A comparative planning study on the treatment of gastric cancer patients with tomotherapy, coplanar and non-coplanar three-dimensional conformal radiotherapy (3D-CRT)

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ABSTRACT

Background: The main purpose of this study is to investigate different methods of radiotherapy (RT) using coplanar three-dimensional conformal RT (3D-CRT (cp)), non-coplanar 3D-CRT RT (3D-CRT (ncp)) and helical tomotherapy (HT) techniques to find the optimal method to treat gastric cancer patients. ***Materials and Methods:*** Twenty patients with gastric cancer were retrospectively enrolled. Three different treatment plans including HT, 3D-CRT (cp) and 3D-CRT (ncp) were generated and optimized for each patient. All plans were then evaluated with respect to dosimetric parameters exported from dose-volume histogram curves of target and organ-at-risk (OAR). SPSS software was used for statistical analysis. ***Results:*** The conformity index in the target was similar for all plans ($p > 0.05$), but HT showed significantly better homogeneity compared to the two 3D-CRT methods (p-value < 0.05). Compared to the 3D-CRT (cp) and 3D-CRT (ncp) plans, the HT plans significantly reduced the mean dose, V13 and V20 values of the kidneys (p-Value < 0.05); V5 values of both kidneys were lower in the 3D-CRT (ncp) plan compared to 3D-CRT (cp) and HT. The difference was statistically significant. Moreover, the results proved that the 3D-CRT (ncp) could better preserve kidneys rather than 3D-CRT (cp). Dmean of the liver for HT plans (20.03) was significantly higher than those for both coplanar and non-coplanar 3D-CRT plans (17.86 and 17.7, respectively). ***Conclusion:*** Generally, HT plans appear to be the best, but in the case of selecting an optimum method, it is necessary to pay attention to the location of tumors compared to OARs.

INTRODUCTION

Gastric cancer is one of the most common cancers in Iran [1] and the fourth most common cancer across the world [2]. Although the percentage of advanced gastric cancer has decreased in some Asian countries as a result of routine screening, it is often diagnosed in the advanced stage. The standard treatment for gastric cancer is partial or total gastrectomy, but loco-regional recurrence and distant metastasis are serious problems that make the treatment outcome usually unacceptable [3,4]. The gastric surgical adjuvant trial intergroup 0116 (INT0116) reported the results which made chemotherapy and radiation therapy from the traditional palliative treatment a necessary adjuvant therapy for patients suffering from gastric cancer [5]. However, the radiation standard in gastric cancer is still limited, and various techniques are applied in different radiotherapy departments [6].

Conventionally, either two-dimensional (2D) or three-dimensional conformal RT (3D-CRT) has been applied as adjuvant radiotherapy. 3D-CRT technique has represented better dose distribution and normal tissue sparing over 2D [3]. In recent years, some studies have confirmed the feasibility of using modern techniques like intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) to treat gastric cancer in an attempt to achieve a more conformal and homogeneous dose to the planning target volume (PTV) with lower side effects compared to 3D-CRT [7-10]. On the other hand, normal tissue volume receiving low radiation doses increases using the IMRT method, and consequently the risk of secondary cancer may grow. Moreover, modern facilities and other preparations are needed compared to 3D-CRT [11,12]. Therefore, it is crucial to choose an optimum technique to reduce the toxicity of critical organs close to the stomach.

In another method using helical tomotherapy (HT), radiation is delivered through a rotating gantry while the binary multi-leaf collimator leaves open per rotation and close entirely between projections. This kind of dose delivery may form target dose conformity and OAR sparing [13,14].

Another approach to reduce dose to organs at risk (OAR) in treatment planning is using non-coplanar

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beams, using multiple fixed or rotating radiation beams that do not have the same geometric plane [15].

