Risk factors for pericardial effusion after chemoradiotherapy for thoracic esophageal cancer—comparison of four-field technique and traditional two opposed fields technique

Noriko Takata*,1,2, Masaaki Kataoka1, Yasushi Hamamoto2, Shintaro Tsuruoka2, Hiromitsu Kanzaki1, Kotaro Uwatsu1, Kei Nagasaki2 and Teruhito Mochizuki2

1Department of Radiotherapy, Shikoku Cancer Center Hospital, Kou 160, Minami-Umemoto, Matsuyama, Ehime 791-0280, Japan
2Department of Radiology, Ehime University Hospital, Shitsukawa, Tohon, Ehime 791-0295, Japan

*Corresponding author. Department of Radiology, Ehime University Hospital, Shitsukawa, Tohon, Ehime 791-0295, Japan. Tel: +81-89-960-5371; fax: +81-89-960-5375; Email: takata.noriko.tg@ehime-u.ac.jp

(Received 20 December 2017; revised 24 February 2018; editorial decision 14 March 2018)

INTRODUCTION

Esophageal cancer is the eighth most common malignancy in the world, and the sixth most common cause of cancer-related death [1]. Concurrent chemoradiotherapy (CCRT) is a standard treatment for locally advanced esophageal cancer in patients with a relatively good general condition. However, long-term heart and lung toxicity has been reported after definitive chemoradiotherapy for thoracic esophageal cancer [2]. The cardiac adverse events include pericarditis/pericardial effusion, myocardial injury, vascular stenosis, valvar injury, and/or conduction abnormalities. Acute cardiac injury often manifests as pericarditis and is usually transient, although it can also be chronic [3]. Subacute/delayed pericardial disease can occur at intervals of months to years after radiotherapy, and includes pericarditis and chronic pericardial effusion, which is usually asymptomatic. Although most cases resolve spontaneously, ~20% progress to chronic and/or constrictive pericarditis [4].

The traditional irradiation technique for thoracic esophageal cancer is the two opposed fields technique (TFT). However, in an
attempt to minimize cardiac adverse events, the four-field technique (FFT) (two opposed anteroposterior fields combined with two opposed oblique fields) has become frequently used in clinical practice. This is because FFT is a simple technique for reducing the heart volume (especially the left ventricle) that receives high doses, compared with the TFT, although it is unclear whether FFT can decrease the incidence of pericardial effusion. Therefore, this retrospective study evaluated dose–volume histogram (DVH) data for the pericardium to determine whether FFT decreased the incidence of pericardial effusion, compared with TFT, among patients who received definitive CCRT for thoracic esophageal cancer.

**MATERIALS AND METHODS**

**Patients**

Between January 2007 and June 2015, 169 patients with newly diagnosed middle and/or lower thoracic esophageal cancer received definitive CCRT in one institution. This study's retrospective protocol was approved by our institutional review board (No. 27 in 2016). Patients were excluded if they did not undergo follow-up computed tomography (CT) after more than 6 months from the end of the CCRT (n = 46), or if the initial treatment plan involved the three-field technique (n = 1). In addition, patients in whom the imaging range of planning CT was narrow and the whole pericardium was not imaged were excluded because DVH analysis of the pericardium could not be performed (n = 28). Thus, a total of 94 patients were assigned to the FFT group (n = 51) or the TFT group (n = 43) according to their initial treatment plan. Tumors were staged according to the 7th version of the UICC–AJCC TNM Staging Manual, and based on the findings from fluoro-D-glucose positron emission tomography (FDG-PET)/CT or contrast-enhanced CT.

