Research Square

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# Dosimetric benefits of dynamic wave arc over co-planar volumetric modulated radiotherapy for locally advanced pancreatic cancer

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**Keywords:** Planning study, Locally advanced pancreatic cancer, Dynamic wave arc

**Posted Date:** August 21st, 2020

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# Abstract

**Background:** Dose reduction to the duodenum is important to decrease gastrointestinal toxicities in patients with locally advanced pancreatic cancer (LAPC) treated with definitive radiotherapy. We aimed to investigate whether dynamic wave arc (DWA), a volumetric-modulated beam delivery technique with simultaneous gantry/ring rotations passing the waved trajectories, is superior to coplanar VMAT (co-VMAT) with respect to dose distributions in LAPC.

**Methods:** DWA and co-VMAT plans were created for 13 patients with LAPC in the pancreatic head or body. The prescribed dose was 45.6 or 48 Gy in 15 fractions. The dose volume indices (DVIs) for the gross tumor volume, planning target volume (PTV), stomach, duodenum, small bowel, large bowel, kidney, liver, and spinal cord were compared between the corresponding plans. The values of the gamma passing rate, monitor unit (MU), and beam-on time were also compared.

**Results:** DWA significantly reduced the volumes of the duodenum receiving 39, 42, and 45 Gy by 1.1, 0.8, and 0.2 $cm^3$, respectively. However, the mean liver dose and maximal dose of the spinal cord were increased in DWA by 1.0 and 1.1 Gy, respectively. Meanwhile, there was no significant difference in the target volumes except for dose irradiated to 2% of PTV (PTV $D_{2\%}$) (110.4% in DWA vs. 109.6% in co-VMAT). There were also no significant differences in the other DVIs. Further, the gamma passing rate was similar in both plans. The MU and beam-on time increased in DWA by 31 MUs and 15 seconds, respectively.

**Conclusion:** Compared with co-VMAT, DWA generated significantly lower duodenal doses with acceptable trade-offs in LAPC.


# Background

Pancreatic cancer has poor prognosis and is one of the leading causes of cancer-related deaths worldwide (1). Surgical resection is the standard treatment for early stage pancreatic cancer, but 30–35% of patients are in a locally advanced stage upon diagnosis (2).These patients with locally advanced pancreatic cancer (LAPC) are commonly treated with systemic chemotherapy, but the median overall survival is only 11.9–13.6 months (3).A previous study on LAPC patients treated with first-line chemotherapy reported that 41% of the patients died without developing any distant metastases (4).For such patients without distant metastasis, radiotherapy could contribute to better survival outcomes by control of locoregional tumor.

Delivering high doses to the target organ while avoiding the organs-at-risk (OARs) is important in radiotherapy. In general, three-dimensional conformal radiation therapy (3D-CRT), which is a beam delivery technique without intensity modulation within the field of radiation, based on computed tomography (CT) images of a patient's internal organs has been used. The pancreas is surrounded by radiosensitive organs, such as the stomach, liver, colon, and kidneys. During irradiation to the irregularly [illegible] these radiosensitive organs to be irradiated with

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high doses, thus causing gastrointestinal (GI) toxicities such as ulcer, hemorrhage, perforation, and stenosis. Conventionally fractionated 3D-CRT combined with chemotherapy has a response rate of 60%, but gastroduodenal ulcers are observed in 42.3% of the patients [5, 6].

Compared with 3D-CRT, high-precision radiotherapy, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated radiotherapy (VMAT), enables dose escalation to the target organs with minimal exposure to the OARs. Further, several reports showed that IMRT combined with chemotherapy improved overall survival (OS) and locoregional progression-free survival (LRPFS) and decreased both acute and late GI toxicities (5–7). A comparison study of 3D-CRT, IMRT, and VMAT for locally advanced cancer of the pancreatic head showed better sparing of the OARs, especially the duodenum, small bowel, and right kidney, and fewer acute GI toxicities in VMAT than that in 3D-CRT or IMRT (8).

