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## FULL PAPER

# Predictive factors for pericardial effusion identified by heart dose–volume histogram analysis in oesophageal cancer patients treated with chemoradiotherapy

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**Objective:** To identify predictive factors for the development of pericardial effusion (PCE) in patients with oesophageal cancer treated with chemotherapy and radiotherapy (RT).

**Methods:** From March 2006 to November 2012, patients with oesophageal cancer treated with chemoradiotherapy (CRT) using the following criteria were evaluated: radiation dose >50 Gy; heart included in the radiation field; dose–volume histogram (DVH) data available for analysis; no previous thoracic surgery; and no PCE before treatment. The diagnosis of PCE was independently determined by two radiologists. Clinical factors, the percentage of heart volume receiving >5–60 Gy in increments of 5 Gy (V5–60, respectively), maximum heart dose and mean heart dose were analysed.

**Results:** A total of 143 patients with oesophageal cancer were reviewed retrospectively. The median

follow-up by CT was 15 months (range, 2.1–72.6 months) after RT. PCE developed in 55 patients (38.5%) after RT, and the median time to develop PCE was 3.5 months (range, 0.2–9.9 months). On univariate analysis, DVH parameters except for V60 were significantly associated with the development of PCE ( $p < 0.001$ ). No clinical factor was significantly related to the development of PCE. Recursive partitioning analysis including all DVH parameters as variables showed a V10 cut-off value of 72.8% to be the most influential factor.

**Conclusion:** The present results showed that DVH parameters are strong independent predictive factors for the development of PCE in patients with oesophageal cancer treated with CRT.

**Advances in knowledge:** A heart dosage was associated with the development of PCE with radiation and without prophylactic nodal irradiation.

Oesophageal cancer has a poor prognosis, accounting for 11,970 (3.4%) of Japan's total cancer deaths in 2011.<sup>1</sup> Compared with Western countries, oesophageal squamous cell carcinomas are more common in Asian countries, including Japan.<sup>1,2</sup> According to several reports, chemoradiotherapy (CRT) prolongs survival in patients with unresectable oesophageal cancer,<sup>3–7</sup> and it may be considered tolerable treatment compared with surgical resection in patients with oesophageal cancer.<sup>8</sup>

Although CRT may improve the prognosis, adverse events may occur that shorten the overall survival in patients with oesophageal cancer treated with CRT.<sup>9</sup>

There have been two reports with long-term follow up concerning the late toxicity of CRT. Radiation Therapy Oncology Group 85-01<sup>4</sup> reported a 2% incidence of grade 3 heart toxicity, and Ishikura et al<sup>10</sup> reported an

approximate incidence of 7.2% for severe heart toxicity.<sup>9</sup> Development of a pericardial effusion (PCE) is the most frequent cardiac adverse event in patients with oesophageal cancer treated with CRT.<sup>10</sup>

Dose–volume histogram (DVH) analysis is suitable for studying radiation-induced adverse events. There has been only one report dealing with the risk factors for the development of PCE using DVH analysis of the pericardium, and it showed a strong correlation.<sup>11,12</sup>

To reduce damage to organs at risk, multiple field irradiation, intensity-modulated radiation therapy and proton beam therapy are used.

The aim of the present study was to define the predictive factors for the development of PCE in patients with oesophageal cancer treated with CRT without prophylactic

nodal irradiation. Predictive factors for PCE were analysed retrospectively using heart DVH analysis.

## METHODS AND MATERIALS

### Patient population

From March 2006 to November 2012, patients with oesophageal cancer were treated with CRT or radiotherapy (RT) at Kansai Medical University, Hirakata, Japan, on the basis of the inclusion and exclusion criteria.

*Inclusion criteria:* radiation dose >50 Gy, heart included in the radiation field, DVH data available for analysis and pathological diagnosis was confirmed. *Exclusion criteria:* previous thoracic surgery, PCE before treatment and chest irradiation history.

### Pre-treatment evaluation

Pre-treatment evaluation included oesophageal endoscopy and enhanced CT and fluorine-18 fludeoxyglucose position emission tomography (<sup>18</sup>F-FDG-PET). TNM staging was evaluated by Union for International Cancer Control (UICC) v. 7.0.<sup>13</sup>

### Treatment

All RT was planned by three-dimensional (3D) CT planning. Simulation CT was performed with 2-mm thick slices.

