Assessment of Field-in-Field, 3-Field, and 4-Field Treatment Planning Methods for Radiotherapy of Gastro-Esophageal Junction Cancer

Ghazal Mehri-Kakavand[1], Mohamad Pursamimi[1], Wrya Parwaie[2], Mahdi Ghorbani[3]*, Mehdi Khosravi[4], Seyyed Mohammad Hosseini[5,6], Ali Soleimani Meigooni[7]

[1]MSc, Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]PhD, Department of Medical Physics, Faculty of Paramedical Sciences, Ilam University of Medical Sciences, Ilam, Iran
[3]PhD, Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]MSc, Vali-e-Asr Radiotherapy and Oncology Center, Qom University of Medical Sciences, Qom, Iran
[5]PhD Candidate, Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[6]PhD Candidate, Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran
[7]PhD, Comprehensive Cancer Centres of Nevada, Las Vegas, USA

ABSTRACT

Background: Gastro-esophageal (GE) junction cancer is the fastest-growing tumor, particularly in the United States (US).

Objective: This study aimed to compare dosimetric and radiobiological factors among field-in-field (FIF), three-field (3F), and four-field box (4FB) radiotherapy planning techniques for gastro-esophageal junction cancer.

Material and Methods: In this experimental study, thirty patients with GE junction cancer were evaluated, and three planning techniques (field-in-field (FIF), three-field (3F), and four-field box (4FB)) were performed for each patient for a 6-MV photon beam. Dose distribution in the target volume, the monitor units (MUs) required, and the dose delivered to organs at risk (OARs) were compared for these techniques using the paired-sample *t*-test.

Results: A significant difference was measured between the FIF and 3F techniques with respect to conformity index (CI), dose homogeneity index (HI), and tumor control probability (TCP) for the target organ, as well as the D_{mean} for the heart, kidneys, and liver. For the spinal cord, the FIF technique showed a slight reduction in the maximum dose compared to the other two techniques. In addition, the $V_{20\ Gy}$ of the lungs and the normal tissue complication probability (NTCP) of all OARs were reduced with FIF method.

Conclusion: The FIF technique showed better performance for treating patients with gastro-esophageal junction tumors, in terms of dose homogeneity in the target, conformity of the radiation field with the target volume, TCP, less dose to healthy organs, and fewer MU.

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Keywords

Radiotherapy; Radiation Dosage; Esophagogastric Junction; Cancer; Three-Field; Four-Field; Field-In-Field

Introduction

Esophagogastric orgastro-esophageal (GE) junction cancer is the fastest growing tumor in the western population, particularly in the United States (US) [1, 2]. Concurrently, various studies have found a similar increase in the incidence of the disease in many parts of the world [3-4]. The fatal nature of the disease has attracted the interest of physicians and investigators. The increase in the incidence of GE

*Corresponding author: Mahdi Ghorbani
Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: mhdghorbani@gmail.com

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junction cancer is primarily attributed to the growing rate of obesity, which in turn increases the risk of gastro-esophageal reflux disease and eventually esophagus adenocarcinoma [4]. Surgery, chemotherapy, and radiation therapy, either alone or in combination with each other are the most widely used procedures for treating locally advanced esophageal cancer [5].

Radiotherapy plays a significant role in cancer treatment, especially in patients with GE junction cancer [6-7]. The medical linear accelerator is now acknowledged as a crucial instrument for radiation therapy and the fight against cancer [8]. Therefore, radiation therapy should be administered in such a way that normal tissues receive the minimum dose while the maximum dose is delivered to the tumor tissue [9-10]. As mentioned, radiation therapy has a definite role in the treatment of esophageal cancer. However, the main challenge is delivering the exact dose required to the tumor site while minimizing normal tissue toxicity [11-12].

However, wedges, compensators, beam-shaping devices, blocks, and computer-controlled multileaf collimators (MLCs) are used to spare organs at risk organs at risk (OARs), these modifications increase the dose emitted on normal tissues due to considerable beam scattering. On the other hand, wedges are not suitable for large therapeutic planes [13, 14]. The field-in-field (FIF) technique is a type of forward-intensity modulated radiation therapy (IMRT) [15]. The IMRT aimed to deliver a lower dose to the surrounding normal tissues while increasing dose uniformity at the target volume. The FIF approach was utilized in various studies to optimize dose distribution during radiotherapy [16, 17]. Ghadimi et al. [13] performed a study to analyze and compare the dosimetric parameters of the three-dimensional conformal radiotherapy (3D-CRT) and FIF methods in patients with esophageal cancer. Less-weighted fields were selected for the FIF plans to improve the dose distributions for the 3D-CRT plans. The optimized FIF plans were determined by a trial-and-error process and evaluation of the 3-D dose distributions and dose-volume histograms (DVHs). By using MLCs and sequential irradiation, several subfields were merged into the main fields. The results indicated that the FIF method had better dosimetric parameters than the 3D-CRT technique due to better dose distribution in the planning target volume (PTV) and a reduction in the dose delivered to OARs. Allaveisi et al. [14] also evaluated and compared the performance of the FIF and four-field box (4FB) techniques in terms of dosimetric and radiobiological parameters in patients with esophageal cancer. However, the FIF plans were constructed similar to the 4FB plans, the differences, including: the generation by MLCs and not using wedges for the FIF plans resulted in the advantages for the FIF plans over the 4FB plans in terms of more homogeneous dose distribution, a lower D_{max} value, fewer monitor units (MUs), and better dose conformity on the PTV [14]. Pursamimi et al. [9] evaluated the performance of the FIF, three-field (3F), and 4FB radiotherapy planning techniques in patients with pancreatic cancer undergoing 3D-CRT. The results showed that the FIF plans were superior to those of 3F and 4FB with the same prescribed dose and at the target site. The results also showed fewer MUs and lower emissions toward OARs in the FIF technique compared to the other techniques.

