

Plan Quality Comparisons Between Three-dimensional Conformal Radiotherapy, Intensity-modulated Radiotherapy, and Volumetric Modulated Arc Therapy Based on Four-dimensional Computed Tomography for Gastric Mucosa-associated Lymphoid Tissue Lymphoma: a Planning Study

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Abstract

Background: Previous planning studies in radiotherapy (RT) for gastric mucosa-associated lymphoid tissue (MALT) lymphoma have been based on three-dimensional computed tomography (3D-CT) images, which do not contain information on the respiratory motion of the stomach. Therefore, we compared the plan quality between 3D conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT) for gastric MALT lymphoma using four-dimensional computed tomography (4D-CT).

Methods: Three different treatment plans of four-field 3D-CRT, seven-field IMRT, and double arc VMAT were created based on 4D-CT images of seven patients with gastric MALT lymphoma. An RT dose of 30 Gy was prescribed to the planning target volume (PTV) in 20 fractions. We calculated the minimum dose coverage for 95% of the PTV (D_{95}), homogeneity index (HI), and conformity index (CI) of the PTV, and organs at risk (OARs) doses for the liver, kidneys, spinal cord, and small bowel. Plan quality metric (PQM) scores were also calculated for a comprehensive and objective assessment.

Results: There was no significant difference among the three plans in D_{95} of PTV. HI of PTV for the IMRT plan was significantly better than that of the VMAT ($p = 0.047$) and 3D-CRT ($p = 0.047$) plans. HI of PTV for the VMAT plan was significantly better than that of the 3D-CRT plan ($p = 0.047$). CIs of PTV for the IMRT and VMAT plans were significantly better than that of the 3D-CRT plan ($p = 0.047$ and $p = 0.047$, respectively). D_{mean} of the liver for 3D-CRT was significantly higher than that for the IMRT ($p = 0.047$) and VMAT ($p = 0.047$) plans. The PQM scores of the VMAT and IMRT plans were significantly higher than that of the 3D-CRT plan ($p = 0.047$ and $p = 0.047$, respectively). The PQM score of the IMRT plan was significantly higher than that of the VMAT plan ($p = 0.047$).

Conclusions: The IMRT plan yields the best plan quality for gastric MALT lymphoma. In terms of plan quality, as opposed to the 3D-CRT plan, we recommend the IMRT and VMAT plans.

Background

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent B-cell lymphoma, which can arise in almost all organs. The stomach is the most frequent site, and most gastric MALT lymphoma cases are localized to stomach. Stage IE accounts for 70–80% of all gastric MALT lymphoma cases [1]. Radiotherapy (RT) is a curative treatment for localized gastric MALT lymphoma and is particularly in persisting cases or those with relapse after helicobacter pylori (HP) eradication when HP is negative. National Comprehensive Cancer Network (NCCN) guidelines recommend an RT dose of 30 Gy in 20 fractions for the treatment of this condition [2].

The target volume for gastric MALT lymphoma is very large. Clinical target volume (CTV) is defined as the gross tumor volume (GTV) plus whole stomach volume, outlined from the gastroesophageal junction to beyond the duodenal bulb. Furthermore, an additional margin is required to cover variations in stomach size and shape, respiratory motion, and set-up errors [3]. As patients with gastric MALT lymphoma have a

long-term prognosis, with an approximate 10-year overall survival of 90% [4]. Therefore, late adverse events from RT should be avoided.