Primary tumour and lymph nodes were defined by CT, <sup>18</sup>F-FDG-PET and endoscopy, as gross tumour volume primary (GTVp) and GTV node (GTVn), respectively. The clinical target volume primary was GTVp plus 2- to 3-cm superior and inferior margins. The clinical target volume node was GTVn plus a margin. Planning target volume (PTV) was clinical target volume plus a 0.5- to 1-cm margin, without prophylactic nodal irradiation. In Stage IV patients, the RT field included primary PTV and lymph nodes of the neighbourhood only.

The calculation algorithm was the AAA method. Patients were irradiated with 1.8–2.0 Gy per fraction, using 10-MV photons from a linear accelerator. Conventional beam RT was delivered with 36–40 Gy anteroposterior opposed beams. A boost dose of 14.4-PTV 20 Gy was given to the PTV for off-cord planning. Multiple field irradiation was not attempted to avoid the heart.

Chemotherapy consisted of 5-fluorouracil (5-FU) plus a platinum base, either cisplatin or nedaplatin. Nedaplatin (CDGP) shows anti-tumour activity similar to that of cisplatin and has less renal and gastrointestinal toxicity.<sup>14,15</sup>

The chemotherapy regimens used with RT consisted of 5-FU and cisplatin or nedaplatin (FP, 5-FU plus cisplatin regimen; FN, 5-FU plus nedaplatin regimen). The doses and schedules were determined and administered as previously reported<sup>6,14,16</sup> (Table 1).

### Evaluation of pericardial effusion and clinical factors

The adverse effects were assessed according to the Common Terminology Criteria for Adverse Event v. 3.0. PCE was assessed by chest CT every 6 months after RT, and the diagnosis of PCE was independently determined by two radiologists (Table 2).

Table 1. Patient's characteristics

Characteristics	Patients, <i>n</i> = 143
Age (years)	
Median (range)	67 (51–95)
>65	88
Gender	
Male	115
Eastern Co-operative Oncology Group performance status	
0	102
1	35
2	6
Primary	
Upper thoracic oesophagus	32
Middle thoracic oesophagus	70
Lower thoracic oesophagus	41
Stage (Union for International Cancer Control v. 7)	
I	17
II	7
III	54
IV	65
Histopathology	
Squamous cell carcinoma	141
Radiation dose (Gy)	
Median (range)	60 (50–60)
=60 Gy	130
Chemotherapy	
High-dose FP	65
Low-dose FP	23
5-fluorouracil plus nedaplatin regimen	36
Other	6
Non	13

FP, 5-fluorouracil plus cisplatin regimen.

Observation end points were invasive chest events such as salvage surgery or oesophageal stenting.

The following clinical factors were investigated in relation to PCE: sex, age, Eastern Co-operative Oncology Group performance status (PS), location of primary tumour, total dose, clinical stage, histology, chemotherapy, hypertension, atrial fibrillation, heart failure, history of cardiac disease and diabetes. The clinical factors, the percentage of heart volume receiving >5–60 Gy in increments of 5 Gy (V5–60, respectively), the maximum heart dose and the mean heart dose were analysed.

### Statistical analysis

The time to develop PCE was calculated from the end of RT to the time of the last follow-up CT, and Kaplan–Meier method

Table 2. Pericardial effusion grades Common Terminology Criteria for Adverse Events (CTCAE v. 3.0)

Grade	Pericardial effusion (CTCAE v. 3.0)
Grade 1	Asymptomatic effusion
Grade 2	–
Grade 3	Effusion with physiological consequences
Grade 4	Life-threatening consequences (e.g. tamponade); emergency intervention indicated
Grade 5	Death

was used to determine the probability of PCE. To evaluate the impact of each factor on the development of PCE, univariate and logistic regression analyses were used. Therefore, the measure of association in this study was the odds ratio (OR) along with 95% confidence interval (95% CI).

Cut-off values were calculated by recursive partitioning analysis (RPA) from the DVH parameters and clinical factors.

Using Spearman’s rank correlation coefficients, the correlation coefficients of the DVH parameters were analysed. RPA was performed to identify the factors that were the most influential for the development of PCE. The significance of RPA values was determined using logistic regression analysis.

Statistical analyses were performed with the SPSS® software package, SPSS II for Windows v. 11 (SPSS, Tokyo, Japan) and R software package v. 2.14 (R project for Statistical Computing, Vienna, Austria). A *p*-value of <0.05 was considered significant.