A continuous non-coplanar delivery technique, termed dynamic wave arc (DWA), was recently developed (9). It allows simultaneous rotation of both radiation head unit and the O-ring-shaped gantry, thus delivering sequential non-coplanar beams both safely and quickly without the need to rotate the couch. The clinical benefit of DWA was first reported in 15 patients with varying treatment sites, namely, breast boost, prostate, lung stereotactic body radiation therapy, and bone metastases (10). Since then, DWA has been added to noncoplanar VMAT techniques to achieve better flexibility in dose shaping while keeping dosimetrically effective delivery. DWA has been reported to have dosimetric advantages over coplanar VMAT (co-VMAT) in tumors located in the midline of the body, such as skull base tumors and prostate cancers [11, 12]. A study on the application of DWA in cases of LAPC using preclinical versions of the treatment planning system (TPS) concluded that it has comparable dosimetric distributions to co-VMAT (13). However, there are no previous reports focused on the dosimetric advantage of DWA in pancreatic head and body cancer, which is also located in the midline of the body, using the clinically integrated version of RayStation TPS (RaySearch Laboratories, Stockholm, Sweden). Thus, this study aimed to investigate the superiority of DWA to co-VMAT with respect to dose distributions in locally advanced pancreatic head and body cancer, using a TPS.

# Methods

### Study design and patients

This planning study evaluated 13 patients with LAPC in the pancreatic head (n = 10) or body (n = 3) who were treated with IMRT in our institution. The clinical stages (Union for International Cancer Control 7th edition) were T3N0M0 in 5 patients, T4N0M0 in 7 patients, and T4N1M0 in 1 patient. The eligible criteria to this study are as follows: 1) primary tumors are located in the head or body of pancreas, 2) Planning tumor volume (PTV) sizes are less than 410 $cm^3$ and 3) PTV is included in the field size of the Vero4DRT system (maximum, 15 cm × 15 cm).

### Simulation and delineation of the target organ and organs at risk

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Patients were immobilized with a vacuum pillow (BodyFIX, Medical Intelligence, Schwabmuchen, Germany) in a supine position with both arms raised above the head. Expiratory breath-hold treatment-planning CT was performed via an intravenous contrast-enhancing agent(without oral contrast agents) using either a LightSpeed RT scanner (GE Medical Systems, Waukesha, WI, USA) with slice thickness of 2.5 mm or SOMATOM Definition AS (Siemens Medical Systems, Erlangen, Germany) with slice thickness of 2 mm.

The gross tumor volume (GTV) included the tumor and metastatic lymph nodes. The clinical target volume (CTV) was defined as the GTV plus a-5 mm margin as well as the retropancreatic space and the para-aortic lymph node region between 10 mm superior to the celiac axis and 10 mm inferior to the superior mesenteric artery. The (PTV) was defined as CTV plus a 5-mm margin. The target organs and OARs were contoured based on the end-expiration phase CT. OARs were defined for the stomach, duodenum, small bowel, large bowel, kidneys, liver, and spinal cord. The planning OAR volumes (PRVs) were created with a 5-mm margin for the duodenum, small bowel, and spinal cord and a 10-mm margin for the stomach.

**Treatment planning**

The co-VMAT and DWA plans were created for the Vero4DRT system (Hitachi, Tokyo, Japan) using RayStation version 4.7. Dose distribution was calculated using collapsed-cone convolution algorithm with a dose grid of 2.5 mm (LightSpeed RT scanner) or 2.0 mm (SOMATOMDefinition AS).The prescribed dose was 48 Gy in 15 fractions to 95% of PTV boost volume, defined as PTV excluding PRVs, while keeping the 36 Gy isodose line covering 98% of PTV volume.