Overall, previous studies have generated conflicting results; hence, the optimal RT technique remains controversial. To the best of our knowledge, few planning studies are comparing the coplanar and non-coplanar 3D-CRT techniques and are comparing them with state-of-the-art methods such as tomotherapy for gastric cancer. This effort may provide a comprehensive insight for selecting optimal treatment modalities in centers with limited facilities. The purpose of the current study was to evaluate the applicability of helical tomotherapy, coplanar and non-coplanar 3D-CRT techniques to determine the appropriate RT technique for patients with gastric cancer. Dose-volume histograms (DVHs) were created and dosimetric parameters such as the homogeneity index (HI), conformity index (CI), and other corresponding dosimetric parameters of OARs were analyzed to select optimum RT techniques.

MATERIALS AND METHODS

Patient selection

This retrospective study was approved by the Ethics Committee at Isfahan University of Medical Sciences (acceptance date and number: 02/27/2022; IR.ARI.MUI.REC.1400.115). A total of 20 consecutive patients with histologically confirmed adenocarcinoma of stomach were selected in this comparative planning study. All patients were treated with postoperative chemoradiotherapy between 2020 and 2022. Chemotherapeutic regimen, consisting of 5-fluorouracil plus oxaliplatin and capecitabine, was used for all patients. The patients had undergone partial (nine patients) or total (eleven patients) gastrectomy prior to the acquisition of the planning CT-scan.

According to the 8th edition of the American Joint Committee on Cancer staging system [16], sixteen patients were at stage III, three at stage II and one with stomach cancer stage I. Thirteen patients had negative and the others had positive surgical margins. Patients' characteristics were listed in table 1.

Table 1. Patients' characteristics.

	N	%
Median age	(40-78 y) 61.7 y	
Men/Women	14/6	70/30
Surgery type		
Total gastrectomy	11	55
Subtotal gastrectomy	9	45
Stage	III (16)	80
	II (3)	15
	I (1)	5

CT simulation procedures

The patients underwent free breathing CT simulation in the supine position with both arms raised above the head. Both intravenous and oral contrast-enhanced CT simulation were performed with a CT-Simulator (model Siemens Somatom 16 CT Scanner, Germany). The slice thickness was 3 mm. Then, all CT images were exported to the treatment planning systems.

Definition of clinical target volume and OARs

The target volumes and organs at risk (OAR) were contoured on axial CT slices in all patients by the same radiation oncologist to avoid possible variations among physicians. The contouring in this study is in accord with the International Commission on Radiation Units and Measurements 50 and 62 reports for all patients. Individual patient data of preoperative CT images, endoscopic, and pathological findings were used to define the CTV. The clinical target volume (CTV) consisted of the tumor bed, anastomoses, and the regional lymph node (perigastric, celiac, splenic, peripancreatic, paraaortic, and hepatoduodenal) depending on tumor location and T-stage [17]. The PTV was constructed by adding 10 mm margin to the CTV isotropically. The normal tissues consisting of kidneys, liver, heart and spinal cord were delineated as OARs.

Treatment planning

3D-CRT and tomotherapy plans were generated based on CT images of all patients. The total prescribed dose was 45 Gy, divided into 25 fractions across all radiotherapy methods used in this study. Moreover, all plans were required to have the same PTV coverage and dose constraints according quantitative analysis of normal tissue effects in clinics' (QUANTEC) recommendation [18].

For each patient, three radiation plans were designed. The first 3D-CRT plan using a three coplanar field (3D-CRT (cp)) arrangement comprised an anterior field, posterior field, and left lateral field with angles of 0°, 180° and 90°, respectively. The second 3D-CRT plan was designed in order to keep kidney dose at a minimum. It used three non-coplanar fields (3D-CRT (ncp)) including an anterior, a posterior and a vertex field. The adjustments of the beam angles, wedge angles, couch rotation and other parameters were used to optimize the target coverage and avoid the OARs exposure, especially the kidneys. Moreover, MLC leaves were created to achieve the optimum plan. Both 3D-CRT plans were carried out using the TiGRT (version 1.2 LinaTech, Sunnyvale, CA, USA) treatment planning system.