A review of previous studies [9, 13-14] indicates that no study has yet analyzed the dosimetric and radiobiological outcomes of FIF technique in patients with GE junction cancer. Therefore, the aim of this study was to compare the FIF, 3F, and 4FB techniques in radiotherapy of GE junction cancer in terms of dosimetric and radiobiological parameters.

Material and Methods

This study is an experimental study.

Patients' characteristics

Thirty patients with a confirmed diagnosis

of GE junction cancer (Figure 1), including 15 males and 15 females, aged 35-60 years (mean: 46), referred to Vali-e-Asr Oncology and Radiotherapy Center (Qom, Iran) were enrolled that their characteristics are presented in Table 1. In the first step of treatment, axial Computed Tomography (CT) images were acquired in the supine position with hands above the head using the Neusoft CT scanner (NeuViz 16, Neusoft Medical Systems, PR, China). The treatment strategy in the form of 3D-CRT was designed using a PCRT3D treatment planning system (RF Tecnicas Radiofizicas, Zaragoza, Spain).

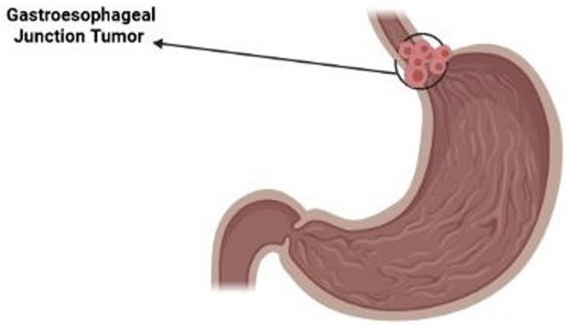

Figure 1: Adenocarcinoma of the gastro-esophageal (GE) junction

Table 1: Characteristics of the patients with the gastro-esophageal (GE) junction cancer in the present study

Characteristics	Number
Number of male patients	15
Number of female patients	15
Age, mean (range) in years	40 (35-45)
Stage	T2-T3
Prescribed dose (Gy)	50.4
PTV volume (cc)	810.80±214.62
Heart volume (cc)	628.78±141.36
Right kidney volume (cc)	130.98±27.90
Left kidney volume (cc)	139.98±32.85
Right lung volume (cc)	2017.58±418.23
Left lung volume (cc)	1635.39±437.92
Liver volume (cc)	1359.60±408.45
Spinal cord volume (cc)	58.67±15.13

PTV: Planning target volume

Target volume and organs at risk

At the baseline, the gross tumor volume (GTV) for each patient was contoured according to the guidelines of the Radiation Therapy and Oncology Group (RTOG) [18]. The initial clinical target volume (CTV) was also determined based on GTV plus 15 mm margin and considered as the area in which tumor cells were likely located. In addition, the PTV was created with an isotopic margin of 10 mm around the defined CTV (Figure 2). This isotopic margin considered the uncertainties resulting from patient adjustment, position changes, and patient movements for all beams. As OARs, the spinal cord, heart, liver, right kidney, left kidney, right lung, and left lung were contoured on the axial CT scans.

Comparative treatment planning study

Individual FIF, 3F, and 4FB radiotherapy planning techniques were developed for each patient. A 6-MV photon beam was designed by Shinva linear accelerator (Shinva Medical, Shandong, China) equipped with an MLC. The dose rate was equal to 200 MU/min for all the beams delivered. The 4FB treatment plan included anterior, posterior, and two lateral fields. The weight of the beams, the angles of the wedges, and the orientation of the wedges were adjusted so that at least 95% of the prescribed dose (50.4 Gy) was delivered to the PTV. The angle of the fields varied due to differences in patients' anatomy and the treatment volume, determined by the radiation oncologist for each individual. Thus, a wedge was used in one or more fields as needed. The 3F treatment plan consisted of an anterior field, a posterior field, and a left lateral field, and wedges were used for all the fields. At least 95% of the 50.4 Gy required dose was delivered to the PTV by adjusting the wedge

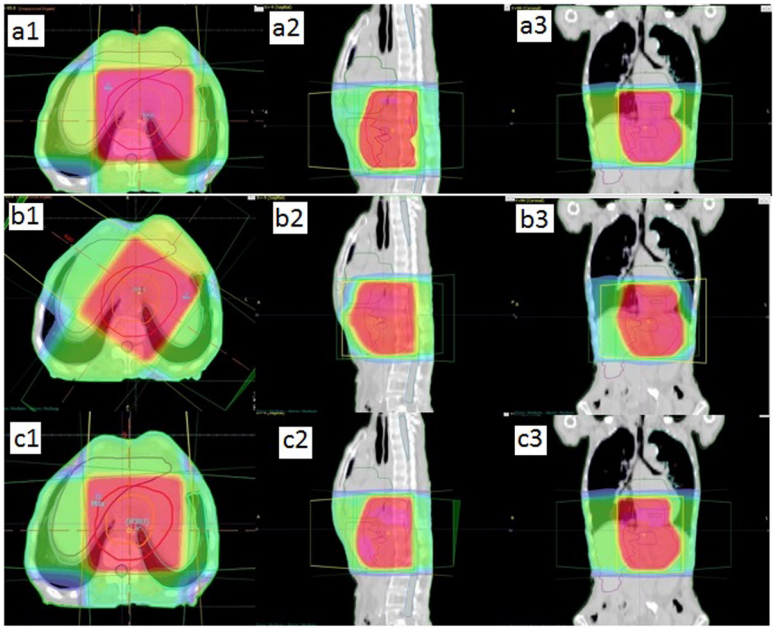

Figure 2: Isodose curves and colour wash dose distributions in cross-sectional, sagittal, and coronal views for a sample gastro-esophageal (GE) junction cancer patient for three-field (3F) (a1-a3), four-field box (4FB) (b1-b3), and field-in-field (FIF) (c1-c3) techniques