The co-VMAT treatment plans consisted of one arc that rotated clockwise from 181˚ to 179˚. Optimization was performed until the following criteria were met: (1) the maximum dose was set to be < 56 Gy, and (2) the dose to the OARs and PRVs should meet the dose constraints (Table 1) while keeping the dose coverage to PTV as mentioned above. If the PRV dose constraints cannot be fulfilled, a 5% reduction of the prescribed dose (45.6 Gy to 95% of PTVboost-34.2 Gy to 98% of PTV) was allowed. DWA treatment plans were based on a fixed single trajectory selected from the list of preinstalled trajectories for pancreatic cancer plans (Fig. 1). The plans were performed with a reciprocating motion of ring rotation in the positive or negative direction simultaneously with the gantry rotating from 182° to 178° (clockwise direction). Optimization was performed to fulfill the same criteria as used in the co-VMAT plans.

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Table 1
Dose constraints for the planning study

| OARs/PRVs | Dose constraints |
|---|---|
| Stomach, duodenum, small bowel, and large bowel | $V_{39Gy} \leq 25\ cm^3$ |
| | $V_{42Gy} \leq 5\ cm^3$ |
| | $V_{45Gy} \leq 1\ cm^3$ |
| Stomach, duodenum, small bowel (PRV) | $V_{36Gy} \leq 45\ cm^3$ |
| | $V_{39Gy} \leq 30\ cm^3$ |
| Spinal cord | $D_{max}$<36 Gy |
| Spinal cord (PRV) | $D_{2cm^3}$<39 Gy |
| Kidneys | $V_{20Gy}$ < 30% |
| Liver | $D_{mean}$ ≤30 Gy |

### Patient-specific quality assurance

The patient-specific quality assurance of co-VMAT and DWA was performed using the ArcCHECK (Sun Nuclear Corp., Melbourne, FL,USA). The measured dose distribution was compared with the calculated results of treatment plans. The gamma analysis with global 3%/3-mm gamma criteria was conducted to compare the calculated and delivered dose distributions. The gamma passing rate for areas receiving isodoses above 10% was calculated using a global difference approach for the absolute dose. In addition, data on the monitor unit (MU) and beam-on time for co-VMAT plans and DWA plans were collected.

### Plan evaluation and statistical analysis

The dose volume indices (DVIs) for the following parameters were compared between co-VMAT plans and DWA plans: dose irradiated to 98%, 95%, 50%, and 2% of GTV and PTV (D98%, D95% D50%, D2%); irradiated volumes of the stomach, duodenum, large bowel, and small bowel to 39, 42, 45, and 48 Gy (V39 Gy, V42 Gy, V45 Gy, and V48 Gy); V20 Gy of the kidney; the mean liverdose (liver Dmean); and maximum dose of the spinal cord (spinal cord Dmax). The DVIs, gamma passing rate, MU values, and beam-on time were compared using the paired t-test on two paired samples. All statistical analyses were performed using R (version 3.5.1). A *p* value of < 0.05 was considered statistically significant.

# Results

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### Dose-volume indices

The PTV ranged from 120.3 $cm^3$ to 406.1 $cm^3$. There was no significant difference in GTV and PTV doses except for PTV $D_{2\%}$ between DWA and co-VMAT. PTV $D_{2\%}$ was significantly higher in DWA plans than that in co-VMAT, but the difference was only 1% (111.5 ± 2.6% vs. 110.5 ± 2.4%, $p < 0.01$). The details for the target volumes are shown in Table 2. Figure 2 shows the dose distribution in a representative case using co-VMAT and DWA. For the OARs, DWA yielded significantly lower irradiated volume of the duodenum ($V_{39Gy}$, $V_{42Gy}$, and $V_{45Gy}$) than co-VMAT by 1.1, 0.8, and 0.2 $cm^3$, respectively (Fig. 3). Meanwhile, DWA led to increase of liver $D_{mean}$ and spinal cord $D_{max}$ by 1.0 and 1.1 Gy, respectively (Table 3). There was no significant difference in DVIs of the stomach, small bowel, large bowel, or kidneys between the two plans.

