Risk Factors for Pericardial Effusion in Patients with Stage I Esophageal Cancer Treated with Chemoradiotherapy

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Abstract. *Aim: We investigated clinical and dosimetric factors influencing the risk of developing pericardial effusion (PCE) in patients with Stage I esophageal cancer undergoing definitive chemoradiotherapy. Patients and Methods: Sixty-nine patients with Stage I esophageal cancer who underwent definitive chemoradiotherapy were retrospectively analyzed. Treatment comprised of three-dimensional conformal radiotherapy (60 Gy in 30 fractions) with concurrent chemotherapy. Clinical and dosimetric factors associated with PCE development were analyzed. Results: The median follow-up was 37 months (range=8-111 months); the crude PCE incidence rate was 52.2%. Grade 2 and 3 incidence rate was 47.8% and 4.3%, respectively. The median time to PCE onset was 5.7 months after radiotherapy. In multivariate analysis, pericardial V30 ≥41.6%, age ≥66 years, body mass index (BMI) ≥19 and diabetes mellitus (DM) were significant predictors of developing PCE. Conclusion: The present study suggests that higher pericardial V30, advanced age, high BMI and DM are risk factors for developing PCE.*

The incidence of superficial (Stage I) esophageal cancer has recently increased, mainly because of remarkable advances in diagnostic techniques, such as endoscopic examination with ultrasound and Lugol dye staining. Surgery and endoscopic resection are recognized as the main treatment modalities for Stage I esophageal cancer (1-3). However, in view of the rapidly increasing aging population in Japan, it is difficult to perform curative surgery in this population because such treatment often worsens their quality of life. Radiotherapy has been reported as an alternative treatment modality for Stage I esophageal cancer (4-7); a recent Japanese trial reported an excellent 4-year survival rate of 80.5% in patients with Stage I esophageal cancer treated with definitive chemoradiotherapy (8).

Although the number of long-term survivors treated with chemoradiotherapy is increasing, treatment-related toxicities including cardiac injuries are now recognized as an important issue and these late toxicities significantly impair patients' quality of life (9-13).

Pericardial effusion (PCE) is considered an adverse effect following cardiac irradiation, with the incidence of post-radiation PCE reported as 28%-43% in esophageal cancer. Wei *et al*. reported that several dose-volume histogram (DVH) parameters of the pericardium and heart were associated with the risk of developing PCE, whereas no clinical factor was found to significantly influence the risk in patients with inoperable esophageal cancer. Fukada *et al*. also concluded that mean pericardial dose and advanced disease (clinical stage ≥II) were risk factors for PCE (14-16). However, the correlation between PCE and radiotherapy for Stage I esophageal cancer was not extensively investigated. Here we present a retrospective analysis to identify clinical and dosimetric factors influencing the risk of developing PCE in patients with Stage I esophageal cancer treated with definitive chemoradiotherapy.

Patients and Methods

Patient population and pre-treatment evaluation. This study was approved by the institutional review board at our-institution. We retrospectively reviewed the medical and radiation records of all patients with newly-diagnosed Stage I esophageal cancer treated with definitive chemoradiotherapy between December 2001 and December 2011 at our institution. All patients participating in this study gave informed consent prior to treatment. Patients were recruited on the basis of the following criteria: histologically-confirmed squamous cell carcinoma, performance status (Eastern

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Cooperative Oncology Group (ECOG)) 0-1, adequate organ function, treatment with three-dimensional conformal radiotherapy (3D-CRT), treatment without induction chemotherapy and availability of follow-up records.

The pretreatment evaluation included complete medical history, physical examination, complete blood cell count, biochemical screening profile, chest radiography, abdominal and thoracic computed tomography (CT) and esophageal endoscopy with biopsy. Clinical tumor, node, metastases staging was defined according to the 7th UICC-AJCC staging system.