angles, wedge orientations, and beam weights. A wedge can be used during the three-field and four-field (box) techniques, if needed, but no wedge is applicable for the FIF technique. It was planned that at least 95% of the 50.4 Gy authorized dose would reach the tumor volume by adjusting the beam weights, wedge angles, and wedge directions. Two plans were used to design the FIF therapeutic strategy. The first plan constituted 4FB with a PTV margin of 5 mm and without any wedge. After selecting the appropriate International Commission on Radiation Units and Measurements (ICRU) point, the second plan was designed with the other four fields to shield high-dose (>108%) regions. Additionally, these weights of beams changed to produce a desirable dose with acceptable homogeneity in the PTV [9, 14, 19]. Almost 95% of the total dose prescribed was delivered through the first plan, and the remaining 5% via the second plan. The dose prescribed for patients was 50.4 Gy for PTV (in 1.8 Gy fractions, administered as five fractions per week). It should also be noted that the patients underwent routine treatment, and these three techniques were only planned without any delivery to the patients.

The DVHs corresponding to the three treatment techniques were obtained for the PTV, heart, right & left kidneys, right & left lungs, liver, and spinal cord. The parameters compared between the three treatment techniques for the PTV included the mean dose (D_{mean}), maximum dose (D_{max}), minimum dose (D_{min}), conformity index (CI), homogeneity index (HI), and tumor control probability (TCP). For OARs, the mean dose (D_{mean}), maximum dose (D_{max}), the equivalent uniform dose (EUD), the normal tissue complication probability (NTCP) (for the heart, kidneys, lungs, liver, and spinal cord), and $V_{20\ Gy}$ (the percent volume receiving greater than or equal to 20 Gy, for the lungs) were compared between the three treatment techniques. Uncertainty was expressed as the standard deviation for each reported value. Finally, the number of MUs required was compared between the three therapeutic methods.

Dosimetric parameters

After calculating DVH, the CI of radiation was calculated as the ratio of the tissue volume covered by the reference isodose (i.e., 95% of the isodose according to the ICRU) [20], to the target volume (i.e., PTV):

$$CI = V_{PTV} \times \frac{V_{TV}}{TV_{PV}^{2}} \quad (1)$$

In this equation, V_{TV} is the treatment volume of the prescribed isodose line; V_{PTV} is the volume of PTV, and TV_{PV} represents the volume of V_{PTV} inside V_{TV}. The value of CI ranges from 0 to 1; the higher the CI, represents higher dose conformity within PTV [21, 22]. In addition, HI is defined as follows:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{prescribed}} \times 100\% \quad (2)$$

where $D_{2\%}$ represents the minimum dose of the target volume; $D_{98\%}$ is the maximum dose inside the target volume, and $D_{Prescribed}$ is the prescribed dose. The main reason for the selection of these doses ($D_{2\%}$ and $D_{98\%}$) in this formula is that the calculation of a true minimum or maximum dose relies on dose calculation parameters. The smaller the HI value represents a more homogeneous dose distribution within the target volume [13, 17, 23].

Using Niemierko's phenomenological model, the radiobiological parameters of TCP and NTCP values were also assessed [24]. Initially, EUD was calculated to determine TCP and NTCP based on Equation 3. The EUD represents the biologically effective dose when it is homogeneously distributed over a tumor mass. Biological effects will be equal to those of a non-homogeneous dose distribution [25].

$$EUD = \left(\sum_{i=1} (V_i EQD_i^{\alpha}) \right)^{\frac{1}{\alpha}} \quad (3)$$

In this formula, α is the unitless model parameter for the normal structure of the tumor [25]; V_i is also a unitless item representing the fraction of the volume receiving a dose of D_i in Gy. Finally, equivalent dose (EQD) is the biologically equivalent physical dose, based on 2 Gy per fraction defined in the following equation:

$$EQD = D \times \left(\frac{\frac{\alpha}{\beta} + \frac{D}{n_f}}{\frac{\alpha}{\beta} + 2} \right) \quad (4)$$

where n_f and $d_f = D/n_f$ are the number of fractions and dose per fraction during the therapeutic course, respectively. Furthermore, α/β shows the tissue-specific linear-quadratic parameter for the intended organ [14, 26]. In this study, EUDs were calculated using the parameters listed in Table 2.

