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Analysis of cardiac toxicity after definitive chemoradiotherapy for esophageal cancer using a biological dose–volume histogram

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ABSTRACT

This study aimed to evaluate the relationship between cardiac toxicity after definitive chemoradiotherapy (CRT) for esophageal cancer and the dose–volume histogram (DVH) of organs at risk (OARs) [using biological effective dose (BED)]. We analyzed the data of 83 patients with esophageal cancer treated using definitive CRT between 2001 and 2016. Furthermore, we evaluated pericardial effusion (PE) as a measure of cardiac toxicity. The median total irradiation dose was 60 (50.4–71) Gy. Symptomatic PE was observed in 12 (14%) patients. The heart and pericardium V5–V100$_{\text{-BED}}$ were significantly higher in patients with symptomatic PE than in those without symptomatic PE (heart: V5–V95$_{\text{-BED}}$, $P < 0.001$; V100$_{\text{-BED}}$, $P = 0.0053$, and pericardium: V5–V40$_{\text{-BED}}$, V55–V95$_{\text{-BED}}$, $P < 0.001$; V45–50$_{\text{-BED}}$, V100$_{\text{-BED}}$, $P < 0.05$, respectively). Receiver operating characteristic curve analysis showed that the dose–volume parameter of the pericardium and the heart that was most strongly associated with an adverse cardiac event was V80$_{\text{-BED}}$, and the mean dose and the cut-off value were 27.38% and 61.7 Gy$_{\text{-BED}}$, respectively. Multivariate analysis showed that the pericardium V80$_{\text{-BED}}$ and the mean heart dose$_{\text{-BED}}$ were risk factors for symptomatic PE ($P < 0.001$, respectively). We revealed the relationship between the irradiated dose of the OARs and symptomatic PE using a BED-based dose–volume histogram. Pericardium V80$_{\text{-BED}}$ and mean heart dose$_{\text{-BED}}$ were the most relevant risk factors for symptomatic PE.

Keywords: chemoradiotherapy; esophageal cancer; symptomatic pericardial effusion; biological effective dose

INTRODUCTION

Definitive chemoradiotherapy (CRT) plays an important role as a non-surgical treatment for esophageal cancer and is a treatment that can lead to long-term survival [1, 2]. However, although long-term survival can be obtained, late adverse events after CRT for esophageal cancer have been reported [3, 4]. In particular, the association of cardiac effects with pericardial effusion (PE), heart failure, ischemic heart disease, and others has been pointed out, and there have been several recent studies that have examined the relationship between irradiation dose to the heart and late adverse events [5, 6]. These studies evaluated the relationship between cumulative doses to organs at risk (OARs) and late adverse cardiac events.

Definitive radiotherapy (RT) for esophageal cancer has been widely used to treat patients with three-dimensional conformal RT (3D-CRT), starting with anteroposterior opposed fields for the initial plan and followed by oblique opposed fields to spare the spinal cord for the boost plan, and is also commonly performed in two stages (initial and boost plan) using multifield irradiation, such as four-field irradiation with anteroposterior and oblique opposite fields. Thereby, the OARs, including the heart, are irradiated with various fractionated doses. Late toxicity in RT is known to be affected by doses per fraction to OARs. Biological effects to the OARs are different if the fractionation schemes vary at the same cumulative dose. Thereby, the assessment of the cumulative irradiated dose to the OARs could be misleading.

Biological effective dose (BED) has been widely used in clinical RT practice for conversion between different fractionation schemes and has been recommended as the tool for estimating the biological

effects on malignant tumors and normal tissues. However, there are few studies that have evaluated the relationship between irradiation dose and late cardiac toxicity, as indicated by BED and the BED-based dose–volume histogram (BEDVH) in the heart. In this study, we evaluated the relationship between irradiation dose (converted to BED) and late cardiac toxicity.

MATERIALS AND METHODS

Eligibility

Between 2001 and 2016, 359 patients with histologically confirmed esophageal cancer received definitive CRT in our institution. The inclusion criteria were as follows: no prior treatment for thoracic malignancies, excluding endoscopic resection; no active double cancer at diagnosis of esophageal cancer; World Health Organization performance status of 0–2; total irradiation dose of >50 Gy; upper to esophageal gastric junction (EGJ) esophageal cancer in which the heart was included in the irradiation fields; no residual tumor, recurrence, or multiple cancer observed within 2 years after CRT; and follow-up duration of ≥ 2 years after CRT. As a result, 83 patients were eligible.

