Comparing treatment plans for proximal and middle/distal stomach cancer: intensity-modulated radiotherapy, volumetric-modulated arc therapy, and tomotherapy

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Background: Adjuvant chemoradiotherapy is viewed as a definitive treatment after resection of stomach cancer (SC). To protect normal tissue, several highly conformal radiotherapy modalities evolved. Therefore, we aimed to compare dosimetric parameters of helical tomotherapy (TOMO), volumetric-modulated arc therapy (VMAT), and intensity-modulated radiotherapy (IMRT) in the adjuvant treatment of SC in different locations.

Methods: This retrospective study was conducted from January 2013 to May 2017 and included 11 patients with gastric cancer receiving adjuvant chemoradiotherapy after total gastrectomy. Both IMRT and VMAT plans were generated on the Pinnacle treatment planning system and TOMO plans were generated using a helical tomotherapy system. Adjuvant radiotherapy was prescribed with a total radiation dose of 50.4 Gy in 28 fractions.

Results: In proximal SC, TOMO achieved a significantly lower dose for the heart, total kidney, left kidney, and liver than that of IMRT or VMAT (P<0.05). In middle/distal SC, lower total kidney mean dose and V20 were observed with TOMO compared with IMRT (P=0.010 and 0.011, respectively) and VMAT (P=0.049; P=0.014).

Conclusions: For the adjuvant treatment of gastric cancer, TOMO not only provided superior dose sparing for total kidney, left kidney, liver V_{20} and liver V_{30} in patients with proximal gastric cancer but also significantly lowered the heart dose in proximal SC when compared to IMRT or VMAT plan.

Keywords: Stomach cancer (SC); intensity-modulated radiotherapy (IMRT); volumetric-modulated arc therapy (VMAT); tomotherapy

Introduction

Stomach cancer (SC) is one of the most common causes of death from cancer worldwide (1). The disease is pervasive worldwide, especially in Asia, and is often diagnosed in advanced stages. According to the stage stratified by clinical stage groupings, and based on data in the National Cancer Database, less than 40% of patients are alive 5 years after a diagnosis of locally advanced gastric cancer with regional
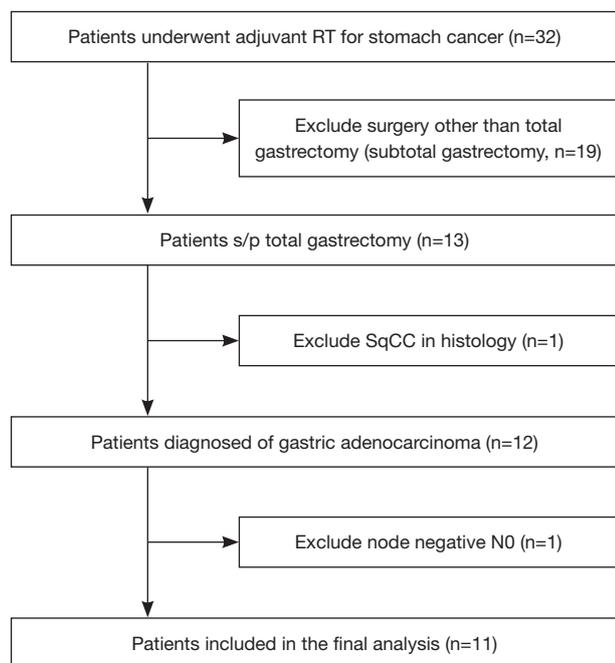
Figure 1 Flowchart of patient selection. SqCC, squamous cell carcinoma.

lymph node (LN) metastasis. However, since the successful intervention in eradication of *Helicobacter pylori* and the widespread availability of food refrigeration, there has been a significant downward trend in the overall incidence of gastric cancer over the past 50 years. Moreover, progress in cancer treatment including modern radiotherapy (RT) and chemotherapy provide more treatment options for SC. Regarding the decrease in the rates of locoregional and distant recurrence following surgery, a study showed that multimodality therapies, such as adjuvant chemoradiation therapy, benefit patients with gastric cancer in intermediate stages (2). A randomized phase III trial, Intergroup 0116 (INT-0116), was conducted to compare observation versus postoperative chemoradiotherapy following R0 resection of the gastroesophageal (GE) junction and gastric adenocarcinoma (3). The landmark INT-0116 trial and the updated 10-year follow-up revealed that there was a marked benefit from adjuvant chemotherapy and RT for curatively resected gastric cancer and GE junction cancer, especially in T3 or greater primaries and positive LNs. Besides the diminishing incidence of gastric cancer, a notable tumor distribution was observed. That is, a significant anatomic shift of gastric tumor has been recognized in recent years, whereby the rate of non-cardia tumors has declined while

the incidence of cardia tumors has increased (4). Blaser *et al.* indicated an 11-fold increase in proportion of proximal SC from 0.4% to 4.5% in past five decades in Japan (5).

Although advances in RT have occurred over decades, the application of contemporary RT techniques as an adjuvant-based treatment for gastric cancer has not been clarified. Regarding concern for surrounding healthy tissue, a comparison on the normal tissue sparing of modern planning techniques with regard to different tumor locations of SC should be elucidated. Serarslan *et al.* has reported IMRT appears to achieve superior OAR protection than either wedge-based conformal RT or field-in-field IMRT in antrum-located SC (6). Current highly conformal treatment modalities, including intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and helical tomotherapy (TOMO) should be analyzed carefully with respect to the dose distributions in the target volume and organs at risk (OARs) based on different anatomical subsites for gastric cancer.

Accordingly, the aims of this study were to compare modern RT planning techniques on the basis of similar target coverage and to determine which technique fits a particular location of gastric cancer more in respect to the dose distribution to planning target volume (PTV) and OARs, namely the heart, lungs, bilateral kidneys, liver, small bowel, and spinal cord.