The goal of RT for gastric MALT lymphoma is to deliver a sufficient dose to the large target volume while avoiding the organs at risk (OARs), such as the kidneys and the liver. Two-dimensional RT (2D-RT) and three-dimensional conformal RT (3D-CRT) have been traditionally used for the treatment of gastric MALT lymphoma [5]. In this decade, the use of intensity-modulated radiotherapy (IMRT) has been increasing for the treatment of abdominal tumors [6, 7]. IMRT can provide the desired intensity modulation by using several gantry angles and dividing each radiation beam into numerous beamlets whose intensities are adjusted individually [8]. More recently, volumetric modulated arc therapy (VMAT) has been introduced for the treatment of various tumors [9]. VMAT can provide the full range of beams by gantry rotation, and change the parameters of dose rate, field shape, and speed of gantry rotation as the beam is rotated [8]. Some groups performed a planning study and reported that these state-of-the-art RT techniques provide a better dose distribution for gastric MALT lymphoma than that provided by 2D and 3D-CRT [5, 10]. However, they performed planning and evaluated plans based on three-dimensional computed tomography (3D-CT) images, which do not contain the information of the respiratory motion, which changes not only the position, but also the shape and volume of the stomach [11, 12]. Another group compared 3D-CRT, IMRT, and VMAT under the deep-inspiration breath hold (DIBH) technique and suggested the dosimetric superiority of IMRT and VMAT over 3D-CRT [13]. However, DIBH can only be performed in a limited number of institutions.

Four-dimensional computed tomography (4D-CT) images, which provide information on the variability of respiratory motion, have been introduced into RT planning. Jang et al. compared the target volume, volume of OARs, and dose distribution of 3D-RT and 4D-CT images from 18 patients with gastric MALT lymphoma [14]. They reported that the target volume and volume of the liver and kidneys, contoured using free-breathing 3D-CT images, were significantly smaller than those contoured using 4D-CT. The reason for this was that the respiratory motion of the target volume and OARs is not reflected into free-breathing 3D-CT images. They also found that 3D-CT image-based planning may result in inadequate dose coverage of the target volume and OAR dose underestimation. The International Lymphoma Radiation Oncology Group recommends determining the target volume by 4D-CT or by fluoroscopy, to track variations in stomach position during respiration [3]. However, to our knowledge, the plan quality of modern treatment techniques has not been evaluated and compared based on 4D-CT images.

The purpose of this study was to evaluate and compare the quality of 3D-CRT, IMRT, and VMAT plans for gastric MALT lymphoma patients based on 4D-CT images.

Methods

Patients

This retrospective study was approved by the institutional research ethics board of our hospital. All patients were enrolled with prior written informed consent to treatment and the use of image data. We

used 4D-CT images of seven patients with stage IE gastric MALT lymphoma who received RT at our institution between February 2019 and June 2020.

CT simulation procedures

To minimize variations in stomach volume, patients were instructed to fast for at least eight hours before planning simulation. They underwent CT simulation by using a Discovery RT CT scanner (GE Healthcare, Chicago, IL) in the supine position with their arms raised. 4D-CT scan was performed using a Smart Deviceless 4D application with the parameters of 120 kV, 70 mA, a gantry rotation time of 0.5 s, a slice thickness of 2.5 mm, and cine mode [15]. The cine durations were set to the respiratory cycles plus the gantry rotation time, and the cine images were sorted into 10 respiratory phases by a phase-binning algorithm. The average intensity projection (AIP) of CT images was generated from projection data of all respiratory phases. All CT images were exported to the treatment planning system (Eclipse, Version 15.6; Varian Medical Systems, Palo Alto, CA) and registered by the hardware arrangement.

Definition of target volumes and OARs

Two radiation oncologists with an experience of 5 and 17 years defined the target volumes and OARs, after reaching a consensus according to the Radiation Therapy Oncology Group contouring atlases [16]. In all patients, GTV was identified based on the endoscopic examination findings, and we confirmed that GTV was contained within the whole stomach. The CTV was defined as the whole stomach, which was delineated on the AIP CT image data sets using fused 4D-CT images to cover stomach of all 10 respiratory phases (CTV-4D) [15]. A margin of 10 mm, which included intra- and inter-fractional variations in stomach volume, respiratory movement, and patient set-up, was added to CTV-4D for generating the planning target volume (PTV) [3, 17]. OARs defined as the kidneys, liver, small bowel, and spinal cord were also delineated on the AIP CT images [15].