Treatment

All patients received 3D-CRT. The gross tumor volume (GTV) was defined as the total volume of the primary lesion (GTVp) and the metastatic lymph node (GTVn). In patients with superficial legions, before planning CT, metallic clips were placed using endoscopy to indicate the craniocaudal extent of the primary lesion. The clinical target volume of the primary lesion (CTVp) was defined as the GTVp with a 2-cm margin in the longitudinal direction of the esophagus and a 3–5-mm margin around the GTVp. The clinical target volume of the metastatic lymph node (CTVn) was defined as the GTVn with a 3–5-mm margin. The clinical target volume of the subclinical regional lymph nodes (CTV subclinical) was determined according to the primary tumor sites—supraclavicular, upper mediastinal, and middle mediastinal lymph nodes (LNs) for upper esophageal cancers; upper to lower mediastinal and perigastric LNs for middle thoracic or lower esophageal cancers; and middle mediastinal lesion to the region of the celiac trunk for EGJ tumors. The clinical target volume for boost irradiation (CTV boost) was defined as the CTVp plus the CTVn. The planning target volume (PTV) was defined as the CTV with a 5–12-mm margin. The PTV initial was defined as the volume including all the CTVs. Moreover, the PTV boost was defined as the volume of the CTV boost.

The irradiation fields for the PTV initial consisted of the anteroposterior opposed fields or multiple fields up to 40 Gy at 2 Gy per fraction. After 40 Gy, the fields for PTV boost consisted of oblique opposed fields or multiple fields to keep the spinal dose to ≤ 40 Gy (up to 20–26 Gy at 2 Gy per fraction).

Chemotherapy was performed with the platinum-based regimen and appropriately modified according to the patient's condition. Cisplatin plus fluorouracil (5-FU), nedaplatin plus 5-FU, and others were administered in 52, 20 and 11 patients, respectively. Patients with advanced disease generally received adjuvant chemotherapy after CRT.

Treatment responses were evaluated by chest–abdominal computed tomography (CT) and endoscopic biopsy after treatment. Subsequently, physical examination was generally performed every 3 months, and endoscopy and CT every 3–6 months.

Analysis

In this study, we analyzed symptomatic adverse cardiac events according to the Common Terminology Criteria for Adverse Events version 4.0. The onset time of the adverse events was calculated from the completion of CRT.

Contouring the heart and the pericardium

We contoured the whole heart and pericardium for OARs. In this study, the cranial edge of the heart was defined as the caudal edge of the right pulmonary artery, and the caudal edge of the heart was defined as the cardiac apex. The pericardium was the inner 3-mm ring of the heart.

BED and dose summation

We defined the alpha-to-beta ratio (α/β) of an OAR as 3 Gy to assess late adverse events. BED was calculated as $nd \times (1 + n/\alpha/\beta)$ (n, number of fractions; d, dose/fraction). The original dose distribution of each plan was converted to the BED-based dose distribution using the program implemented in Velocity® (Varian Medical Systems, USA). The voxel size on the reconstructed CT image was 2.5 mm. In cases with two (initial + boost) or more plans, the BED-based dose distribution of each plan was summed. When different CT images were used in each plan, the BED-based dose distribution in different CT images was summed up using the deformable image registration on Velocity®.

Dose evaluation

The BED-based dose–volume histogram (BEDVH) of each OAR was evaluated using the BED-based dose distribution. The percentage volume of the OAR irradiated with ≥ 40 Gy was defined as V40. Dose–volumes were assessed for each 5 Gy from V5 to V100, and the mean dose was derived from the DVH.

Risk factor investigations

The following clinical factors were investigated for associations with the risk of adverse cardiac events: sex, age, alcohol, smoking, diabetes, cardiovascular disease, liver disease, clinical stage, performance status, and treatment-related factors (including radiation dose, treatment planning method, chemotherapeutic regimen, and BEDVH factors).

Statistical evaluation

The cumulative incidence of adverse cardiac events was presented as Kaplan–Meier curves. To detect a statistically significant difference between the two subgroups, we used the log-rank test and the Mann–Whitney U test. The Cox proportional hazards regression model was used for multivariate analysis. Receiver operating characteristic (ROC) curves were used to identify the dose–volume parameters that were most strongly associated with adverse cardiac events. To detect optimal cut-off values from ROC curves, the point on the curve closest to the upper left corner was determined. In analysis of the data, $P < 0.05$ was considered to be statistically significant.