Patients' characteristics. Of 78 patients with Stage I esophageal cancer treated with chemoradiotherapy, 69 were eligible. Nine patients were excluded from analysis because of either missing detailed patient data (n=5) or unavailability of cardiac DVHs (n=4). Patient characteristics are listed in Table I. The median follow-up period was 37 months (range, 8-111) and median age was 69 years (range, 49-84). All tumors were histologically confirmed as squamous cell carcinoma. Fifteen (21.7%) and 54 (78.3%) patients were diagnosed as T1a and T1b, respectively. Elective nodal regions were included in the clinical target volume (CTV) of eight (11.6%) patients. All patients completed the treatment course. Chemotherapy regimens were cisplatin plus 5-fluorouracil (5-FU) (n=64, 92.7%), docetaxel (n=3, 4.3%) and nedaplatin plus 5-FU (n=2, 2.9%). Cisplatin or nedaplatin was administered at a dose of 70 mg/m^2 by slow drip infusion on days 1 and 29, and 5-FU was administered at a dose of 700 mg/m^2 per day by continuous infusion for 24 h on days 1-4 and 29-32. Docetaxel was administered at a dose of 70 mg/m^2 by slow drip infusion on days 1, 8, 15, 22, 29 and 36.

Treatment. Treatment comprised 3D-CRT (60 Gy in 30 fractions) with concurrent chemotherapy. Patients underwent simulation on a CT simulator in supine position under normal, quiet respiration during acquisition. A commercial treatment planning system (XiO TPS; Elekta, Stockholm, Sweden) was used to design fields. Radiotherapy was delivered by 10 MV photons from a linear accelerator.

Gross tumor volume was not defined because of T1 disease. To determine tumor location for treatment planning, two fiducial markers were placed when patients underwent endoscopy before simulation CT: at the upper and lower tumor edges. CTV defined the esophagus between the upper and lower markers plus a margin of 2 cm in the craniocaudal direction. In principle, elective nodal regions were not included in CTV. Planning target volume (PTV) was generated by a margin of 1-2 cm in addition to CTV. Dose prescriptions were subsequently made in reference to the ICRU reference points (isocenters) of PTV.

Radiotherapy was initially performed using anterior–posterior opposing fields to 40 Gy. Treatments then continued, avoiding the spinal cord, with obliquely opposing fields to 60 Gy. All patients were treated with 60 Gy in 30 fractions over 6 weeks.

The heart surface was delineated manually on each axial CT slice, which was defined as the inferior border of the right pulmonary artery to the apex of the heart. ''Pericardial volume'' was defined as a ''shell'' extending from the heart contours. The manually contoured heart served as the inner boundary of the shell, which was extended outward by 0.5 cm.

Dosimetric analysis. The following dosimetric factors were calculated from cardiac or pericardial DVHs: mean dose for the heart or pericardium and percentages of cardiac or pericardial volume receiving ≥5 to 60 Gy in increments of 5 Gy (V5-V60). Convolution dose calculations with heterogeneity correction were applied in all cases.

Table I. *Univariate analysis of clinical factors influencing the risk of PCE.*

Characteristic	n (%)	*p*-Value
Age(years)		
≥66	41 (59.4)	0.032
<66	28 (40.6)	
Gender		
Male	65 (94.2)	0.355
Female	4 (5.8)	
BMI		
≥19	52 (75.4)	0.006
<19	17 (24.6)	
Tumor location		
Proximal (Ce + Ut)	9 (13.0)	0.129
Distal (Mt + Lt)	60 (87.0)	
Smoking history		
Current and former	56 (81.2)	0.944
Never smoked	13 (18.8)	
Hypertension		
Yes	21 (30.4)	0.109
No	48 (69.6)	
Diabetes mellitus		
Yes	9 (13.0)	0.039
No	60 (87.0)	
Heart disease		
Yes	5 (7.2)	0.501
No	64 (92.8)	
Chemotherapy		
Cisplatin + 5-fluorouracil	64 (92.8)	0.350
Nedaplatin + 5-fluorouracil	3 (4.3)	
Docetaxel	2 (2.9)	
Serum creatinine (mg/dl)		
≥0.9	22 (31.9)	0.006
<0.9	47 (68.1)	

BMI; Body mass index; Ce; cervival esophagus; Ut; upper thoracic esophagus; Mt; middle thoracic esophagus; Lt, lower thoracic esophagus.