Treatment planning procedures

3D-CRT, IMRT, and VMAT plans were generated based on AIP CT images. The 3D-CRT plan consisted of four beams (gantry angles of 0°, 90°, 180°, and 270°) with 15-MV X-ray. Multileaf collimator apertures were created, encompassing the PTV with a 5 mm margin in all directions. The IMRT plan using sliding window technique consisted of seven beams (gantry angles of 24°, 75°, 126°, 177°, 231°, 282°, and 333°) with 6-MV X-ray. The VMAT plan consisted of a double arc of 360° with 6-MV X-ray [13]. The prescribed dose was 30 Gy in 20 fractions. The goal of each plan was as follows: the minimum coverage dose for 95% of the PTV (D_{95}) > 95% of the prescribed dose, mean dose (D_{mean}) of the liver < 12.5 Gy, D_{mean} of each kidney < 10 Gy, maximum dose (D_{max}) of the spinal cord < 30 Gy, and D_{max} of the small bowel < 31.5 Gy [13]. The dose calculation was performed with the anisotropic analytical algorithm and a grid size of 2.5 mm.

Dosimetric parameters for plan evaluation

Each plan was analyzed using a dose-volume histogram (DVH). The PTV coverage was evaluated based on D_{95} . The homogeneity index (HI) of the PTV was calculated as follows [18]:

$$HI = \frac{D_1 - D_{99}}{D_p}$$

where D_1 and D_{99} are the minimum dose covering 1 and 99% of the PTV, respectively; and D_p is the prescription dose. The lower HI suggests a better homogeneity.

The conformity index (CI) of the PTV was calculated as follows [13]:

$$CI = \frac{BV_{95}}{PTV}$$

where BV_{95} is the volume of the body receiving 95% of the prescribed dose. The closer CI is to 1, the better conformity.

The OAR dose was evaluated by the D_{mean} for parallel organs (kidneys and liver), and the D_{max} for serial organs (small bowel and spinal cord).

We used an RT plan analysis software; Plan IQ (Version 2.3.2; Sun Nuclear, Melbourne, FL), which obtains a comprehensive and objective assessment of treatment plans by calculating the plan quality metric (PQM). The PQM score settings were based on previous reports and clinical importance (Table 1) [13, 18]. The PQM score (%) was calculated as follows [13]:

$$PQM \text{ score } (\%) = \frac{PQM_{raw}}{PQM_{max}} \times 100$$

where PQM_{raw} means the total score of each dosimetric parameter, and PQM_{max} means the sum of the perfect score of each dosimetric parameter, which was set to 120.

Table 1
Plan quality metric scores for each dosimetric parameter

Score	Target			OAR				
	D ₉₅ (cGy)	HI	CI	Liver D _{mean} (cGy)	Right kidney D _{mean} (cGy)	Left kidney D _{mean} (cGy)	Spinal cord D _{max} (cGy)	Small bowel D _{max} (cGy)
0	< 2550	0.2 ≤	0	2000 ≤	1800 <	1800 <	3000 <	
1	2550	0.18	< 0.2, 1.8 <	1950	1800	1800	3000	
2	2600	0.16	0.2, 1.8	1900	1700	1700	2900	
3	2650	0.14	0.3, 1.7	1850	1600	1600	2800	
4	2700	0.12	0.4, 1.6	1800	1500	1500	2700	
5	2750	0.1	0.5, 1.5	1750	1400	1400	2600	
6	2800	0.08	0.6, 1.4	1700	1300	1300	2500	2700
7	2850	0.06	0.7, 1.3	1650	1200	1200	2400	2750
8	2900	0.04	0.8, 1.2	1600	1100	1100	2300	2800
9	2950	0.02	0.9, 1.1	1550	1000	1000	2200	2850– 2950, 3050–3150
10	3000	0	1	1500	950	950	2100	3000
11				1450	900	900	2000	
12				1400	850	850	1900	
13				1350	800	800	1800	
14				1300	750	750	1700	
15				1250	700	700	1600	
16				1200	650	650	1500	
17				1150	600	600	1400	
18				1100	550	550	1300	
19				1050	500	500	1200	

OAR: organ at risk, PTV: planning target volume, D₉₅: the minimum coverage dose of 95% of the PTV, HI: homogeneity index, CI: conformity index, D_{mean}: mean dose, D_{max}: maximum dose.