Methods

Patient data

We enrolled 32 newly diagnosed patients with gastric cancer receiving adjuvant RT after gastrectomy from January 2013 to May 2017. Our study is approved by local IRB and our IRB number is TMU-JIRB No.:N210712030. The first eligible criterion was pathology-proven gastric adenocarcinoma in patients that had received a total gastrectomy. The location of the primary lesion was recorded. Overall, 11 gastric cancer patients with six proximal and five middle/distal lesions were evaluated. A patient selection flowchart is presented in *Figure 1*. All anatomical locations of stomach adenocarcinoma were included. Other eligibility criteria were patients aged 20 to 90 years who had a favorable Eastern Cooperative Oncology Group (ECOG) performance status (score 0, 1, or 2). Tumors were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system [2010] and were categorized as pathological

Table 1 Patient and tumor characteristics (N=11)

Patient characteristic	Groups	Proximal (n=6), n (%)	Middle/Distal (n=5), n (%)
Gender	Female	0 (0)	1 (20.0)
	Male	6 (100.0)	4 (80.0)
Age (years)	<65	4 (66.7)	4 (80.0)
	≥65	2 (33.3)	1 (20.0)
	Median (range)	61.0 (48.0–87.0)	
ECOG	0	3 (50.0)	3 (60.0)
	1	2 (33.3)	1 (20.0)
	2	1 (16.7)	1 (20.0)
BMI	Underweight (≤18.5)	2 (33.3)	0 (0)
	Normal weight (18.5–24.9)	4 (66.7)	5 (100.0)
	Overweight (25–29.9)	0 (0)	0 (0)
	Obesity (BMI ≥30)	0 (0)	0 (0)
GERD	–	5 (83.3)	2 (40.0)
	+	1 (16.7)	3 (60.0)
Tobacco use	–	3 (50.0)	3 (60.0)
	+	3 (50.0)	2 (40.0)
Alcoholic drinking	–	5 (83.3)	3 (60.0)
	+	1 (16.7)	2 (40.0)
Helicobacter pylori infection	–	6 (100.0)	4 (80.0)
	+	0 (0)	1 (20.0)
Previous stomach surgery	–	6 (100.0)	5 (100.0)
	+	0 (0)	0 (0)
Pernicious anemia	–	6 (100.0)	5 (100.0)
	+	0 (0)	0 (0)
Surgery	Total gastrectomy	6 (100.0)	5 (100.0)
	Subtotal gastrectomy	0 (0)	0 (0)
LN dissection	D1	3 (50.0)	1 (20.0)
	D2	3 (50.0)	4 (80.0)
AJCC stage	IIIA	2 (33.3)	1 (20.0)
	IIIB	1 (16.7)	2 (40.0)
	IIIC	2 (33.3)	1 (20.0)
	IV	1 (16.7)	1 (20.0)

P/M/D, proximal/ middle/distal; Tx, treatment.

T3–T4b and positive nodes. Because the PTV varied considerably owing to the location of the primary tumor and extent of surgical resection, the primary tumor bed and regional LNs were the target of radiation as per a consensus approved by the Multidisciplinary Gastrointestinal Tumor Board at Shuang Ho Hospital. The patient characteristics were summarized in *Table 1*.

Simulation and target delineation

All patients were immobilized in a vacuum bag in the supine position with their arms placed above their head. A computed tomography (CT) scan of the chest and abdomen was completed after at least 4 hours of fasting and oral contrast was used to identify intestinal loops. Respiration control and abdominal compressor were not used. We performed RT planning on a contrast-enhanced CT image with an interval of 5 mm in slide thickness. The target volumes and OARs were contoured according to the International Commission on Radiation Units and Measurements (reports 50 and 62) and all delineations were performed on individual axial CT slices (7). The clinical target volume (CTV) comprised the original tumor bed and regional draining LSNs at risk, depending on the tumor location. The PTV was defined as a 5–10-mm expansion to the CTV to account for daily setup error and organ motion. OARs comprised the heart, lungs, bilateral kidneys, liver, small bowel, and spinal cord. The small bowel was delineated an additional 1 cm in both the superior and inferior edge of the PTV.

Planning requirement and techniques

The treatment plans were generated using IMRT, VMAT, and TOMO techniques. Irrespective of whether or not the patients had an initial prospective IMRT, VMAT, or TOMO plan, all treatments were re-planned retrospectively to enable a comparison of optimized IMRT, VMAT, and TOMO dosimetric parameters. All RT plans were completed by the same medical physicist. A total radiation dose of 50.4 Gy in 28 fractions was prescribed as adjuvant RT for gastric cancer, which is required to obtain a similar PTV coverage in all plans. The objective of planning was to deliver 97% of the prescription dose (D97) to cover at least 97% of the PTV. All treatment plans aimed to achieve a minimum dose higher than 97% and a maximum dose lower than 115% of the prescribed dose. The dose constraints for IMRT, VMAT, and TOMO plans are listed in *Table 2* (8).

IMRT and VMAT planning with a 10-MV photon beam were performed on the Pinnacle treatment planning system (version 9.8.0; Philips, Fitchburg, WI, USA) and irradiation was delivered using a linear accelerator equipped with multileaf collimators. The IMRT plans comprised six coplanar beams. We accomplished IMRT plans by trial and error and angles of 20°, 80°, 170°, 220°, 300° and 340° for proximal gastric cancer and angles of 30°, 80°, 100°, 140°, 280° and 340° for middle/distal gastric cancer were found to achieve the provided constraints. VMAT plans comprised double arcs with a collimator angle of 10°, rotating clockwise from 181° to 180° and then 180° to 181° counterclockwise. A maximum delivery time of 200 seconds/arc was used during the optimization.

A 6-MV photon energy beam with a helical fan-beam was used in TOMO. TOMO plans with a field width of 2.5 cm, pitch of 0.287, and modulation factor of 3.5 were generated using a TOMO planning system (Hi-Art Tomotherapy 4.1.2; TomoTherapy Inc., Madison, WI, USA).

CT contours and OARs were drawn in Pinnacle version 9.8 and transmitted to the TOMO planning system. Treatment plans were assessed on the basis of similar PTV coverage and were compared with each technique in relation to the conformity and homogeneity, as well as the dose distribution in OARs. The conformity index (CI) and homogeneity index (HI) were calculated as follows:

$$CI = \left(V_{T,ref} / V_T\right) \times \left(V_{T,ref} / V_{ref}\right) \quad [1]$$

$V_{T,ref}$ is the volume of the target covered by the reference isodose line, V_T is the PTV, and V_{ref} is the volume covered by the reference isodose line. A value closer to 1 implies better conformity of the dose to the PTV (9).

$$HI = \left(D_2 - D_{98}\right) / D_{pre} \quad [2]$$

D_X represents the minimum dose to the x% of the PTV exposed to the highest dose and D_{pre} is the prescribed dose. D_2 represents the average maximum dose for the PTV, whereas D_{98} represents the average minimum dose for the PTV. A lower HI suggests superior uniformity of the distributed dose (6).