Evaluation of pericardial effusion. PCE was assessed from follow-up chest CT scans. Patients were followed-up every 3 months for the first 2 years after therapy and thereafter every 6 months in principle. Toxicity assessments were performed by CTCAE version 4.0. Radiation-related cardiac effects other than PCE were not evaluated because patients did not receive cardiac function tests routinely during follow-up visits.

Statistical analysis. The time to PCE was calculated from the end of radiotherapy to the date at which PCE was observed. Patients without PCE were censored at the final follow-up or death. The PCE rate was calculated using the Kaplan–Meier method. Clinical and dosimetric factors were analyzed for PCE in univariate (log-rank test) and multivariate analysis (Cox proportional hazards model). A

Table II. *Univariate analysis of dosimetric factors influencing the risk of PCE.*

DVH parameters	Cut-off value	*p*-Value
Mean heart dose	≥14.2 Gy	0.019
Heart V5	≥62.6%	0.011
Heart V10	≥57.5%	0.011
Heart V15	≥55.1%	0.012
Heart V20	≥52.3%	0.012
Heart V25	≥48.6%	0.012
Heart V30	≥31.3%	0.014
Heart V35	≥26.4%	0.008
Heart V40	≥19.8%	0.018
Heart V45	≥7.4%	0.036
Heart V50	≥5.9%	0.011
Heart V55	≥4.3%	0.011
Heart V60	≥0.7%	0.076
Mean pericardium dose	≥25.5 Gy	0.004
Pericardium V5	≥49.9%	0.014
Pericardium V10	≥47.0%	0.014
Pericardium V15	≥57.8%	0.005
Pericardium V20	≥58.8%	0.003
Pericardium V25	≥34.4%	0.013
Pericardium V30	≥41.6%	0.007
Pericardium V35	≥39.1%	0.007
Pericardium V40	≥35.7%	0.003
Pericardium V45	≥10.2%	0.027
Pericardium V50	≥16.5%	0.008
Pericardium V55	≥4.9%	0.008
Pericardium V60	≥1.8%	0.056

DVH, Dose-volume histogram; V5-60, percentages of volume receiving more than respective dose.

Table III. *Multivariate analysis of clinical and dosimetric factors influencing the risk of developing PCE.*

Parameter	HR	95% CI	*p*-Value
Pericardium V30 ≥41.6%	3.49	1.69-7.23	<0.001
Age ≥66	2.52	1.17-5.72	0.017
BMI ≥19	3.89	1.32-16.7	0.011
Diabetes mellitus	3.54	1.33-8.50	0.013
Serum creatinine ≥0.9 mg/dl	1.89	0.92-3.82	0.084

HR, Hazard ratio; CI, confidence interval; BMI, body mass index; V30, percentages of volume receiving more than 30 Gy.

p-value of <0.05 was considered statistically significant. We used JMP pro 10 (SAS Institute Inc., Cary, NC, USA) for the statistical analysis.

The following clinical factors were investigated for their association with PCE: age, gender, ECOG performance status, body mass index (BMI), hypertension, diabetes mellitus (DM), heart disease, serum creatinine, tumor location, smoking history and types of chemotherapy. Other dosimetric factors analyzed included mean heart and pericardial dosage and cardiac and pericardial V5-V60. The Pearson's analysis was performed to calculate the correlation between dosimetric factors.

