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Original Article

Simultaneous Integrated Boost Volumetric Modulated Arc Therapy for Middle or Lower Esophageal Cancer Using Elective Nodal Irradiation: Comparison with 3D Conformal Radiotherapy

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We investigated the feasibility of simultaneous integrated boost (SIB) volumetric modulated arc therapy (VMAT) using elective nodal irradiation (ENI) for middle or lower esophageal cancer and compared it with three-dimensional conformal radiotherapy (3D-CRT). The study included 15 patients. The prescribed doses included a standard dose (50.4 Gy) and a high dose (60 Gy) for the planning target volume (PTV) of the involved lesions. The objective of the whole lung volume receiving ≥ 20 Gy (V_{20Gy}) was < 30%, and the mean lung dose (MLD) was < 20 Gy. The volumes of the lung receiving 5 Gy (V_{5Gy}) and the heart receiving 30-50 Gy ($V_{30\text{-}50Gy}$) were kept as low as reasonably achievable. As a result, SIB-VMAT showed superior dose conformity for the PTV ($p < 0.001$). Although the lung V_{5Gy} was significantly increased ($p < 0.001$), the V_{20Gy} and MLD showed no significant increase. The heart $V_{30\text{-}50Gy}$ showed a > 20% reduction in the mean against 3D-CRTs. Our results demonstrate the feasibility of SIB-VMAT for the treatment of middle or lower esophageal cancer with ENI. Although attention should be paid to the low-dose area of the lungs, SIB-VMAT would be a promising treatment option with improved outcomes for esophageal cancer.

Key words: esophageal cancer, middle and lower thoracic, volumetric modulated arc therapy, 3D-CRT, elective nodal irradiation

Volumetric modulated arc therapy (VMAT) is a highly conformal intensity-modulated radiation technique that is widely used for the treatment of prostate, cervical, head and neck, and many other cancers [1-6]. Compared to intensity-modulated radiation therapy (IMRT), VMAT can achieve comparable clinical outcomes in a shorter treatment time [7,8]. The feasibility and benefits of VMAT for the treatment of esophageal cancer were recently reported [9-11]. VMAT can deliver concentrated doses to planning target volumes (PTVs) and reduced doses to the heart without significantly increasing the dose to the normal lungs. Although some investigators have compared the efficacy of IMRT and VMAT to that of three-dimensional conformal radiotherapy (3D-CRT) [9-11], the definition of PTV in their reports was based on the involved field irradiation (IFI). There are also twosome reports indicating the efficacy of three-field regional lymph node dissection in esophageal cancer [12,13].

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The benefits of large-field elective nodal irradiation (ENI) in chemoradiotherapy for thoracic esophageal cancer are controversial [14, 15]. However, in accordance with the concept of three-field regional lymph node dissection in curative surgery, ENI has been widely used in Japanese institutions, and its efficacy has been reported [16-18].

The problems with using ENI for middle or lower thoracic esophageal cancer are that (1) the high dose area is very close to the heart, and (2) the elective nodal area covers the whole lung level. Severe radiation pneumonitis (RP) and long-term toxicity of the heart are significant problems encountered during the treatment of esophageal cancer [14]. We thus considered that it would be useful to evaluate the feasibility of VMAT with ENI. There are no previous reports comparing VMAT with ENI and 3D-CRT with ENI for middle or lower thoracic esophageal cancer.

In addition, the outcomes of chemoradiotherapy in esophageal cancer are still rather dismal, with a poor prognosis generally related to locoregional failure [19-21]. One of the ways to improve the local control rate would be a dose escalation to the involved area [22, 23]. A recent study reported a favorable outcome using high-dose (≥60 Gy) IMRT [24]. Simultaneous integrated boost (SIB) VMAT can easily achieve the dose escalation to the involved tumors without changing the dose to the elective nodal area [25-27]. Therefore, we conducted the present study to evaluate whether SIB-VMAT with ENI is feasible for middle or lower thoracic esophageal cancer, and we compared this combination with 3D-CRT at a standard dose (50.4 Gy) and a high dose (60 Gy).

Patients and Methods

This study was approved by our institutional Ethics Committee (No. 692). Informed consent to participate was obtained from all of the patients. This was a planning study, and we created and compared two plans: one using SIB-VMAT and the other using 3D-CRT with the computed tomography (CT) data from the same patients.

