***Title*: Respiratory gating and multifield technique radiotherapy for esophageal cancer**

Short Running: Gating and multifield for esophageal cancer

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ABSTRACT

Purpose: To investigate the effects of a respiratory gating and multifield technique on the dose-volume histogram (DVH) in radiotherapy for esophageal cancer.

Methods and Materials: Twenty patients underwent four-dimensional computed tomography for esophageal cancer were included. We retrospectively created the four treatment plans for each patient, with or without the respiratory gating and multifield technique: No gating-2-field, No gating-4-field, Gating-2-field, and Gating-4-field plans. We compared the DVH parameters of lung and heart in the No gating-2-field plan with the other three plans.

Result: In the comparison of the parameters in No gating-2-field plan, there are significant differences in the Lung V_{5Gy}, V_{20Gy}, mean dose with all three plans and the Heart V_{25Gy} - V_{40Gy} with Gating-2-field plan, V_{35Gy}, V_{40Gy}, mean dose with No Gating-4-field plan and V_{30Gy} - V_{40Gy}, mean dose with Gating-4-field plan. The lung parameters were smaller in Gating-2-field plan and larger in No gating-4-field and Gating-4-field plans. The heart parameters were all larger in No gating-2-field plan.

Conclusion: The lung parameters were reduced by the respiratory gating technique and increased by the multifield technique. The heart parameters were reduced by both techniques. It is important to select the optimal technique according to the risk of the complications.

Keywords: Respiratory gating, Multifield, Esophageal cancer, Organ at risk, Dosimetry

Introduction

Some esophageal cancer patients who undergo radiotherapy suffer from adverse events due to the extensive radiation field. Late adverse events involving the lung (such as radiation pneumonitis and fibrosis) and those of the heart (such as pericarditis and myocardial infarction) are challenges to address toward improving the long-term prognosis of these patients. Ishikura *et al*. reported that among 78 patients with esophageal cancer treated with definitive chemoradiotherapy who achieved complete remission, 24 patients had > grade 2 late cardiopulmonary toxicities [1]. Radiation pneumonitis occurred in four patients (5.1%) and pericardial effusion occurred in 16 patients (20.5%); four patients (5.1%) died of myocardial infarction or heart failure.

Lung adverse events have a relationship with the lung volume receiving 20 Gy or more (V_{20Gy}) and mean lung dose [2]. Heart adverse events have a relationship with the heart $V_{25–40Gy}$ [3, 4]. To reduce the incidence of these adverse events, several techniques have been developed. For types of cancer that may move significantly due to the patient's respiratory motion, the respiratory gating technique has been used to reduce the internal margin. The respiratory gating technique allows us to decrease the effect of respiratory motion.

In lung cancer, the use of the respiratory gating technique was reported to reduce the dose-volume histogram (DVH) parameters of the organ at risk (OAR). The respiratory motion of the esophagus and in patients with esophageal cancer have been investigated using four-dimensional computed tomography (4D-CT), expiratory-inspiratory CT and magnetic resonance imaging (MRI). Yamashita *et al.* reported that the average and maximum displacements of the esophagus in the superior-inferior direction were 1.1 mm (max. 5.5 mm), 3.0 mm (14.5 mm), and 5.1 mm (16.3 mm) for the upper, middle, and lower thoracic esophagus, respectively [5]. Patel *et al*. proposed that the following internal target volume (ITV) margins

are necessary for esophagus primary tumors: 1.5 cm in the superior–inferior direction, 0.75 cm in the anterior-posterior direction, and 0.75 cm in the left-right direction [6]. It may thus be potential to reduce the ITV by using respiratory gating radiation.

One of the most frequently used general techniques in radiotherapy is the multifield technique. For comparisons of two field plan [anterior-posterior - posterior-anterior; AP-PA] - which is the most conventional field - the multifield technique can reduce the high-dose area, although the low-dose is increased alternatively.

The effects of these techniques in the treatment of esophageal cancer have not been reported. In this study, we investigated how the respiratory gating technique and multifield technique affect the lung and heart doses in radiotherapy for esophageal cancer by comparing some three-dimensional conventional radiotherapy (3D-CRT) plans that include or do not include the respiratory gating or multifield techniques.