**RESULTS**

From March 2006 to November 2012, 290 patients with oesophageal cancer were treated with CRT or RT at the Kansai

Figure 1. Cumulative development of pericardial effusion (PCE) by the Kaplan-Meier method. Cumulative prevalence of PCE is 48.2% from the end of radiotherapy.

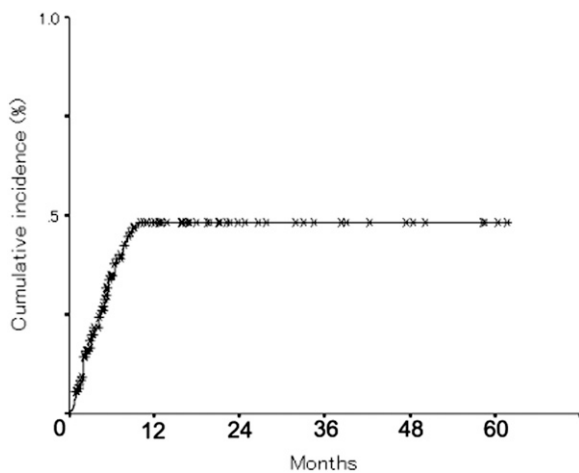


Table 3. Patients with symptomatic late cardiac adverse effects grade 3 or greater

Case number	Age (years)	Gender	Clinical stage	Chemotherapy	Radiation dose (Gy)	Mean heart dose (Gy)	Heart V10 (Gy)	Follow-up time by CT (months)	PCE grade	Cardiac adverse effect	Progression time of PCE (months)	Treated adverse effect	History of cardiac conditions	Outcome/survival
1	69	Male	II	FP	60	40.3	84.1	13.6	4	Pericardial tamponade by PCE	13.6	Pericardial drainage	No	CR/I died
2	77	Male	III	FP	60	30.8	72.0	4.5	4	Supraventricular tachycardia	4.8	Catheter ablation	No	PR/alive
3	73	Male	III	5-fluorouracil plus nedaplatin regimen	60	36.4	79.5	46.3	4	Pleural effusion	38.9	Pleurodesis	Hypertension	CR/alive
4	72	Male	I	Low-dose FP	60	28.8	72.7	48.5	3	Heart failure	31.1	Medical	Hypertension	CR/alive
									3	Atrial fibrillation	20.7	Medical	Hypertension	CR/alive

CR, complete response; FP, 5-fluorouracil plus cisplatin regimen; PCE, pericardial effusion; PR, partial response.

The symptomatic cardiac adverse effects and the relationship with PCE are not clear. Because we analysed grade 1, the development of PCE in this study, this table is independent of the results of the analysis.

Table 4. Univariate analysis of dose–volume histogram (DVH) parameters associated with the development of pericardial effusion (PCE)

Heart DVH parameter	Heart volume (PCE has occurred), median % (range)	Heart volume (PCE has not occurred), median % (range)	Odds ratio	Univariate analysis, 95% confidence interval	<i>p</i> -value
Maximum heart dose	61.5 (65.7–49.4)	60.8 (66.0–40.4)	1.16	1.02–1.33	0.028
Mean heart dose	34.3 (44.3–18.7)	25.3 (45.9–5.2)	1.14	1.08–1.20	<0.001
Heart V60	3.7 (20.9–0)	0.3 (60.0–0)	1.04	0.99–1.10	0.123
Heart V55	18.9 (36.2–0)	7.4 (52.4–0)	1.07	1.03–1.11	<0.001
Heart V50	23.4 (44.1–0)	10.6 (58.1–0)	1.07	1.04–1.11	<0.001
Heart V45	29.0 (59.4–7.6)	14.3 (63.6–0)	1.07	1.04–1.11	<0.001
Heart V40	56.3 (78.5–12.6)	35.0 (77.9–0.6)	1.06	1.04–1.08	<0.001
Heart V35	60.8 (81.7–31.4)	43.3 (86.4–0.2)	1.06	1.04–1.09	<0.001
Heart V30	63.7 (83.6–34.4)	45.8 (89.5–8)	1.07	1.04–1.10	<0.001
Heart V25	67.2 (87.6–37.6)	48.2 (91.8–9.1)	1.07	1.04–1.10	<0.001
Heart V20	72.5 (98.7–42.9)	52.5 (93.5–10.4)	1.07	1.04–1.10	<0.001
Heart V15	75.6 (100–45.9)	55.3 (94.8–12.0)	1.07	1.04–1.10	<0.001
Heart V10	78.6 (100–50.0)	58.4 (96.2–12.9)	1.07	1.04–1.10	<0.001
Heart V5	82.5 (100–56.2)	63.5 (98.8–14.5)	1.07	1.04–1.11	<0.001

We showed the volume of hearts in patients where PCE did or did not occur.