The HT plans were made applying Precision (version 10, Varian Medical Systems, USA) which is a helical fan-beam IMRT using inverse planning software. A field width of 5 cm, pitch of 0.433, and modulation factor of 3 was used for HT plans. The photon beam energy was 6 MV in all modalities.

Evaluation and comparison of treatment plans

Dose distributions and DVH for the PTV and OARs were compared using the 3D-CRT (cp), 3D-CRT (ncp) and helical tomotherapy techniques. The evaluated dosimetric parameters for PTV were the mean dose (D_{mean}), maximum dose (D_{max}), conformity index (CI), and homogeneity index (HI).

The homogeneity index (HI) and conformity index (CI) for the PTV were defined by equations 1 and 2 (19,20):

$$HI = \frac{(D_{2\%} - D_{98\%})}{D_{50\%}} \quad (1)$$

In this formula, $D_{x\%}$ is the amount of dose absorbed in that x% of the PTV.

$$CI = \frac{(V_{RI})}{TV} \quad (2)$$

Where; VRI is 95% isodose volume and TV is the target volume.

For the OARs, several dose–volume metrics were used for the comparisons: D_{mean}, D_{max}, V5, V13 and V20 for both kidneys; D_{mean}, D_{max}, V5, V30 and V40 for the liver, maximum dose for the spinal cord, and D_{mean}, D_{max}, V10, V20 and V30 for the heart.

Statistical analysis

The data were analyzed with SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA) and presented as the mean ± standard deviation. The statistical significance level was considered as p-Value < 0.05.

RESULTS

Patient characteristics are summarized in table 1. The median age of patients was 61.7 years (range 40–78 years), and the mean PTV volume was 552.37 cc (range, 301.3– 759.76 cc). Figure 1 shows representative dose distributions for 3D-CRT (cp), 3D -CRT (ncp), and HT plans; and the corresponding DVHs are displayed in figure 2 within a representative patient.

The dosimetric parameters for PTV are summarized in table 2. The average maximum and mean doses in PTV were the highest in the 3D-CRT (ncp) plans, followed by the 3D-CRT(cp) and HT plans. The difference between all plans was significant ($p < 0.05$). The plan conformity was similar for all three techniques and provided sufficient results (mean CI was about 0.99). The HT plans had the best homogeneity compared to both 3D -CRT plans ($p < 0.05$).

The dosimetric data of OARs for each plan type is presented in table 3. The Dmean values of both kid-neys were lower in HT plans than those in 3D-CRT (cp) and 3D-CRT(ncp) plans ($p < 0.05$). Indeed, com-pared to the 3D-CRT(cp) plan (11.18 + 1.67 vs 8.8 + 1.4), the 3D-CRT(ncp) plan significantly reduced the mean dose of right kidney. Although the left and right kidney's D_{max} was significantly lower in HT plans than that in both 3D-CRT techniques ($p < 0.05$), there were no significant differences between 3D-CRT(cp) and 3D-CRT(ncp) techniques ($p > 0.05$). In the case of V13 and V20, a statistically significant benefit was achieved for HT plans for both kidneys ($p < 0.05$), but when considering the V5 value, the 3D-CRT(ncp) plan achieved better results compared to others ($p < 0.05$). Moreover, 3D-CRT(ncp) plan achieved significantly lower results compared to the 3D-CRT (cp) plan in the case of V5, V13, and V20 of kidneys (p-Value < 0.05).