Table 2
Dose volume indices of the target volumes

| Target | Indices | DWA (Mean ± SD) | co-VMAT (Mean ± SD) | *p* value |
|---|---|---|---|---|
| GTV | $D_{98\%}$ (%) | 96.1 ± 5.1 | 96.7 ± 5.4 | 0.104 |
| | $D_{95\%}$ (%) | 98.4 ± 4.5 | 99.2 ± 4.9 | 0.206 |
| | $D_{50\%}$ (%) | 106.8 ± 2.9 | 106.6 ± 2.8 | 0.481 |
| | $D_{2\%}$ (%) | 110.4 ± 3.2 | 109.8 ± 3.0 | 0.114 |
| PTV | $D_{98\%}$ (%) | 79.0 ± 4.3 | 79.4 ± 4.2 | 0.133 |
| | $D_{95\%}$ (%) | 84.1 ± 4.8 | 84.6 ± 4.8 | 0.092 |
| | $D_{50\%}$ (%) | 106.3 ± 1.9 | 106.1 ± 2.0 | 0.174 |
| | $D_{2\%}$ (%) | 111.5 ± 2.6 | 110.5 ± 2.4 | 0.001* |

Asterisks (*) indicate statistical significance.

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Table 3
Dose volume indices of the organs at risk other than gastrointestinal organs

| Organ | Indices | DWA (Mean ± SD) | co-VMAT (Mean ± SD) | *p* value |
|---|---|---|---|---|
| Rt kidney | $V_{20Gy}$ ($cm^3$) | 4.6 ± 5.5 | 6.9 ± 8.4 | 0.124 |
| Lt kidney | $V_{20Gy}$ ($cm^3$) | 13.2 ± 7.2 | 12.1 ± 7.8 | 0.322 |
| Liver | $D_{mean}$ (Gy) | 6.9 ± 3.5 | 5.9 ± 3.4 | < 0.001* |
| Spinal cord | $D_{max}$ (Gy) | 30.1 ± 3.2 | 29.0 ± 3.3 | 0.053 |
| Abbreviations are the same as in Tables 1 and 2. | | | | |

### Comparison of gamma passing rate, monitor unit, and beam-on time

The mean (range) 3%/3-mm gamma passing rate was 96.5% (90.5%-99.6%) for DWA and 96.7% (92.3%-100%) for co-VMAT, with no significant difference in the gamma passing rate. Meanwhile, the MU values were significantly higher in DWA than that in co-VMAT (620.02 ± 74.3 vs. 588.7 ± 72.7, $p = 0.001$). The beam-on time in DWA was significantly higher than that in co-VMAT (104.1 ± 24.2 seconds vs. 88.8 ± 10.9 seconds, $p = 0.04$).

## Discussion

Concurrent chemoradiotherapy has been shown to increase resectability and decrease postoperative recurrence in LAPC cases (5). Pancreatic cancer is known to have fairly low radiosensitivity (14), and thus higher doses are needed for better local control. However, this also leads to a higher frequency of GI toxicities. The present study showed the dosimetric benefits of DWA over co-VMAT in decreasing the intermediate and high doses to the duodenum, while preserving the PTV coverage.

Clinical trials assessing the benefits of escalated dose radiation with an IMRT technique in LAPC have shown significantly increased local control and OS [6, 15] Goto et al. investigated the clinical outcomes of hypofractionated IMRT in LAPC cases and reported a significantly increased LRPFS and OS in cases treated with doses ≥ 45 Gy in 15 fractions. Krishnan et al. also reported significant improvements in LRPFS and OS in LAPC patients treated with dose-escalated IMRT (biologically effective dose [BED], > 70 Gy). However, although dose-escalating IMRT trials have shown promising results, GI toxicities remain a major concern. Further reduction of GI toxicities is needed to adequately satisfy the need for dose escalation to achieve better local control.