Methods and Materials

Patients

The subjects were consecutive esophageal cancer patients treated at our institute between April 2011 and December 2013. The patients who underwent 4D-CT for treatment planning with clips at both sides of their esophageal tumor were included. The patients who underwent a chest operation or had massive pleural effusion were excluded. A final total of 20 patients were included in the study, which was approved by the Institutional Review Board of Niigata University Hospital (IRB number 2191)

Planning CT

The 4D-CT images were scanned using a GE Lightspeed RT 16 multi-slice CT scanner (General Electric Medical Systems, Waukesha, WI) with a slice thickness of 2.5 mm. The patients were audio-coached to use a 3-sec respiratory cycle. A Varian Real-Time Position Management system (Varian Medical Systems, Palo Alto, CA) was used to measure the respiratory motion. The scans were sorted into 10 phase-bins (0–90) of the respiratory cycle, using an Advantage 4D workstation (GE Healthcare, Princeton, NJ).

Delineation and treatment plans

We delineated and made treatment plans using a Varian Eclipse Treatment Planning System, software version 8.6 (Varian Medical Systems). We delineated the gross tumor volume (GTV) and the clinical target volume (CTV) at three phases: the end-inspiratory phase (phase 0), the intermediate phase (phase 30), and the end-expiratory phase (phase 50). The CTV for the primary tumor was defined as the esophagus between the clips plus 2 cm craniocaudally. The CTV for metastatic lymph nodes was equal to the GTV. The CTV was extended to the elective nodal area for all patients because of high incidence of lymph node metastasis [7]. Mediastinal and perigastric lymph nodes were included in elective nodal area for upper, middle, lower thoracic esophageal cancer. Supraclavicular lymph nodes were included for upper and middle thoracic esophageal cancer and celiac lymph nodes were included for lower thoracic esophageal cancer.

We made a composite of the CTV at the three phases (0, 30, 50) and used it as the ITV of all respiratory phases (i.e., No gating) radiation (ITV_No gating). We used the composite of the CTV at two phases (30, 50) as the ITV of the expiratory phase (i.e., Gating) radiation (ITV_Gating). We made the planning target volume (PTV_No gating and PTV_Gating) by expanding each ITV by 5 mm. The

delineation of the OARs including lungs, heart and spinal cord was made on the intermediate CT-set (phase 30).

The treatment plans consisted of an initial plan (40 Gy in 20 fractions for the esophageal tumor, metastatic lymph nodes and the elective lymph node area) and a boost plan (20 Gy in 10 fractions for the primary tumor and metastatic lymph nodes) delivered using 10-MV photon beams with 100% of the prescribed dose to the reference point. Dose distributions were calculated based on the intermediate phase CT-set (phase 30) for all plans. The leaf margin to PTVs was set 5 mm.

To examine the effect of the multifield technique, we created two initial plans (two-field plans [AP-PA] and four-field plans [AP-PA and two oblique fields]) for each PTV_ No gating and PTV_Gating plan. We created a total of four initial plans for each patient: No gating-2-field, No gating-4-field, Gating-2-field, and Gating-4-field.

The boost plans were created with two oblique opposite fields avoiding the spinal cord in principle. We compared the effects of the four treatment plans (initial plan + boost plan) in this study.

Statistical analysis

To evaluate the effects of the respiratory gating technique and multifield technique on the DVH parameters of the lung and the heart, we compared the most conventional plan (i.e., the No gating-2-field) with the other three plans (No gating-4-field, Gating-2-field, and Gating-4-field). We compared the DVH parameters including the dose that covers 95% (D95) of the CTV and PTV, the V_{5Gy},V_{20Gy}, and mean dose to the lung (MLD) , and the V_{25G},V_{30Gy},V_{35Gy}, V_{40Gy} and mean dose to the heart (MHD) .

To evaluate the effects of the respiratory gating technique, we compared the PTV size and the

major axis of the field (i.e., the AP field of the initial plan and the anterior oblique field of the boost plan) between the No-gating and Gating plans.

All statistical analyses were performed using JMP ver. 11.0.0 software (SAS Institute, Cary, NC).The two-tailed paired t-test was used for comparisons, and p-values <0.05 were accepted as significant.

Results

The patients' characteristics are shown in Table 1. The position of the esophageal tumor was most frequently in the middle thoracic portion. The TMN stage I was the most frequent. The D95 values of the CTV and PTV are shown in Table 2. Although there were significant differences in Initilal CTV between No-gating-2-field plan and Gating-4-field plan and in Initial PTV between No-gating-2-field plan and No-gating-4-field plan, the maximum difference was 0.6 Gy.