Statistical analyses

Statistical analyses was conducted using Statistical Package for Social Sciences (SPSS) 19 (IBM SPSS Inc., Armonk, NY) and data were demonstrated as the mean and standard deviation. The differences in dosimetric parameters among three planning techniques, and two groups, each with a

Table 2 Organs at risk dose constraints based on a Quantitative Analyses of Normal Tissue Effects in the Clinic Summary (8)

OARs	Prescribed dose limit
Heart	D_{mean} <26 Gy
	V_{30} <46%
	V_{25} <10%
Lung	V_{20} <30%
Spinal cord	D_{max} <50 Gy
Whole liver	D_{mean} <30 Gy
Bilateral whole kidneys	D_{mean} <18 Gy
	V_{20} <32%
	V_{23} <30%
	V_{28} <20%
Small bowel	V_{45} <195 c.c.

OARs, organs at risk; V_x, percentage of volume receiving at least x Gy.

different tumor location, were evaluated using Wilcoxon's signed-rank test: IMRT *vs.* VMAT, IMRT *vs.* TOMO, and VMAT *vs.* TOMO. Dosimetric results of various planning techniques and comparison of organs at risk in the proximal and middle/distal location tumor were assessed using independent paired *t*-test. A P value <0.05 was regarded as statistically significant.

Results

Patient characteristics

Patient data of the 11 participants in this study were collected retrospectively from January 2013 to May 2017 and comprised six patients with proximal gastric cancer and five with middle/distal gastric cancer after receiving total gastrectomy combined with adjuvant chemotherapy and RT in Shuang Ho Hospital. There was only one female patient and the median age of these patients was 61 years (ranging from 48 to 87 years). Regarding the ECOG performance status, more than half of the patients had a score of zero. Regarding body mass index, none of the patients were overweight at the diagnosis. Nine patients had stage III cancer, which included three stage IIIA, three stage IIIB, and three stage IIIC based on the seventh edition of the AJCC. Two patients were stage IV with solitary liver metastases and were treated on a salvage basis. All patients

received total gastrectomy with regional LN dissection. Seven patients (63%) underwent D2 dissection (LN ≥15). No difference was observed between the proximal and middle/distal groups with respect to age at diagnosis, sex, ECOG performance status, stage, and surgical procedure.

Target volume doses

TOMO, VMAT, and IMRT all achieved desirable PTV coverage, with 97% of the prescribed dose (D_{97}) covering at least 97% of the PTV. No significant difference was observed in hot spot doses and HI among the three techniques. However, TOMO seemed to have a superior CI to IMRT in patients with proximal gastric cancer (P=0.033). In terms of the monitor units (MUs), there were fewer MUs (shorter treatment time) in IMRT and VMAT than in TOMO. The dosimetric parameters for target volumes are summarized in *Table 3*.

OAR doses

IMRT *vs.* VMAT

In the six patients diagnosed with proximal gastric cancer, IMRT lowered small bowel mean dose and V_{35} (P=0.046 and P=0.046, respectively) compared to VMAT. For middle/distal tumors, VMAT lowered the dose in the bilateral kidney V_{20} and V_{30} (P=0.030 and P=0.020, respectively) compared with IMRT. The dose-volume histogram (DVH) results were shown in *Figure 2*.

IMRT *vs.* TOMO

In comparison with IMRT, TOMO lowered the heart $D_{1/3}$ (P=0.046); left kidney V_{20} (P=0.001), V_{23} (P=0.003), and V_{28} (P=0.001); total kidney D_{mean} (P<0.001), V_{20} (P=0.009), V_{23} (P=0.001), and V_{28} (P<0.001); right kidney V_{23} (P=0.023); liver V_{20} (P=0.028) and V_{30} (P=0.009) and small bowel V_{40} (P=0.028) in patients with proximal gastric cancer. For patients with middle/distal gastric cancer, there was significantly lower total kidney D_{mean} (P=0.010), V_{20} (P=0.011), and V_{23} (P=0.014) when planning with TOMO rather than IMRT. The dose-volume histogram (DVH) results were shown in *Figure 2*.

VMAT *vs.* TOMO

For proximal gastric cancer, the TOMO treatment plan lowered the heart $D_{1/3}$ (P=0.046); left kidney V_{20} (P<0.001), V_{23} (P<0.001), and V_{28} (P=0.006); total kidney Dmean (P=0.005), V_{20} (P=0.013), V_{23} (P=0.018), and V_{28} (P=0.027); liver V_{20} (P=0.046) and V_{30} (P=0.019); and small bowel V_{40} (P=0.028) compared with VMAT. In patients with middle/distal gastric tumor, TOMO significantly improved dose sparing to total kidney D_{mean} (P=0.049) and V_{20} (P=0.014). The dose-volume histogram (DVH) results were shown in *Figure 2*.

Proximal *vs.* middle/distal

When comparing the dosimetric results between patients with proximal and middle/distal gastric cancer, TOMO significantly lowered the treatment time (MU) in the patients with middle/distal gastric cancer. In comparison with the heart dose in patients with proximal and middle/distal gastric cancer, all heart parameters, including heart D_{mean}, heart $D_{1/3}$ and V_{30} were significantly higher in proximal gastric tumors than in the distal counterparts when planning with IMRT and VMAT. Moreover, the lung dose tended to be lower in middle/distal gastric tumors than in proximal tumors. *Table 4* presents the dosimetric results for the planning parameters and a comparison for OARs in the proximal versus middle/distal tumor locations. *Figures 3* and *4* show representative cases of proximal and middle/distal gastric cancer respectively.