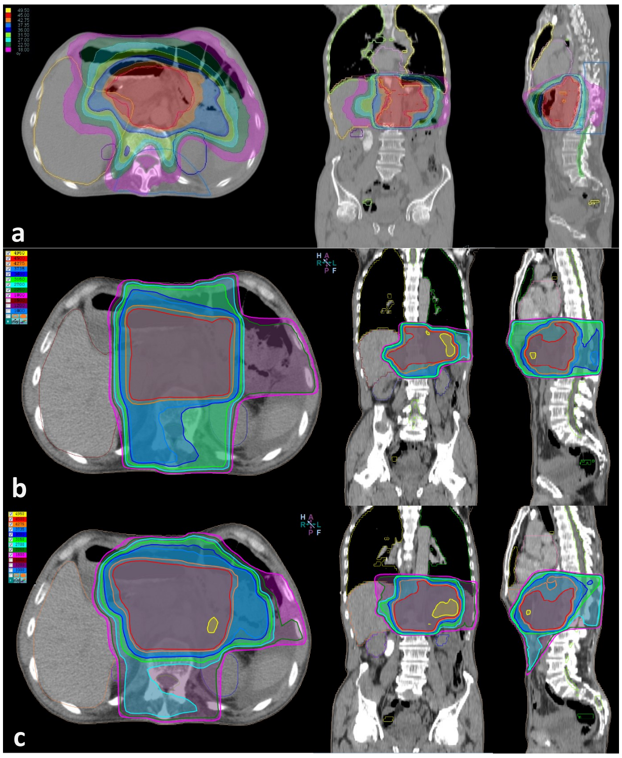

Figure 1. Dose distributions of the same patient in axial, coronal, and sagittal views with helical tomotherapy **(a)**, coplanar three-dimensional conformal radiotherapy **(b)**, and non-coplanar three-dimensional conformal radiotherapy **(c)**. Isodose lines in the image showing the irradiation dose to OARs.

Table 2. Dosimetric comparison for PTV based on three various radiotherapy techniques (3D-CRT(cp): coplanar three-dimensional conformal radiotherapy, 3D-CRT(ncp): non-coplanar three-dimensional conformal radiotherapy, HT: helical tomotherapy, HI: homogeneity index, CI: conformity index).

Parameter	3D-CRT (cp)	3D-CRT (ncp)	(C) HT	p-Value		
				A vs. B	A vs. C	B vs. C
D_{mean}	46.33± 0.14	47.08± 0.24	45.85± 0.13	0.017	0.008	0.001
D_{max}	50.8± 0.13	51.2± 0.37	48.36± 0.33	0.026	0.001	0.000
CI	0.99± 0.0008	0.99± 0.001	0.99± 0.009	0.15	0.066	0.158
HI	0.12± 0.003	0.14± 0.005	0.07± 0.03	0.082	0.007	0.007

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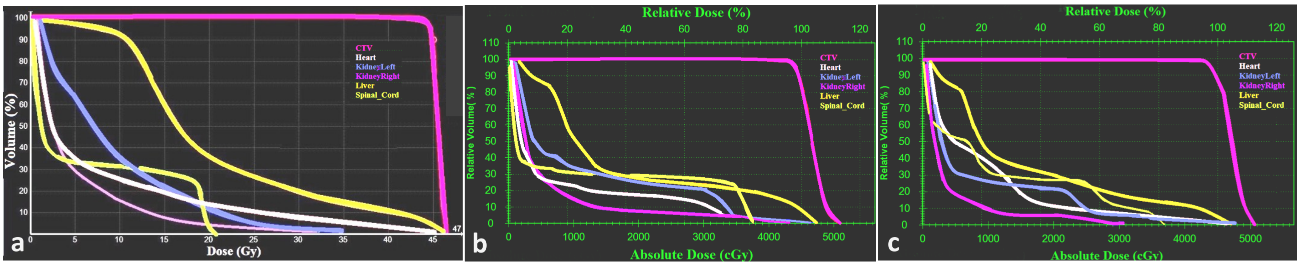

Figure 2. DVH curves of target and OARs for an actual treatment plan for one patient helical tomotherapy **(a)**, coplanar three-dimensional conformal radiotherapy **(b)**, and non-coplanar three-dimensional conformal radiotherapy **(c)**.

Table 3. Dosimetric results for OARs in radiotherapy of gastric cancer patients based on three various radiotherapy techniques (3D-CRT(cp): coplanar three-dimensional conformal radiotherapy, 3D-CRT(ncp): non-coplanar three-dimensional conformal radiotherapy, HT: helical tomotherapy, R: Right, L: Left, VX (%) indicates the volume, where the dose is higher than X% of the prescribed dose).