Patient characteristics and details of the initial therapy. CT data from 15 patients diagnosed with squamous cell carcinoma of the middle or lower thoracic esophagus were used in this study. All of the patients had received radiation therapy in our institution by 3D-CRT, IMRT, or VMAT during the period from June 2015 to October 2017. We started using IMRT and VMAT in December 2016, and thereafter we treated essentially all patients with esophageal cancer with VMAT. Patients with pacemakers were an exception; VMAT was not indicated in these cases due to the low-dose irradiation to the pacemaker. The primary lesions involved the middle thoracic esophagus (7 patients), lower thoracic esophagus (3 patients), and middle plus lower thoracic esophagus (5 patients) (Table 1).

CT scans for the plan and linear accelerator. All patients underwent CT-based planning. The CT was performed in the treatment position using a helical scanner. For each patient, 3-mm-thick images for 3D-CRT and 2-mm-thick images for VMAT were obtained. All plans were developed using the Elekta Synergy linear accelerator with an Agility multileaf (160 leaves) collimator (MLC) (Elekta, Stockholm,

Table 1 Characteristics and treatment details of the 15 patients with squamous cell carcinoma

Variable	
Age, years; median (range)	77 (58–86)
Male	14
Female	1
Primary site:	
Mt	7
MtLt	4
Lt	3
LtMt	1
Clinical stage*	
I	8
II	4
III	3
Treatment details:	
Radiation therapy alone	9
Chemoradiotherapy	6
Cumulative dose, Gy; median (range)	60 (50.4–66)
Radiation technique, initial treatment:	
3D-CRT	9
Initial field: 3D-CRT, boost field: VMAT	1
IMRT	2
VMAT	3

*Japanese classification of esophageal cancer, 11th edition. 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; LtMt, middle and lower thoracic esophagus (main lesion exist at Lt); Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; MtLt, middle and lower thoracic esophagus (main lesion exist at Mt); VMAT, volumetric modulated arc therapy.

Sweden) with a leaf width of 5 mm.

Pretreatment evaluation, targets, and organs at risk (OARs). The pretreatment evaluation included endoscopy and CT of the esophagus. The extent of the gross tumor volume at the primary site (GTVp) was determined by endoscopy and CT. The gross tumor volume of the lymph nodes (GTVn) was defined using CT when the nodes were ≥ 1 cm in their shortest axis. The clinical target volume of the primary site (CTVp) was delineated with 2-2.5 cm superior-inferior margins and 0.5 cm lateral and anterior-posterior margins for the GTVp. The clinical target volume of the involved lymph node (CTVn) was delineated with 0.3 cm uniform margins for the GTVn.

The clinical target volume for ENI (CTVe) was defined as follows: regardless of the subsite of the primary tumor, the lower cervical, peri-esophageal, mediastinal, and perigastric nodes were included in the elective nodal area. Celiac nodes were also included when the lower esophagus was involved. "CTV1" consisted of the CTVp, CTVn, and CTVe. "CTV2" consisted of the CTVp and CTVn. The planning target volume (PTV) was defined as CTV plus a 1-1.5 cm margin in the craniocaudal direction and a 0.5-1 cm margin in the lateral direction to account for respiratory organ motion and daily setup errors.

An example of a PTV is shown in Fig. 1. Normal tissue organs included both of the lungs (as a single organ), the heart, spinal cord (including the spinal canal), both of the kidneys (as a single organ), liver, and stomach. The heart was contoured according to the Radiation Therapy Oncology Group (RTOG) contouring atlases for OARs in Thoracic Radiation Therapy (https://www.rtog.org/LinkClick.aspx?fileticket=qlz0qMZXfQs%3d&tabid=361, accessed July 19, 2018), and the pericardium was defined as the sac-like structure (thickness: 5 mm) at the surface of the heart [28, 29]. The PTV was not subtracted from the volumes of the OARs when calculating the dose-volume histogram (DVH).