Table 1. Patient characteristics and analysis of symptomatic PE

Characteristics	$N = 83(\%)$	5-year incidence of symptomatic PE	Univariate analysis (P)
Age (years)			
<69	38 (45%)	19%	0.8564
≥69	45 (55%)	13%	
Sex			
Female	12 (15%)	16%	0.8478
Male	71 (85%)	16%	
Performance status			
0–1	78 (94%)	14%	0.0765
2	5 (6%)	40%	
Diabetes mellitus			
Yes	9 (11%)	14%	0.6829
No	74 (89%)	16%	
Alcohol			
Yes	71 (85%)	17%	0.6027
No	12 (15%)	8%	
Smoking			
Yes	72 (87%)	15%	0.6088
No	11 (13%)	18%	
Cardiovascular disease			
Yes	12 (15%)	0%	0.1477
No	71 (85%)	18%	
Liver disease			
Yes	11 (13%)	29%	0.1922
No	72 (87%)	4%	
Clinical stage			
I	43 (52%)	12%	0.4716
II–IV	40 (48%)	20%	
Radiation dose			
≤60 Gy	43 (52%)	13%	0.4913
>60 Gy	40 (48%)	18%	
Chemotherapy			
CDDP +5-FU	52 (63%)	21%	0.0982
Others	31 (37%)	7%	
Irradiation method			
Two-portal group	32 (38%)	35%	0.0286
Multiportal group	51 (62%)	9%	
$V80_{\text{-BED}}$ of pericardium			
<27.3%	67 (81%)	5%	<0.001
≥27.3%	16 (19%)	58%	
Mean heart $dose_{\text{-BED}}$			
<61.7 $Gy_{\text{-BED}}$	66 (80%)	5%	<0.001
≥61.7 $Gy_{\text{-BED}}$	17 (20%)	54%	

PE = pericardial effusion, CDDP = cisplatin, 5-FU,=5-fluorouracil, BED = biological effective dose.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 1. Patients were divided into the two-portal group and the multiportal group. The two-portal group included patients who received anteroposterior opposed fields for the initial plan followed by oblique opposed fields for the boost plan. The multiportal group included patients who received multiportal fields for the initial plan followed by multiportal fields for the boost plan. To eliminate hotspots on the dose distribution, patients in whom only a small dose of oblique fields (<15% of the prescribed dose) was added to the anteroposterior opposed fields using the field-in-field technique was included in the two-portal group.

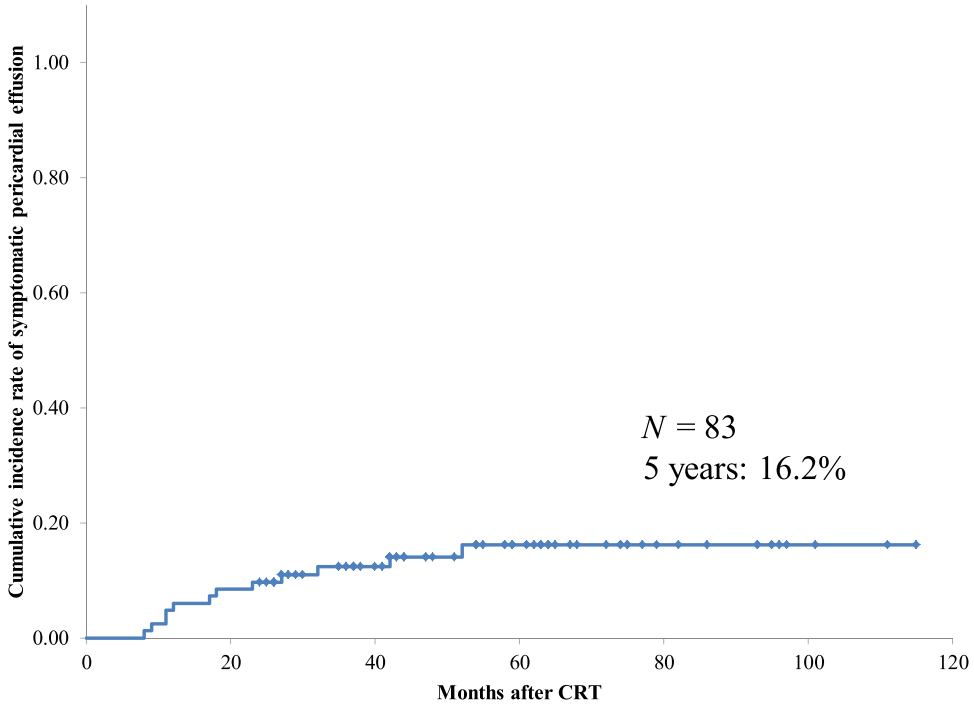

Fig. 1. Cumulative incidence rate of symptomatic pericardial effusion from the Kaplan–Meier curve.