**Treatment**

Treatment plans were created using the Eclipse planning system (Varian Medical Systems, Palo Alto, CA), and 3-mm CT slices that were acquired during free breathing (HiSpeed NX/i Smart Gantry system; General Electric Healthcare, Little Chalfont, UK). The gross tumor volume (GTV) was defined as the primary tumor plus any metastatic lymph nodes. Primary tumors were identified based on the CT, FDG-PET/CT, and/or endoscopy findings. If the primary tumor could not be identified on the CT and/or FDG-PET/CT images, metallic clips were placed on the esophageal wall on the oral and anal sides of the primary tumor during the endoscopy before the CT simulation. Metastatic lymph nodes were also identified using the CT and/or FDG-PET/CT images. The clinical target volume (CTV) for the primary tumor was defined as the tumor's volume plus margins of 2–3 cm in the cranio-caudal direction and 0.5 cm in the other directions. The nodal CTV was defined as the volume of any metastatic lymph nodes plus margins of 0.5 cm in all directions. The overall CTV was defined as the primary and nodal CTVs, although prophylactic treatments [elective nodal irradiation (ENI)] were also included in the CTV for some patients, based on the physician’s discretion. The prophylactic treatments target regions where lesions might be present. The planning target volume (PTV) was defined as the overall CTV plus margins of 0.5 cm in all directions.

The patients had received a dose of 60 Gy in 30 fractions over 6 weeks using 10-MV X-rays from a linear accelerator (Clinac 21-EX, Varian Medical Systems). The first 40 Gy were delivered to the PTV using either TFT or FFT (initial plan), and the remaining 20 Gy were administered using off-cord boost plans in principle. When off-cord boost plans were made, CT simulation was newly performed. In off-cord boost plans, the spinal cord and any prophylactic regions were excluded from the radiation fields, and the final 20 Gy were delivered to the reduced PTV. Some of the patients who were treated using FFT did not need a change to an off-cord plan because their initial plans were able to keep the dose of the spinal cord below 40 Gy while administering 60 Gy to the PTV. The chemotherapy regimens were based on cisplatin (70 mg/m² on Days 1 and 29) and 5-fluorouracil (700 mg/m² on Days 1–4 and 29–32), although the doses were decreased if necessary. All patients received concurrent chemoradiotherapy as the initial treatment.

**Dosimetric analysis**

The pericardium was defined as the sac-like structure (thickness: 3 mm) at the surface of the heart and the roots of the great vessels. The entire pericardial volume was contoured on the treatment planning CT images according to the RTOG Contouring Atlases for Organs at Risk in Thoracic Radiation Therapy [5]. The pericardial DVH was subsequently generated using the treatment planning system. The pericardium was contoured both on CT images for initial plans and on CT images for boost plans. Using image-fusion function by rigid image registration of the treatment planning system, CT images for the boost plan were superimposed on CT images for the initial plan. Then, we made the sum-plan, including the initial plan and the boost plan on CT images for the initial plan. DVH analysis was performed using the sum-plan. The percent volumes that received doses of ≥5 Gy, ≥10 Gy, ≥20 Gy, ≥30 Gy, ≥40 Gy, ≥50 Gy and ≥60 Gy were expressed as V5 Gy, V10 Gy, V20 Gy, V30 Gy, V40 Gy, V50 Gy and V60 Gy, respectively.

**Evaluation of pericardial effusion and follow-up**

In principle, follow-up CT was performed every 2–3 months during the first 3 years and then every 2–6 months thereafter. The time to the appearance of pericardial effusion was calculated from the beginning of CCRT. All patients were followed-up using CT for ≥6 months. Grading of pericardial effusion was performed according to the Common Terminology Criteria for Adverse Events (version 4.0); Grade 0 = no pericardial effusion, Grade 2 = asymptomatic small-to-moderately sized effusion, Grade 3 = effusion with physiological symptoms, Grade 4 = effusion with life-threatening symptoms that required urgent intervention, and Grade 5 = death.

**Statistical analysis**

The cumulative incidences of pericardial effusion were compared using the Kaplan–Meier method and the log-rank test. Differences in the V5 Gy, V10 Gy, V20 Gy, V30 Gy, V40 Gy, V50 Gy and V60 Gy values were evaluated using the Wilcoxon test. Logistic regression analyses were used to investigate the risk factors for
pericardial effusion. However, as some factors could confound each other, we selected optimal factors using stepwise regression analysis (a combination of forward selection and backward elimination). The optimal risk factors were subsequently used in logistic regression analysis. Statistical analyses were performed using JMP software (version 12.0; SAS Institute Inc., Cary, NC).