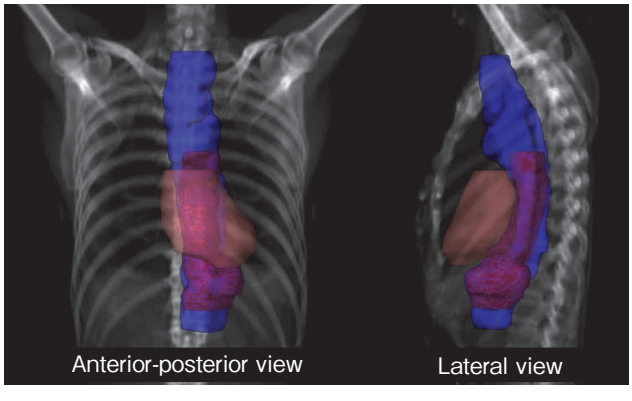

Fig. 1 Anterior-posterior and lateral views of a sample planning target volume (PTV). *Blue*: The PTV1 (elective nodal area). *Red*: The PTV2 (involved lesion). *Pink*: heart. The heart is adjacent to the PTV2 in middle or lower esophageal cancer.

3D-CRT planning. Treatment plans for 3D-CRT were generated by the Pinnacle ver. 9.6 treatment planning system (Philips Medical Systems, Andover, MA, USA). Tissue heterogeneity corrections were applied to all dose calculations. We used a 3D convolution/superposition algorithm that is considered an accurate dose-calculation method apart from the Monte Carlo simulation for dose calculations. A 10-MV beam was used in all of the 3D-CRT plans. The dose calculation grid size was 2-mm in all cases.

The prescribed dose was 41.4 Gy (in 23 fractions of 1.8 Gy/fraction) to the PTV1 in the standard-dose plan and 40 Gy (in 20 fractions of 2 Gy/fraction) to the PTV1 in the high-dose plan. Radiation to the PTV1 was delivered using the four-field technique in the standard-dose plan, and using the anterior-posterior opposed fields in the high-dose plan as described previously [16, 17]. A booster dose of 9 Gy (in 5 fractions of 1.8 Gy/fraction) in the standard-dose plan and 20 Gy (in 10 fractions of 2 Gy/fraction) in the high-dose plan was administered to the PTV2 using oblique fields to avoid the spinal cord. The treatment portal covered the PTV plus a 0.5-0.7 cm margin to account for the penumbra. The field-in-field technique was used to improve the dose distribution of the PTV if needed. The normalization point was set to the isocenter or a proper reference point to cover the PTV.

VMAT planning. Treatment plans for SIB-VMAT were generated by the Monaco ver. 5.11 treatment planning system (Elekta). Tissue heterogeneity corrections were applied to all dose calculations. A 6-MV beam was used in all of the SIB-VMAT plans as described previously [9-11]. The X-ray voxel Monte Carlo (XVMC) algorithm was used for dose calculations. The dose calculation grid size and the statistical uncertainty of the calculation were set to 2 mm and 1% per plan, respectively. A double-arc with an avoidance sector plan was generated in this study.

The VMAT had gantry angles of 135°-180°, 180°-225°,

and 330°-30° (Fig. 2), which were chosen based on previous reports [9, 30]. The collimator angle was set at 0° in all of the plans. The prescribed doses were 45 Gy to the PTV1 in both the standard-dose plan (in 28 fractions) and high-dose plan (in 30 fractions). A total dose of 50.4 Gy in the standard-dose plan (in 28 fractions) and 60 Gy in the high-dose plan (in 30 fractions) was prescribed to the PTV2.

Planning objectives of VMAT. We normalized each SIB-VMAT plan so that 100% of the prescribed dose was delivered to 50% of the PTV2. The planning objectives for the PTV1 and PTV2 were ≥95% of the target volume receiving ≥95% but no more than 107% of the prescribed dose of <1% of the target volume as reported by Nicolini [9]. The whole lung volume receiving ≥20 Gy (V_{20Gy}) was <0%, and the mean lung dose (MLD) was <20 Gy [31]. The volume receiving ≥5 Gy (V_{5Gy}) was kept as low as reasonably achievable.

In all of the plans, the volume of the heart receiving 30-50 Gy ($V_{30\text{-}50Gy}$) was kept as low as reasonably achievable. The maximum dose limit for the spinal cord was 46 Gy. The mean dose constraints for the kidney and liver doses were <15 Gy and <30 Gy, respectively.

Parameters analyzed. The quantitative evaluation of the plan was performed using the standard dose-volume histogram (DVH). For the PTV, the $D_{98\%}$, $D_{95\%}$, $D_{5\%}$, and $D_{2\%}$ (dose received by 98%, 95%, 5%, and 2% of the volume) values are reported. The homogeneity index (HI) is expressed in terms of $D_{5\%}$-$D_{95\%}$ (the difference between the dose covering 5% and 95% of the PTV).