Niemierko [24] proposed a logistic function to calculate NTCP based on EUD to determine the late response of normal tissues to radiation:

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD} \right)^{4 \times \gamma_{50}}} \quad (5)$$

where TD_{50} is the tolerance dose (TD) for a 50% complication rate at an interval time when the entire organ of interest receives ho-

Table 2: Parameters for applying Niemierko's approach to compute the equivalent uniform dose (EUD)

Tissue	Volume type	TD_{50}/TCD_{50} (Gy)	γ_{50}	α	α/β
GE junction	Tumor	TCD_{50}=49.09	2.16	-13	10
Heart	OAR	TD_{50}=50	3	3	2
Kidney	OAR	TD_{50}=28	3	1	3
Lung	OAR	TD_{50}=24.5	2	1	3
Liver	OAR	TD_{50}=40	3	3	1.5
Spinal cord	OAR	TD_{50}=66.5	4	13	2

GE: Gastro-esophageal; TD: Tolerance dose; TCD: Tumor control dose; OAR: Organs at risk

mogeneous irradiation, and γ_{50} is a unitless model parameter specific to the normal tissue or tumor of interest and marks the slope of the dose-response curve [14, 19]. Similarly, the following equation was used to calculate the TCP of the tumor:

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\times\gamma_{50}}} \quad (6)$$

In this formula, TCD_{50} is the absorbed dose resulting in a 50% control rate over a homogeneously exposed tumor, and γ_{50} is a unitless model parameter characterizing the slope of the dose–response curve [9, 27, 28]. Here, TCD stands for tumor control dose. The number of the MU required was recorded and compared between the therapeutic techniques.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 28, SPSS Inc., Chicago, USA) software was used to conduct statistical analyses. The Kolmogorov-Smirnov test was employed to determine whether the distribution of the data was normal. The paired-sample *t*-test was performed to compare variables with normal distribution, and a significant difference between the two groups was defined as P-value<0.05. The Chi-square test was also used to compare variables with non-normal distribution.

Results

In this study, all parameters were evaluated using the Kolmogorov-Smirnov statistical test, showing normal distribution for all with a 95% confidence interval.

The isodose distribution in the 3F, 4FB, and FIF techniques in a patient with GE junction cancer is shown in Figure 2. In addition, Figure 3 demonstrates the DVHs of PTVs and OARs for the 3F, 4FB, and FIF techniques in patients with GE junction cancer.

Dosimetric parameters obtained by DVH analysis for PTVs and OARs using the three therapeutic techniques are presented in Tables 3 and 4.

1. Planning target volume

According to the results presented in Table 3, the values of TCP, EUD, and D_{mean} for PTV were significantly different between the three treatment plans (FIF *vs*. 3F and FIF *vs*. 4FB, P-value<0.05). TCP, EUD, and D_{mean} did not significantly differ between the 3F and 4FB procedures, indicating that these approaches did not outperform the other (P-value>0.05). Table 3 shows a significant difference in D_{min} comparing the FIF plan with each of 3F and 4FB (P-value<0.05). However, there was no significant difference in D_{min} between 3F and 4FB (P-value>0.05), showing that these techniques were compared with each other.

In addition, there were significant differenc-

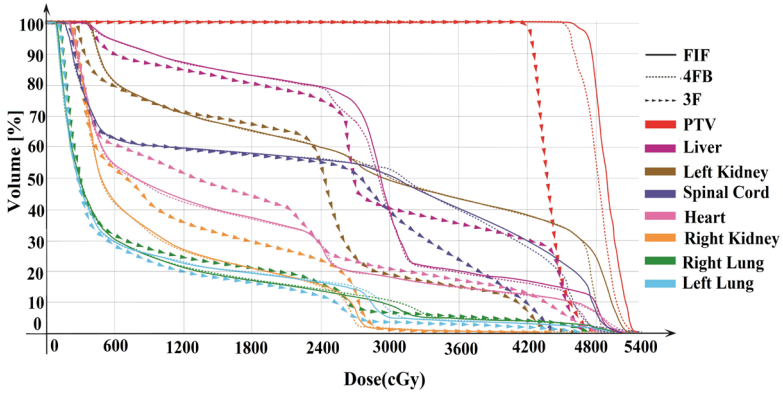

Figure 3: Dose-volume histogram (DVH) for an example patient with cancer of the gastro-esophageal (GE) junction cancer obtained from three-field (3F), four-field box (4FB) and field-in-field (FIF) techniques.

Table 3: Dosimetric and radiobiologic results for planning target volume (PTV) obtained by three-field (3F), four-field box (4FB), and field-in-field (FIF) treatment planning techniques for treatment of gastro-esophageal (GE) cancer.

Parameter	3F	4FB	FIF	P-value
D_{mean} (Gy)	51.16±0.57	51.30±0.53	50.59±0.33	*<0.01 (4FB vs. FIF)
				*<0.01 (FIF vs. 3F)
				0.56 (3F vs. 4FB)
D_{max} (Gy)	54.53±1.17	54.03±1.06	52.50±0.38	*<0.01 (4FB vs. FIF)
				*<0.01 (FIF vs. 3F)
				*<0.01 (3F vs. 4FB)
D_{min} (Gy)	45.56±2.85	46.21±2.03	45.81±1.87	*<0.01 (4FB vs. FIF)
				0.36 (FIF vs. 3F)
				*0.04 (3F vs. 4FB)
CI	1.95±0.24	1.89±0.21	1.82±0.23	0.25 (4FB vs. FIF)
				*0.03 (FIF vs. 3F)
				0.31 (3F vs. 4FB)
HI	0.11±0.02	0.10±0.02	0.07±0.01	*<0.01 (4FB vs. FIF)
				*<0.01 (FIF vs. 3F)
				*<0.01 (3F vs. 4FB)
EUD (Gy)	50.89±1.44	50.82±1.26	50.38±1.34	*0.03 (4FB vs. FIF)
				*0.03 (FIF vs. 3F)
				1 (3F vs. 4FB)
TCP (%)	57.83±6.05	57.99±5.86	55.58±6.01	*0.02 (4FB vs. FIF)
				*0.04 (FIF vs. 3F)
				1 (3F vs. 4FB)
MU	307.76±21.88	273.51±27.94	249.98±18.21	*<0.01 (4FB vs. FIF)
				*<0.01 (FIF vs. 3F)
				*<0.01 (3F vs. 4FB)