Discussion

Our study presented a dosimetric comparison of SC in different locations. As mentioned previously, adjuvant RT has played a crucial role in the postoperative setting for resectable gastric cancer since the landmark INT-0116 trial. However, the radiation technique traditionally employed in INT-0116 is considered to be outdated. Consequently, in this study, radiation was delivered using highly conformal radiation techniques such as IMRT, VMAT, and TOMO to attain extensive normal tissue sparing. Furthermore, we examined whether there was a dosimetric advantage in applying a particular planning technique to gastric tumors in different locations, which has never been discussed in the literature, and which drew our attention due to a marked anatomic shift in gastric cancer. That is, the incidence of gastric cardia tumors has increased while the incidence of distal gastric tumors has decreased (4). We endeavored to identify the optimal RT techniques for treating gastric cancer in shared or similar locations. In our study, patients diagnosed with gastric cancer who received a total gastrectomy were categorized into proximal (cardia) and middle/distal (body and antrum) groups.

Studies have demonstrated that IMRT has an edge

Table 3 (Left) dosimetric results for planning target volume and organs at risk in locally advanced gastric cancer; (right) dosimetric results of an analytic data comparison[†] for IMRT vs. VMAT, IMRT vs. TOMO, and VMAT vs. TOMO

Variable	IMRT		VMAT		TOMO		IMRT vs. VMAT		IMRT vs. TOMO		VMAT vs. TOMO	
	Proximal	Middle/Distal	Proximal	Middle/Distal	Proximal	Middle/Distal	P	M/D	P	M/D	P	M/D
D_{97} (PTV$_{48.88}$) (%)	97.24±0.27	97.19±0.18	97.23±0.30	97.28±0.20	98.26±0.94	97.99±1.14	1.000	1.000	0.200	0.563	0.237	0.802
CTV$_{48.88}$ (%)	99.90±0.17	99.95±0.12	99.88±0.11	99.93±0.15	99.47±1.17	99.82±0.41	1.000	1.000	1.000	1.000	1.000	1.000
Hot spot (Gy)	5,444.75±138.81	5,504.40±117.78	5,519.97±100.92	5,602.04±142.66	5,452.00±104.30	5,539.60±91.99	0.464	0.144	1.000	0.967	1.000	0.362
HI	0.07±0.04	0.10±0.03	0.10±0.02	0.12±0.03	0.08±0.04	0.10±0.03	0.578	1.000	1.000	1.000	1.000	1.000
CI	0.82±0.03	0.83±0.02	0.80±0.05	0.82±0.04	0.85±0.02	0.85±0.02	0.571	1.000	0.033*	0.879	0.062	0.657
MU (sec in Tomo)	462.43±82.69	418.94±116.12	468.25±61.01	447.80±112.06	6,432.70±571.74	5,337.74±556.70	1.000	1.000	0.028*	0.043*	0.028*	0.043*
Right kidney												
Mean dose (cGy)	989.40±461.79	974.76±668.93	1,002.50±419.16	853.12±608.77	845.83±415.80	828.80±470.45	1.000	1.000	0.153	0.978	0.297	1.000
V$_{20}$ (%)	17.14±9.49	14.20±14.68	16.03±9.40	10.75±11.18	9.46±8.03	6.29±8.34	1.000	0.810	0.112	0.551	0.264	0.402
V$_{23}$ (%)	11.55±6.88	10.00±10.25	13.21±8.60	7.32±8.55	6.23±5.60	3.08±4.36	1.000	0.726	0.023*	0.354	0.207	0.345
V$_{28}$ (%)	7.01±5.99	4.31±4.62	8.91±6.75	3.63±5.29	3.27±3.38	0.22±0.37	1.000	1.000	0.071	0.333	0.214	0.652
Left kidney												
Mean dose (cGy)	1,499.63±276.12	1,407.20±433.64	1,431.77±232.25	1,334.18±488.85	754.33±580.50	1,145.80±584.26	0.429	1.000	0.081	0.224	0.147	0.240
V$_{20}$ (%)	25.13±6.34	22.73±6.82	22.69±5.00	19.46±10.34	13.50±5.95	15.28±11.02	0.483	0.804	0.001*	0.223	<0.001*	0.090
V$_{23}$ (%)	20.23±5.01	16.70±6.84	18.78±4.34	15.43±8.90	10.48±4.33	12.53±9.24	0.632	1.000	0.003*	0.538	<0.001*	0.095
V$_{28}$ (%)	13.69±3.74	10.50±5.57	13.47±4.05	10.98±7.63	6.76±3.49	8.66±6.78	1.000	1.000	0.001*	1.000	0.006*	0.143
Total kidney												
Mean dose (cGy)	1,255.52±251.90	1,225.28±572.06	1,229.88±254.07	1,123.18±547.99	1,002.00±269.10	1,014.00±545.75	0.429	0.146	<0.001*	0.010*	0.005*	0.049*
V$_{20}$ (%)	21.33±5.57	19.26±10.70	19.64±4.72	15.73±10.45	11.77±5.51	11.20±9.00	0.227	0.030*	0.009*	0.011*	0.013*	0.014*
V$_{23}$ (%)	15.98±3.49	14.19±8.73	16.23±4.20	12.01±8.55	8.39±4.04	8.34±6.51	1.000	0.020*	0.001*	0.014*	0.018*	0.063
V$_{28}$ (%)	10.41±3.39	8.25±5.47	11.35±3.69	7.96±6.32	5.05±2.95	5.14±4.39	1.000	1.000	<0.001*	0.253	0.027*	0.356
Liver												
Mean dose (cGy)	1,664.62±127.73	1,763.56±291.20	1,722.27±93.53	1,908.54±591.61	1,555.00±158.24	1,813.80±666.64	0.600	1.000	0.320	1.000	0.122	1.000
V$_{20}$ (%)	31.15±4.58	34.38±5.70	32.10±2.62	41.93±23.42	22.71±6.96	40.35±22.12	0.917	0.893	0.028*	0.686	0.046*	0.500
V$_{30}$ (%)	16.66±1.25	18.99±8.22	18.24±2.08	20.05±11.30	9.93±3.74	18.42±11.57	0.420	1.000	0.009*	1.000	0.019*	0.751

Table 3 (*Continued*)

Table 3 (*Continued*)