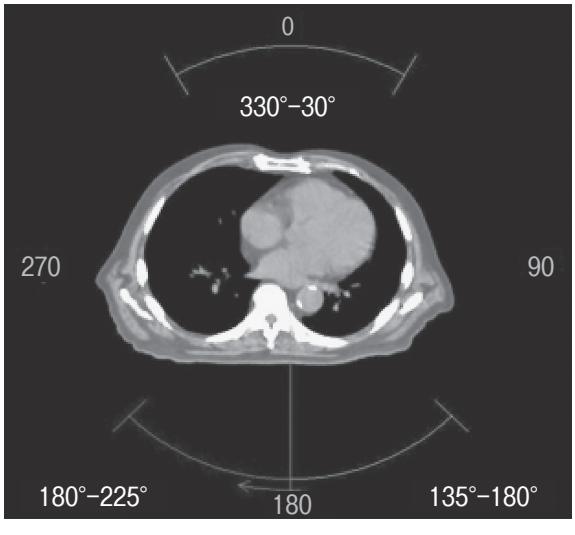

Fig. 2 The arc arrangement of a double-arc with avoidance sector. The VMAT consisted of gantry angles of 135°–180°, 180°–225°, and 330°–30°.

The degree of conformity of the plan was measured using the RTOG conformity index (RCI) and the Paddick conformity index (PCI). The formula for the PCI [32] is: $(TV_{PIV})^2/(TV \times PIV)$, in which TV is the target volume and PIV is the prescription isodose volume. TV_{PIV} is target volume covered by PIV. The formula for the RCI [33] is: PIV/TV. An RCI value of 1.0 indicates ideal conformity, and a value >1.0 or <1.0 indicates over- or under-coverage, respectively. A PCI value of 1.0 indicates ideal conformity, but a value <1.0 is due to both over- and under-coverage of the PTV. For the OARs, the analysis included the mean dose and the set of appropriate $V_{x\,(Gy)}$ values.

Follow-up after the initial therapy. After the initial therapy, CT and endoscopy were performed every 1-3 months in the first year, and every 3-6 months in the second year. For the assessment of toxicity, the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0 was adopted. On the basis of the onset time, late toxicities were those that were detected 6 months after the start of the treatment.

Statistical analysis. To compare the two different plans for each patient, we used Student's paired *t*-test (when the data showed a normal distribution) or the paired Wilcoxon signed-rank test (when the data showed a non-normal distribution). *P*-values <0.05 were considered significant. The mean value of the difference (3D-CRT minus VMAT) and the 95% confidence interval (CI) for the difference in parameters between each plan was calculated. Statistical analyses were performed using the JMP v.10.0 software (SAS Institute, Cary, NC, USA).

Results

Tables 2 and 3 summarize the descriptive statistics of the 3D-CRT and VMAT for the standard- and high-dose plans. VMAT significantly improved the conformity index compared to 3D-CRT. In the heart and pericardium, VMAT realized a significantly lower value for all parameters (all *p*-values were <0.001). A >20% reduction of $V_{30\text{-}50Gy}$ was confirmed in the heart. In the lung, VMAT showed a significantly higher V_{5Gy} in both the standard- and high-dose plans ($p<0.001$). VMAT showed no significant difference in the V_{20Gy} for the

Table 2 Summary of the DVH analysis for the standard-dose plan: comparison between 3D-CRT and VMAT