Incidence of pericardial effusion

The median follow-up duration in all patients was 58 months (26–116 months), and 65 patients survived in the analysis, with a median follow-up duration of 58 months (24–115 months). PE of Grade (G)2, G3, G4 and G5 was observed in 49, 9, 3 and 0 patients, respectively. Among the patients with symptomatic PE, the 5-year incidence rate was 16.2% (Fig. 1). The median onset time of symptomatic PE was 17.5 months (5–52 months). Angina pectoris was observed in 2 patients (2.4%, 1 case each of G3 and G4, with onset time of 47 and 27 months, respectively). Arrhythmia was observed in 3 patients (3.6%, 1 case each of G2, G3 and G5, with onset time of 109, 34 and 59 months, respectively), and valvular insufficiency was observed in 1 patient (1.2%, G5, with onset time of 110 months).

Dosimetric analysis of symptomatic PE

The mean V5–V100$_{\text{-BED}}$ of the heart and the pericardium in patients with G3 or more PE (symptomatic PE) and G0 to G2 PE were plotted in Fig. 2a and 2b. The heart V5–V100$_{\text{-BED}}$ was significantly higher in patients with symptomatic PE than in those without symptomatic PE (V5–V95$_{\text{-BED}}$, $P < 0.001$; V100$_{\text{-BED}}$, $P = 0.0053$, respectively), similar to that in the pericardium (V5–V40$_{\text{-BED}}$, V55–V95$_{\text{-BED}}$, $P < 0.001$; V45–50$_{\text{-BED}}$, V100$_{\text{-BED}}$, $P < 0.05$). The mean heart dose$_{\text{-BED}}$ of each patient with symptomatic PE was 67.1 Gy$_{\text{-BED}}$, which was significantly higher than that of other patients (48.6 Gy$_{\text{-BED}}$, $P < 0.001$). Moreover, the mean value of the mean pericardial dose$_{\text{-BED}}$ of each patient with symptomatic PE was 60.5 Gy$_{\text{-BED}}$, which was significantly higher than those of other patients (44.1 Gy$_{\text{-BED}}$, $P < 0.001$). The results of the ROC curve analysis of the dose–volume parameters of the heart and the pericardium are presented in Tables 2 and 3, respectively. The dose–volume parameter of the pericardium that was most strongly associated with symptomatic PE was V80$_{\text{-BED}}$, and the area under the ROC curve (AUC) was 0.9108. The cut-off value was 27.38%, in which sensitivity and specificity were 75% and 91%, respectively. The dose–volume parameter of the heart that was most strongly associated with symptomatic PE was the mean heart dose$_{\text{-BED}}$, and the AUC was 0.9073. The cut-off value for the mean heart dose$_{\text{-BED}}$ was 61.7 Gy$_{\text{-BED}}$, in which sensitivity and specificity were 75% and 89%, respectively.

Risk factor analysis

Univariate analysis of risk factors for symptomatic PE is presented in Table 1. We selected the V80$_{\text{-BED}}$ of the pericardium and the mean heart dose$_{\text{-BED}}$ as the most relevant dose-volume parameters according to the ROC curve analysis. In the univariate analysis, the radiation method, the V80$_{\text{-BED}}$ of the pericardium, and the mean heart dose$_{\text{-BED}}$ were significant risk factors for symptomatic PE among the clinical and treatment background parameters. In performing multivariate analysis, the V80$_{\text{-BED}}$ of the pericardium and the mean heart dose$_{\text{-BED}}$ were strongly correlated with each other. Therefore, multivariate analysis was performed separately for each dosimetric parameter. As the result, the V80$_{\text{-BED}}$ of the pericardium and the mean heart dose$_{\text{-BED}}$ were significant factors in symptomatic PE in multivariate analysis (Table 4). The cumulative incidence rate of symptomatic PE according to the cut-off value of the V80$_{\text{-BED}}$ of the pericardium and the mean heart dose$_{\text{-BED}}$ are shown in Fig. 3 and b. The 5-year incidence rate of symptomatic PE in patients with a pericardium V80$_{\text{-BED}}$ of $\geq$27.38% was significantly higher than that in other patients (58% and 5%, respectively; $P < 0.001$). As well, the 5-year incidence rate of symptomatic PE in patients with a mean heart dose$_{\text{-BED}}$ of $\geq$61.7 Gy was