RESULTS

The median patient age was 67 years (range: 38–87 years), and the male/female ratio was 84/10 (Table 1). Some differences were found between the FFT and TFT groups, with early-stage cancer being more frequent in the FFT group, and the initial field length tending to be longer in the TFT group. The overall follow-up periods ranged from 6.7 months to 96.6 months (median: 33.9 months). Pericardial effusion was observed in 74 patients (79%), and appeared at 1–18.5 months (median: 5.3 months) after the CCRT. The cumulative incidences of pericardial effusion in the FFT group were 73% at 1 year, 78% at 2 years and 78% at 3 years. These rates were not significantly different, compared with the rates in the TFT group (77%, 82% and 82%, respectively; *P* = 0.6395). The cumulative incidence of pericardial effusion is shown in Fig. 1. Of the 74 patients with pericardial effusion, 32 (31 Grade 2 and one Grade 3) had recurrence before or after the onset of pericardial effusion or simultaneously. A total of 23 patients with Grade 2 pericardial effusion experienced recurrence after the appearance of the pericardial effusion, which was considered to be unrelated to the recurrence or salvage therapy. Seven patients with Grade 2 pericardial effusion suffered from recurrence at the same time as appearance of pericardial effusion. Because the pericardial effusion decreased and remained small in size in follow-up CT, these pericardial effusions were diagnosed as being unrelated to the recurrence. In one patient with Grade 2 pericardial effusion, the pericardial effusion appeared 5 months after the recurrence in the gastric lymph node. Because the recurrence site was outside the first CCRT field, it was treated with salvage CCRT. The pericardial effusion finally disappeared. One patient with Grade 3 pericardial effusion recurred 5 months after the pericardial effusion. In this

Table 1. Patient characteristics according to treatment techniques

|                        | TFT (n = 43) | FFT (n = 51) | P value |
|------------------------|-------------|-------------|---------|
| Age (years)            | Median 68 (38–87) | 66 (45–84) | 0.1247  |
| Sex                    | Male 39 91% | 45 88% | 0.6997  |
|                        | Female 4 9% | 6 12%       |         |
| Tumor involving lower thoracic esophagus | Yes 18 42% | 18 35% | 0.5141  |
|                        | No 25 58% | 33 65%       |         |
| T stage                | 1 6 14% | 29 57% | 0.0002  |
|                        | 2 18 42% | 12 24%       |         |
|                        | 3 13 30% | 9 19%        |         |
|                        | 4 6 14% | 1 2%          |         |
| N stage                | 0 16 37% | 36 71% | 0.0032  |
|                        | 1 10 23% | 10 20%       |         |
|                        | 2 15 35% | 4 8%          |         |
|                        | 3 2 5% | 1 2%          |         |
| Clinical stage         | 1 13 30% | 36 71% | 0.0012  |
|                        | 2 8 19% | 4 8%          |         |
|                        | 3 21 49% | 10 20%       |         |
|                        | 4 (M1 LYM) | 1 2% | 1 2% |         |
| Field length           | <20 cm 13 30% | 25 49% | 0.0644  |
|                        | ≥20 cm 30 70% | 26 51% |         |

TFT = two field technique, FFT = four-field technique.

Fig. 1. Cumulative incidence of pericardial effusion. TFT = two opposed fields technique, FFT = four-field technique, CRT = chemoradiotherapy.