Parameter	50.4 Gy				
	3D-CRT Median (range)	VMAT Median (range)	Mean of (3D-CRT-VMAT)	3D-CRT vs. VMAT (95% CI)	*P* value
PTV2 (301 ± 81 ml)					
D2% (Gy)	52 (51–53.9)	52.2 (51.9–52.5)	−0.1	(−0.4 to 0.3)	0.777*
D5% (Gy)	51.8 (50.9–53.2)	51.8 (51.5–52.1)	0.1	(−0.2 to 0.4)	0.603*
D95% (Gy)	48.5 (45.2–49.8)	48.8 (48.1–49.3)	−0.5	(−1.1 to 0.1)	0.112*
D98% (Gy)	47.7 (41.6–49.2)	48.4 (47.5–49)	ND	ND	0.043†
D5%–D95% (Gy)	3.4 (1.9–6.4)	3 (2.3–3.9)	0.6	(0.1 to 1.1)	0.026*
RCI	3.13 (1.99–4.81)	2.03 (1.52–2.82)	1.12	(0.78 to 1.45)	<0.001*
PCI	0.3 (0.21–0.41)	0.49 (0.35–0.61)	−0.18	(−0.22 to −0.15)	<0.001*
Lungs (3338 ± 943 ml)					
Mean (Gy)	12.6 (9.3–14.8)	12.7 (10.5–14.8)	−0.6	(−1.2 to 0.1)	0.072*
V5Gy (%)	56.4 (42.8–62)	60.6 (47.4–70.9)	−6.9	(−9.9 to −3.9)	<0.001*
V10Gy (%)	42.7 (30–48)	37.3 (29.8–48.4)	0.9	(−2.2 to 3.9)	0.54*
V20Gy (%)	22.2 (17.5–34.7)	22.9 (16.6–27.8)	1.2	(−1.5 to 3.9)	0.35*
Heart (612 ± 173 ml)					
Mean (Gy)	37 (27.2–45.8)	29 (24–34.1)	7.3	(5.8 to 8.9)	<0.001*
V30Gy (%)	78.4 (54.6–93.4)	41.7 (30.9–61.4)	33.4	(29.3 to 37.4)	<0.001*
V40Gy (%)	46.8 (22.9–75.7)	18.9 (10.5–35.8)	26.8	(21.4 to 32.2)	<0.001*
V50Gy (%)	25.6 (6.4–56.3)	1.1 (0.4–3.7)	22.2	(15.5 to 29)	<0.001*
Pericardium (179 ± 27 ml)					
Mean (Gy)	30.5 (23.8–38.7)	26.8 (21.3–33.3)	3.4	(2.7 to 4.2)	<0.001*
V30Gy (%)	59.7 (41.6–76.6)	38.8 (26.5–55)	18.7	(17 to 20.4)	<0.001*
V40Gy (%)	36.8 (22.4–55)	26.8 (15.5–42.3)	9.9	(6.7 to 13.1)	<0.001*
V50Gy (%)	17.6 (9.8–29.9)	8.2 (4.9–14.6)	ND	ND	<0.001†
Liver (1074 ± 219 ml)					
Mean (Gy)	9.5 (5.2–15.1)	8.9 (4.2–14.9)	0.3	(−0.1 to 0.7)	0.155*
V30Gy (%)	13.6 (6–24.5)	13.7 (3.8–25.3)	−0.4	(−1.5 to 0.7)	0.484*
Kidneys (254 ± 52 ml)					
Mean (Gy)	3.6 (0.6–12.3)	4.3 (0.4–6.1)	0.7	(−0.3 to 1.8)	0.169*
Spinal cord (57 ± 14 ml)					
Max (Gy)	44 (42.9–45)	41 (39.3–42.7)	2.9	(2.3 to 3.5)	<0.001*
Stomach (180 ± 60 ml)					
Mean (Gy)	30.1 (10.1–39.1)	31.6 (10.2–37.7)	−0.4	(−1.1 to 0.3)	0.233*

DVH, dose-volume histogram; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; CI, confidence interval; PTV, planning target volume; Dx%, dose received > x% of volume; VxGy, volume receiving > x Gy; RCI; RTOG conformity index; PCI, Paddick conformity index; ND, Not Determined.
* Student's paired *t*-test, † Wilcoxon signed-rank test

standard-dose plan ($p = 0.35$) but showed a significantly lower V_{20Gy} for the high-dose plan ($p = 0.004$). Other parameters showed no significant differences in the lungs. The results of the DVH analysis for other OARs (showing slight differences) are provided in Tables 2 and 3.

The median follow-up time was 16 months after the initial therapy. The incidence of late toxicities including pneumonitis and pericardial effusion of grade 2 or more is shown in Table 4. There was one grade 4 pericardial effusion, and the patient needed pericardial drainage and fenestration at 27 months after treatment.