Organ Parameter	(A) 3D-CRT(cp)	(B) 3D-CRT(ncp)	(C) HT	p-Value		
				A versus B	A versus C	B versus C
R kidney D_{mean}	11.18± 1.67	8.8 ± 1.4	5.6 ± 0.52	0.000	0.001	0.008
R kidney D_{max}	42.57 ± 2.47	41.4 ± 2.8	35.16 ± 1.5	0.429	0.002	0.006
R kidney V_5 (%)	41.42 ± 5.7	33.6 ± 5.3	42.2 ± 5.8	0.000	0.72	0.004
R kidney V_{13} (%)	27.9 ± 4.8	20.48 ± 4.2	8.6 ± 0.98	0.000	0.000	0.007
R kidney V_{20} (%)	21.05 ± 4.17	18.3 ± 4.09	3.39 ± 0.61	0.000	0.001	0.002
L kidney D_{mean}	17/17 ± 2.3	16.33 ± 2.6	10.71 ± 0.6	0.2	0.005	0.021
L kidney D_{max}	46/59 ± 0.54	47.41 ± 1.09	44.34 ± 0.65	0.261	0.003	0.008
L kidney V_5 (%)	57/26 ± 6.6	51.78 ± 7.2	68.93 ± 6.08	0.001	0.000	0.000
L kidney V_{13} (%)	48/11 ± 7.4	45.54 ± 7.4	27.95 ± 2.1	0.000	0.014	0.028
L kidney V_{20} (%)	44/89 ± 7.5	40.25 ± 7.5	15.05 ± 1.6	0.000	0.001	0.004
Liver D_{mean}	17.86 ± 0.75	17.7 ± 0.82	20.03 ± 0.49	0.58	0.001	0.003
Liver D_{max}	47.77 ± 1.2	49.11 ± 0.48	48.03 ± 0.51	0.266	0.853	0.171
Liver V_5 (%)	87.36 ± 1.3	85.95 ± 1.16	94.14 ± 1.3	0.236	0.000	0.000
Liver V_{30} (%)	25.3 ± 2.01	22.02 ± 1.97	20.96 ± 1.4	0.000	0.003	0.393
Liver V_{40} (%)	19.14 ± 1.6	15.1 ± 1.5	10.36 ± 1.2	0.000	0.000	0.000
Spinal cord D_{mean}	8.7 ± 0.7	9.26 ± 0.6	7.3 ± 0.33	0.12	0.064	0.005
Spinal cord D_{max}	40.21 ± 1.2	41.47 ± 1.5	30.66 ± 1.5	0.093	0.000	0.000
Heart D_{mean}	7.04 ± 1.4	8.6 ± 1.4	7.6 ± 1.2	0.007	0.431	0.217
Heart D_{max}	45.11 ± 1.1	43.5 ± 2.5	45.7 ± 0.49	0.533	0.537	0.378
Heart V_{10} (%)	17.6 ± 4.2	31.5 ± 6.1	22.8 ± 4.07	0.000	0.016	0.027
Heart V_{20} (%)	13.58 ± 3.7	12.2 ± 3.4	14.08 ± 2.3	0.165	0.821	0.38
Heart V_{30} (%)	9.9 ± 3.4	7.08 ± 2.2	7.7 ± 1.2	0.059	0.423	0.677

Liver Dmean values were significantly lower in both 3D-CRT plans than those in HT plans ($p < 0.05$), but there are no significant differences between 3D-CRT(cp) and 3D-CRT(ncp) plans. The estimated criterion for the liver the mean dose was below 30 Gy for all plans. With regard to the liver, the V30, and V40 were significantly lower with HT compared to both 3D-CRT plans ($p < 0.05$ for all cases except for V30 of 3D-CRT(ncp) vs HT ($p = 0.393$)). Although liver V5 values were significantly higher in HT plans than those in 3D-CRT plans ($p = 0.00$), the difference in V5 between 3D-CRT(cp) and 3D-CRT(ncp) plans did not differ significantly (p=0.236).