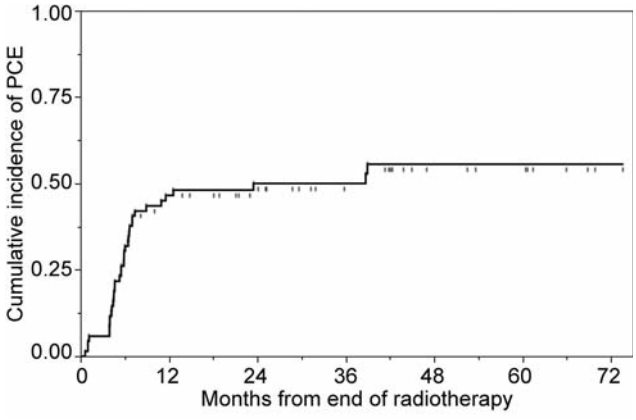

Figure 1. *Cumulative incidence rate of PCE.*

Results

The crude PCE incidence rate was 52.2% (36/69 patients). The median time to onset of PCE after radiotherapy was 5.7 months and the actuarial incidence rate at 1 year was 46.6%. Figure 1 shows the PCE incidence rate from the end of radiotherapy using the Kaplan–Meier method. Grade 2 and 3 rates were 47.8% and 4.3%, respectively; no cases progressed to grade ≥4 PCE.

In univariate analysis, age ≥66 years, BMI ≥19, DM and serum creatinine ≥0.9 mg/dl were found to significantly influence the risk of PCE. Table I lists the associations of clinical factors with the PCE incidence rate. A wide range of DVH parameters of the pericardium and heart was associated with the risk of PCE, including mean dose and V5, V10, V15, V20, V25, V30, V35, V40, V45, V50 and V55 of the pericardium and the heart (Table II). These dosimetric factors shared predictive power with regard to PCE incidence rate because of their multi-collinearity (data not shown).

We selected pericardial V30 for the multivariate analysis, which revealed pericardial V30 ≥41.6%, age ≥66 years, BMI ≥19 and DM as significant predictors of developing PCE (Table III); thus, pericardial V30 was established as the strongest parameter associated with the risk of developing PCE. Figure 2 shows that when pericardial V30 was >41.6% or <41.6%, the rate of PCE at 18 months was 68.0% and 36.7%, respectively (p=0.007). Figure 3 shows that the greater the number of risk factors, the more likely that PCE would develop. Interestingly, patients with three or four risk factors inevitably developed PCE.

Discussion

We determined the incidence rate, as well as dosimetric and clinical predictive factors of developing PCE in patients with Stage I esophageal cancer treated with definitive chemo-

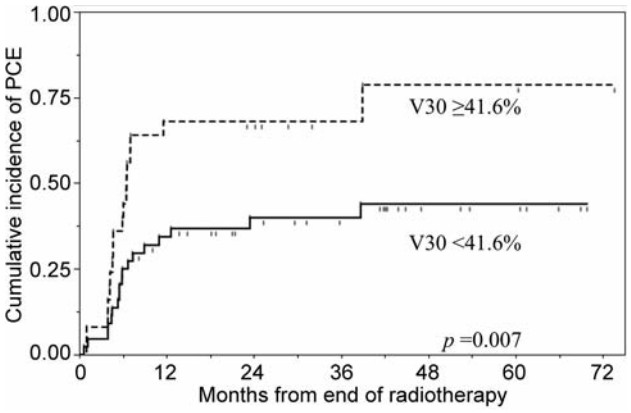

Figure 2. *Cumulative incidence rate of PCE with respect to pericardial V30. Patients were divided into two groups based on pericardial V30: <41.6% and ≥41.6%.*

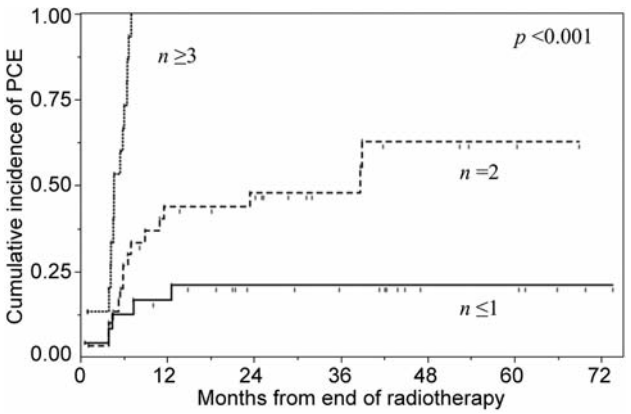

Figure 3. *Cumulative incidence rate of PCE with respect to number (n) of risk factors. The risk factors are pericardial V30 ≥41.6%, BMI ≥19, age ≥66 years and diabetes mellitus.*

radiotherapy. Wei *et al*. reported a crude PCE incidence rate of 27.7%, with a median time to onset after radiotherapy of 5.3 months despite a short mean follow-up of 8.4 months (14). Fukada *et al*. reported a crude PCE incidence rate of 43%, with a median time to onset of 12 months and median follow-up of 34 months (15). In the current study, the crude incidence rate was 52.2%, with a median time to onset of 5.7months. These reports suggest that PCE is a common toxicity that develops within the first year following radiotherapy.