3F: Three-field; 4FB: Four-field box; FIF: Field-in-field; CI: Conformity index; HI: Homogeneity index; EUD: Equivalent uniform dose; TCP: Tumor control probability; MU: Monitor unit
*: The P-value is less than 0.05 and this indicates a significant difference between the two techniques.

es in comparing the D_{max}, HI, and MU for PTV between different treatment plans (FIF vs. 3F and FIF vs. 4FB) (P-value<0.05). In terms of CI, there was a significant difference between the FIF and 3F techniques (P-value<0.05); however, CI showed no significant difference comparing 4FB *vs*. FIF or 3F *vs*. 4FB (P-value>0.05).

2. Organs at risk

2.1. Heart

As shown in Table 4, NTCP and D_{mean} for the heart revealed no significant difference comparing 4FB *vs*. FIF and 3F *vs*. 4FB. However, both NTCP and D_{mean} were significantly different comparing FIF *vs*. 3F (P-value<0.05). In terms of EUD in the heart, there was a significant difference comparing FIF vs. 3F and 3F *vs*. 4FB (P-value<0.05), but not for 4FB *vs*. FIF (P-value>0.05). Finally, D_{max} for the heart was significantly different between the treatment plans (4FB *vs*. FIF, FIF *vs*. 3F, and 3F *vs*. 4FB) (P-value<0.05).

2.2. Kidneys

For the right kidney, NTCP, EUD, and D_{mean} showed statistically significant differ-

Table 4: Dosimetric results for the organs at risk (OARs) in the three-field (3F), four-field box (4FB), and field-in-field (FIF) treatment planning techniques.

OAR	Parameter	3F	4FB	FIF	P-value
Heart	D_{mean} (Gy)	20.33±4.79	18.17±4.40	17.16±5.03	0.94 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					0.05 (3F vs. 4FB)
	D_{max} (Gy)	54.48±1.67	52.81±1.59	51.49±0.77	*0.01 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	EUD (Gy)	24.04±3.08	22.33±3.99	21.79±3.14	0.49 (4FB vs. FIF)
					*0.03 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	NTCP (%)	0.05±0.09	0.02±0.04	0.02±0.04	1 (4FB vs. FIF)
					*0.02 (FIF vs. 3F)
					0.15 (3F vs. 4FB)
Right kidney	D_{mean} (Gy)	19.24±4.63	14.04±3.80	13.92±3.65	1 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	D_{max} (Gy)	42.39±5.96	46.10±6.73	45.65±6.63	*0.02 (4FB vs. FIF)
					0.07 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	EUD (Gy)	9.44±2.26	6.89±1.88	6.76±1.74	1 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	NTCP (%)	< 0.01	< 0.01	< 0.01	1 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
Left kidney	D_{mean} (Gy)	22.15±3.59	20.06±2.58	20.64±3.27	1 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	D_{max} (Gy)	52.03±2.11	51.19±0.98	50.65±1.07	0.15 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*0.03 (3F vs. 4FB)
	EUD (Gy)	10.90±1.15	10.22±0.99	10.03±0.77	0.58 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	NTCP (%)	0.05±0.18	0.02±0.07	0.01±0.06	0.35 (4FB vs. FIF)
					0.35 (FIF vs. 3F)
					0.35 (3F vs. 4FB)

OAR	Parameter	3F	4FB	FIF	P-value
Right lung	D_{mean} (Gy)	10.24±2.76	9.99±2.82	9.86±2.78	0.79 (4FB vs. FIF)
					0.79 (FIF vs. 3F)
					0.79 (3F vs. 4FB)
	D_{max} (Gy)	52.52±1.14	51.67±1.47	50.39±1.04	*<0.01 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	$V_{20\ Gy}$ (%)	19.20±3.34	16.87±3.98	17.30±3.61	1 (4FB vs. FIF)
					0.06 (FIF vs. 3F)
					*0.03 (3F vs. 4FB)
	EUD (Gy)	5.03±1.36	4.91±1.39	4.87±1.36	0.88 (4FB vs. FIF)
					0.88 (FIF vs. 3F)
					0.88 (3F vs. 4FB)
	NTCP (%)	<0.01	<0.01	<0.01	0.76 (4FB vs. FIF)
					0.76 (FIF vs. 3F)
					0.76 (3F vs. 4FB)
Left lung	D_{mean} (Gy)	10.40±1.39	9.77±1.31	9.56±1.29	0.55 (4FB vs. FIF)
					*0.01 (FIF vs. 3F)
					0.07 (3F vs. 4FB)
	D_{max} (Gy)	53.47±1.30	52.69±1.19	51.21±0.70	*<0.01 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					0.26 (3F vs. 4FB)
	$V_{20\ Gy}$ (%)	24.53±7.09	22.02±7.04	21.70±6.99	0.95 (4FB vs. FIF)
					*0.02 (FIF vs. 3F)
					*0.02 (3F vs. 4FB)
	EUD (Gy)	5.25±0.70	4.84±0.59	4.73±0.58	0.5 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*0.01 (3F vs. 4FB)
	NTCP (%)	<0.01	<0.01	<0.01	0.44 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*0.04 (3F vs. 4FB)
Liver	D_{mean} (Gy)	26.30±2.99	29.55±3.20	29.31±3.23	0.77 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					*<0.01 (3F vs. 4FB)
	D_{max} (Gy)	52.35±1.43	51.94±1.30	51.42±1.08	0.41 (4FB vs. FIF)
					*0.03 (FIF vs. 3F)
					0.95 (3F vs. 4FB)
	EUD (Gy)	25.61±1.33	26.49±1.26	26.34±1.27	1 (4FB vs. FIF)
					0.1 (FIF vs. 3F)
					*0.02 (3F vs. 4FB)
	NTCP (%)	0.56±0.35	0.82±0.41	0.77±0.42	0.64 (4FB vs. FIF)
					*0.04 (FIF vs. 3F)
					*0.01 (3F vs. 4FB)