Discussion

We compared SIB-VMAT and 3D-CRT for middle and lower esophageal cancers using ENI at doses of 50.4 Gy and 60 Gy. The results demonstrated that SIB-VMAT could generate plans with superior dose conformity for the target volume and with a significant reduction in doses for the heart and pericardium without worsening the major parameters of the lung (V_{20Gy} and

Table 3 Summary of the DVH analysis for the high-dose plan: Comparison between 3D-CRT and VMAT

Parameter	60 Gy				
	3D-CRT median (range)	VMAT median (range)	mean of (3D-CRT-VMAT)	3D-CRT vs. VMAT (95% CI)	*P* value
PTV2 (301 ± 81 ml)					
D2% (Gy)	62 (60.2–64.4)	63 (62.6–63.6)	−1.2	(−1.8 to −0.6)	<0.001*
D5% (Gy)	61.7 (60–63.5)	62.5 (62.1–62.9)	−0.9	(−1.5 to −0.4)	0.0014*
D95% (Gy)	57.6 (52.4–58.9)	57.3 (57–58)	ND	ND	0.903†
D98% (Gy)	56.1 (48.2–58)	56.4 (56–57.6)	ND	ND	0.351†
D5%–D95% (Gy)	4.2 (2.2–8.6)	5.3 (4–5.7)	ND	ND	0.048†
RCI	2.8 (1.78–4.45)	1.28 (1.18–1.59)	ND	ND	<0.001†
PCI	0.33 (0.22–0.45)	0.74 (0.62–0.8)	−0.4	(−0.43 to −0.37)	<0.001*
Lungs (3338 ± 943 ml)					
Mean (Gy)	14 (10.2–16)	13.3 (10.6–16.9)	−0.1	(−0.9 to 0.6)	0.667*
V5Gy (%)	56.3 (42–62.4)	63.1 (54.2–72.3)	−9.3	(−12.2 to −6.4)	<0.001*
V10Gy (%)	40.3 (27.4–47.9)	39.4 (30.2–51.8)	−1.7	(−5.1 to 1.8)	0.31*
V20Gy (%)	28.2 (19.3–33.2)	22.2 (13.8–30.4)	4.5	(1.7 to 7.3)	0.004*
Heart (612 ± 173 ml)					
Mean (Gy)	44 (32.3–54.2)	33.9 (28.1–35.5)	ND	ND	<0.001†
V30Gy (%)	81.4 (57.4–94.7)	55.1 (42.9–63.6)	24.6	(19.7 to 29.5)	<0.001*
V40Gy (%)	74.4 (51.6–91.3)	31.2 (21.2–36.8)	42.5	(38.1 to 47)	<0.001*
V50Gy (%)	40.3 (13.1–71.2)	15.9 (8.4–21.7)	21.6	(14.7 to 28.5)	<0.001*
Pericardium (179 ± 27 ml)					
Mean (Gy)	34.7 (27.2–45.4)	30.3 (24.3–36.6)	5.3	(4.3 to 6.4)	<0.001*
V30Gy (%)	61.7 (43.8–81.2)	42.4 (30–57.9)	19.2	(16.5 to 21.9)	<0.001*
V40Gy (%)	52.7 (38.9–72.1)	28.8 (17.7–44.8)	23.3	(21.1 to 25.4)	<0.001*
V50Gy (%)	31.4 (15.8–43.5)	17.5 (11–29.2)	10	(7.7 to 12.3)	<0.001*
Liver (1074 ± 219 ml)					
Mean (Gy)	11.5 (5.5–16.4)	9.6 (3.9–15.5)	0.8	(0.1 to 1.4)	0.023*
V30Gy (%)	14.1 (6.3–25.1)	14.1 (3.6–26.2)	0.5	(−0.5 to 1.6)	0.263*
Kidneys (254 ± 52 ml)					
Mean (Gy)	3.2 (0.6–11.8)	4.3 (0.4–13.7)	−1	(−1.8 to −0.2)	0.017*
Spinal cord (57 ± 14 ml)					
Max (Gy)	44.8 (39.4–47.1)	39.7 (38.5–41)	4.7	(3.7 to 5.8)	<0.001*
Stomach (180 ± 60 ml)					
Mean (Gy)	30.4 (10.7–45)	30.7 (10.7–42.3)	1	(−0.1 to 2.1)	0.07*

DVH, dose-volume histogram; 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; CI, confidence interval; PTV, planning target volume; Dx%, dose received > x% of volume; VxGy, volume receiving > x Gy; RCI; RTOG conformity index; PCI, Paddick conformity index; ND, Not Determined.
* Student's paired *t*-test, † Wilcoxon signed-rank test

Table 4 Late toxicities higher than grade 2

Radiation technique	3D-CRT (n = 9)	IMRT/VMAT (n = 6)
Pneumonitis		
Grade 2 (%)	2 (22.2)	0 (0)
Pericardial effusion		
Grade 2 (%)	3 (33.3)	2 (33.3)
Grade 4 (%)	1 (11.1)	0 (0)

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

MLD). Although attention should be paid to the increase in the low-dose area (V_{5Gy}) of the lungs, the results of this study could provide great value in clinical settings.

