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Dosimetric comparison between helical tomotherapy and intensity-modulated radiotherapy for esophageal carcinoma

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Abstract

Objective: To compare the effectiveness of different radiotherapy techniques – tomotherapy (TOMO) and intensity-modulated radiation therapy (IMRT) – for patients with esophageal carcinoma on the basis of dosimetric analysis.

Methods: The target areas and organs at risk in 10 patients with esophageal carcinoma were underlined and transmitted to the Raystation and TOMO planning systems. The homogeneity index (HI) and conformal index (CI) values, and dose distributions to organs at risk were compared on the basis of dose–volume histograms parameters.

Results: The median of HI of gross planning target volume by TOMO (HI = 0.0575) showed superior homogeneity dose distribution compared with the IMRT technique (HI = 0.0735, $P = 0.047$). The median of CI of planning target volume by TOMO (CI = 0.785) showed improved conformity of dose distribution compared with IMRT (CI = 0.6825, $P = 0.009$). The median of the maximum dose to planning gross tumor volume (PGTV) and planning target volume by TOMO was significantly decreased compared with IMRT. The median of total lung doses, total heart doses, and maximum doses to the spinal cord were all significantly reduced by TOMO compared with IMRT.

Conclusions: Compared with IMRT, TOMO could provide better conformal target coverage, more homogeneity dose distribution, and significantly decreased the radiation dose to the lungs, heart, and spinal cord.

KEYWORDS

esophageal carcinoma, intensity-modulated radiation therapy, organs at risk, tomotherapy

1 | INTRODUCTION

In China, esophageal cancer is a highly aggressive malignancy and the fourth most common cause of cancer-related deaths.[1] Esophageal cancer is often diagnosed at a relatively late stage and has a very poor prognosis.[2,3] It was shown that chemoradiotherapy is the major treatment method for locally advanced or unresectable esophageal cancer.[4] The use of intensity modulated radiation therapy (IMRT) to treat esophageal cancer has been shown to have superior dose homogeneity and tumor coverage, and reduced dose delivered to the surrounding normal tissue when compared with 3-D conformal radiotherapy.[5,6] However, the 5-year overall survival rate of esophageal cancer is just 15–25%.[7] The most common failure pattern of concurrent chemoradiotherapy is local failure.[8] Recurrences in the target region are extremely rare, and reduction of the incidence is largely dependent on adequate irradiation,[9] which indicates to us that the greatest challenge of esophageal cancer radiotherapy is achieving an adequate dose to the gross tumor volume while minimizing toxicity to the surrounding critical normal tissues.[10]

With the constant development of equipment and technology, the methods for tumor radiotherapy have diversified. Advanced radiation therapy techniques, which were developed to lower the normal tissue toxicity, might allow for further treatment intensification and re-irradiation in previously irradiated regions. Helical tomotherapy is a

modality of IMRT delivered by a continuously moving slip ring gantry in synchrony with the couch motion, and with a fan radiation beam modulated by a binary multi-leaf collimator. The application of mega-voltage computed tomography (CT) provides a viable solution to adaptive radiotherapy and dose-guided radiotherapy.[11–14]

The present retrospective dosimetric study was carried out to compare treatment plans of IMRT with TOMO for esophageal cancer.

2 | METHODS

2.1 | Patients

Between July 13, 2014 and February 25, 2015, 10 patients (10 males) with non-metastatic esophageal cancer were treated with CT-based IMRT planning in the Department of Radiation Oncology at Zhejiang Cancer hospital, Zhejiang, Chia. A total of 10 patients were diagnosed with squamous cell cancer of the esophagus. The median age of these patients was 53-years (range 49–68 years). The Karnofsky Performance Scale scores of all patients were >70 points. None of these patients had received surgical treatment. Based on the CT images, IMRT and TOMO treatment plans were generated to compare the dose distributions.

2.2 | Thermoplastic mask immobilization and CT laser simulation positioning

Treatments were planned with patients in the supine position under thermoplastic mask immobilization of the head, neck, and shoulders. Planning CT images were taken at 3-mm slices using a dedicated CT scanner. Version 4.5.1.14 of RayStation (RaySearch Laboratories AB, Stockholm, Sweden) was used for treatment planning.