Previous reports have showed the association between DVIs and GI toxicities, but the prescribed doses [16–19]. The BED is commonly used to compare

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such various doses and fractionation schedules with an alpha/beta ratio of 10 Gy (BED10) for acute toxicities and 3 Gy (BED3) for late toxicities in the duodenum. Considering the DVIs converted to BED10 and BED3, the DVIs for the duodenal toxicities can be lowered with DWA (Table 4). Our data indicate that the use of DWA may be beneficial to decrease both acute and late duodenal toxicities, which is crucial for dose escalation in LAPC. However, it remains unclear whether the dosimetric superiority directly reduces GI toxicities because the toxicities are caused by multiple treatment-related factors such as chemotherapy and low platelet count [20, 21].

Table 4
Proposed dose constraints for the duodenum in previous reports

| Author | Prescribed dose | Technique | Toxicity | Proposed constraints for the duodenum | DVIs by DWA in this study<br>Mean(range) |
|---|---|---|---|---|---|
| Nakamura, et al. [16] | 54 Gy/30 fr | 3D-CRT | Acute<br>≥Gr 3upper GI bleeding | $V_{50Gy}$ ≦33 $cm^3$*<br>($BED_{10}$, 59 $Gy_{10}$) | $V_{45Gy}$ = 0.2 $cm^3$(0-1.3 $cm^3$)*<br>($BED_{10}$,59 $Gy_{10}$) |
| Huang, et al. [17] | 36–42 Gy/15 fr | 3D-CRT<br>IMRT | Acute<br>≥Gr 3 | $V_{25Gy}$ ≦45%<br>($BED_{10}$, 31–32 $Gy_{10}$) | $V_{25Gy}$ = 34% (5–75%)<br>($BED_{10}$, 33 $Gy_{10}$) |
| | 30–38 Gy/15–19 fr | | | $V_{35Gy}$ ≦20%<br>($BED_{10}$, 43–45 $Gy_{10}$) | $V_{35Gy}$ = 12% (0–39%)<br>($BED_{10}$ = 46 $Gy_{10}$) |
| Kelly, et al. [18] | 50.4 Gy/28 fr<br>57.5–75.4 Gy/28–39 fr | 3D-CRT<br>IMRT | Acute<br>≥Gr 2 | $V_{\geq 55Gy}$ ≥1 $cm^3$<br>($BED_{10}$, 65–66 $Gy_{10}$) | $V_{\geq 48Gy}$ = 0 $cm^3$(0-0.04 $cm^3$)<br>($BED_{10}$, 63 $Gy_{10}$) |
| Liu, et al. [19] | 50 Gy/15–20 fr | IMRT | Acute and late<br>≥Gr 2 | $V_{45Gy}$ ≥ 0.5 $cm^3$<br>($BED_{10}$, 56–60 $Gy_{10}$; and $BED_3$, 83–95 $Gy_3$) | $V_{45Gy}$ = 0.2 $cm^3$(0-0.7 $cm^3$)<br>($BED_{10}$, 59 $Gy_{10}$; and $BED_3$, 93 $Gy_3$) |

* Volumes for the stomach plus duodenum are shown.

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There is a trade-off relationship of irradiated dose among OARs surrounding the pancreas. In co-VMAT, decreasing the irradiated dose of one organ will lead to an increased dose in another organ. With DWA, non-coplanar trajectories shift irradiation toward soft tissues or bones and avoid passing directly through radiosensitive organs. Therefore, the irradiated doses of the duodenum could be decreased with a trade-off of slight increase in the mean liver dose and the maximum dose of the spinal cord. The other trade-off is the increase of the MUs followed by prolongation of treatment time. However, the differences of 31 MUs and 15 seconds could be justified with the dosimetric benefit of DWA.

There are some limitations in the present study. First, the sample size is small, but it is still larger than that in a previous report on DWA that used a preclinical version of TPS (13). Second, we focused on centrally located LAPC, and thus the benefit of DWA in tail pancreatic cancer or LAPC with larger PTV remains unknown. Given that this is a planning study, further investigation is warranted to explore the types of cancer and with which trajectories DWA can be optimal.