Table 2. DVH parameters according to treatment techniques

| Dosimetric factors | TFT (n = 43) | FFT (n = 51) | P value |
|--------------------|-------------|-------------|---------|
| V5 Gy (%)          | 77.2        | 74.6        | 0.4616  |
| V10 Gy (%)         | 72.3        | 62.4        | 0.3038  |
| V20 Gy (%)         | 65.9        | 61.1        | 0.2646  |
| V30 Gy (%)         | 57.1        | 52.7        | 0.1451  |
| V40 Gy (%)         | 48.2        | 33.5        | <0.0001 |
| V50 Gy (%)         | 25.7        | 22.8        | 0.0757  |
| V60 Gy (%)         | 7.9         | 7.8         | 0.8734  |
| Mean Dose (Gy)     | 31.8        | 28.6        | 0.0259  |

TFT = two field technique, FFT = four-field technique.
patient, pericardial drainage was performed 16 months after the appearance of pericardial effusion, and the result of the cytologic examination was negative. For these reasons, the cases of pericardial effusion in this study were considered unrelated to the recurrence or salvage therapy.

Table 2 shows the results of the DVH analysis according to the treatment techniques. The mean pericardial doses were 31.8 Gy and 28.6 Gy for the FFT and TFT groups, respectively. The pericardial V40 Gy and mean dose in the FFT group were significantly smaller than those in the TFT group ($P < 0.0001$ and $P = 0.0259$, respectively). However, no significant differences were observed when the V5 Gy, V10 Gy, V20 Gy, V30 Gy, V50 Gy and V60 Gy values were compared between the two groups.

Grade 3 pericardial effusion was observed in the TFT group (7%, 3/43), but was not observed in the FFT group (0/51; $P = 0.0921$, Fisher's exact test). No cases of Grade 4 or 5 pericardial effusion were identified. The median time from the beginning of CCRT to pericardial drainage in the patients with Grade 3 pericardial effusion was 23 months (22 months, 23 months and 25 months), and the V40 Gy values in these patients were 40.3%, 47.6% and 78.8%, respectively. Grade 3 pericardial effusion was not observed in patients with a pericardial V40 Gy of < 40%.

Table 3a and b shows the univariate analyses of clinical factors that were related to all-grade and Grade 3 pericardial effusion. Significant differences were observed in field length ($< 20$ cm vs $> 20$ cm) for all-grade pericardial effusion. Grade 3 pericardial effusion was significantly associated with TFT ($P = 0.0283$). Table 4a and b shows the univariate analyses of dosimetric factors. Significant differences were observed in all dosimetric parameters between patients with and without pericardial effusion, although only V40 Gy was significantly associated with Grade 3 effusion. In the multivariate analysis of pericardial effusion, stepwise regression analysis with a cut-off $P$ value of 0.25 was performed including all clinical and DVH factors, because we did not know which factors were related to pericardial effusion. The results revealed that two factors, involving lower esophagus and V20 Gy, were picked-up for evaluation. In the multivariate analysis, only V20 Gy was a significant risk factor for Grade 2–3 pericardial effusion ($P = 0.001$) (Table 5). Multivariate analysis

### Table 3a. Univariate analysis of clinical factors influencing all Grade pericardial effusion

| Clinical factors                  | Grade 2, 3 ($n = 74$) (%) | Grade 0 ($n = 20$) (%) | Odds ratio | 95% CI     | $P$ value |
|----------------------------------|---------------------------|------------------------|------------|------------|-----------|
| Age ($<65$ vs $>65$)             | $<65$ 35                  | 40                     | 1.2        | 0.4–3.4    | 0.6894    |
| Sex (male vs female)             | male 88                   | 95                     | 2.6        | 0.5–50.1   | 0.3201    |
| T stage (1, 2 vs 3, 4)           | 1, 2 66                   | 80                     | 2.0        | 0.7–7.7    | 0.2222    |
| N stage (0, 1 vs 2, 3)           | 0, 1 76                   | 80                     | 1.3        | 0.4–4.9    | 0.6813    |
| Clinical stage (1, 2 vs 3, 4)    | 1, 2 64                   | 70                     | 1.3        | 0.5–4.2    | 0.5863    |
| Involving lower esophagus (no vs yes) | No 57                  | 80                     | 3.1        | 1.0–11.4   | 0.0492    |
| Field technique (TFT vs FFT)     | TFT 47                    | 40                     | 0.7        | 0.3–2.0    | 0.5598    |
| Field length ($<20$ cm vs $>20$ cm) | $<20$ cm 34              | 65                     | 3.6        | 1.3–10.8   | 0.0122    |

TFT = two field technique, FFT = four-field technique.