2.3 | Contour delineation of the target areas and organs at risk

The gross tumor volume (GTV), the clinical target volumes (CTVs), the planning target volume (PTV), and organs at risk (OARs; including lungs, heart, and spinal cord) were contoured by the original treating radiation oncologist, according to the principles of International Commission on Radiation Units and Measurements (ICRU) Report 83.[15] GTV was defined as the primary tumor and any involved lymph nodes by imaging studies including CT scan, positron emission scan (PET) scan, magnetic resonance imaging (MRI), and endoscopic ultrasound. CTV was defined as the GTV with a 3.0-cm superior–inferior expansion and with a 0.5-cm radial expansion. The PTV was defined as 0.5 cm beyond the CTV.

2.4 | Radiotherapy treatment planning

The target areas and OARs were transmitted to the Raystation and TOMO planning systems. Dosimetric quality was evaluated by two senior physicists and two deputy chief physicians in terms of target dose homogeneity and OARs, through the application of a set of dose metrics. All patients received 61.6 Gy to gross disease in 28 daily fractions. The aim of all plans was to achieve a minimum dose >95% and a maximum dose <110% (V95% and V110%) of the prescribed dose. Both IMRT plans and TOMO plans used 6 MV X-ray beams, and the source–axis distance was 100 cm. Inhomogeneity corrections were applied during treatment planning. Other parameters for TOMO plans included field width, modulated factor, and helical pitch at 2.5 cm, 3.0, and 0.287, respectively. Dose constraints for normal OARs were: spinal cord maximal doses (D_{max}) <45 Gy; lung mean doses (D_{mean}) <13 Gy, volume of at least 5 Gy (V_5) <60%, volume of at least 10 Gy (V_{10}) <40%, volume of at least 20 Gy (V_{20}) <30%, and volume of at least 30 Gy (V_{30}) <25%; heart D_{mean} <25 Gy, V_{30} <40%, and V_{40} <30%.

2.5 | Assessment of radiotherapy plan

The assessment of the treatment plan mainly includes two sections: the treatment planning parameters of tumor target volume and OARs. The treatment planning parameters of tumor target volume include: (i) dose–volume histogram (DVH); (ii) the homogeneity index (HI), defined as: $HI = (D_{2\%} - D_{98\%}) / D_{Rx} \times 100\%$, $D_{2\%}$ and $D_{98\%}$ were defined as the dose received by 2% and 98% of the volume (smaller HI values closer to 0 indicate superior homogeneity, whereas larger values closer to 1 indicate inferior homogeneity. HI values were used for effectively evaluating the uniformity of the dose distribution);[16] (iii) conformal index values (CI), defined as: $CI = (V_{t,ref} / V_t) \times (V_{t,ref} / V_{ref})$, V_t was the target volume, $V_{t,ref}$ was the target volume covered by the reference isodose, V_{ref} was all volume of the reference isodose (the CI values vary from 0 to 1, the larger values indicate better conformity of dose to the PTV);[17] (iv) the dose received by 99% and 1% of the volume ($D_{99\%}$ and $D_{1\%}$), respectively defined as metrics for the minimum dose (D_{min}) and D_{max}; and (v) other parameters, such as $D_{95\%}$, $D_{50\%}$, and $D_{5\%}$. For each patient, the planning parameters of OARs were analyzed: the maximum dose to the spinal cord; the mean lung dose, and volumes of lung receiving a dose of at least 5, 10, and 20 Gy (V_5, V_{10}, and V_{20}); and the mean heart dose, the volume of heart receiving a dose of at least 20, 40, and 50 Gy (V_{20}, V_{40}, and V_{50}).

2.6 | Statistical analysis

To determine statistical significance, non-parametric statistics tests for two paired samples (Wilcoxon signed-rank test) were carried out. A *P*-value of <0.05 was considered to be significant. All statistical tests were carried out with SPSS for Windows (Version 16.0. SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Isodose distribution and DVHs

As shown on Table 1, case 2 suffered from cervical esophageal carcinoma, case 10 suffered from esophagogastric junction cancer, and the other eight patients all suffered from thoracic esophageal cancer. The two plans could meet the standards of prescribed doses and the limit of acceptable doses for the OAR. Isodose curve distribution (Fig. 1) of

