intensity-modulated radiation therapy; VMAT Volumetric Modulated Arc therapy; PTV: planned tumor volume, OAR: Organs at risk $D_{n\%}$: dose received by n% of the volume; Gy: Gray (unit); Vx%: the volume receiving of the prescribed dose; HI: homogeneity index; CI: conformity index; D_{mean}: the mean dose for the organ; Dmax: maximum dose received (Gy); MU: monitor units

Abdominal irradiation affects the kidneys, which are radiosensitive. It is recommended to keep the Dmean ≤ 18 Gy and V20 ≤ 32 Gy to avoid toxicity [15,16]. Our study shows that both IMRT and VMAT achieved lower Dmean for the kidneys compared to 3D-CRT, with no significant difference between IMRT and VMAT. Sadia et al.'s study aligns with our findings regarding the right kidney [12]. In another study conducted by Tahir Cakir etal the right and left kidney Dmean did not differ significantly between IMRT and 3DRT [17]. Other studies such as Pelin Altinok et al had lower Dmean for IMRT &VMAT than 3DRT in both left and right kidney [10]. In our study, Dmean dose to the left kidney was significant for VMAT &IMRT, while Dmean of the right kidney showed no significance for the three techniques. Our finding is in consistent with the Makhtar study in that, IMRT & VMAT provided superior protection Dmean for both kidneys compared to 3DRT (P= 0.005 and p=0.018 respectively) thus they are appropriate for patients who has chronic renal disease or one kidney.

In contrast the liver, which is a parallel organ to the target and adjacent to the draining lymph node, can suffer from radiation inducing liver toxicity and elevation of liver enzymes achieved if Dmean exceeds 31 Gy and increases by 4% with each 1Gy [19]. Four years later, Liang SX et al demonstrated Dmean above 23Gy with increased incidence of liver disease by 6% [20]. In our study, liver constrains Dmean ≤ 25Gy resulting in significant reduction in IMRT and VMAT for both V35 and V45, thus improving liver sparing compared to 3D-CRT. This result is consistent with the studies by Pelin Altinok and Zhang T et al. [10, 11]

For the spinal cord, the Dmax was improved with VMAT, though the difference from IMRT and 3D-CRT was not significant. Ma et al demonstrated improvement of Dmax of spinal cord with IMRT more than VMAT [21]. Our findings are consistent with Altinok and Tahir et al [10,17], who found higher Dmean doses for 3D-CRT compared to IMRT and VMAT.

Heart toxicity can be induced by radiation dose above 40Gy [22]. The best was VMAT in minimizing and sparing heart with Dmax reaching 22.47 Gy, followed by IMRT 25.91Gy then highest maximum dose was recorded by 3DRT reaching 37.20 Gy with significant value consistent with the finding of Sheng-Fang study [23], except that, the heart V45 were comparable in IMRT and VMAT plans (p= 0.893) and VMAT plans provided superior CI ((p=0.033). Dmean for heart was comparable in three techniques this was in line with Tahir et al study [17].

In conclusion, VMAT and IMRT are both effective in sparing OAR. However, VMAT offers significant advantages in sparing OARs, with lower Dmax values than IMRT and 3D-CRT. In addition, the best conformal plans were yielded with VMAT for PTV

Recommendation:

3DRT technique is not recommended in adjuvant treatment of gastric cancer as it have high incidence of increasing doses and volumes to OAR in addition to its inferiority in proper coverage of PTV. VMAT offers better coverage for the target with potential shorter treatment time, reducing by that the target motion and increasing accuracy during treatment.

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