Variable	Mean ± SD						P value					
	IMRT		VMAT		TOMO		IMRT vs. VMAT		IMRT vs. TOMO		VMAT vs. TOMO	
	Proximal	Middle/Distal	Proximal	Middle/Distal	Proximal	Middle/Distal	P	M/D	P	M/D	P	M/D
Heart												
Mean dose (cGy)	1,683.68±737.78	506.40±340.66	1,584.02±671.27	581.80±429.44	1,264.00±555.86	440.40±272.76	0.227	1.000	0.083	1.000	0.095	1.000
$D_{1/3}$ (cGy)	2,060.52±997.99	440.75±422.14	1917.69±907.49	470.18±363.10	1,389.50±661.63	359.12±207.61	1.000	1.000	0.046*	0.178	0.046*	0.043*
V_{30} (%)	17.72±12.23	3.38±3.30	15.72±10.23	4.34±4.80	8.61±5.93	2.11±2.38	0.477	1.000	0.082	0.234	0.064	0.583
Spinal cord D_{max} (cGy)	4,225.68±589.38	3,472.46±1,142.82	4,222.62±555.26	3,849.66±736.40	4,069.17±225.78	3,672.20±836.94	0.917	0.138	0.345	0.686	0.249	0.893
Small bowel												
Mean dose (cGy)	26.07±6.69	27.84±9.68	27.94±5.96	29.69±7.40	26.62±7.46	28.28±8.37	0.046*	0.686	0.753	0.500	0.345	0.500
V_{35} (c.c.)	64.75±75.42	79.6220±67.60	69.80±78.65	78.92±64.31	54.82±67.55	72.06±59.13	0.046*	0.893	0.075	0.225	0.075	0.225
V_{40} (c.c.)	42.72±53.98	64.47±58.80	47.78±58.62	64.90±56.29	32.10±42.04	56.11±47.13	0.293	0.686	0.028*	0.345	0.028*	0.345
V_{45} (c.c.)	29.80±30.92	39.13±52.15	34.99±34.68	39.29±52.76	22.16±22.76	29.71±38.44	0.669	1.000	0.474	1.000	0.361	1.000
Whole lung												
Mean dose (cGy)	545.60±307.07	246.08±131.93	576.50±354.70	259.40±133.89	590.83±336.43	274.20±133.07	0.638	0.311	0.267	0.136	1.000	0.876
V_5 (%)	27.83±14.79	13.15±7.34	29.77±16.67	14.11±7.72	29.80±17.33	13.01±8.70	0.259	0.063	0.477	1.000	1.000	1.000
V_{10} (%)	18.26±10.90	7.46±4.14	19.79±12.87	7.76±4.20	20.33±14.20	7.19±5.47	0.422	1.000	0.691	1.000	1.000	1.000
V_{20} (%)	8.08±5.26	2.67±1.45	8.79±6.88	2.81±1.38	8.32±6.78	4.57±5.15	1.000	1.000	1.000	1.000	1.000	1.000
V_{30} (%)	3.96±3.32	0.96±0.72	4.20±4.22	1.04±0.80	3.71±3.27	1.15±0.94	1.000	0.459	1.000	1.000	1.000	1.000

*, quick reference guide is based on the significant P value ($P<0.05$); otherwise, data without * means statistical insignificance. IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated radiation therapy; TOMO, tomotherapy; SD, standard deviation; Heart $D_{1/3}$, the mean dose covering one-third volume of the heart; V_x, the percentage of organ receiving more or equal to x Gy; D_{max}, maximum dose of certain OAR.
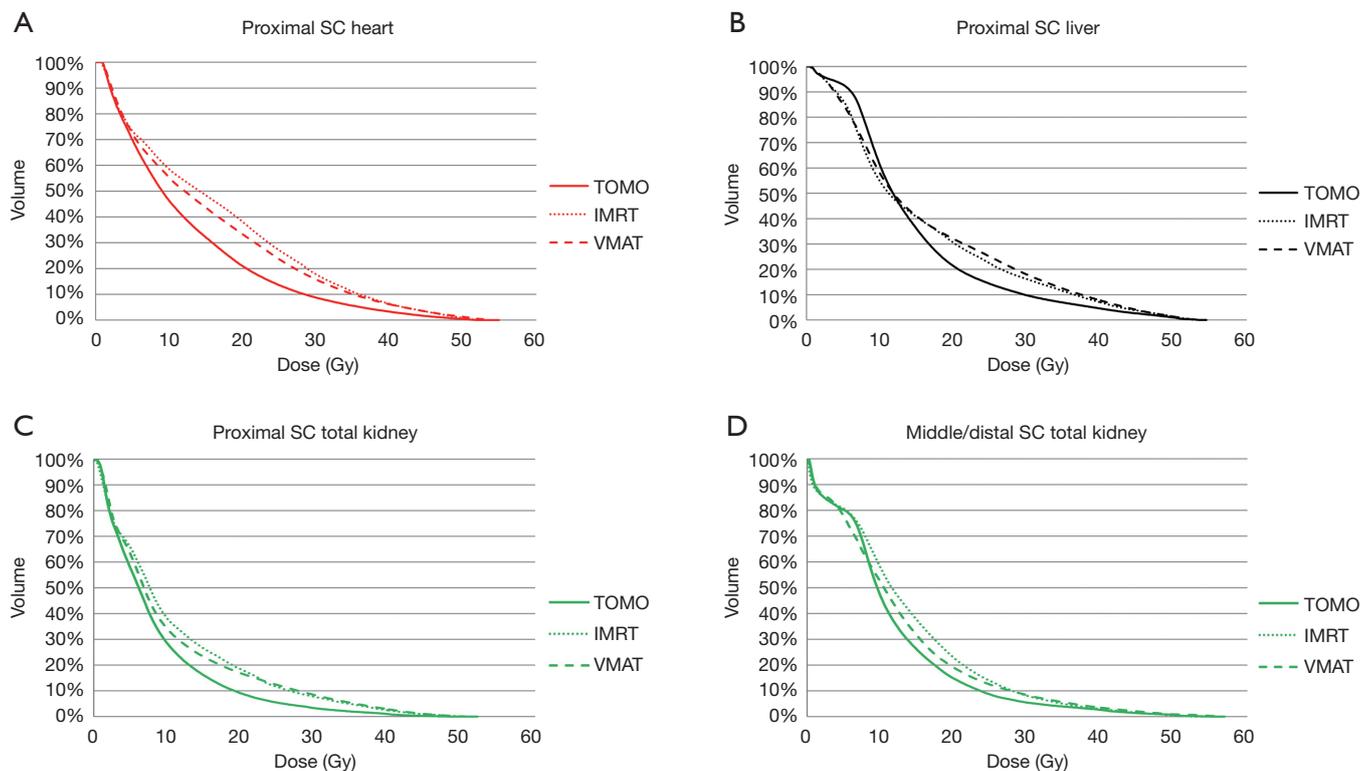
Figure 2 The dose-volume histogram (DVH) comparing TOMO, IMRT and VMAT in (A) heart dose in proximal stomach cancer, (B) liver dose in proximal SC, (C) total kidney dose in proximal SC, (D) total kidney dose in middle and distal SC.