TABLE 1 Characteristics of 10 esophageal cancer patients

Patients	Distance from the incisors	Stage	Volume (cm^3)		PGTV CI		PGTV HI	
			PGTV	PTV	IMRT	TOMO	IMRT	TOMO
1	20–25cm, 30cm	T1N3M0, IVA	52.46	674.25	0.31	0.659	0.065	0.03
2	19cm	T3N1M0, III	80.27	560.07	0.47	0.486	0.088	0.06
3	25-29cm	T3N2M1, IVB	138.31	827.3	0.43	0.508	0.068	0.07
4	28cm	T3N2M1, IVB	101.53	622.1	0.50	0.770	0.056	0.06
5	28-32cm	T3N1M1, IVB	167.89	654.42	0.56	0.728	0.098	0.04
6	23cm	T3N2M0, III	126.37	426.95	0.68	0.679	0.101	0.06
7	28-35cm	T3N1M1, IVB	67.87	484.86	0.39	0.614	0.086	0.06
8	30-35cm	T3N1M0, III	96.12	392.18	0.55	0.543	0.076	0.09
9	22-33cm	T3N1M0, III	71.07	487.11	0.60	0.700	0.055	0.04
10	36cm-cardia	T3N2M1, IVB	132.77	557.91	0.54	0.406	0.071	0.08

CI, conformal index; HI, homogeneity index; PGTV, planning gross tumor volume; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; TOMO, tomotherapy

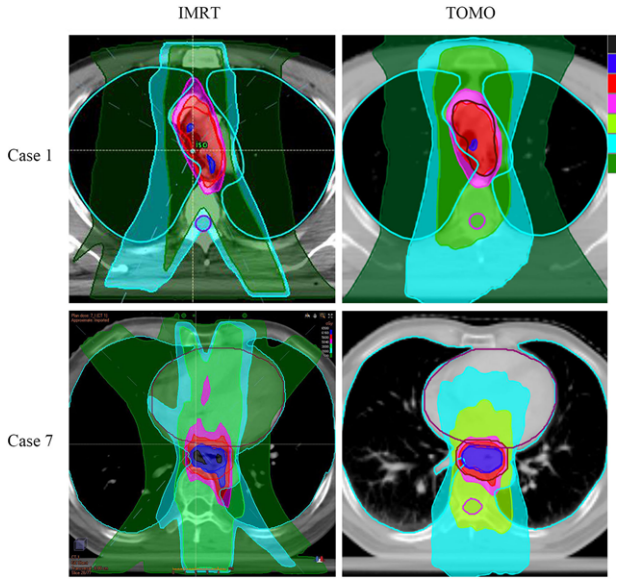

FIGURE 1 Isodose curves of two radiotherapy plans for two patients with esophageal carcinoma. IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy

IMRT and TOMO in two patients (case 1 and case 7) with EC in the supine position. TOMO plans showed better conformal PTV coverage and steeper dose gradients. The DVHs of these two patients for PGTV, PTV, heart, lung, and spinal cord for TOMO and IMRT are shown in Figure 2.

3.2 | Comparison of dosimetric parameters of the target areas

For the PGTV, TOMO produced similar coverage in terms of mean dose or minimum dose compared with IMRT. As shown in Table 2, the median maximum dose to PGTV by TOMO was 64.9 Gy, which was significantly decreased compared with plans by IMRT (D_{max} = 66.51 Gy, P = 0.005). The median HI of PGTV was smaller in TOMO (HI = 0.0575) than in IMRT (HI = 0.0735, P = 0.047), showing more homogeneity dose distribution by TOMO. The median CI of PGTV was increased by TOMO (CI = 0.6365) compared with the IMRT technique (CI = 0.521, P = 0.059). Although there was no statistical difference in CI of PGTV between TOMO and IMRT, it also showed more conformity of dose distribution by TOMO, and it might have been caused by the small number of patients. For the PTV, the D_{mean}, D_{min} and HI of TOMO plans were similar to the IMRT technique. TOMO produced a lower median maximum dose to PTV (D_{max} = 64.1 Gy) when compared with IMRT (D_{max} = 64.9 Gy, P = 0.028). The median CI of PTV was also significantly improved by TOMO (CI = 0.785) compared with IMRT (CI = 0.6825, P = 0.009). As shown on Table 1, case 10 suffered from esophagogastric junction cancer, the CI and HI for the PGTV was not improved by TOMO compared with IMRT. This showed that TOMO might not be superior to IMRT for esophagogastric junction cancer.