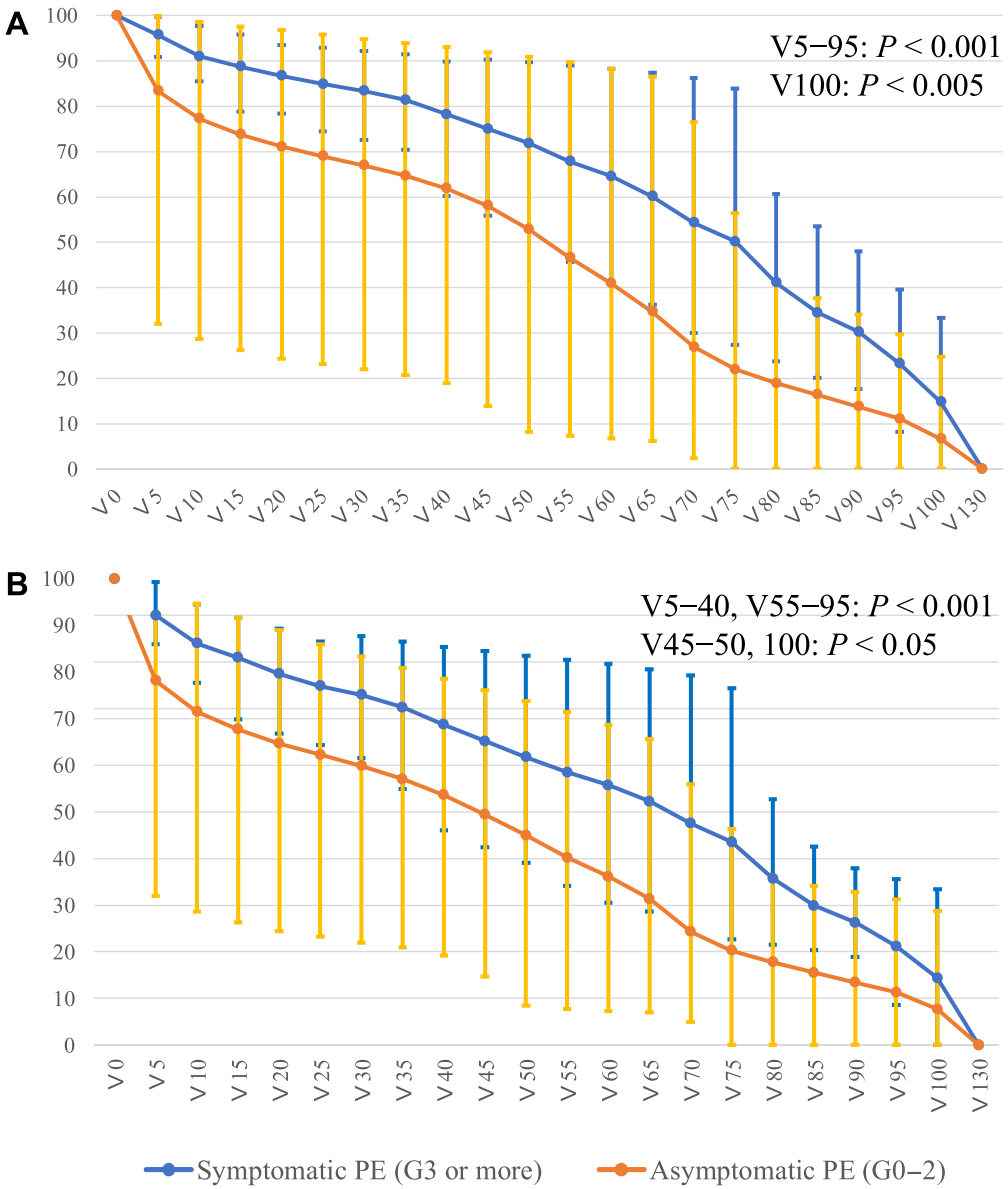

Fig. 2. (a) BED-based dose–volume histogram curves of the heart according to symptomatic or asymptomatic pericardial effusion. (b) BED-based dose–volume histogram curves of the pericardium according to symptomatic or asymptomatic pericardial effusion. PE = pericardial effusion.

significantly higher than that in other patients (54% and 5%, respectively; $P < 0.001$).

DISCUSSION

In our study, symptomatic PE after CRT for esophageal cancer was observed in 12 of 83 patients (14.5%). In the univariate analysis, the $V80_{\text{-BED}}$ of the pericardium (cut-off value, 27.38%), the mean heart $dose_{\text{-BED}}$ (cut-off value, 61.7 $Gy_{\text{-BED}}$) and the irradiation method were significant factors. In the multivariate analysis, the pericardial $V80_{\text{-BED}}$ and the mean heart $dose_{\text{-BED}}$ were the significant prognostic factors for symptomatic PE.