Medical University Hirakata Hospital. A total of 143 patients with oesophageal cancer were reviewed retrospectively on the basis of the criteria shown in [Table 1](#).

Stages III and IV (UICC v. 7) accounted for the majority of cases in this study. Squamous cell carcinoma was observed in 141 patients, with adenocarcinoma in 2.

The median prescribed RT dose was 60 Gy (range, 50–60 Gy). The median of the mean heart dose was 28.9 Gy (range, 5.2–45.9 Gy). Seven patients were prescribed 50.4 Gy. Overall, 130 patients were treated with CRT, and 13 were treated with RT alone.

A total of 65 patients received high-dose FP, while 23 received low-dose FP and 36 received FN. Six patients received other chemotherapy regimens, including cisplatin alone (four patients), paclitaxel alone (one patient) and carboplatin plus 5-FU (one patient). Three patients received induction chemotherapy.

The median follow-up time was 15.0 months (range, 2.1–72.6 months). Follow-up by chest CT was 1–6 months for 35% of all patients, 7–12 months for 23% of all patients, 13–24 months for 22% of all patients and more than 25 months for 20% of all patients. Median numbers of CT scans were three times (range, 1–8) in 1–6 months, twice (range, 0–6) in 7–12 months, twice (range, 1–6) in 13–24 months and four times (range, 1–10) in more than 25 months, respectively.

PCE developed after RT in 55 patients (38.5%); PCE grades 1 and 4 were seen in 40 patients and 1 patient, respectively. The median time to develop PCE was 3.5 (range, 0.2–9.9) months. The cumulative prevalence of PCE is described in [Figure 1](#) by the Kaplan–Meier method.

Symptomatic cardiac adverse events occurred in four cases. In one severe case (PCE grade 4), the patient developed symptomatic PCE for which pericardial drainage was performed 13.6 months after completion of RT. In another case, symptomatic heart failure occurred at 31.1 months, which was treated medically. An intractable pleural effusion then developed, and bilateral pleurodesis was performed at 38.9 months (pleural effusion grade 4).

In another case, aggravation of paroxysmal supraventricular tachycardia developed, and catheter ablation was performed at 4.8 months (paroxysmal supraventricular tachycardia grade 4). In a case without PCE, atrial fibrillation occurred after 20.7 months ([Table 3](#)).

On univariate analysis, all DVH parameters except V60 were significantly associated with the development of PCE ([Table 4](#)). No clinical factors were significantly related to the development of PCE, and we describe analysis by radiation dose, chemotherapy and clinical factors in [Table 5](#). DVH parameters were a continuous variable, and we added more analysis. Spearman's rank correlation coefficients for DVH parameters of 5–60 Gy in increments of 5 Gy were analysed. There were close correlations among the DVH parameters except V60 (range of Spearman's

Table 5. The association of radiation dose, chemotherapy factors and cardiac clinical factors in the development of pericardial effusion

Dose/factors	Patients, <i>n</i> = 143	Odds ratio	Univariate analysis, 95% confidence interval	<i>p</i> -value
Radiation dose (Gy)				
Median (range)	60 (50–60)	–	–	–
=60 Gy	130	2.22	0.58–8.46	0.24
Chemotherapy				
High-dose FP	65	–	–	–
Low-dose FP	23	1.12	0.41–3.05	0.83
5-fluorouracil plus nedaplatin regimen	36	1.87	0.81–4.32	0.14
Other	6	1.05	0.18–6.18	0.96
Non	13	2.44	0.73–8.18	0.15
Induction chemotherapy	6	1.64	0.32–8.40	0.56
Hypertension	30	1.29	0.57–2.93	0.54
Atrial fibrillation	6	1.64	0.32–8.40	0.56
Heart failure	2	1.61	0.10–26.30	0.74
Cardiac disease	2	1.61	0.10–26.30	0.74
Diabetes	16	2.26	0.79–6.48	0.13

FP, 5-fluorouracil plus cisplatin regimen.