Target	OAR			
20	1000	400	400	1100
OAR: organ at risk, PTV: planning target volume, D_{95} : the minimum coverage dose of 95% of the PTV, HI: homogeneity index, CI: conformity index, D_{mean} : mean dose, D_{max} : maximum dose.				

Statistical analysis of dosimetric parameters

For the comparison of treatment plans, the Friedman test was used for analysis of variance (ANOVA), and the Wilcoxon signed-rank test was used for post-hoc analysis with a Bonferroni correction. Differences with p-values of < 0.05 were considered to be statistically significant. Statistical analyses were performed with the SPSS software (Version 26.0; IBM, Armonk, NY).

Results

The results of the DVH parameters and the PQM scores of the three treatment plans are shown in Table 2. Examples of dose distributions for each plan are shown in Fig. 1.

Table 2

Dosimetric parameters and plan quality metric scores of the three plans (mean \pm standard deviation)

		3D-CRT	IMRT	VMAT	p-value*	p-value#		
						3D-CRT vs. IMRT	3D-CRT vs. VMAT	IMRT vs. VMAT
PTV	D ₉₅ (cGy)	2895 \pm 58	2936 \pm 16	2932 \pm 19	0.368	–	–	–
	HI	0.15 \pm 0.03	0.04 \pm 0.01	0.07 \pm 0.02	< 0.001	0.047	0.047	0.047
	CI	1.56 \pm 0.16	1.23 \pm 0.05	1.19 \pm 0.05	0.002	0.047	0.047	0.094
Liver	D _{mean} (cGy)	1587 \pm 190	1291 \pm 213	1376 \pm 175	0.004	0.047	0.047	0.234
Right kidney	D _{mean} (cGy)	400 \pm 184	544 \pm 272	561 \pm 297	0.066	–	–	–
Left kidney	D _{mean} (cGy)	729 \pm 662	760 \pm 467	699 \pm 492	0.368	–	–	–
Spinal cord	D _{max} (cGy)	2415 \pm 564	1845 \pm 101	1980 \pm 142	0.066	–	–	–
Small bowel	D _{max} (cGy)	3060 \pm 74	3017 \pm 76	3006 \pm 161	0.276	–	–	–
PQM score (%)		57.11 \pm 9.24	74.49 \pm 8.05	70.36 \pm 8.58	0.002	0.047	0.047	0.047
3D-CRT: three-dimensional conformal radiotherapy, IMRT: intensity-modulated radiotherapy, VMAT: volumetric modulated arc therapy, PTV: planning target volume, D ₉₅ : the minimum coverage dose of 95% of the PTV, HI: homogeneity index, CI: conformity index, D _{mean} : mean dose, D _{max} : maximum dose, PQM: plan quality metric, * ANOVA, # post-hoc Wilcoxon signed-rank test with a Bonferroni correction.								

PTV coverage, homogeneity, and conformity

There was no significant difference in D₉₅ among the three plans ($p = 0.368$). The box plots of HI and CI are shown in Fig. 2. The HI of the IMRT plan was significantly lower than that of the VMAT ($p = 0.047$) and 3D-CRT ($p = 0.047$) plans. The HI of the VMAT plan was significantly lower than that of the 3D-CRT ($p = 0.047$) plan. CIs of the IMRT and VMAT plans were significantly lower than those of the 3D-CRT plan ($p = 0.047$ and $p = 0.047$, respectively). There was no significant difference in CI between the IMRT and VMAT plans ($p = 0.094$).