Definitive CRT for esophageal cancer is now widely used as non-surgical therapy. In some cases, long-term survival has been achieved, and late cardiac toxicity due to CRT has emerged as a problem. Ishikura *et al.* [3] reported late cardiac toxicity after definitive CRT for esophageal cancer. They showed that the incidence rates of G2 to G4 PE, heart failure, and G5 acute myocardial infarction were 20.5%, 2.5% and 2.5%, respectively. Beukema *et al.* [7] conducted a systematic review and reported that the incidence rate of symptomatic cardiac toxicity was as high as 10.8% in definitive RT for esophageal cancer, and PE was the most common late toxicity. Frandsen *et al.* [8] identified RT as an independent risk factor for post-treatment cardiac complications among various treatment modalities for esophageal

Table 2. Results of receiver operating characteristic curve analyses of the heart.

	AUC	Cut-off value	Sensitivity	Specificity
$V5_{\text{-BED}}$	0.8392	93.02%	92%	78%
$V10_{\text{-BED}}$	0.8504	86.92%	92%	76%
$V15_{\text{-BED}}$	0.8732	85.21%	92%	79%
$V20_{\text{-BED}}$	0.8873	83.29%	92%	83%
$V25_{\text{-BED}}$	0.8873	81.10%	92%	82%
$V30_{\text{-BED}}$	0.8873	78.28%	92%	79%
$V35_{\text{-BED}}$	0.8885	76.40%	83%	79%
$V40_{\text{-BED}}$	0.8521	73.82%	75%	83%
$V45_{\text{-BED}}$	0.8345	69.43%	75%	82%
$V50_{\text{-BED}}$	0.8322	63.97%	75%	80%
$V55_{\text{-BED}}$	0.8298	56.63%	75%	76%
$V60_{\text{-BED}}$	0.8592	54.56%	75%	82%
$V65_{\text{-BED}}$	0.8756	41.08%	92%	75%
$V70_{\text{-BED}}$	0.8803	34.24%	92%	73%
$V75_{\text{-BED}}$	0.9002	33.79%	75%	86%
$V80_{\text{-BED}}$	0.8950	31.45%	75%	86%
$V85_{\text{-BED}}$	0.8920	22.83%	83%	79%
$V90_{\text{-BED}}$	0.8873	20.21%	83%	80%
$V95_{\text{-BED}}$	0.8357	15.15%	92%	72%
$V100_{\text{-BED}}$	0.7523	10.17%	83%	73%
Mean heart dose	0.9073	61.65 $Gy_{\text{-BED}}$	75%	89%

AUC = area under curve, cut-off value = cut-off value of the heart.

Table 3. Results of receiver operating characteristic curve analyses of the pericardium

	AUC	Cut-off value	Sensitivity	Specificity
$V5_{\text{-BED}}$	0.8545	87.93%	91%	79%
$V10_{\text{-BED}}$	0.8773	82.16%	91%	79%
$V15_{\text{-BED}}$	0.8914	80.46%	83%	88%
$V20_{\text{-BED}}$	0.8838	74.76%	83%	81%
$V25_{\text{-BED}}$	0.8685	76.63%	75%	89%
$V30_{\text{-BED}}$	0.8509	74.37%	75%	89%
$V35_{\text{-BED}}$	0.8439	71.06%	75%	89%
$V40_{\text{-BED}}$	0.8122	65.2%	75%	86%
$V45_{\text{-BED}}$	0.7923	62.81%	66%	89%
$V50_{\text{-BED}}$	0.7969	59.7%	66%	89%
$V55_{\text{-BED}}$	0.7993	57.15%	66%	89%
$V60_{\text{-BED}}$	0.8181	41%	83%	72%
$V65_{\text{-BED}}$	0.8415	38.7%	83%	79%
$V70_{\text{-BED}}$	0.8756	30.37%	83%	77%
$V75_{\text{-BED}}$	0.8932	30.24%	75%	86%
$V80_{\text{-BED}}$	0.9108	27.38%	75%	91%
$V85_{\text{-BED}}$	0.9061	20.35%	100%	75%
$V90_{\text{-BED}}$	0.8991	19.03%	91%	79%
$V95_{\text{-BED}}$	0.8439	15.93%	91%	78%
$V100_{\text{-BED}}$	0.7441	11.14%	83%	75%
Mean pericardial dose	0.8897	55.56 $Gy_{\text{-BED}}$	75%	93%

AUC = area under curve, cut-off value = cut-off value of the pericardium.