The DVH parameters of the OAR are shown in Figure 1 and Table 3. In our comparison of the lung parameters in the No gating-2-field plan, we observed significant differences in the V_{5Gy}, V_{20Gy}, and the MLD with the Gating-2-field plan, and in the V_{5Gy}, V_{20Gy}, and the MLD compared to the No Gating-4-field plan. There were also significant differences in the V_{5Gy}, V_{20Gy}, and MLD between the No gating-2-field plan and the Gating-4-field plan. Compared to the No gating-2-field plan, all of the parameter values were smaller in the Gating-2-field plan and larger in the No Gating-4-field and Gating-4-field plans. In addition, the lung V_{20Gy} and MLD were decreased by 0.5% and 0.2 Gy by the respiratory gating technique, and increased by 1.8% and 1 Gy by the multifield technique. By using both techniques, the Lung V_{20Gy} and MLD were increased by 1.4% and 0.8 Gy.

In our comparison of the heart parameters using the No gating-2-field plan, there were significant difference in the V_{25Gy}, V_{30Gy}, V_{35Gy}, and V_{40Gy} with the Gating-2-field plan, and in the V_{35Gy}, V_{40Gy} and MHD with the No Gating-4-field plan and in the V_{30Gy}, V_{35Gy}, V_{40Gy}, and MHD with the Gating-4-field plan. The parameters were all smaller in the Gating-2-field, No Gating-4-field, and Gating-4-field plans compared to the No gating-2-field plan. The heart V_{40Gy} was decreased by 1.3% by the respiratory gating technique, decreased by 17.8% by the multifield technique, and decreased by 19.2% with the use of both techniques.

The PTV size and radiation field length with and without the respiratory gating technique are shown in Table 4. These values all show significant differences between the plans. They are all smaller in the Gating plans. The mean difference was 30.4 cm^3 at the Initial PTV and 10.2 cm^3 at the Boost PTV, 0.5 cm at the initial plan field and 0.4 cm at the boost plan field.

Discussion

In the present study, the lung dose are reduced by the respiratory gating technique and increased by the multifield technique, whereas the heart dose was reduced by both techniques. The efficiency of respiratory gating radiation has been reported in lung cancer and liver cancer [8, 9]. There is no report about respiratory gating radiation in esophageal cancer, to our knowledge. The PTV size can be reduced by using the respiratory gating technique. In lung cancer, Muirhead *et al.* reported that the PTV size was decreased by 83.21cm^3 with the use of the respiratory gating technique [10]. In our study, the reduction in the Initial PTV was 30.3cm^3, which is smaller than that in lung cancer in the Muirhead study. The reason for the difference in the reduction may be due to a difference in the degree of the tumor motion. Mageras *et al*. reported that the maximum lung tumor motion in the superior-inferior direction was > 2.5 cm [11].

This is larger than that the motion of esophageal tumors. With the multifield technique, the high-dose area is decreased, but the low-dose is concomitantly increased. There is thus a trade-off of the high-dose area of the heart and the low-dose area of the lung in the radiotherapy of esophageal cancer. The effects of the respiratory gating and multifield techniques differ by the organ. In esophageal cancer, we need to understand the effects of these two techniques on the lung and heart individually.

Dose reductions achieved with the respiratory gating technique in lung cancer have been described. Underberg *et al.* reported that the MLD and V_{20Gy} were decreased 0.9 Gy and 1.9% by respiratory gating in lung cancer [12], and Hau *et al.* stated that the MLD and V_{20Gy} were decreased by 1.33 Gy and 2.2% by respiratory gating in lung cancer [13]. Muirhead *et al.* reported that the MLD and V_{20Gy} were decreased by 0.57–2.35 Gy and 0.58%–2.27 % by inspiratory or expiratory gating in lung cancer [9]. In 0.5%, which are smaller than the values achieved in these prior studies of lung cancer. It is possible that the benefit of gating is smaller in esophageal cancer because of the volume of the target volume. Starkschall *et al.* [14] proposed that respiratory gating radiation is advantageous for the lung V_{20Gy} and MLD for patients whose GTVs are < 100 cm^3. In our study, the initial PTV was large at 576 cm^3, because the radiation fields for esophageal cancer are very extensive for prophylactic lymph node area irradiation.The lung dose was increased by using the multifield technique. In the study of intensity-modulated radiotherapy for esophageal cancer, Kole *et al.* observed that the lung V_{5Gy} was significantly increased and the average MLD and V_{20Gy} values were increased without a significant difference [15]. The use of the multifield technique for patients who have one or more risk factors for lung adverse events should be considered very carefully.