### Table 3b. Univariate analysis of clinical factors influencing Grade 3 pericardial effusion

| Clinical factors                  | Grade 3 ($n = 3$) (%) | Grade 0, 2 ($n = 91$) (%) | Odds ratio | 95% CI     | $P$ value |
|----------------------------------|------------------------|---------------------------|------------|------------|-----------|
| Age ($<65$ vs $>65$)             | $<65$ 33                | 36                        | 1.1        | 0.1–25.0   | 0.9167    |
| Sex (male vs female)             | male 100                | 89                        | 2.7E-08    | 0–7.9      | 0.4073    |
| T stage (1, 2 vs 3, 4)           | 1, 2 33                 | 70                        | 4.7        | 0.4–104.5  | 0.1946    |
| N Stage (0, 1 vs 2, 3)           | 0, 1 33                 | 78                        | 7.1        | 0.6–157.3  | 0.1050    |
| Clinical stage (1, 2 vs 3, 4)    | 1, 2 33                 | 66                        | 3.9        | 0.4–85.2   | 0.2586    |
| Involving lower esophagus (no vs yes) | No 67                  | 62                        | 0.8        | 0.04–8.7   | 0.8561    |
| Field technique (TFT vs FFT)     | TFT 100                 | 44                        | 1.2E-08    | 0–0.7      | 0.0283    |
| Field length ($<20$ cm vs $>20$ cm) | $<20$ cm 67          | 41                        | 1.4        | 0.1–30.1   | 0.7970    |

TFT = two field technique, FFT = four-field technique.
DISCUSSION

Compared with radiotherapy alone, CCRT is a standard treatment for locally advanced or unresectable esophageal cancer and provides superior survival and local control [6]. Late cardiopulmonary toxicities have recently been recognized [2], although there is no clear quantitative dose and/or volume dependence for most cardiac toxicity. No previous data are available for comparing dose volumes between FFT and TFT for esophageal cancer, although FFT is a simple irradiation technique that is thought to decrease the heart volume that receives high doses. When we compared FFT and TFT, we found that the V40 Gy and mean dose values in the FFT group were significantly smaller than those in the TFT group. Nevertheless, there was selection bias in our sample, as the FFT group included more patients with early clinical stage, while the TFT group had a longer mean initial field length (22.8 cm vs 20.8 cm). If this difference in field length was substantial, we would expect noticeable differences in all DVH parameters, including the low-dose spectrum. Thus, it appears that the differences in the V40 Gy and mean dose values were related to other factors, including the field techniques. However, FFT did not decrease the incidence of all-grade pericardial effusion, compared with TFT, although TFT was a significant risk factor for

| Parameters      | Median pericardial volume | Univariate analysis |
|-----------------|----------------------------|---------------------|
|                 | Grade 2, 3                 | Grade 0             | Odds ratio<sup>a</sup> | 95% CI     | P value |
| V5 Gy (%)       | 79.7 (51.8–100.0)          | 66.5 (45.7–88.5)    | 1.08                      | 1.03–1.13  | 0.0004  |
| V10 Gy (%)      | 74.2 (46.5–97.6)           | 61.1 (40.8–84.7)    | 1.08                      | 1.03–1.13  | 0.0003  |
| V20 Gy (%)      | 68.2 (38.8–88.2)           | 53.4 (33–80.2)      | 1.08                      | 1.03–1.13  | 0.0003  |
| V30 Gy (%)      | 55.9 (32.1–83.3)           | 44.5 (19.5–74.3)    | 1.08                      | 1.03–1.13  | 0.0005  |
| V40 Gy (%)      | 43.8 (19.2–78.8)           | 34.2 (8.9–57.1)     | 1.06                      | 1.02–1.11  | 0.0024  |
| V50 Gy (%)      | 24.5 (10.9–47.3)           | 16.5 (6.7–35.8)     | 1.13                      | 1.05–1.23  | 0.0009  |
| V60 Gy (%)      | 8.0 (0.3–21.6)             | 4.5 (0.4–14.8)      | 1.19                      | 1.04–1.39  | 0.0228  |
| Mean dose (Gy) | 31.7 (16.7–44.1)           | 25.6 (14.3–37.9)    | 1.16                      | 1.06–1.28  | 0.0005  |