OAR dose

The box plots of D_{mean} of the liver are shown in Fig. 2. D_{mean} of the liver for 3D-CRT was significantly higher than that for IMRT ($p = 0.047$) and VMAT ($p = 0.047$). There was no significant difference between the IMRT and VMAT plans in the D_{mean} of the liver ($p = 0.234$). There was no significant difference among the three plans in the D_{mean} of right kidney ($p = 0.066$) and left kidney ($p = 0.368$), D_{max} of the spinal cord ($p = 0.066$), and D_{max} of the small bowel ($p = 0.276$).

PQM score

The PQM score box plots are shown in Fig. 2. The PQM scores of the VMAT and IMRT plans were significantly higher than that of the 3D-CRT plan ($p = 0.047$ and $p = 0.047$, respectively). The PQM score of the IMRT plan was significantly higher than that of the VMAT plan ($p = 0.047$).

Discussion

Our study based on planning 4D-CT images suggested that the IMRT and VMAT plans have a dosimetric superiority over the 3D-CRT plan, in terms of homogeneity and conformity of the PTV, dose to the liver, and PQM score. Choi et al. performed a planning study to compare four-fields 3D-CRT, seven-fields step-and-shoot IMRT and double arc VMAT in nine patients based on free-breathing 3D-CT images [13]. They added an isotropic margin of 15 mm to the whole stomach to account for respiratory movement during treatment and an additional isotropic margin of 5 mm to cover set-up errors. The prescribed dose was 30 Gy in 20 fractions. They reported that the IMRT and VMAT plans provided significantly better CI of PTV and significantly lower D_{max} of the spinal cord compared with the 3D-CRT plan, and that other dosimetric parameters were similar among the three treatment plans. By using 4D-CT images, we confirmed a similar tendency, whereby the IMRT and VMAT plans achieved a dosimetric superiority over the 3D-CRT plan in point of appropriate dose to PTV and reduced dose to OARs.

In terms of plan quality superiority among the IMRT and VMAT plans, Choi et al. found no significant difference in PTV coverage, homogeneity, conformity, and OAR doses between the IMRT and VMAT plans. On the other hand, our results suggested that the IMRT plan provides better dose distributions than the VMAT plan in terms of homogeneity of the PTV and PQM score. A possible reason for the difference between their result and ours is a difference in our definitions of the target volume. Unlike the study by Choi et al., we defined target volumes based on 4D-CT images. Respiratory movement is not isotropic; Uchinami et al. estimated the motion of the stomach in 10 patients with gastric lymphoma using 4D-CT and reported that the average respiratory amplitudes of the centroid stomach were 4.1 mm, 2.9 mm, and 10.1 mm in the anterior-posterior, left-right, and superior-inferior direction, respectively [12]. Another possible reason is that Choi et al. used the step-and-shoot technique, while we used a sliding window technique for the IMRT plan. It is reported that sliding window IMRT provides better plan quality compared with step-and-shoot IMRT under certain conditions [19].

Although VMAT had been introduced after IMRT, the results of the previous reports on dosimetric superiority of these techniques are conflicting between the studies. Yoo et al. compared seven-field IMRT with single and double arc VMAT in ten prostate cancer patients with or without pelvic lymph nodes [20]. The RT dose of 46.8 Gy was prescribed for primary PTV (PTV_P), which contained prostate, seminal vesicles, and pelvic lymph nodes. It was followed by an RT dose of 28.8 Gy for boost PTV (PTV_B), which contained prostate and seminal vesicles. For the primary plan, HI and CI of PTV_P for the IMRT plan were significantly better than those for the single arc VMAT plan, whereas those were similar with those for two arc VMAT plan. The D_{mean} of the bladder, rectum, and small bowel for the IMRT plan was significantly lower than that for the single and two arc VMAT plans. For the boost plan, the HI of PTV_B for the IMRT plan was significantly better than that for the single arc VMAT plan and was almost the same as that for the two arc VMAT plan. The CI of PTV_B for the IMRT plan was similar to that for the single arc VMAT plan and was significantly worse than that for the two arc VMAT plan. The D_{mean} of the bladder and rectum for the IMRT plan was significantly lower than that for the single arc VMAT plan, whereas those were similar to that for the two arc VMAT plan. Their results may suggest that the dose distribution of the IMRT plan is superior to that of the VMAT plan in cases where the target volume is large and complex, which is applicable to gastric MALT lymphoma in our study.