# Conclusions

DWA was superior to co-VMAT with respect to dose distributions in locally advanced pancreatic head and body cancer. These findings would help further clinical studies of IMRT for LAPC with escalating doses to the tumor as well as keeping less GI toxicities.

# List Of Abbreviations

LAPC: Locally advanced pancreatic cancer; DWA: dynamic wave arc; VMAT: Volumetric Modulated Arc therapy; co-VMAT: coplanar VMAT; DVIs: dose volume indices; PTV: planning target volume; MU: monitor unit; OARs: organs at-risk; 3D-CRT: three-dimensional conformal radiation therapy; GI: gastrointestinal; IMRT: intensity-modulated radiotherapy; CT: computed tomography; OS: overall survival; LRPFS: locoregional progression-free survival; TPS: treatment planning system; GTV: gross tumor volume; CTV: clinical target volume; PRVs: planning OAR volumes; BED: biological effective dose.

# Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kyoto University Hospital (R1446) and was performed in accordance to the Declaration of Helsinki (1975, as revised in 2013). The need for written informed consent was waived.

### Consent for publication

Not applicable.

### Availability of data and materials

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The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

Takashi Mizowaki has an advisory contract with Hitachi, Ltd. Other authors declare that they have no conflict of interest.


### Funding

This work was partially supported by the Japan Agency for Medical Research and Development (AMED) [grant number 20ck0106427h0003].


### Authors' contributions

A.A. performed the planning study and wrote the manuscript. Y.M. supervised the study. R.A. and N.K. contributed the analysis of the results and supported designing the figures. H.H. performed the quality assurance. All the co-authors commented on the manuscript.


### Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.


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# Figures

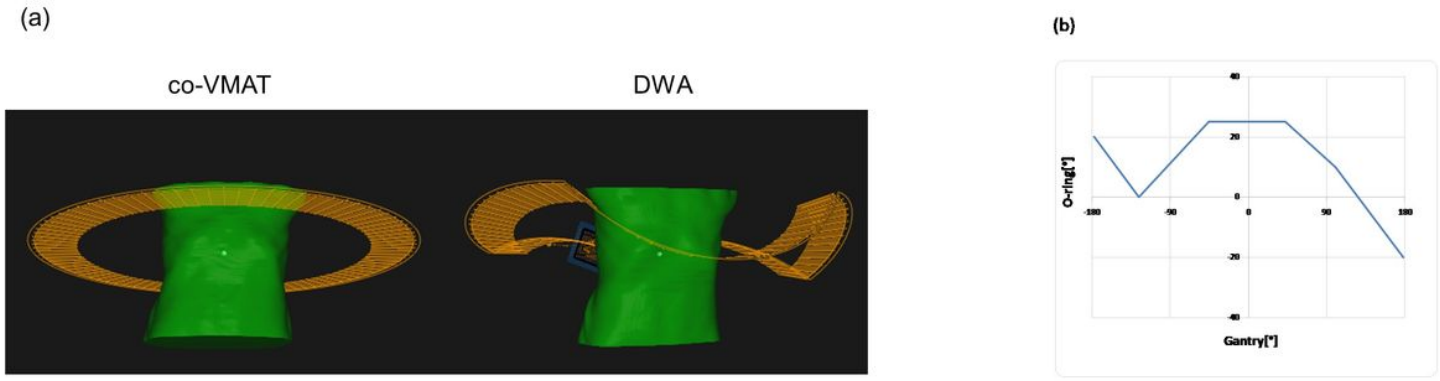


**Figure 1**

Diagrams presenting the gantry and O-ring rotation direction in addition to DWA delivery trajectory. (a) The 2D gantry-ring rotational positions. (b) The control points of the DWA delivery trajectory.