<sup>a</sup>Odds ratio was the value per unit increase.

| Parameters      | Grade 3 | Grade 0, 2 | Odds ratio<sup>a</sup> | 95% CI     | P value |
|-----------------|---------|------------|-------------------------|------------|---------|
| V5 Gy (%)       | 79.5 (63.4–100.0) | 77.2 (45.7–95.4) | 1.04                    | 0.94–1.19  | 0.4344  |
| V10 Gy (%)      | 75.2 (58.0–97.6) | 71.9 (40.8–91.3) | 1.05                    | 0.95–1.19  | 0.3354  |
| V20 Gy (%)      | 69.4 (52.8–86.9) | 65.7 (33–88.2)   | 1.04                    | 0.95–1.18  | 0.4110  |
| V30 Gy (%)      | 57.4 (49.2–83.3) | 53.9 (19.5–79.7) | 1.06                    | 0.97–1.18  | 0.2365  |
| V40 Gy (%)      | 47.6 (40.3–78.8) | 40.7 (8.9–69.5)  | 1.09                    | 1.00–1.21  | 0.0480  |
| V50 Gy (%)      | 26.7 (21.1–41.0) | 22.8 (6.7–47.3)  | 1.07                    | 0.94–1.22  | 1.0700  |
| V60 Gy (%)      | 6.6 (4.7–11.1)   | 7.3 (0.3–21.6)   | 0.98                    | 0.71–1.24  | 0.8738  |
| Mean dose (Gy) | 32.4 (26.5–44.1) | 30.20 (14.3–41.9)| 1.12                    | 0.93–1.42  | 0.2288  |

<sup>a</sup>Odds ratio was the value per unit increase.

| Factors          | Odds ratio | 95% CI     | P value |
|------------------|------------|------------|---------|
| Involving lower esophagus (no vs yes) | 2.12       | 0.63–8.45  | 0.2451  |
| V20 Gy           | 1.07<sup>a</sup> | 1.03–1.13  | 0.0021  |

<sup>a</sup>Odds ratio was the value per unit increase.
symptomatic pericardial effusion (i.e. Grade 3). Based on these data, it appears that FFT generates low pericardial V40 Gy and mean dose values, which might limit the risk of symptomatic pericardial effusion.

The univariate analyses revealed that field length and tumor localization involving the lower esophagus were significant risk factors for all-grade pericardial effusion, although these factors were not significant for symptomatic pericardial effusion (Table 3). In this context, field length is a known risk factor for pericardial effusion, as Fukada et al. reported that a field length of >20 cm was a significant risk factor for the development of pericardial effusion [7]. Moreover, the field length can vary if the patient is treated using ENI or involved field irradiation (IFRT), although there is no clear consensus regarding the role of ENI. Some researchers have suggested that IFRT could be superior to ENI, as it can minimize adverse effects without increasing locoregional failure [8], while other researchers have reported that ENI was effective for preventing regional nodal failure [9]. Although a prospective trial would clarify the survival benefit of ENI, radiotherapy using smaller fields (e.g. IFRT) may be effective for preventing pericardial effusion. Few reports have examined the relationship between tumor location and pericardial effusion, although it does not appear to be a risk factor for pericardial effusion [7, 10]. Thus, our findings from the multivariate analysis are consistent with those results.