over 3D conformal RT in terms of dosimetric parameters and doses of OARs (6,10-12). However, few studies have investigated comparisons of IMRT, VMAT, and TOMO in treating postoperative gastric cancer patients. We examined three contemporary planning techniques (IMRT, VMAT, and TOMO) that are commonly used in RT in Taiwan. As for the amounts of the beam angle design in IMRT, Nazareth *et al.* pointed the beam-angle selection which involves the selection of 5–10 angles from 360 gantry angles is crucial in IMRT planning (13). And Jia *et al.* further added that the beam orientation selection is usually achieved via a cumbersome trial-and-error approach conducted by experienced treatment planners (14). On the basis of same defined goal of the PTV coverage and OARs constraints, our 6-beam IMRT achieved the goal as VMAT did. We did not add more beams not only for the long and intolerable treatment time but also for the evidence that adding more beams in static IMRT increases the MUs and number of segments without any considerable improvement in dose distribution, leading to more leakage radiation and increased critical organ dose (15). We obtained satisfactory

D_{97} covering at least 97% of the PTV, which is higher than the coverage reported in the study of Serarslan *et al.* (6), which discussed the treatment of antrum-located SC using IMRT and CRT. Moreover, our HI is comparable to theirs. We also obtained a similar CI as the data shown in the studies of Onal *et al.* (6,16), and a higher CI than that presented in Serarslan *et al.* (6).

No marked difference was noted in the locations of the tumors in our study and we had balanced cases in the proximal and middle/distal groups. We revealed that TOMO provided superior dose sparing for heart, total kidney, left kidney and liver V_{20} and liver V_{30} in proximal SC compared with IMRT and VMAT. By contrast, the benefit of TOMO planning for middle/distal SC was only observed in the total kidney dose. Moreover, a comparison of different locations was conducted on the basis of the same planning techniques. Heart dose was significantly higher in proximal gastric tumor than in the distal counterparts when planning with all three techniques, which is reasonably contributes to the closer distance to the heart.

The kidneys are vital organs, which are at risk in gastric

Table 4 Dosimetric results for planning parameters and comparison for organs at risk in the proximal *vs.* middle/distal location tumor

Variable	Proximal *vs.* middle/distal (P value)[†]		
	IMRT	VMAT	TOMO
D_{97} ($PTV_{48.88}$) (%)	0.716	0.780	0.680
$CTV_{48.88}$ (%)	0.614	0.471	0.542
Hot spot (Gy)	0.468	0.293	0.178
HI	0.132	0.363	0.351
CI	0.389	0.433	0.728
MU	0.486	0.708	0.011*
Right kidney			
Mean dose (cGy)	0.967	0.642	0.951
V_{20} (%)	0.696	0.416	0.538
V_{23} (%)	0.772	0.286	0.334
V_{28} (%)	0.433	0.190	0.078
Left kidney			
Mean dose (cGy)	0.677	0.673	0.296
V_{20} (%)	0.561	0.513	0.740
V_{23} (%)	0.348	0.434	0.666
V_{28} (%)	0.287	0.505	0.562
Total kidney			
Mean dose (cGy)	0.917	0.704	0.966
V_{20} (%)	0.688	0.473	0.901
V_{23} (%)	0.684	0.312	0.987
V_{28} (%)	0.443	0.295	0.970
Liver			
Mean dose (cGy)	0.469	0.462	0.377
V_{30} (%)	0.563	0.707	0.122
V_{20} (%)	0.750	0.058	0.116
Heart			
Mean dose (cGy)	0.010*	0.018*	0.015*
$D_{1/3}$ (cGy)	0.008*	0.009*	0.009*
V_{30} (%)	0.032*	0.049*	0.048*
Spinal cord Dmax (cGy)	0.105	0.238	0.010*
Small bowel			
Mean dose (cGy)	0.934	0.251	0.163
V_{35} (%)	0.432	0.669	0.173
V_{40} (%)	0.530	0.731	0.276
V_{45} (%)	0.720	0.874	0.712

Table 4 (*Continued*)

Table 4 (*Continued*)

Variable	Proximal *vs.* middle/distal (P value)[†]		
	IMRT	VMAT	TOMO
Whole lung			
Mean dose (cGy)	0.074	0.085	0.074
V_5 (%)	0.067	0.078	0.073
V_{10} (%)	0.062	0.073	0.077
V_{20} (%)	0.053	0.088	0.338
V_{30} (%)	0.080	0.128	0.116

[†], by independent *t*-test; *, quick reference guide for the significant P value ($P<0.05$); otherwise, data without * means statistical insignificance.

cancer RT owing to the radiosensitivity of renal tissue. Cassady studied clinical radiation nephropathy and found that a total kidney dose of 18–23 Gy was associated with a 5% risk of injury within 5 years. Further investigation analyzing kidney function in SC patients treated with RT found that the mean renal dose was less crucial than V_{20}, with the author recommending that <70% of the ipsilateral kidney volume receive 20 Gy (V_{20} <70%) (17). In our study, the total kidney constraint was set at V_{20} <32%. Our results of the kidney mean dose were compatible with another TOMO study, whereby Dahele *et al.* (18,19) reported mean right and left kidney doses of 13.6 Gy (range, 7.9–28.8 Gy) and 17.6 Gy (range, 14.9–19.4 Gy), respectively, which are higher than our results: Right kidney$_{mean}$ =8.4 Gy (range, 4.2–12.6 Gy) and Left kidney$_{mean}$ =9.3 Gy (range, 3.4–15.2 Gy). In proximal gastric cancer, TOMO significantly spared the left kidney and total kidney doses.