3.3 | Doses to lungs, heart, and spinal cord

The median D_{mean} and median D_{max} of the OARs (lungs, heart, and spinal cord) in TOMO and IMRT plans are shown in Table 3. The two plans could meet the limit of acceptable doses for the OAR. The median D_{mean} of total lungs was significantly reduced by TOMO (10.79 Gy) compared with IMRT (11.88 Gy, P = 0.005). The median V_{20}, V_{30}, V_{40}, and V_{50} of lung were significantly reduced by the TOMO plan (16.81%, 9.63%, 4.54%, and 1.95%) compared with plans by IMRT (21.71%, P = 0.005; 12.6%, P = 0.005; 6.22%, P = 0.013; and 2.74%, P = 0.009). The median V_5 and V_{10} of lung were similar by TOMO (V_5 = 55.33%, V_{10} = 33.73%) and IMRT (V_5 = 52.96%, P = 0.878; V_{10} = 37.03%, P = 0.074). As expected, the median D_{mean} of total heart was significantly reduced by TOMO (22.60 Gy) compared with IMRT (24.33 Gy, P = 0.028). Median V_{20}, V_{30}, V_{40}, V_{50}, and V_{60} of heart was significantly reduced by the TOMO plan (36.21%, 20.72%, 11.81%, 5.27%, and 0.47%) compared with plans by IMRT (56.36%, P = 0.022; 30.9%, P = 0.007; 17.23%, P = 0.013; 8.5%, P = 0.022; and 1.07%, P = 0.009). The median D_{max} to the spinal cord were also significantly reduced by TOMO (40.22 Gy) when compared with IMRT plans (41.66 Gy, P = 0.007). These results showed that the doses to the lung, heart or spinal cord were significantly reduced by TOMO when compared with IMRT plans.

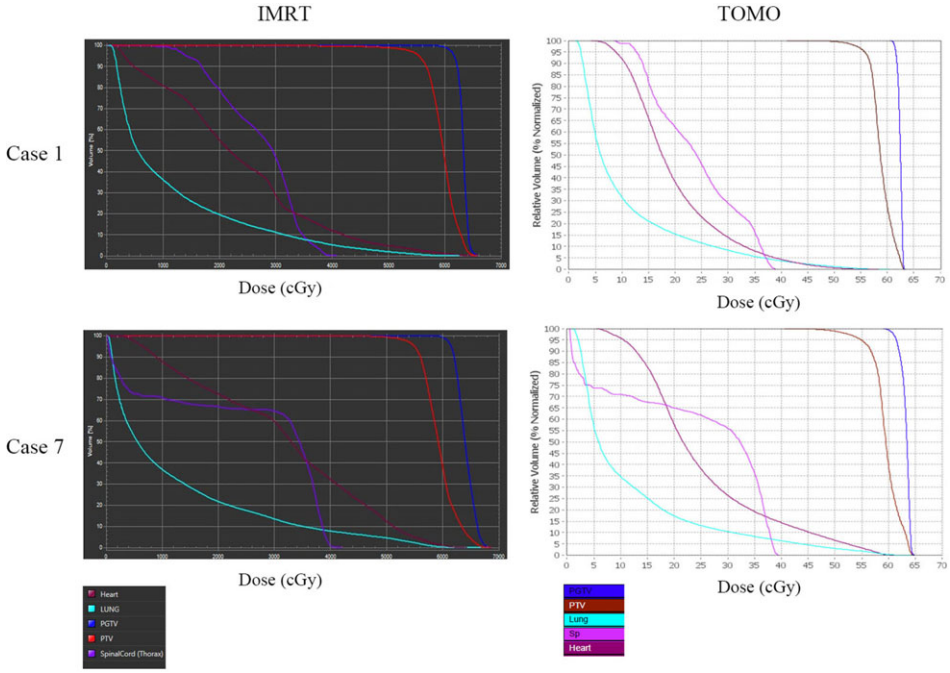

FIGURE 2 Dose volume histograms of two radiotherapy plans for two patients with esophageal carcinoma. IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy

TABLE 2 Median results for PGTVs and planning target volumes by tomotherapy and intensity-modulated radiation therapy plans for 10 esophageal cancer patients

TV	Parameters		Q2 (Q1, Q3)		*P*
			TOMO	IMRT	TOMO *vs* IMRT
PGTV	Dose (Gy)	D_{mean}	63.2 (62.5, 63.46)	63.43 (63.26, 63.86)	0.093
		D_{min}	60.37 (60.17, 60.51)	60.62 (60.3, 60.71)	0.507
		D_{max}	64.9 (64.11, 64.96)	66.51 (65.6, 67.6)	0.005
	HI	0.0575(0.04425, 0.0645)	0.0735 (0.06575, 0.0875)	0.047	
	CI	0.6365 (0.51675, 0.69475)	0.521 (0.43725, 0.5555)	0.059	
PTV	Dose (Gy)	D_{mean}	59.69 (59.27, 60.2)	59.98 (59.62, 60.34)	0.139
		D_{min}	51.96 (50.37, 52.27)	52.88 (52.01, 53.18)	0.114
		D_{max}	64.1 (63.07, 64.38)	64.9 (64.39, 66.13)	0.028
	HI	0.1915 (0.17625, 0.2145)	0.204 (0.1815, 0.21975)	0.169	
	CI	0.785 (0.77925, 0.82425)	0.6825 (0.64725, 0.76375)	0.009	