Some authors have reported that dose–volume factors predict the development of pericardial effusion. For example, Hayashi et al. reported that the most significant predictors of pericardial effusion after chemotherapy and radiotherapy were V5 Gy to V60 Gy of the heart [11]. In addition, Wei et al. have reported that V30 Gy of the pericardium/heart was the only independent risk factor for pericardial effusion after chemoradiotherapy [12]. Furthermore, Tamari et al. evaluated patients with Stage I esophageal cancer who received chemoradiotherapy, and reported that the cumulative rate of pericardial effusion was 52.2%, with pericardial V30 Gy of >41.6% being a significant risk factor [10]. Thus, the volume of the heart/pericardium receiving relatively low doses (i.e. 10–30 Gy) is likely associated with the development of pericardial effusion. In the present study, V20 Gy was a significant risk factor for pericardial effusion in the univariate and multivariate analyses, which suggests that a relatively low dose (e.g. V20 Gy) can be related to all-grade pericardial effusion.

In contrast, symptomatic pericardial effusion seems to be induced by slightly higher doses. For example, Fukada et al. reported that the pericardial V30 Gy–V45 Gy values were significantly higher in patients with symptomatic pericardial effusion, compared with patients with asymptomatic pericardial effusion [13]. Thus, they concluded that the mean pericardial dose was the strongest risk factor for symptomatic pericardial effusion, and that a mean pericardial dose of 36.5 Gy and a pericardial V45 Gy of 58% seemed to be the optimal cut-off values for predicting symptomatic pericardial effusion. Those findings suggest that relatively low doses (10–30 Gy) can induce asymptomatic pericardial effusion, but higher doses (>40 Gy) are needed to induce symptomatic pericardial effusion. The present study only included three patients with Grade 3 pericardial effusion, who could not be evaluated in the multivariate analysis, although these cases all involved TFT and had a pericardial V40 Gy of >40% (40.3%, 47.6% and 78.8%). Moreover, the V40 Gy value in the FFT group was significantly smaller than that in the TFT group, and V40 Gy was significantly associated with symptomatic pericardial effusion. Therefore, FFT appears to have provided a small V40 Gy and may be useful for minimizing the risk of symptomatic pericardial effusion.

The median time to the appearance of pericardial effusion was 5.3 months, with a trend towards a longer time for symptomatic pericardial effusion (~2 years) compared with asymptomatic pericardial effusion. Previous reports have also indicated that most symptomatic pericardial effusion is detected at >1 year [10, 13, 14], and that some cases may not be detected until 5 years after the CCRT [13]. Thus, the onset of asymptomatic pericardial effusion seems to be relatively late, and we suspect that prolonged and careful follow-up is needed in order to detect this event, despite the limited number of patients who experience symptomatic pericardial effusion.

Previous studies have indicated that late toxicities involving the coronary artery, capillary myocardium, valves, and conducting system are decreased when smaller heart volumes receive high doses. For example, Ogino et al. reported that the risk of symptomatic cardiac disease (pericardial effusion, valvular disease, tachycardia, atrial fibrillations, coronary artery disease, and congestive heart failure) appeared to be related to relatively high-dose volumes (i.e. V45 Gy, V50 Gy and V55 Gy) [14]. In addition, a single photon emission computed tomography (SPECT) study revealed that myocardial fatty acid metabolism seemed to be affected by intermediate and high heart doses (40–60 Gy) [15]. Furthermore, a myocardial perfusion SPECT study revealed that the percent volume of the heart receiving intermediate doses (37–40 Gy) seemed to be associated with the development of new perfusion defects during radiation therapy [16]. These reports indicate that decreased cardiac volumes receiving intermediate/high radiation doses were associated with fewer late cardiac adverse events, although we only identified two cases involving non-effusion cardiac events (two cases of myocardial ischaemia), which precluded further analysis.