The maximum dose of the spinal cord showed a reduction for HT plans compared to the 3D-CRT(cp) and 3D-CRT(ncp) plans (30.66 + 1.5 Gy vs. 40.21 + 1.2 and 41.47 + 1.5, respectively). In general, the 3D-CRT(cp) decreased the V10 of the heart, (by ~ 44% and ~ 22%) compared to the 3D-CRT(ncp) and HT ($p < 0.05$). No significant advantage for one technique over the others was observed for other dosimetry parameters. However, the mean dose of the heart revealed a significant statistical reduction for 3D-CRT(cp) plans compared to the 3D-CRT(cp) ($p = 0.007$). With specific consideration of the data, more results would be obtained, which will be discussed in the next part.

DISCUSSION

Various radiotherapy departments, especially centers with limited state-of-the-art equipment, need to select and apply optimal methods to improve tumor coverage and reduce the radiation dose received from OAR.

The current study investigated the effects of different radiotherapy techniques on PTV and OAR dosimetric parameters in patients with gastric cancer. Furthermore, efforts were made to deliver lower dose to OARs without compromising the dose received by the PTV. Based on the obtained results, tomotherapy permitted mean dose reduction to both kidneys in addition to a reduction in mean dose in the heart in patients with gastric tumors in the cardia (table 3). These data suggest that the choice of gastric

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radiotherapy method may depend on tumor location and on the oncologist's preference for saving a specific OAR.

Furthermore, we found that the HT plans achieved more homogeneous dose coverage compared to both 3D CRT methods (table 2). However, similar conformity index was found for all treatment techniques based on the results obtained in the current study.

Our results are in comparison to the studies conducted by Kucuktulu *et al.* [10] and Onal *et al.* [14], who found that the HT technique yielded the best tumor conformity and homogeneity compared to other techniques for adjuvant treatment of stomach cancer. Another previous study compared dosimetric parameters of various modern and conventional radiotherapy techniques in total gastrectomy patients. It revealed that HT significantly provided more homogeneity compared to others [7].

One of the important side effects of radiotherapy for gastric cancer is renal toxicity induced by increased radiation dose to the kidney. Therefore, selection of an optimal radiation technique is essential [19,21]. In the current study, V5 was significantly reduced in both kidneys in the non-coplanar 3D CRT plan compared to other plans (table 3). In addition, mean doses to both kidneys were highest for 3D-CRT(cp), 3D-CRT(ncp) and HT in decending order. The results of tomotherapy and coplanar 3D-CRT plans for the right kidney Dmean are consistent with those in a previous study carried out by Choi [22]. They examined the values of kidneys Dmean in various RT methods, both in deep inspiration breath-hold and in free-breathing techniques. Furthermore, they reported that these values for free-breathing tomotherapy and 3D-CRT were 7.17 vs. 8.45 for the right kidney and 8.79 vs. 10.69 for the left kidney, respectively. Compared to our study, a lower Dmean was achieved using the 3D-CRT method. This difference could be the result of different planning techniques used as they applied four 10 MV energy beams, organized as anterior-posterior opposed beams and two lateral beams, but we used anterior-posterior opposed beams and one lateral beam with an energy of 6 MV. Moreover, our results show superior performance and protection compared to tomotherapy alone [22]. Our non-coplanar 3D-CRT plan of the right kidney yielded similar results to their 3D-CRT plan values.

Renal V20 has been identified as important for assessing kidney function compared to mean dose [23]. Kidney V20 should be less than 70% and contralateral kidney V20 should be less than 30% [14]. Although the right and left kidney V20 results in our study were within the tolerance limits for all plans, the HT plan obtained lower values followed by 3D-CRT(ncp) and 3D-CRT(cp) plans (table 3). This difference was statistically significant for all plans. These results are in accordance with the previous studies [10]. Moreover, the right kidney V20 by the tomotherapy technique in our study was similar to that previously reported. Comparion of both 3D-CRT techniques in our study showed that the non-coplanar setting could better preserve the kidneys (table 3). In the current study, the average values of patients' dosimetric parameters were higher in the left kidney than those in the right kidney. It is due to the fact that the lymph nodes of all patients were placed in the radiation field for treatment.