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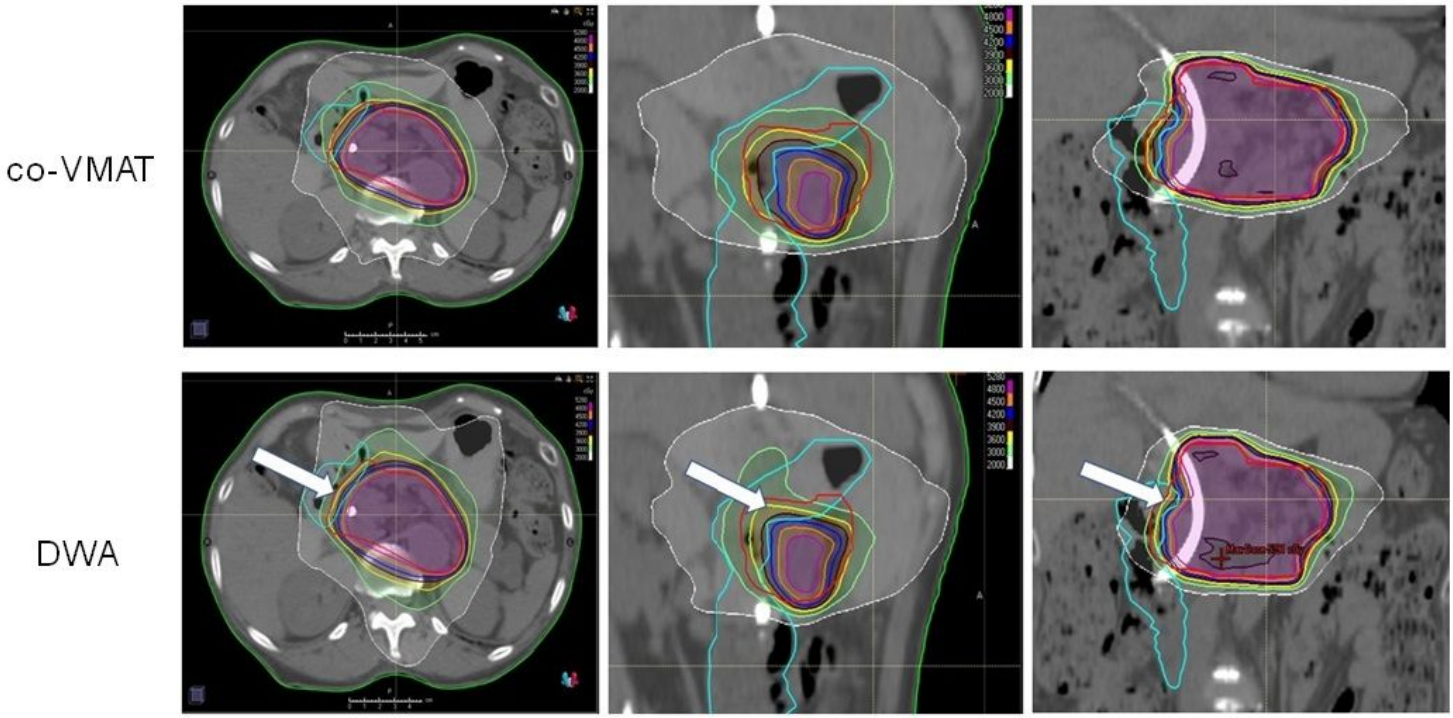


## Figure 2

Dose distribution comparison between DWA and co-VMAT from a representative case. The PTV (red) is covered with an isodose line of 36 Gy (yellow). The white arrows indicate the duodenum (cyan) is spared in the DWA plan.