Radiation dose and chemotherapy were not significant either and cardiac clinical factors were not significant.

rank correlation coefficients, 0.70–0.99; *p* < 0.001). Off-cord planning and a dosage plan of a total of 50 Gy reduced the correlation of V60.

Furthermore, to find the optimal cut-off points for various parameters, RPA was used. The RPA included age, sex, PS, primary location, radiation dose, clinical stage, histology, chemotherapy, medical history and all DVH parameters as variables. RPA showed that only a V10 value of >72.8% was associated with the development of PCE, and this was greater than the predictive factor for development of PCE on logistic regression analysis (OR, 12.2; 95% CI, 5.5–27.4; *p* < 0.001). We show development and patients distributed by cut-off value V10 72.8% in the decision tree (Figure 2). In addition, for planning, RPA showed that a mean heart dose value >30.25% was associated with the development of PCE (OR, 13.9; 95% CI, 6.1–31.7; *p* < 0.001). Two curves for the cumulative prevalence of PCE were plotted as a boundary line from the cut-off value (Figure 3).

**DISCUSSION**

In this study, heart DVH parameters were found to be associated with PCE onset following oesophageal cancer CRT. The PCE cumulative incidence using the Kaplan–Meier method was compatible with two other studies from the graphs.<sup>11,17</sup>

In this study, the PCE development period was 3.5 months (range, 0.2–9.9 months). The development curve reported by us and by Wei et al<sup>11</sup> reached a plateau, but Fukada et al<sup>17</sup> noted PCE development for a few years thereafter. This difference

appears to be owing to differences in irradiation volume based on two-dimensional (2D) and 3D simulations.

Wei et al<sup>11</sup> reported that, although only partial significance was seen in heart DVH, there was a correlation with pericardial DVH, and pericardial DVH was the more effective factor. The

Figure 2. Recursive partitioning analysis using clinical factors and dose-volume histogram parameters. In each terminal node, the upper row shows the number that developed PCE, and the lower row shows the number of patients. PCE, pericardial effusion.

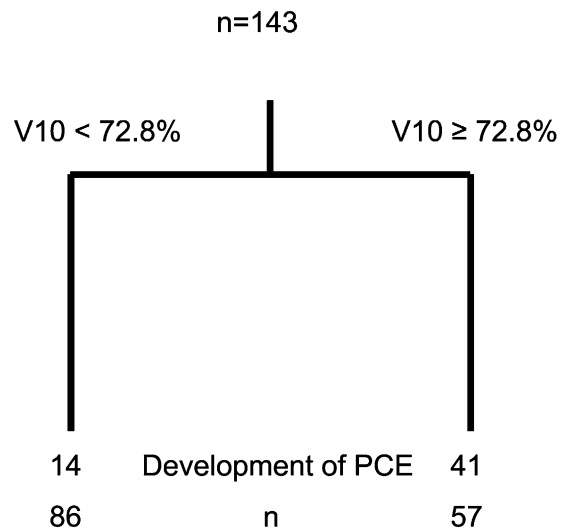
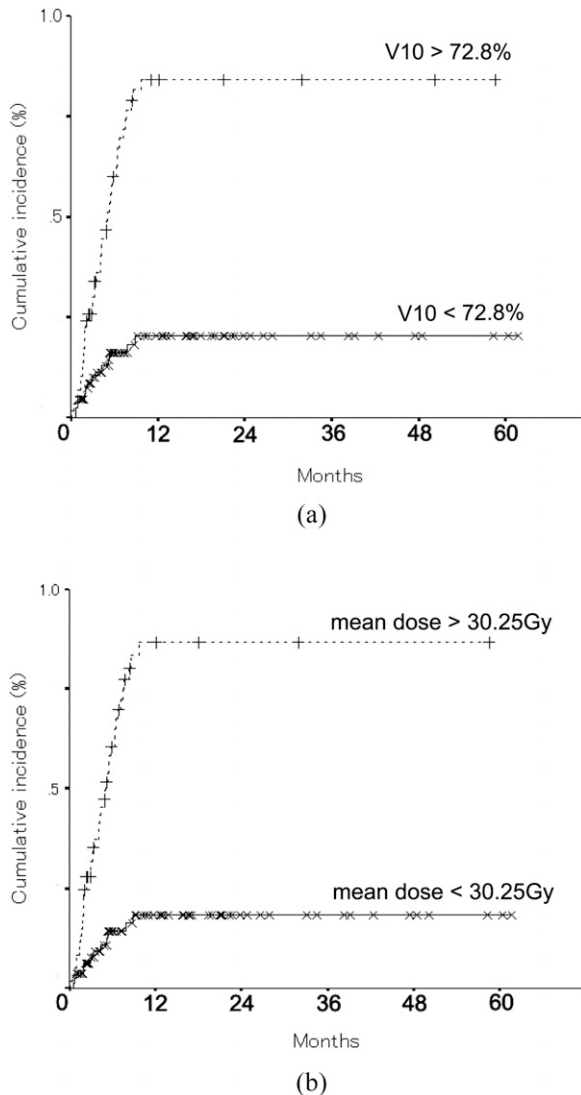