Regarding the heart dose reduction allowed by the use of the respiratory gating technique, there are only a few reports. In left-side breast cancer, Qi *et al.* described a reduction of the MHD and the left ascending aorta dose obtained by using the respiratory gating technique [16]; this was due to the shift of

the heart by the inspiration. The esophagus is located at the mediastinum, and esophageal cancer is frequently present at middle thoracic portion, where the back of the heart is located. The heart dose thus becomes high, and there is little effect of a heart shift by the respiratory gating technique. In our study, the reduction of the heart V_{30Gy} and V_{40Gy} values were 0.7% and 1.3% respectively by the respiratory gating technique. This is due to the reduction the target volume. With our use of the multifield technique, the heart V_{30Gy} and V_{40Gy} were reduced by 1.7% and 17.7%, respectively. The V_{40Gy} was especially decreased. The multifield technique may more useful to reduce the risk of heart adverse events. Fukada *et al*. reported that compared to the patients who underwent a two-dimensional (2D) anterior-posterior field plan, the pericardial effusion was reduced in the patients who underwent a 3D multifield plan [17], and the pericardial V_{40Gy} and V_{45}Gy were significantly smaller with the 3D multifield plan. Although there may be differing effects of 2D and 3D plans, using the multifield technique could reduce the incidence of cardiac adverse events.

Our study has several limitations. We used the same PTV margin for the Gating and No gating PTVs. However, a larger PTV margin may be necessary when using a Gating PTV compared to a No gating PTV, because the uncertain aspects of the respiratory gating technique such as the time-lag of the machine must be taken into account. There was also a bias regarding the cancer stage of the patients analyzed in this study, because we selected patients whose treatment included clips at both sides of the esophageal cancer (12 of the 20 patients were cT1N0M0). In addition, we compared only the DVH parameters in some virtual plans; we did not investigate whether adverse events can be reduced by these techniques in the clinical setting. The clinical adverse events produced by the respiratory gating and multifield techniques as described herein should be investigated in future studies. Considering to these points, we have recently begun a research to compare clinical outcomes of the each treatment technique.

Conclusion

The lung dose was reduced by the respiratory gating technique and increased by the multifield technique. In contrast, the heart dose was reduced by both techniques. It is important to examine the risk of heart and lung complications and select the optimal treatment technique before radiotherapy for patients with esophageal cancer.

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Table 1　Patient charastaristics

Variable	Stratification	Data
Age (years)	Median(Range)	70(54-84)
Sex	Male	18
	Female	2
Location	Upper thoracic portion	3
	Middle thoracic portion	14
	Lower thoracic portion	3
Stage	I	13
	II	1
	III	4
	IV (supraclavicular)	2

Table 2 D95 of CTV and PTV

	No gating-2-field plan	No gating-4-field plan	p-value	Gating-4-field plan	p-value	Gating-4-field plan	p-value
Initial CTV (Gy)	39.7 ± 1.4	39.5 ± 1.1	0.19	39.1 ± 1.5	0.01	39.3 ± 1.4	0.07
Boost CTV(Gy)	57.4 ± 4.6	57.3 ± 4.5	0.42	57.6 ± 4.5	0.24	57.5 ± 4.5	0.30
Initial PTV (Gy)	34.4 ± 2.7	38.8 ± 1.2	0.02	38.3 ± 1.4	0.11	38.3 ± 1.2	0.19
Boost PTV (Gy)	56.3 ± 4.3	55.7 ± 4.8	0.16	56.5 ± 4.3	0.27	55.9 ± 4.8	0.24