Univariate analysis revealed serum creatinine ≥0.9 mg/dl, BMI ≥19, age ≥66 years and DM as significant factors influencing the risk of developing PCE. Furthermore, a wide range of DVH parameters of the pericardium and heart was associated with the risk of developing PCE. Finally, multivariate analysis revealed pericardial V30 ≥41.6%, age ≥66 years, BMI ≥19 and DM as significant predictors of developing PCE. Several previous studies showed that clinical factors are associated with the risk of late complications, including cardiotoxicity, after radiotherapy. Although Pignon *et al*. concluded that old age was not associated with acute and late complications after curative thoracic radiotherapy, they documented insufficiently about cardiotoxicity (17). Darby *et al*. reported that DM and BMI >30 were significant factors of ischemic heart disease in breast cancer patients treated with radiotherapy (18). To our knowledge, there is no study showing clinical factors influencing the risk of PCE after radiotherapy. Only one study has investigated the clinical and dosimetric factors associated with the risk of PCE in patients undergoing chemoradiotherapy for esophageal cancer (14). The major difference between the findings of that study and those of our study, investigating the correlation between PCE and radiotherapy, is that our analysis determined that several clinical factors in addition to DVH correlated with PCE development. By contrast, the study by Wei *et al*. found that several DVH parameters of the pericardium and heart were associated with the risk of developing PCE in patients with inoperable esophageal cancer, but none of the clinical factors were found to significantly influence it. This disparity in findings may be a reason why Wei *et al*. did not investigate significant clinical factors such as BMI. Another possible reason is that the radiotherapy field size in our study may have been smaller than that used by Wei *et al*. because we do not usually include elective nodal regions in CTV. Therefore, clinical factors may be overshadowed by dosimetric factors, which are more influential in radiotherapy, considering that a large area of the heart is often subjected to a high dose in patients with esophageal cancer.

Dosimetric factors, as well as clinical factors, are important to developing PCE. We believe that our findings are important for clinical practice because the risk of post-radiation PCE may be reduced by the use of an appropriate radiation technique, such as intensity-modulated radiation therapy (IMRT) or proton beam therapy (19, 20), particularly in the case of advanced age, obesity and DM. Lin *et al*. reported that the incidence of cardiac death had significantly increased after 3D-CRT compared with that after IMRT (21). However, optimal dose restrictions for the heart and the pericardium were not established. Although we and Wei *et al*. selected pericardial V30 as the predictive factor, our results did not show pericardial V30 as the best predictive factor because a wide range of DVH parameters was associated with the risk of developing PCE. Further investigations are required to answer this question.

The findings in this study should be interpreted with caution. First, there is no consensus on the delineation of the heart and pericardium. Although the pericardium is defined

as a virtual structure, dosimetric parameters of the pericardium are better correlated with PCE than those of the heart. Accurate dose evaluation is difficult because of organ motion. Second, our treatment planning system and linear accelerator were changed in December 2008. For this study, we recreated the previous treatment regimen and determined dosimetric parameters using the new treatment planning system (Xio). Therefore, the recreated dosimetric distribution may have been different from the actual distribution.

In conclusion, our results indicate that PCE is a common cardiotoxicity after radiotherapy in Stage I esophageal cancer patients treated with definitive chemoradiotherapy. Higher pericardial V30, advanced age, high BMI and DM are also risk factors for PCE. These findings will be of use when using definitive radiotherapy in such patients.

Conflicts of Interest

None.

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