Predictive factors for radiation pneumonitis in oesophageal cancer patients treated with chemoradiotherapy without prophylactic nodal irradiation

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Objective: The objective of this study was to identify clinical and dosimetric factors for the development of radiation pneumonitis (RP) among patients with oesophageal cancer treated with three-dimensional radiotherapy without prophylactic nodal irradiation.

Methods: 125 patients with oesophageal cancer had undergone dose–volume histogram (DVH) metrics and received chemoradiotherapy (CRT). Several clinical and dosimetric factors with regard to the lung were evaluated as predictive factors for the development of symptomatic RP.

Results: 26 patients (20.8%) developed symptomatic RP classified as greater than or equal to Grade 2. By univariate analysis, body weight loss, tumour length, Stage IV, response to treatment and all DVH parameters proved to be significant factors for the development of RP ($p < 0.05$). By multivariate analysis, Stage IV and all dosimetric factors were independent predictive factors for the development of symptomatic RP ($p < 0.05$). Recursive partitioning analysis indicated that V10 values of 24.8% or more and Stage IV were associated with higher development of RP (odds ratio 6.53).

Conclusions: Our study demonstrated that severe RP was also developed in patients treated with the minimal radiation field. Stage IV and the dosimetric factors were identified as independent predictive factors for symptomatic RP in oesophageal cancer patients treated with CRT without prophylactic nodal irradiation.

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Definitive chemoradiotherapy (CRT) has been established as a curative option for patients with carcinoma of the oesophagus, and its clinical efficacy has expanded [1–4]. Because thoracic irradiation can cause late development of adverse events that involve the heart, lung and oesophagus, including death, radiation therapy management has become an important clinical issue, especially for patients with prolonged survival and follow-up [5–9]. Efforts to reduce adverse events have become increasingly important.

Radiation pneumonitis (RP) is a major adverse event after thoracic irradiation, which occasionally results in death. In several studies, predictive factors for RP, including clinical factors and dosimetric parameters, have been reported for patients with lung cancer receiving definitive radiotherapy (RT) [10–14]. However, in oesophageal cancer, few reports are available on predictive factors for RP [15, 16]. To our knowledge, the predictive factors for the development of RP have not been evaluated in detail for oesophageal cancer patients treated with minimal radiation field.

The objective of the present study was to determine the predictive values of clinical and dosimetric factors for

the development of symptomatic RP in oesophageal cancer patients treated with three-dimensional (3D) RT without prophylactic nodal irradiation.

Methods and materials

Patients

This was a retrospective cohort study of oesophageal cancer patients treated with CRT at the Aichi Cancer Center Hospital between November 2006 and June 2009. There were a total of 125 patients who met the following inclusion criteria: (1) carcinoma of oesophagus; (2) histological diagnosis of primary oesophageal squamous cell carcinoma; (3) total radiation dose ≥ 50 Gy; (4) concomitant chemotherapy consisting of 5-fluorouracil and cisplatin; (5) dose–volume histogram (DVH) data available for analysis; (6) no previous thoracic RT; and (7) no previous thoracic surgery.

Pre-treatment staging

Pre-treatment staging evaluations included physical examination, laboratory tests, oesophagogastrroduodenoscopy, barium oesophagography and contrast-enhanced CT scans from the neck to upper abdomen. Positron

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emission tomography (PET) scans were performed especially after 2005 if the clinician thought it necessary to reveal distant metastasis such as bone metastasis. PET scans were also performed until 2005. Pre-treatment staging was performed according to the sixth edition of the American Joint Committee on Cancer Cancer Staging Manual during a team conference, which included thoracic surgeons, radiologists, gastroenterologists and medical oncologists [17]. The treatment strategy was also decided at this conference. In general, patients with Stage I disease were treated by surgery alone, endoscopic mucosal resection or CRT. Patients with Stage II–IV disease were treated by surgery plus chemotherapy or CRT.