OAR	Parameter	3F	4FB	FIF	P-value
Spinal cord	D_{mean} (Gy)	22.71±4.02	21.79±4.33	21.56±4.32	*<0.01 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					0.3 (3F vs. 4FB)
	D_{max} (Gy)	49.91±1.33	49.60±2.37	49.21±2.49	*<0.01 (4FB vs. FIF)
					*<0.01 (FIF vs. 3F)
					0.32 (3F vs. 4FB)
	EUD (Gy)	40.66±1.62	40.32±2.32	39.89±2.39	0.43 (4FB vs. FIF)
					0.16 (FIF vs. 3F)
					0.54 (3F vs. 4FB)
	NTCP (%)	0.04±0.02	0.04±0.03	0.04±0.3	0.62 (4FB vs. FIF)
					0.62 (FIF vs. 3F)
					0.62 (3F vs. 4FB)

OAR: Organ at risk; 3F: Three-field; 4FB: Four-field box; FIF: Field-in-field; EUD: Equivalent uniform dose; NTCP: Normal tissue complication probability
*: The P-value is less than 0.05 and this indicates a significant difference between the two techniques

ences comparing FIF *vs.* 3F and 3F *vs*. 4FB (Table 4, *P*-value<0.05), but not for FIF *vs*. 4FB (*P*-value>0.05). On the other hand, D_{max} for the right kidney was significantly different between the 4BF and FIF techniques (*P*-value<0.05), but not between FIF *vs*. 3F and 3F *vs*. 4FB (*P*-value>0.05).

For the left kidney, while no significant difference was seen between the techniques in terms of NTCP (*P*-value>0.05), EUD, D_{max}, and D_{mean} showed significant differences between the FIF and 3F plans (*P*-value<0.05), but not between FIF and 4FB (*P*-value>0.05).

2.3. Lungs

For the right lung, comparisons between the three techniques revealed significant differences for none of NTCP, EUD, and D_{mean} (*P*-value>0.05), but D_{max} (*P*-value<0.05). In addition, $V_{20\ Gy}$ was significantly different comparing FIF *vs*. 3F (*P*-value<0.05), but not between FIF *vs*. 4FB and 3F *vs*. 4FB (*P*-value>0.05, Table 4).

As shown in Table 4, NTCP, EUD, and $V_{20\ Gy}$ parameters for the left lung were comparable between the 4FB and FIF techniques (*P*-value<0.05) with significant differences comparing FIF *vs*. 3F and 3F *vs*. 4FB techniques (*P*-value<0.05). In terms of D_{max} for the left lung, the FIF technique showed a statistically significant difference compared with both 4FB and 3F methods (*P*-value<0.05), but there was no significant difference between the 3F and FIF techniques (*P*-value>0.05). Regarding D_{mean} for the left lung, a significant difference was only observed between the FIF and 3F techniques (*P*-value<0.05).

2.4. Liver

As shown in Table 4, NTCP for the liver was significantly different comparing FIF *vs*. 3F and 3F *vs*. 4FB techniques (*P*-value<0.05), but not between 4FB and FIF techniques (*P*-value>0.05). In terms of EUD, there was only a significant difference comparing the 3F and 4FB treatment plans, and D_{max} showed a significant difference only between the FIF and 3F techniques (*P*-value<0.05). In addition, D_{mean} for the liver was significantly different in FIF *vs*. 3F and in 3F *vs*. 4FB (*P*-value<0.05); however, there was no significant difference between the 4FB and FIF techniques (*P*-value>0.05).

2.5. Spinal cord

According to Table 4, NTCP and EUD for the spinal cord were not significantly different between the three techniques (*P*-value>0.05). On the other hand, D_{max} for the spinal cord showed a significant difference only between the FIF and 3F techniques (*P*-value<0.05).

Also, the comparison of D_{mean} between the 3Fmethod and each of the FIF and 4FB techniques showed a statistically significant difference (P-value<0.05).