Radiation-induced liver disease has been a critical issue for patients with primary liver cancer treated with radiation. Because of the large radiation volume required for adjuvant RT of SC and the fact that the liver consumes a considerable proportion of the space in the upper abdomen, it is crucial to protect the liver from radiation injury when using adjuvant chemoradiation therapy to treat gastric cancer (20). In our study, TOMO planning was superior to both IMRT and VMAT in liver V_{20} and liver V_{30} (the percentage of the organ receiving more or equal to 30 Gy) in the proximal gastric cancer subgroup. According to an investigation by Gu *et al.* (11), liver V_{30}–V_{40} is correlated with liver function injury. Therefore, we extrapolate that TOMO could reduce damage to liver function in patients with proximal gastric cancer receiving adjuvant RT.
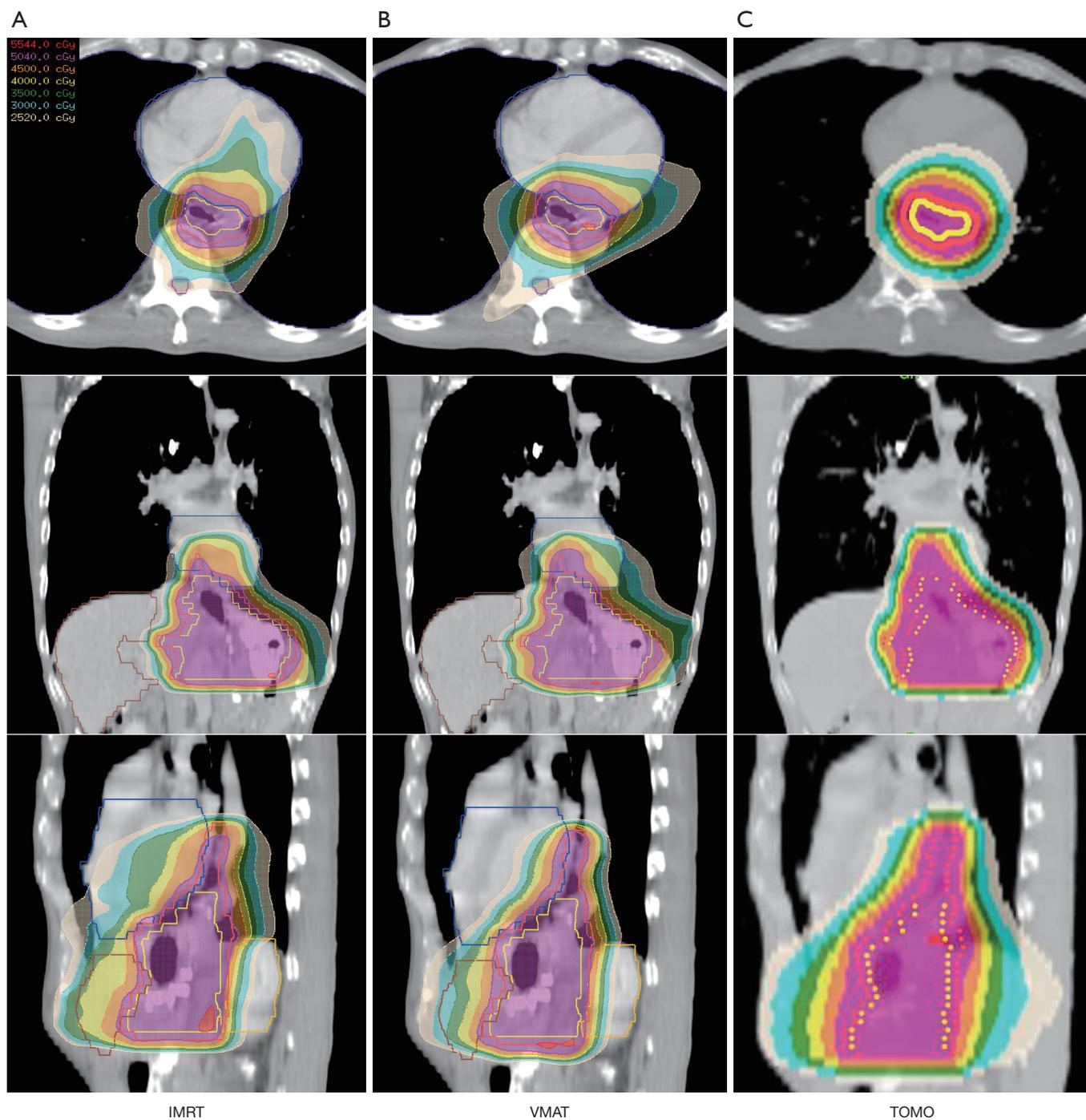
Figure 3 Representative case of proximal gastric cancer displaying the isodose curves in the axial view at the level of the heart and the relevant coronal/sagittal view: (A) intensity-modulated radiation therapy; (B) volumetric-modulated arc therapy; and (C) tomography.