Since the stomach is anatomically close to the heart, reducing the radiation dose to the heart is important in order to reduce the risk of side effects in the heart [24]. In the current study, gastric cancer was more commonly found in the non-cardiac region of the stomach (87%), with approximately 13% in the cardia region.

In general, our study revealed that heart dosimetry parameters showed no significant differences among all groups except V10 (table 3). In details, the results of 3D-CRT (cp) planning suggested that, compared to other methods, mean heart dose could be reduced in patients with cardia region tumors. According to the data presented in table 3, heart V20 and V30 values were reduced by 3D-CRT (ncp) plans in patients with non-cardia region tumor, and by HT plans in patients with cardia region tumor. Overall, our results were consistent with those obtained by Wang *et al.* [25], which assumed that the tomotherapy method could provide superior dose distribution for targets with more complex shapes, especially for patients undergoing proximal partial or total gastrectomy (CI = 0.92 ± 0.03). In another study, Serarsalan *et al.* [12] reported a dosimetric comparison of different radiotherapy methods for similar locations of stomach tumors to prevent discrepancies in the result. They found that IMRT offers better tumor conformity (0.75 vs. 0.60 and 0.58) and OARs protection compared to field-in-field intensity-modulated RT and wedge-based conformal RT, making it the most appropriate technique for antrum-located gastric cancer.

Chemotherapy often affects liver function. Therefore, more attention should be paid to the liver of patients who undergo adjuvant radiotherapy. The risk of liver toxicity can be assessed by dosimetric parameters such as mean dose and V30 [21]. We showed that the HT plans resulted in significantly higher liver mean dose than both 3D-CRT techniques, but the tolerance doses were not higher; however, the V30 of the liver was obtained lower for HT plans among all methods (table 3). Similar results were found for the liver in volume-based criteria V30 in other studies. However, they revealed a superior mean dose for the liver by the tomotherapy technique. This discrepancy between studies reflects different priorities given to organs as dose constraints, and the application of various parameters by physicists during the treatment

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planning process to improve the dose sparing of the kidneys and other OARS as much as possible.

The technique that most effectively fulfilled the maximum spinal cord dose was the HT technique. However, there was no significant difference between coplanar and non-coplanar 3D-CRT plans (table 3). Overall, our findings are consistent with those in a recent study that compared different radiotherapy modalities for total gastrectomy patients [7]. The highlight of our results showed that HT achieved the most favorable maximal dose of the spinal cord improvement over mentioned study (30.66 vs. 36.35 Gy).

One of the strengths of this study is that it performed a dosimetric comparison between various conventional and modern radiotherapy techniques and suggested the most appropriate treatment combination strategy regarding target coverage and OAR doses. However, our study was retrospective and subject to all limitations associated with such studies. In addition, the relatively small number of patients with the same gastric tumor location limits our ability to make strong recommendations. In addition to demonstrating the benefits of using non-coplanar planning compared to 3D-CRT coplanar planning in reducing some dose parameters like kidney, the increased treatment time required for table rotation and issues such as the mechanical load on the treatment device should also be considered.

CONCLUSION

We compared coplanar and non-coplanar 3D-CRT and HT methods for patients with gastric cancer. The HT plans had a dosimetric superiority over both 3D-CRT techniques in terms of the homogeneity index of the PTV, dose to the kidneys, and Dmax of the spinal cord. The results show that the optimal plan for decreasing the dose received by the heart varies according to the location of the tumor. Indeed, 3D-CRT (ncp) method can reduce some dosimetric parameters of OARs like D_{mean} and V20 of kidney, etc. compared to 3D-CRT (cp) which resulted in better sparing of OARs.

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Author contribution: A.K. and A.Sh. designed and conceived the study; A.K., L.M. and M.K. collected and analyzed the data; A.K. prepared the figures and drafted the manuscript; L.M., M.K. and A.Sh. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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