Discussion

Wedge-based beams are frequently employed in conformal treatment planning in radiation therapy to account for the tissue heterogeneity and abnormalities by malignant tumors [14, 29]; however, the use of wedges has some shortages, such as inapplicability for large target areas and scattering of emissions towards normal tissues [30, 31]. Compared with 3D CRT, the FIF technique uses simple (i.e., non-wedged) beams and can be performed at each center equipped with MLCs. Also, the FIF technique delivers excellent dose coverage for PTV [13, 14, 23, 32] and acceptable performance for protecting OARs during radiotherapy for esophageal, pancreatic, and early-stage breast cancers [9, 14, 29, 33]. However, no study has been conducted on the feasibility of this technique in patients with GE junction cancer. Therefore, the present study investigated the potential advantages of the FIF technique in comparison with the 3F and 4FB methods for treating patients with GE junction cancer in terms of radiobiological and diametrical parameters. Regarding PTV, the parameters of D_{mean} and D_{max} were calculated for different therapeutic plans (i.e., 3F, 4FB, and FIF). In this investigation for PTV, the FIF technique outperformed the 3F and 4FB techniques in terms of dosimetric outcomes, such as D_{mean} and D_{max} that in PTV, were significantly lower in the FIF technique compared to the 3F and 4FB methods (Table 3), related to the shielding regions at higher doses in the FIF approach. In a study on esophageal cancer, Allaveisi et al. [14] reported a lower D_{max} of PTV in the FIF technique compared to the 4FB technique but no significant difference in terms of D_{mean} of PTV between the two methods. The results of Allaveisi et al. [14] were consistent with the results of the current study for D_{max} but inconsistent for D_{mean}. Ghadimi et al. [13] reported that the FIF technique delivered lower D_{mean} and D_{max} values for PTV compared with the 3F technique. These findings were consistent with the results of the present study.

In terms of CI for PTV, no discernible difference was discovered between the FIF and 4FB approaches. However, the FIF technique showed a smaller CI compared with the 4FB technique and a significantly improved CI compared with the 3F method. The better CI obtained in the FIF technique could result from the external shielding of the target areas that received doses close to the target dose. In terms of HI (i.e., homogeneity index) for PTV, the FIF technique could deliver a significantly better dose homogeneity at the target site than the other two techniques. The improvement of HI in the FIF technique can be due to the reduction of the maximum dose at the target site and consequently, a reduction in the variation of the target dose. In line with the current research, Allaveisi and Moghadam [14] conducted a study on esophageal cancer and revealed that the FIF technique resulted in better dose homogeneity of PTV compared with the 4FB technique; however, there was no discernible difference in dosage conformance between the two procedures. In their experiment on breast cancer radiation therapy, Ercan et al. [16] also declared that the FIF technique had a significantly better dose distribution homogeneity in PTV compared with two tangential wedge-based fields, supporting the outcomes of the current study in terms of dose homogeneity in PTV. Moreover, Sasaoka et al. [23] compared the dosimetric of whole breast radiotherapy (WBRT) using the FIF technique with that of conventional tangential field-radiotherapy with physical wedges for WBRT and reported that the former technique had a better dosage homogeneity. Prabhakar et al. [34] conducted a study on upper abdomen malignancies, including the malignancies of the gastro-esophageal junction, stomach, gall-

bladder, and pancreas and stated that the FIF technique was superior to wedge-based methods in terms of dose conformity in PTV, which was in parallel with the findings of the current study.

In the present study, besides CI and HI (as dosimetric parameters), the TCP index, as a PTV radiobiological parameter, was also measured and compared between the three different techniques (Table 3). The FIF technique delivered a significantly better TCP value compared with the two other techniques, indicating better tumor control for GE junction cancer. Allaveisi et al. [14] also compared the FIF and 4FB techniques in terms of TCP index for esophageal tumors with no significant difference between the two techniques, which contradicts the finding of the current study. In a study on pancreatic tumors, Pursamimi et al. [9] also reported that the FIF technique was not superior to the 3F and 4FB techniques in terms of tumor response.

The NTCP parameters were compared for OARs between the three different plans (Table 4). In terms of D_{mean}, the use of the FIF technique significantly reduced the mean doses required for OARs (the heart, right kidney, left kidney, and left lung) compared with the 3F technique but not 4FB. Evaluation of the mean dose emitted on the liver showed a lower value in the 3F technique compared with the FIF technique because only one of the fields passes through the liver in the former while both opposite lateral fissures pass through the organ in the other two techniques. The FIF technique could reduce the mean dose emitted towards OARs compared with the 3F technique, but no significant difference was observed compared with the 4FB method. Allaveisi et al. [14] compared the FIF and 4FB methods in terms of the mean dose for OARs (the heart, liver, left lung, and right lung) in patients with esophageal cancer and found that FIF was not superior to 4FB in terms of mean dose reduction, which agreed with our observation. In addition, Altinok et al. [35] compared the FIF and 3D CRT techniques in terms of the mean dose delivered to OARs (the right kidney, left kidney, liver, and spinal cord) in patients with gastric cancer and reported a lower mean dose exposition to OARs in the former approach compared to the latter, which was also consistent the results of the present study.

Table 4 summarizes the maximum doses received by OARs. The maximum doses delivered to the heart, right lung, left lung, and spinal cord were significantly lower in the FIF technique compared with the 3F and 4FB. Regarding this index, the FIF technique could significantly reduce the maximum dose exposed to the left kidney and liver compared with the 3F method and the maximum dose delivered to the right kidney compared with the 4FB technique. Although the use of the FIF technique reduced the maximum dose exposed to the heart, left kidney, right lung, and left lung in patients with GE junction cancer, this trend was not shown for all the OARs under study, sparing the right kidney and liver. For the spinal cord, no significant difference was recognized between the FIF method and the other two techniques. Overall, the FIF technique probably reduced the maximum dose delivered to OARs, which can be important in preventing possible complications during treating GE junction tumors. The proximity of the prescribed dose to the spinal cord's tolerance dose should be considered. However, the three techniques had slight differences in terms of the maximum doses delivered to the spinal cord. Onal et al. [32] analyzed conventional FIF and tangential wedge-beam techniques in the patients undergoing breast irradiation after breast-conserving surgery and reported that there was no significant difference between these techniques in terms of the maximum dose delivered to OARs (i.e., the lung, heart, and contralateral breast). Ghadimi et al. [13] also compared FIF with 3D-CRT in patients with esophageal cancer and revealed that the former was associated with a lower maximum dose to the spinal cord compared with the lat-

ter, which agreed with the current study. Yavas et al. [36] reported that the FIF technique significantly reduced the maximum dose delivered to OARs (the rectum, bladder, bowel, thighs, and bone marrow) compared to 3D-CRT in the patients undergoing radiotherapy for early-stage endometrial cancer. In another study, Prabhakar et al. [34] reported a reduction in the doses delivered to critical organs, such as the kidneys and especially, the spinal cord, in the patients receiving FIF rather than wedge-based treatment. These results were in accordance with those of the present study.