The present study has several limitations. First, this was a retrospective study in a single institution with a limited sample size. Second, the limited number of patients with symptomatic pericardial effusion precluded a detailed statistical evaluation. Finally, late cardiac events that occurred after several years could not be evaluated. In addition, the influence of salvage chemoradiotherapy for recurrent disease and/or recurrent disease could not be evaluated in patients in whom tumor recurrence preceded the appearance of pericardial effusion. Only one patient experienced tumor recurrence in the upper abdomen preceding appearance of pericardial effusion, and that patient received salvage chemoradiotherapy. Because the pericardium was almost outside of the irradiation field of salvage chemoradiotherapy and distant from the recurrent site, the influence of the salvage irradiation and recurrent disease on the pericardium might have been small.

**CONCLUSION**

To the best of our knowledge, this is the first report to indicate that, compared with TFT, FFT decreased the pericardial mean dose and V40 Gy values. Our findings also indicate that a pericardial V40 Gy of >40% may predict the development of symptomatic
pericardial effusion. However, further studies are needed to clarify whether FFT can reduce symptomatic cardiac toxicity.

ACKNOWLEDGEMENTS
The authors thank Ms Natsumi Yamashita M.D., Department of Clinical Research, Shikoku Cancer Center Hospital, for her statistical support. Results from this study were presented at JASTRO 2016.

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

REFERENCES
1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. J Int Cancer 2015;136:E359–86.
2. Ishikura S, Nihei K, Ohtsu A et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–702.
3. Gagliardi G, Constine LS, Moiseенко V et al. Radiation dose–volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76:S77–85.
4. Carmel RJ, Kaplan HS. Mantle irradiation in Hodgkin’s disease. An analysis of technique, tumour eradication, and complications. Cancer 1976;37:2813–25.
5. Radiation Therapy Oncology Group. Atlases for Organs at Risk (OARs) in Thoracic Radiation Therapy. https://www.rtog.org/LinkClick.aspx?fileticket=qh0qMZXfQy%3d&tabid=361 (10 July 2017, date last accessed).
6. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623–7.
7. Fukada J, Shigematsu N, Ohashi T et al. Pericardial and pleural effusions after definitive radiotherapy for esophageal cancer. J Radiat Res 2012;53:447–53.
8. Yamashita H, Takenaka R, Omori M et al. Involved-field radiotherapy (IFRT) versus elective nodal irradiation (ENI) in combination with concurrent chemoradiotherapy for 239 esophageal cancers: a single institutional retrospective study. Radiat Oncol 2015;10:171. doi:10.1186/s13014-015-0482-9.
9. Onozawa M, Nihei K, Ishikura S et al. Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of the thoracic esophagus. Radiother Oncol 2009;92:266–9.
10. Tamari K, Isohashi F, Akino Y et al. Risk factors for pericardial effusion in patients with Stage I esophageal cancer treated with chemoradiotherapy. Anticancer Res 2014;34:7389–94.
11. Hayashi K, Fujiwara Y, Nomura M et al. Predictive factors for pericardial effusion identified by heart dose–volume histogram analysis in esophageal cancer patients treated with chemoradiotherapy. Br J Radiol 2015;88:20140168.
12. Wei X, Liu HH, Tucker SL et al. Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys 2008;70:707–14.
13. Fukada J, Shigematsu N, Takeuchi H et al. Symptomatic pericardial effusion after chemoradiation therapy in esophageal cancer patients. Int J Radiat Oncol Biol Phys 2013;87:487–93.
14. Ogino I, Watanabe S, Iwashita N et al. Symptomatic radiation-induced cardiac disease in long-term survivors of esophageal cancer. Strahlenther Onkol 2016;192:359–67.
15. Takanami K, Arai A, Umezawa R et al. Association between radiation dose to the heart and myocardial fatty acid metabolic impairment due to chemoradiation-therapy: prospective study using I-123 BMIPP SPECT/CT. Radiother Oncol 2016;119:77–83.
16. Zhang P, Hu X, Yue J et al. Early detection of radiation-induced heart disease using 99m Tc-MIBI SPECT gated myocardial perfusion imaging in patients with oesophageal cancer during radiotherapy. Radiother Oncol 2015;115:171–8.