Figure 3. Cumulative development of pericardial effusion by the Kaplan-Meier method. For the cut-off-value of V10 and mean heart dose, we created graphs; (a) two curves were plotted as a boundary line from the cut-off-value heart V10 72.8%, (b) two curves were plotted as a boundary line from the cut-off-value mean heart dose 30.25%.



present study investigated heart DVH, because heart DVH parameters other than V60 were significant.

The prescribed dosage is often 60 Gy in Japan, and squamous cell carcinoma is dominant in our country, affecting about 90% of patients with oesophageal cancer.<sup>2,6,9</sup>

The present study had a prescribed dose of 60 Gy, higher than Wei *et al*,<sup>11</sup> but it appeared to have a lower heart volume irradiated, without prophylactic nodal irradiation. Even with such differences, PCE development had a low association with clinical factors, and heart-related DVH parameters were significant. PCE incidence and duration were not thought to have been associated. However, the

calculated results cut-off values were different, with a V10 cut-off of 72.8%.

Fukada *et al*<sup>17</sup> had the same prescribed dose of 60 Gy, but it was an X-ray simulation, and the radiation field is expected to be broader. Their report was not a planned DVH analysis, and the field size was reported to be more significant than clinical factors. The differences in PCE incidence and duration were thought to be owing to the differences in dose and volume arising from the difference between 3D and 2D radiation.

Without prophylactic nodal irradiation, even a high dosage of 60 Gy might inhibit the development of PCE compared with a dosage of 50.4 Gy. PCE might be inhibited in a reduced field by high accuracy irradiation using advanced RT technique.

In the long-term report by Ishikura *et al*,<sup>10</sup> severe heart-related adverse events occurred in about 7.2% of cases; Kumekawa *et al*<sup>18</sup> reported 8.2% and Morota *et al*<sup>19</sup> reported 5.4%. The present study had four observed cases (2.8%) of severe heart-related adverse events of grade 3 or higher, including pleural effusion (Table 3). The relationship with PCE accumulation owing to arrhythmia and heart failure is unclear, and the one case of cardiac tamponade (PCE grade 4) that underwent pericardiocentesis was believed to be directly related to symptomatic PCE development.

In the present study, there was a low incidence of heart-related adverse events. This may have been owing to the short observation period, and the RT field in the present study may have been smaller than in other studies.

In oesophageal cancer CRT with a median follow up of about 2 years, the potential for PCE and pleural effusion is high, followed by symptomatic radiation pneumonitis and heart-related adverse events appear as late toxicity.<sup>10</sup> On the other hand, Hodgkin's lymphoma and breast cancer have long-term observation periods; there are also long-term reports about radiotherapy-associated cardiac toxicity in Hodgkin's lymphoma and breast cancer, and it has been recommended that the dose to the heart should be kept as low as possible.<sup>20,21</sup>

The differences between oesophageal cancer and other reported tumours include differences related to the short follow-up period coming from the short survival of such patients, cardiotoxic chemotherapy, such as adriamycin, high RT doses and the radiation field. It is also thought that late adverse events were not evident owing to the short follow-up period. For this reason, long-term adverse event data following radiotherapy for oesophageal cancer are needed, and the relationship with irradiation planning needs to be studied.

It is thought that oesophageal cancer RT must be planned by taking into account the dose to the lung, the dose to the heart and the prognosis.

## CONCLUSION

The development of PCE is strongly associated with the radiation dose to the heart, but the clinical symptoms require further study.

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