The dosimetric superiority of the IMRT plan over the VMAT plan is demonstrated in our study; however, the dose distributions of the VMAT plan were sufficiently better than those of 3D-CRT. The advantages of VMAT over IMRT are confirmed in the shorter treatment time and fewer monitor units [9, 21]. Therefore, considering these advantages and the significantly better dose distribution of IMRT and VMAT, these plans could be an appropriate for the treatment of gastric MALT lymphoma.

As comparison of the quality of treatment plans requires the evaluation of many DVH parameters. Therefore, it is difficult to make a direct comparison between treatment plans. To resolve this issue, we used Plan IQ for a comprehensive and objective assessment of the treatment plans. Our results suggested that the PQM score appropriately and comprehensively reflected the tendency of each DVH parameters. This type of RT plan analysis software may be useful to improve and evaluate the quality of treatment plans.

There are some limitations to our study. Firstly, it was a single center retrospective study with a relatively small sample size. Secondly, as this is a planning study, the effects of respiratory motion, such as deformation of the structures and interplay effect in a real clinical setting, on the dose distribution were not considered [22, 23]. Similarly, the clinical superiority of IMRT and VMAT over 3D-CRT is not demonstrated and further studies are underway to address issues.

Conclusions

In this planning study, we compared the quality of the 3D-CRT, IMRT, and VMAT plans for patients with gastric MALT lymphoma based on 4D-CT images. The IMRT and VMAT plans had a dosimetric superiority over the 3D-CRT plan in terms of homogeneity and conformity of the PTV, dose to the liver, and

PQM score. The IMRT plan provides better dose distributions than the VMAT plan in terms of homogeneity of the PTV and PQM score. Taking into account the advantages of VMAT over IMRT in terms of shorter treatment time and fewer monitor units, we recommend the implementation of the IMRT and VMAT plans, rather than 3D-CRT, for patients with gastric MALT lymphoma.

Abbreviations

MALT = mucosa-associated lymphoid tissue

RT = radiotherapy

HP = helicobacter pylori

CTV = clinical target volume

GTV = gross tumor volume

OARs = organs at risk

2D-RT = two-dimensional radiotherapy

3D-CRT = three-dimensional conformal radiotherapy

IMRT = intensity-modulated radiotherapy

VMAT = volumetric modulated arc therapy

3D-CT = three-dimensional computed tomography

DIBH = deep-inspiration breath hold

4D-CT = four-dimensional computed tomography

AIP = average intensity projection

PTV = planning target volume

DVH = dose-volume histogram

HI = homogeneity index

CI = conformity index

PQM = plan quality metric

Declarations

Ethics approval and consent to participate

This study received the full approval from the Institutional Research Ethics Board at the Kumamoto University Hospital (No. 1878). The requirement for individual participant consent was waived by the research ethics board.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of the data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Institutional Research Ethics Board at Kumamoto University Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TM developed the study design; collected, analyzed, and interpreted data; performed statistical analysis; and drafted the manuscript. RT developed the study design; collected, analyzed and interpreted data; and revised the manuscript. YS developed the study design; performed radiotherapy planning; and collected, analyzed, and interpreted data. TW and YK developed the study design; collected and interpreted data. TM, TS, YF, and NO developed the study design and interpreted data. All authors have read and approved the final manuscript.