In terms of the OAR constraints, other than the kidney and liver doses, we usually pay more attention to the dose to the heart and lungs when we encounter proximal SC because of their anatomic locations. Similarly, the cardiac exposure of radiation in treating breast cancer has been a pertinent. A population-based case-control study of
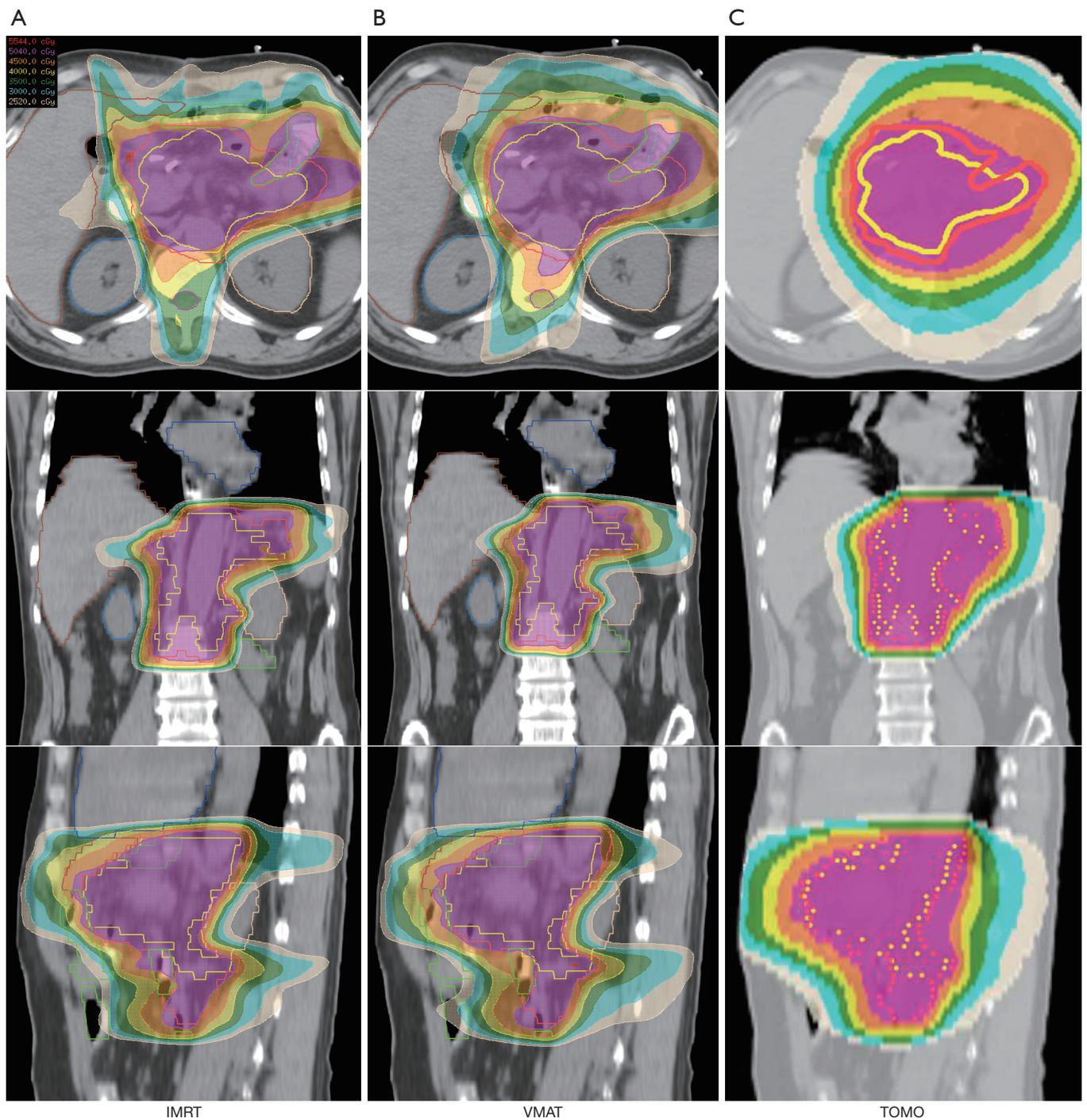
Figure 4 Representative case of middle/distal gastric cancer displaying the isodose curves in the axial view at the level of T12 and the relevant coronal/sagittal view: (A) intensity-modulated radiation therapy; (B) volumetric-modulated arc therapy; and (C) tomography.

the risk of ischemic heart disease in women receiving postoperative RT conducted by Darby *et al.* (18) showed a linear correlation between the mean heart dose and major coronary events, which increased by 7.4% per Gy. Additionally, cardiac radiation exposure increases the risk of heart failure with preserved ejection fraction in older

women (mean age: 69±9 years) after breast irradiation (odds ratio: 16.9), with the odds being even higher than for heart failure with reduced ejection fraction (21). Correspondingly, the stomach is located on the left side of body as is the heart; therefore, the cardiac radiation dose administered in adjuvant RT of gastric cancer is of importance. In this study, we revealed that all parameters of heart dose (D_{mean}, $D_{1/3}$ and V_{30}) in proximal SC were significantly higher than that for middle/distal SC when comparing the heart dose of proximal and middle/distal gastric cancer. When comparing different planning techniques, we observed that TOMO treatment plans surpass either IMRT or VMAT plans on the heart dose in proximal SC. That is, TOMO yields a lower cardiac radiation dose in proximal SC. The highlight of our results indicated that TOMO achieved the most favorable dose improvements in terms of heart sparing in proximal gastric cancer.

A major limitation of this study is that the small sample size might have been too small to show a significant analytical difference between the groups. Other than advanced image-guided RT, we should consider more motion management strategies by using 4D CT, respiratory gating, or an abdominal compressor to reduce the shift of target volumes that are susceptible to substantial respiratory movement. It is believed that tumor motion can compromise the effectiveness and accuracy of radiation treatment. Clinically, either respiration motion or changes in the filling status of gastrointestinal organs causes tumor motion in the abdomen. Hu *et al.* (22) showed combining breath hold with image guided IMRT can minimize the organ motion and make the setup more accurate. Based on their dosimetric comparison, the dose could be escalated to 54 Gy without increasing the critical organs toxicities. With the addition of contemporary conformal techniques and the introduction of image-guided RT, closer target volume margins could be achieved without compromising the PTV coverage in addition to more favorable normal tissue sparing.

In summary, this is the first study to compare conformal RT techniques using IMRT, VMAT, and TOMO with regard to the PTV and OARs in adjuvant RT for gastric cancer in different locations. The results revealed that in the adjuvant treatment of gastric cancer, TOMO not only provided superior dose sparing for total kidney, liver V_{20}, and liver V_{30}, which was especially evident in proximal gastric cancer, but also provided the optimal dose improvements in the heart among the three planning techniques in proximal SC. Further study is required to

validate the clinical use of TOMO in RT treatment plans for patients with gastric cancer.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our study is approved by local IRB and our IRB number is TMU-JIRB No.:N210712030. Informed consent was waived due to the retrospective nature of the study.

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