Table 4. Multivariate analysis

Factor	HR (95% CI)	*P*-value
Series 1		
Irradiation method		
Two-portal group	2.17 (0.63–7.38)	0.2142
Multiportal group		
$V80_{\text{-BED}}$ of pericardium		
<27.3%	12.38 (3.25–47.11)	<0.001
≥27.3%		
Series 2		
Irradiation method		
Two-portal group	0.46 (0.45–5.70)	0.4656
Multiportal group		
Mean heart $dose_{\text{-BED}}$		
<61.7 $Gy_{\text{-BED}}$	13.35 (3.60–49.45)	<0.001
≥61.7 $Gy_{\text{-BED}}$		

PE = pericardial effusion, HR = hazard ratio, CI = confidence interval.

cancer. The incidence rate of PE of G3 or more after definitive CRT for esophageal cancer was reported to be 4–16% [2, 5, 9], similar to the result of our study (16.2%, 5 years). There are studies that have analyzed the correlation between radiation dose to the OAR and late cardiac toxicity, especially PE. Most of these studies evaluated the correlation using the cumulative dose to the OAR. Ogino *et al.* [6] reported the risk factors for symptomatic cardiac toxicity as heart V45–55 (cut-off value, ≥15%, 10% and 5%, respectively) in the dose–volume parameters. Tamari *et al.* [9] noted that pericardial V30 (cut-off value, ≥41.6%) was the most significant factor in dose–volume parameters for symptomatic and asymptomatic PE. Fukada *et al.* [5] reported that the mean heart dose was the most significant risk factor for symptomatic PE. We examined the correlation using BED, not cumulative dose. This is because the dose per fraction is known to be associated with late toxicity. Stavrev *et al.* [10] reported that PE after RT for esophageal cancer was observed only in the group irradiated with 3.5 Gy/fraction (compared with the group irradiated with 1.8 Gy/fraction) and that the dose distribution corrected for the effect of fractionation was important. Therefore, we evaluated the relationship between radiation dose to the OAR and symptomatic PE using dose–volume parameters with the impact of dose per fraction.

The BED is a concept for standardizing physical dose and comparing treatment results in different fractionation schemes based on the Linear Quadratic model. Calculating BED allows a physical dose to be converted into a dose that describes the biological effect of the radiation on a tumor or normal tissue. Aly *et al.* [11] reported that the sequential boost method and simultaneous integrated boost method, both with the same prescribed dose but with different fractionation schemes, were converted into BED for postoperative breast radiation, and differences were observed in BEDVH of OARs. They indicated that the comparison using the BED conversion was necessary to compare the DVH of the radiation plan in different fractionation schemes.

Although the precise α/β ratio is controversial, we defined the α/β ratio of the OAR as 3 Gy, which is often used to assess late toxicity after RT in the calculation of BED. Gillete *et al.* [12] examined the correlation between mediastinal irradiation dose and PE in dogs and estimated the pericardial α/β ratio to be 2.5 Gy and the myocardial α/β ratio to be 3.2 Gy. In contrast, Aly *et al.* [11] defined the cardiac α/β ratio as 3 Gy and compared several irradiation methods in terms of BED. Thus, we believed that consensus was most likely to be obtained by setting the α/β ratio of the heart and the pericardium to 3 Gy.

In this study, we identified the irradiation method, $V80_{\text{-BED}}$ of the pericardium and mean heart $dose_{\text{-BED}}$ as significant factors in the univariate analysis, and $V80_{\text{-BED}}$ of the pericardium and mean heart $dose_{\text{-BED}}$ as significant factors in the multivariate analysis. Thus, our study suggested that reducing the dose to the pericardium and the heart would minimize the risk of symptomatic PE.

Intensity-modulated radiation therapy (IMRT) is a technique that can concentrate the prescription dose to the target while reducing the dose to the OARs. In definitive CRT of esophageal cancer, IMRT can be used to reduce the heart and pericardial dose. Xu D *et al.* [13] reported that IMRT could significantly reduce the average cardiopulmonary dose resulting from 3D-CRT. He *et al.* [14] compared 3D-CRT and IMRT in definitive CRT of esophageal cancer and showed that the incidence rates of PE and pleural effusion were significantly lower in the IMRT group. Lin *et al.* [15] showed that IMRT results in a lower risk of non-disease-related death, especially heart-related death, compared with 3D-CRT in the treatment of esophageal cancer. Since IMRT has an extremely complicated dose distribution, the evaluation using BEDVH seems to be more suitable.