Homogeneity index (HI), $(D_{2\%} - D_{98\%}) / DRx \times 100\%$. Conformal index (CI), $(V_{t,ref} / V_t) \times (V_{t,ref} / V_{ref})$. D_{max}, the dose received by 1% of the volume ($D_{1\%}$); D_{min}, the dose received by 99% of the volume ($D_{99\%}$); IMRT, intensity-modulated radiation therapy; Q1, first quartile (25% quartile); Q2, Second quartile (50% quartile or the median); Q3, third quartile (75% quartile); TOMO, tomotherapy; TV, target volume

4 | DISCUSSION

Currently, radiotherapy is recognized to be one of the most important treatment methods in the management of esophageal cancer.[18–20] For radiotherapy planning, the precise definition of the primary tumor and involved lymph nodes is crucial. TOMO has been proven to deliver a sharper dose gradient compared with conventional IMRT, to improve conformity and dose homogeneity for the target volumes, and minimize the involvement of OARs in several cancers.[21–23] In the present study, the median CI of PTV was significantly improved by TOMO compared with the IMRT technique, showing more conformity in dose distribution by TOMO in cervical and thoracic esophageal carcinoma. Although the median CI of PGTV showed no statistical difference between TOMO and IMRT, it still showed more conformity in dose distribution by TOMO, and the small number of patients caused no statistical difference. For the PTV, the median HI of TOMO plans was slightly lower than the mean HI of IMRT plans, but there was no significant statistical difference. The median HI of PGTV was less by TOMO than by IMRT, and the difference was statistically significant, indicating that TOMO shows superior dose homogeneity to IMRT. On the basis of dosimetric analysis, Chen *et al.* compared different radiotherapy techniques – TOMO, IMRT, and 3-D conformal radiotherapy – for six patients with locally advanced mid-distal esophageal carcinoma who were treated with neoadjuvant chemoradiation followed by surgery.[21] Consistent with the present findings, their results showed that TOMO plans are superior in terms of target conformity and dose

TABLE 3 Median results for lung, heart, and spinal cord by tomotherapy and intensity-modulated radiation therapy plans for 10 esophageal cancer patients

OARs	Parameters	Q2 (Q1, Q3)		*P*
		TOMO	IMRT	TOMO *vs* IMRT
Lungs	D_{mean} (Gy)	10.79 (10.3, 11.63)	11.88 (11.3, 12.24)	0.005
	V_5 (%)	55.33 (48.17, 57.69)	52.96 (51.53, 54.04)	0.878
	V_{10} (%)	33.73 (31.43, 36.58)	37.03 (35.54, 38.9)	0.074
	V_{20} (%)	16.81 (15.72, 17.67)	21.71 (19.73, 22.83)	0.005
	V_{30} (%)	9.63 (8.43, 10.28)	12.6 (11.19, 14.97)	0.005
	V_{40} (%)	4.54 (3.82, 5.54)	6.22 (5.79, 7.92)	0.013
	V_{50} (%)	1.95 (1.38, 2.53)	2.74 (1.94, 3.81)	0.009
Heart	D_{mean} (Gy)	22.60 (17.08, 25.68)	24.33 (18.30, 27.32)	0.028
	V_{20} (%)	36.21(23.07, 59.36)	56.36 (38.11, 66.41)	0.022
	V_{30} (%)	20.72 (10.83, 31.51)	30.9 (26.48, 39.13)	0.007
	V_{40} (%)	11.81 (4.39, 16.23)	17.23 (17.05, 21.98)	0.013
	V_{50} (%)	5.27 (1.77, 7.06)	8.5 (6.51, 10.35)	0.022
	V_{60} (%)	0.47 (0.24, 0.66)	1.07 (0.94, 2.63)	0.009
Sp	D_{max} (Gy)	40.22 (39.48, 40.67)	41.66 (40.85, 41.88)	0.007