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Figures

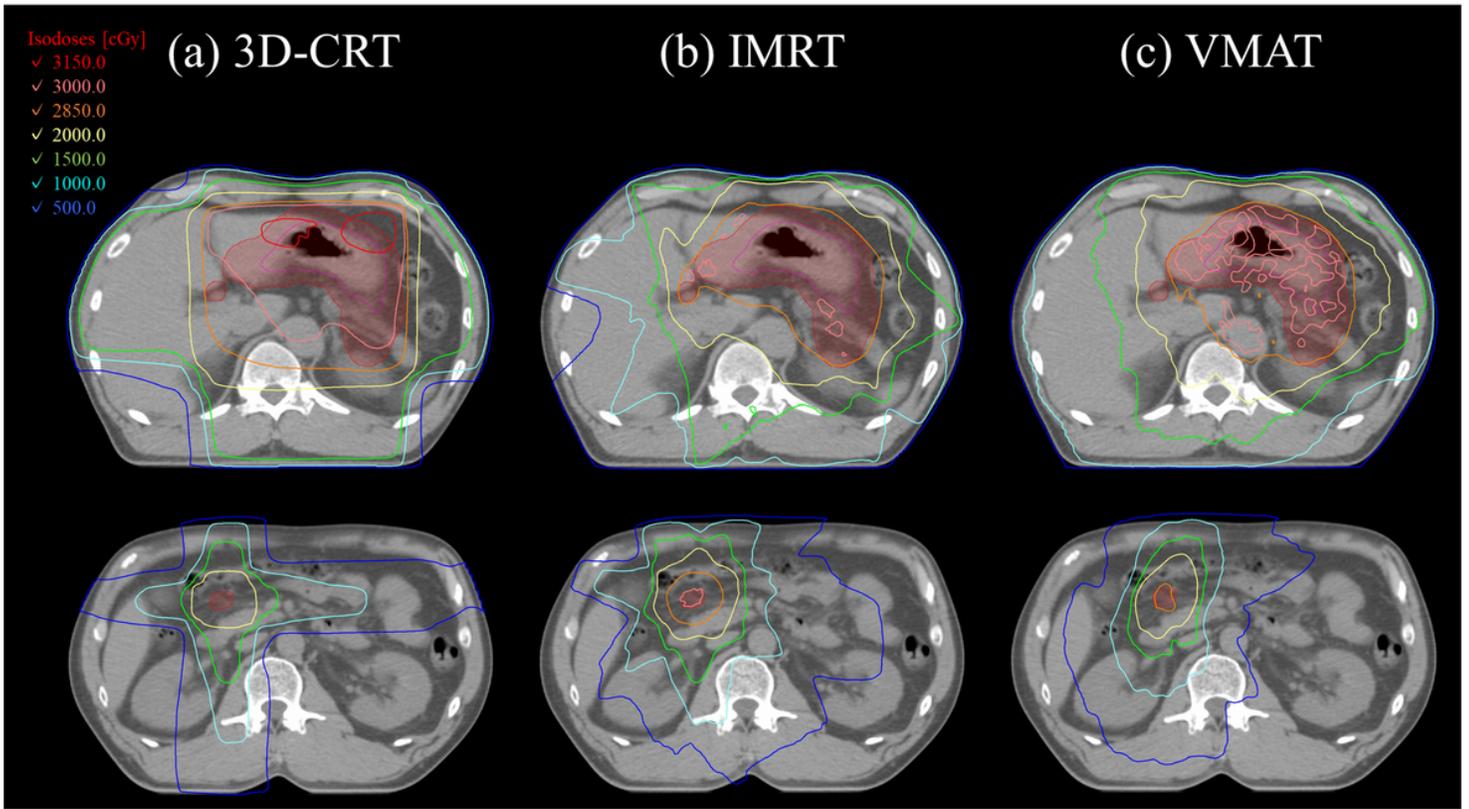


Figure 1

Examples of dose distributions for (a) 3D-CRT, (b) IMRT, and (c) VMAT. CTV-4D and PTV are rendered in pink and red, respectively.