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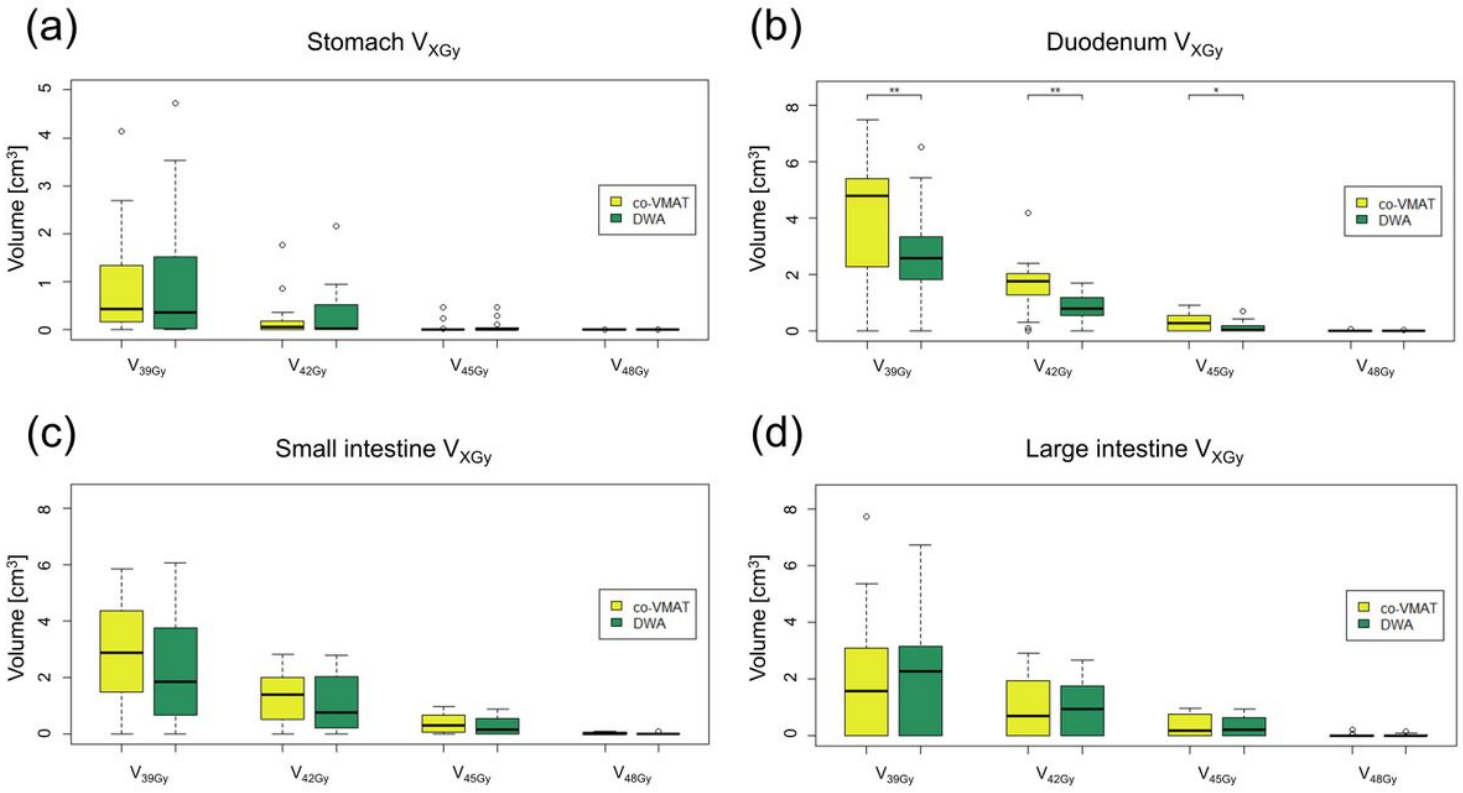


## Figure 3

Box-and-whisker plots of the difference between DWA and co-VMAT in the gastrointestinal organs: (a) stomach, (b) duodenum, (c) small bowel, and (d) large bowel. The central box shows the values from the first to third quartiles. The horizontal line inside the box represents the median, and the vertical line indicates the range, except for outliers and far out values which are shown as ●. * indicates $p<0.05$;** $p<0.01$

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