p-value : vs No gating-2-field plan

Table 3. DVH parameters to the organ at risk

	No gating-2-field plan	Gating-2-field plan	p-value	No gating-4-field plan	p-value	Gating-4-field plan	p-value
Lung V_{5Gy} (%)	46.8 ± 9.1	46.1 ± 9.2	<0.01	49.6 ± 7.2	<0.01	48.9 ± 7.2	0.01
Lung V_{20Gy} (%)	23.8 ± 6.3	23.3 ± 6.2	<0.01	25.6 ± 6.6	<0.01	25.2 ± 6.6	<0.01
MLD (Gy)	11.6 ± 2.2	11.4 ± 2.2	<0.01	12.6 ± 2.2	<0.01	12.4 ± 2.2	<0.01
Heart V_{25Gy} (%)	69.0 ±10.2	68.2 ± 10.5	<0.01	70.2 ± 11.3	<0.01	69.4 ± 11.7	0.24
Heart V_{30Gy} (%)	64.8 ± 9.6	64.1 ± 9.8	<0.01	63.1 ± 11.4	<0.01	62.0 ± 11.8	<0.01
Heart V_{35Gy} (%)	61.8 ± 9.5	61.0 ± 9.7	<0.01	47.3 ± 10.5	<0.01	46.1 ± 10.9	<0.01
Heart V_{40Gy} (%)	54.0 ± 11.9	52.7 ± 12.2	<0.01	36.3 ± 9.9	<0.01	34.8 ± 10.0	<0.01
MHD (Gy)	33.9 ± 5.8	33.9 ± 5.2	0.48	32.9 ± 5.1	0.03	32.3 ± 5.2	<0.01

p-value : vs No gating-2-field plan

Figure 1 Important DVH parameters of organ at risk

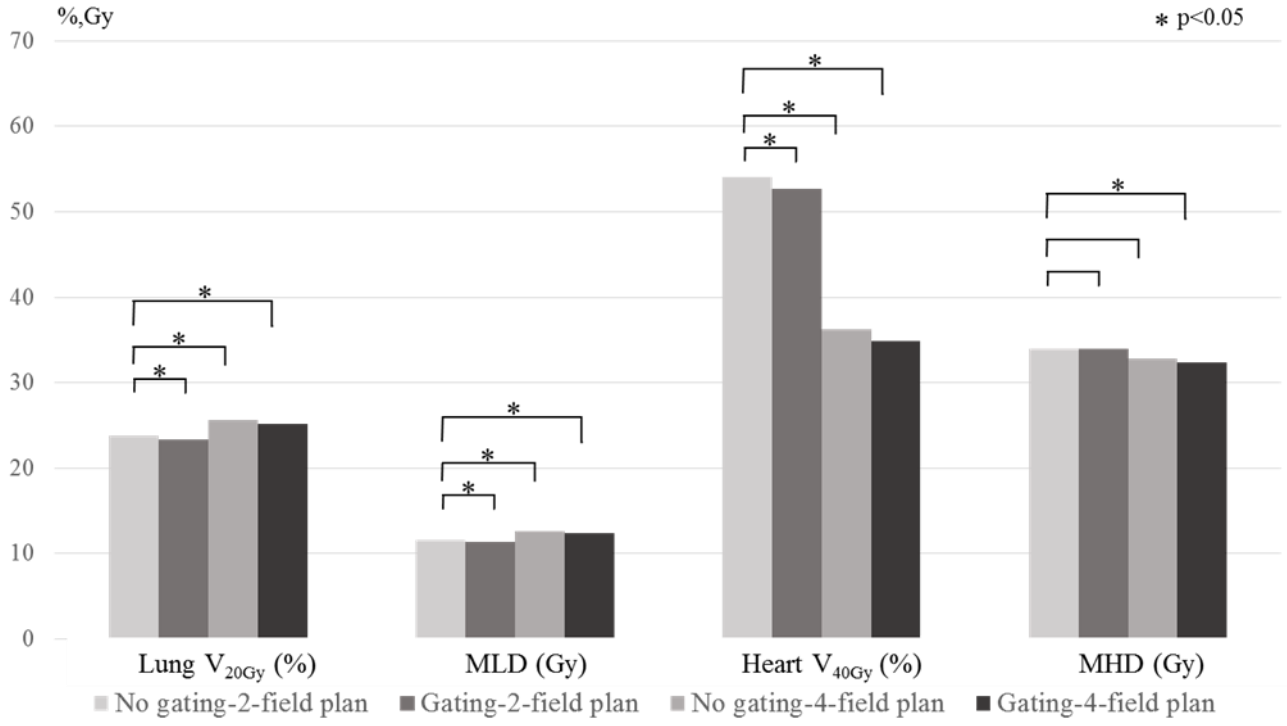

Table 4. PTV size and field major axis

	No gating plan	Gating plan	p-value
Initial PTV (cm^3)	606.7 ± 106.7	576.3 ± 102.0	<0.01
Boost PTV (cm^3)	191.4± 87.0	181.3 ± 84.3	<0.01
Initial field (cm)	28.5 ± 1.4	28.0 ± 1.5	<0.01
Boost field (cm)	14.7 ± 4.1	14.4 ± 4.0	<0.01

Mean ± S.D.