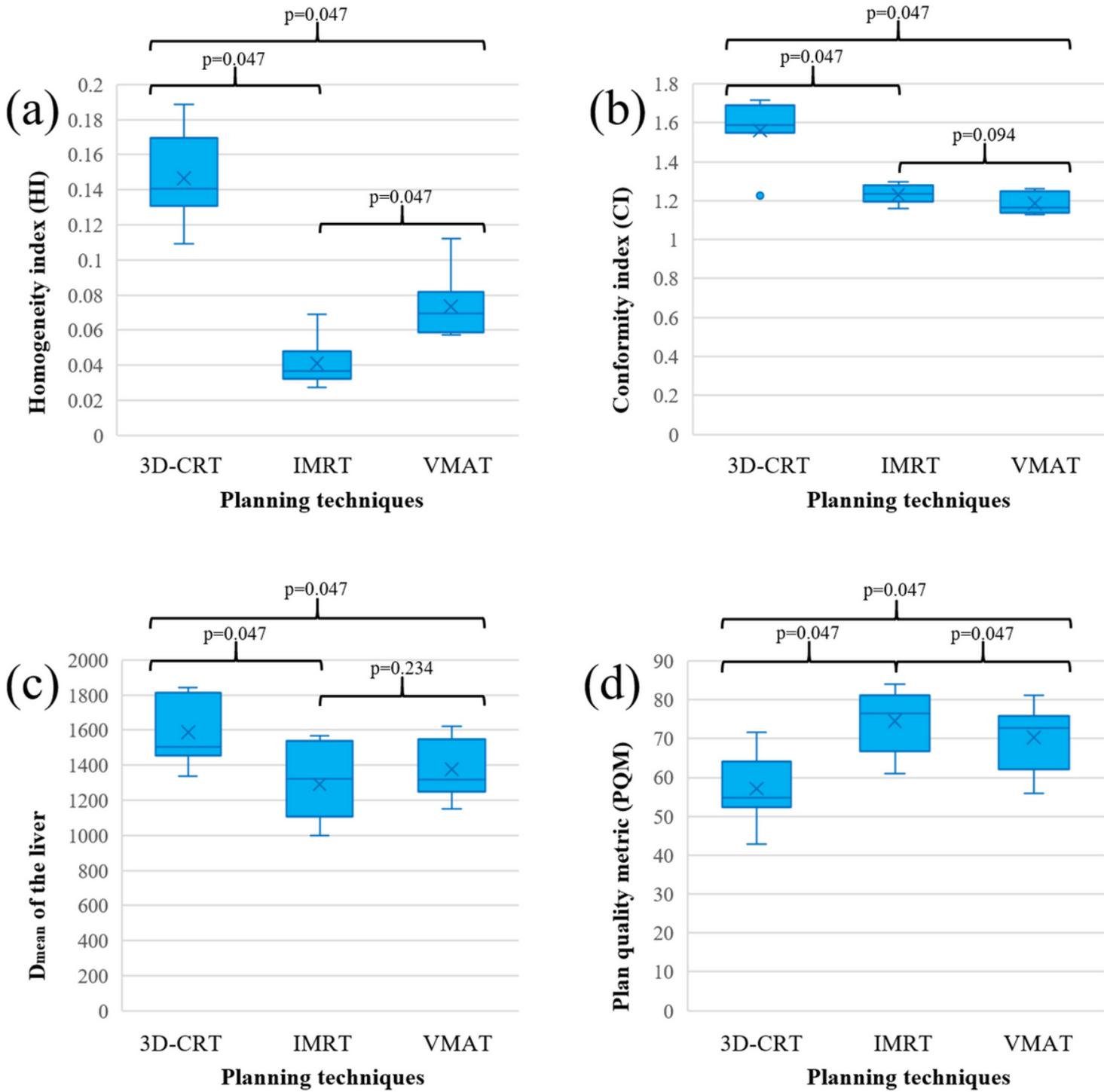


Figure 2

Boxplots of the (a) homogeneity index, (b) conformity index, (c) D_{mean} of the liver, and (d) PQM score for 3D-CRT, IMRT, and VMAT.