In addition, NTCP values for all OARs were determined for the three treatment techniques, showing significantly lower values for the heart, right kidney, left lung, and liver in FIF compared with 3F. However, the FIF technique was not superior to the 4FB technique in reducing NTCP values for OARs, such as the heart, right kidney, left lung, and liver. The NTCP values obtained for the left kidney, right lung, and spinal cord, the three treatment techniques showed no superiority over each other for treating GE junction cancer. Allahveisi et al. [14] compared NTCP values for OARs in patients with esophageal cancer treated with either FIF or 4FB and also reported that the FIF technique (compared to 4FB) reduced the NTCP of the left lung and spinal cord, which was not in line with the current study. However, for other OARs, they reported no significant difference between the two techniques in terms of NTCP values, which was consistent with our findings. In addition, Shanei et al. [27] compared the NTCPs of OARs between the 3D-CRT and IMRT techniques during left breast radiotherapy and demonstrated that IMRT could significantly reduce NTCPs in the lung and heart compared with 3D-CRT.

In the present study, there was no significant difference in $V_{20\ Gy}$ of the right lung between FIF and the other two techniques; however, the mean value of $V_{20\ Gy}$ was lower in the FIF method compared with 3F. On the other hand, the $V_{20\ Gy}$ of the right lung was notably lower for the 4FB technique compared to 3F. For the left lung, $V_{20\ Gy}$ was not significantly different between the FIF and 4FB techniques; however, this value was significantly lower in both FIF and 4FB compared with 3F. Lung $V_{20\ Gy}$ is used as an index for setting dose constraints and assessing treatment outcomes since it is closely related to radiation-induced pneumonitis [13, 14]. Baycan et al. [17] evaluated the homogeneity of dose distribution and the dose delivered to OARs between the FIF-IMRT and 3D-CRT strategies for the left breast in the patients undergoing lumpectomy and also found that FIF was not superior to 3D-CRT in reducing $V_{20\ Gy}$ in the left lung. Ghadimi et al. [13] in a study on esophageal cancer reported that FIF reduced $V_{20\ Gy}$ for the left and right lungs compared with 3D-CRT and their result was consistent with those of the present study for the left lung but inconsistent for the right lung. In accordance, studies have highlighted the effectiveness of the FIF technique in reducing lung $V_{20\ Gy}$ compared with other therapeutic techniques [16, 37-38].

In the current study, fewer MUs were needed to deliver the prescribed dose to the target site for the FIF compared to 3F and 4FB techniques, which is consistent with the lower MUs used in non-wedged fields compared to the wedged fields for delivering the same dose. The FIF technique also has the advantage of a shorter radiation period in each fraction compared with the 3F and 4FB techniques since a higher number of MUs prolongs treatment, which is consistent with that of Prabhakar et al. [34] who reported that the number of MUs was significantly lower in the FIF technique than in the wedge-based techniques. Other studies also delineated that the FIF technique could markedly reduce the number of MUs compared to other therapeutic techniques [13, 14, 16, 31, 32], supporting the results of the present study. It is noteworthy that more MUs in each treatment fraction can widen radiation scattering, leading to secondary cancers. Therefore, the FIF technique performs better

than the other two techniques in terms of patient safety. There are also other studies [39-42] on comparison of the FIF technique with other radiotherapy techniques or modalities in terms of different dosimetric and radiobiologic parameters and a review of the studies is useful.

Conclusion

The use of the FIF technique for treating GE junction cancer leads to a reduction in the doses received by the heart, kidney, lung, liver, and spinal cord compared with other treatment methods, such as 3F and 4FB. This is critical as the reduction of dose to the normal tissue may reduce the rate of complications and harm to the normal tissues during radiation therapy. In addition, the FIF technique provided significantly better homogeneity and conformity in dose in PTV than the 3F and 4FB methods. The FIF technique has also other advantages, including a shorter overall time duration of treatment, lower MU, lower radiation scattering, and less patient load, treated by the linear accelerator. Overall, this study revealed that in some cases, the FIF technique had better dosimetric properties for treating GE junction cancer than the 3F and 4FB techniques. However, FIF is a time-consuming technique due to the large number of beams used, and its application requires practical skills, knowledge, and experience by medical physicists.

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Authors' Contribution

Gh. Mehri-Kakavand, W. Parwaie, M. Khosravi, SM. Hosseini, and A. Soleimani Meigooni made a contribution in data collection, data analysis, and manuscript preparation. M. Pursamimi and M. Ghorbani made a contribution to all steps of the research made a contribution in data collection, data analysis, and manuscript preparation. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

This study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences with the ethical code number of IR.SBMU.CRC.REC.1400.012.

Informed consent

Since there was no extra intervention on the patients due to this study and only patients' information was analyzed, informed consent was not received.

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Conflict of Interest

None

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