There are some limitations in this study. First, it is a retrospective study. Second, a relatively small number of patients were considered eligible. Finally, there is no consensus regarding OAR contouring including the heart. Wu *et al.* [16] reported IMRT contouring guidelines but did not mention OARs. In this study, heart contouring was based on the heart contouring atlas of Feng *et al.* [17], but it is desirable that a consensus about the definition of OAR contouring is obtained.

In conclusion, the 5-year incidence rate of symptomatic PE was 16.2%. Pericardial $V80_{\text{-BED}}$ and mean heart $dose_{\text{-BED}}$ were

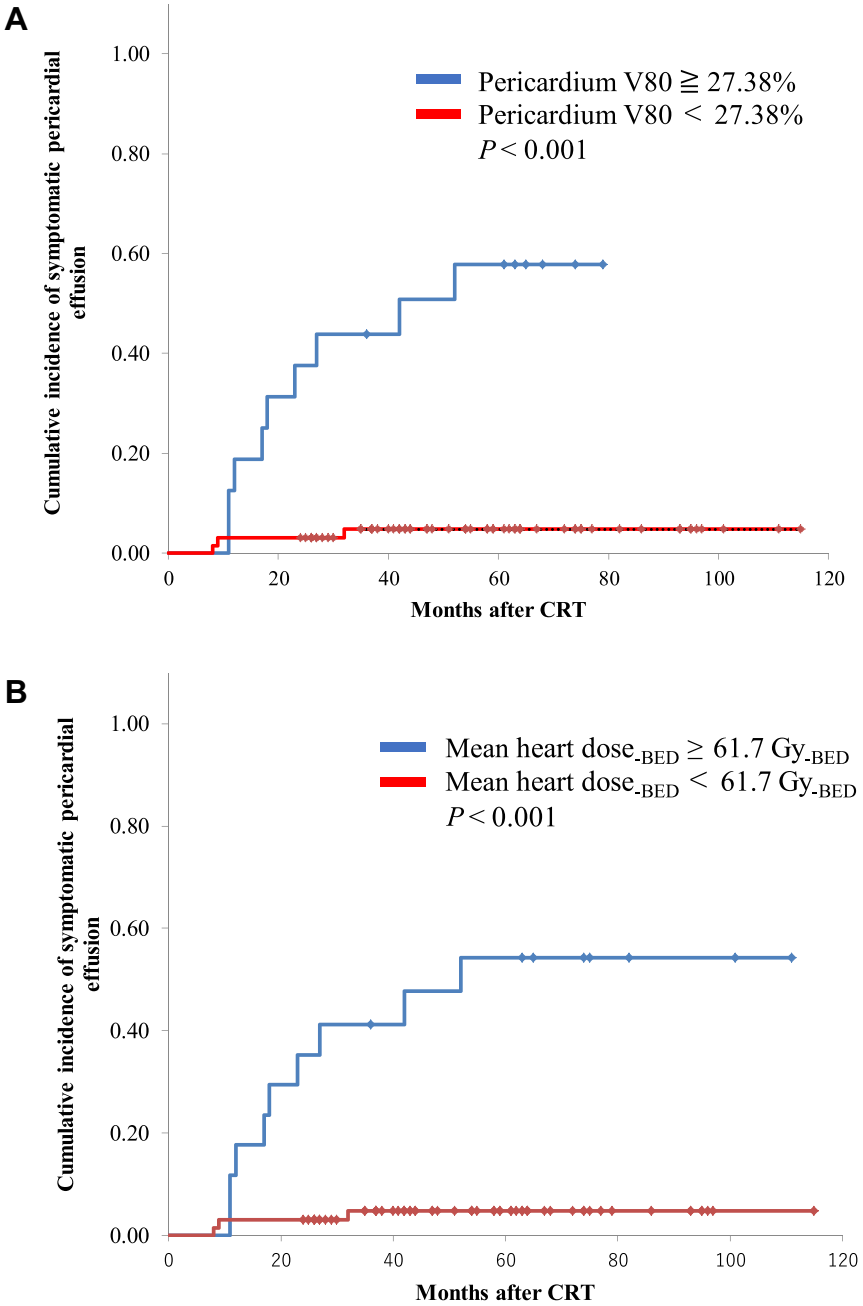

Fig. 3. (a) Cumulative incidence of symptomatic pericardial effusion according to optimal cut-off value of $V80_{-BED}$ of the pericardium from the Kaplan–Meier curve. (b) Cumulative incidence of symptomatic pericardial effusion according to optimal cut-off value of mean heart $dose_{-BED}$ from the Kaplan–Meier curve. CRT: chemoradiotherapy.

the significant factors and were indexes to be noted. We consider such biological dose analysis to be important in this era of high-precision RT.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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