In thoracic radiotherapy for esophageal and lung cancers, the relationships between the heart/pericardium dose and the outcomes or adverse events have been reported. Fukada *et al.* [34] reported that pericardium $V_{45Gy} \geq 58\%$ and its mean dose of ≥ 36.5 Gy are risk factors for symptomatic pericardial effusion (SPE). Ogino *et al.* [28] showed that pericardium $V_{50Gy} \geq 17\%$

is a risk factor for SPE. Other studies have also reported the significance of the heart V_{30Gy} for pericardial effusion [29, 35]. Interestingly, Speirs *et al.* [36] showed the heart dose to be an independent prognostic factor. There are no previous reports comparing SIB-VMAT and 3D-CRT for middle or lower esophageal cancer with ENI, though judging from other reports [28, 29, 34-36], the heart and pericardium $V_{30\text{-}50Gy}$ would be important parameters. The results of our present investigation could lead to improved outcomes, because the use of SIB-VMAT can help achieve a significant reduction in the $V_{30\text{-}50Gy}$ for the heart and pericardium.

When adopting SIB-VMAT for esophageal cancer with ENI, attention should be paid to the increase in the low-dose area (*e.g.*, V_{5Gy}). Nutting *et al.* [37] pointed to a flaw in a large number of fields in the IMRT plan, caused by a low dose spread over the entire lungs. Nicolini *et al.* [10] used two coplanar arcs of 360° with avoidance sectors to exclude direct lateral entrance through the lungs. However, these two studies were based on the IFI. According to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [31], it is prudent to limit the lung V_{20Gy} to ≤30-35% and the MLD to ≤20-23 Gy (with conventional fractionation) in order to reduce the risk of RP to ≤20%.

The influence of V_{5Gy} on RP has also been reported. Yom *et al.* [38] noted that the rate of grade 3 or higher RP among IMRT patients with V_{5Gy} values exceeding 70% was significantly larger compared to the rate among patients with lower V_{5Gy} values (21% vs. 2%). Shaikh *et al.* [39] stated that lung V_{5Gy} was associated with grade 2 or higher RP in a multivariate analysis. A $V_{5Gy} \geq 65\%$ was identified as a risk factor for the increased incidence of grade 2 or higher RP. Although the clinical importance of the V_{5Gy} for the lungs might be controversial, a lung $V_{5Gy} < 65\text{-}70\%$ would be a guide for optimization based on previous reports [38, 39]. We here have shown that SIB-VMAT can meet those criteria for the lungs. In addition, although our sample size was small, the probability of late toxicities of grade 2 or higher RP after IMRT/VMAT was lower than that seen with 3D-CRT.

Locoregional failure is a serious problem in radiotherapy for esophageal cancer [19-21]. The standard dose is considered to be 50.4 Gy [20]. One of the ways to improve the local control rate would be a dose escalation to the involved tumors [22, 23]. Shirakawa *et al.* [40] and Chang *et al.* [24] reported favorable outcomes with high-dose (≥60 Gy) 3D-CRT and IMRT. Although high-dose irradiation with ENI is widely used for definitive treatment in Japan [16, 18], there are no reports with a dose-volume analysis of the heart and lungs using high-dose SIB-VMAT with ENI. The results of our present study demonstrate that SIB-VMAT with ENI can realize dose escalation with a significant reduction in the dose delivered to the heart and pericardium while meeting the dose criteria for the lungs.

This study has some limitations. First, though the efficacy of the flattening filter-free (FFF) beam was reported [10], we could not make a plan using these beams because of machine constraints. FFF beams may have the potential of improving the dose distributions in ENI for middle or lower esophageal cancer. Second, the target volume was set including the inhaled and exhaled positions accounting for respiratory organ motion, and the relevance of respiratory gating was not questioned [10]. The use of respiratory gating might have made it possible to shrink the PTV margin and reduce the doses to the lung and heart.

Our study revealed that the use of SIB-VMAT can achieve a significant reduction in the heart and pericardium doses while meeting the dose criteria for the lungs during the treatment of middle or lower thoracic esophageal cancer with ENI. Although we need to pay attention to the low dose area of the lung, our findings present the possibility of a new treatment strategy for improving the outcomes of middle or lower thoracic esophageal cancer.

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