D_{max}, the dose received by 1% of the volume ($D_{1\%}$); D_{mean}, the mean dose; IMRT, intensity-modulated radiation therapy; OARs, organs at risk; Q1, first quartile (25% quartile); Q2, Second quartile (50% quartile or the median); Q3, third quartile (75% quartile); Sp, spinal cord; TOMO, tomotherapy; V_x, the volume of the organs at risk receiving at least x Gy

homogeneity. In the present study, the CI and HI for the PGTV was not improved by TOMO compared with IMRT for case 10 who suffered from esophagogastric junction cancer. This showed that TOMO might not be superior to IMRT for esophagogastric junction cancer. Recently, Wang *et al.* has reported that TOMO provided superior dose conformity and homogeneity to IMRT and Volumetric Modulated Arc Therapy (VMAT) in 16 patients with gastroesophageal junction and stomach cancer who had received curative surgery, and improved dose sparing of the bowel and bone marrow in these patients.[24] In the present study, the OARs included the lungs, heart, and spinal cord, without bowel or bone marrow, and only one patient had a primary tumor located in the gastroesophageal junction. The total dose and fractional dose in the present study differed from those of the study by Wang *et al*. All patients in their study received adjuvant radiotherapy after curative surgery, which was different from the patients in the present study who received radical radiotherapy to the primary tumor and the regional lymph nodes. All of the above factors caused the distinctive differences between our study and Wang's study, suggesting that the choice of radiotherapy technology for patients with esophagogastric junction cancer is still worthy of further study.

In esophageal cancer radiotherapy, increasing the dose to gross tumor volume might also enhance the risk of severe pneumonitis.[25] Lee *et al*. reported that in 61 patients with esophageal cancer who had received conformal 3-D radiotherapy, 11 (18%) patients developed pneumonia or acute respiratory distress syndrome after surgery and two died (3%).[26] DVH analysis of the patients who developed pulmonary complications revealed a V_{15} (volume of lung treated to 15 Gy) and V10 (volume of lung receiving 10 Gy) of 30% and 40%, respectively. IMRT has been shown to have the potential to significantly reduce radiation doses to the lungs in esophageal cancer radiotherapy. La *et al*. showed that the IMRT technique allowed sparing of a large volume of normal lung from radiation.[27] The median V_5 and the mean lung dose were 53% and 10.9 Gy, respectively, which might have accounted for the low morbidity. In the present study, the median D_{mean} of total lung was significantly reduced to 10.79 Gy by TOMO, and the median D_{mean} by IMRT was 11.88 Gy, $P = 0.005$. Lee *et al*. found that in 61 esophageal cancer patients who received concurrent chemoradiotherapy preoperatively, a significant increase of postoperative pulmonary complications occurred in cases with V_{10} >40%.[26] In another study by Nguyen *et al*. using the IMRT technique for locally advanced esophageal cancer, dose constraints for total lung for complications were: V_5 <50%, V_{10} <40%, V_{15} <30%, and V_{20} <25%.[22] Graham *et al*. found a strong correlation between the parameter V_{20} and the severity of pneumonitis in lung cancer patients.[28] They reported the incidence of grade ≥2 pneumonitis as 7%, 13%, and 36% for patients with V_{20} in the range of 22–31%, 32–40%, and >40%, respectively. Zhang *et al*. reported that the volume of the heart receiving 40 and 50 Gy (V_{40} and V_{50}) in esophageal cancer patients treated with the IMRT technique was 35% and 15%, respectively.[29] Generally, myocardium damage is related to heart volume receiving a high radiation dose (≥45 Gy). In the present study, the D_{mean} of the heart was significantly reduced by TOMO compared with IMRT, and the volume of the heart receiving a high dose (V_{20}, V_{30}, V_{40}, V_{50} and V_{60}) was lower by TOMO. A significant reduction of the D_{max} to the spinal cord was also achieved by TOMO. In summary, we found that TOMO was superior to IMRT to decrease normal organ toxicity.

In the present study, we found that patients with esophageal cancer treated with TOMO could provide superior plans compared with those with IMRT. In the treatment of esophageal cancers, TOMO could provide better conformal target coverage and more homogeneity dose distribution than IMRT. Compared with IMRT, TOMO also provided a significant reduction of radiation dose to the lungs, heart, and spinal cord, while delivering a higher dose to the gross tumor. We suggest that

more early and long-term clinical trials should be carried out to assess the effectiveness of TOMO.

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CONFLICT OF INTEREST

The authors declare that they had read the article and there are no competing interests.

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