Three-dimensional radiotherapy planning

RT was delivered using a linear accelerator (Clinac 21EX, Clinac 2100C; Varian Medical Systems, Palo Alto, CA) with a 6 or 10 MV photon beam. In general, patients received 2 Gy per fraction to a total of 60 Gy with a conventional beam arrangement; that is, anteroposterior opposed fields up to 36–40 Gy and oblique (off-cord) fields. After 2008, 64 patients with mid-thoracic or lower thoracic primary tumours were treated with multiple portal arrangement; that is, a combination of anteroposterior opposed and oblique (off-cord) fields. Patients with bulky disease or large radiation fields received 1.8 Gy per fraction to a total of 50.4 Gy, the prescription dose specified in the International Commission on Radiation Units and Measurements reports no. 50 and no. 62 [18, 19]. All patients were treated after 3D treatment planning using XiO computer software (CMS, St Louis, MO) with tissue inhomogeneity correction, such as a superposition dose calculation algorithm. Treatment planning was based on CT scans with 3–5 mm-thick sections and 3–5 mm intervals that were obtained in the treatment position. The primary gross tumour volume (GTV-P) and involved lymph nodes (GTV-N) were defined. The primary clinical target volume (CTV-P) included the GTV-P with a 20–30 mm margin craniocaudally, and the CTV for the lymph nodes (CTV-N) was defined as the GTV-N without additional margin [20]. The regional nodal site was not added to the CTV for prophylaxis [21]. The planning target volume (PTV) included both CTVs with lateral and anteroposterior 5–10 mm margins and 10–20 mm craniocaudal margins. In addition, 5–8 mm leaf margins were added to the PTV. Spinal cords never received more than 45 Gy, and attempts were made to minimise the radiation dose and volume to the heart. No more than 30% of the combined lung volume was intended to receive more than 20 Gy ($V_{20} < 30\%$).

Normal lung was automatically contoured on the CT images, and the trachea and bronchi were manually excluded. Doses were calculated to reflect tissue density inhomogeneity, and the DVH of the lung (treated as a combined-pair organ) was calculated based on CT-defined lung volumes. From the lung DVH the following parameters were extracted: mean lung dose (MLD), V_5 , V_{10} , V_{15} and V_{20} , where V_{20} was defined as the percentage of CT-defined lung volume receiving >20 Gy. The other V parameters were calculated in the same way.

Data collection

RP was graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v3.0) [21]. Pulmonary toxicity of greater than or equal to Grade 2 (symptomatic RP) occurring any time from the completion of RT up to the most recent follow-up visit after RT was considered an event. The following information was recorded from the medical record and radiological images of each patient: treatment initiation date, RT completion date, age, gender, Eastern Cooperative Oncology Group performance status, pre-treatment body weight loss in last 6 months, smoking status (Brinkman index: number of cigarettes smoked per day $\times$ years of smoking), alcohol history, total radiation dose, treatment technique, tumour length, tumour site, clinical stage, response to treatment according to Response Evaluation Criteria in Solid Tumors version 1.1 [22], final date assessing survival and date of death. The following dosimetric factors were also reviewed: V_5 , V_{10} , V_{15} , V_{20} and MLD.

Chemotherapy

All patients received concurrent chemotherapy consisting of cisplatin 70 mg m^{-2} on day 1 and continuous infusion of 5-fluorouracil $700 \text{ mg m}^{-2} \text{ day}^{-1}$ on days 1 to 4, repeated every 4 weeks [20]. The majority of Stage IIA–IVB patients received consolidation chemotherapy consisting of 5-fluorouracil and cisplatin after concurrent chemotherapy.

Follow-up

A history and physical examination, complete blood cell count, gastrointestinal endoscopy, chest X-ray and CT scanning of the neck, chest and abdomen were performed approximately every 1–2 months for up to 6 months after completion of RT, and every 3–6 months thereafter. Patient vital status and disease status were confirmed by checking medical records at the last follow-up visit. For a patient lost to follow-up, his or her vital status was confirmed from the annual census registration. In that case, if a patient was determined to have died, the cause of death was treated as unknown.

Statistical analysis

The development of symptomatic RP was calculated from the time of completion of RT to the time of death from any cause, to the time of last follow-up or to the time of symptomatic RP. The development of symptomatic RP was calculated by the Kaplan–Meier method. To evaluate the impact of each factor on the development of symptomatic RP, univariate and multivariate logistic regression analysis was applied. Therefore, the measure of association in this study was the odds ratio (OR) along with the 95% confidence interval. Correlation between DVHs was evaluated by Spearman's rank correlation coefficient (ρ). Recursive partitioning analysis (RPA) was performed to identify the factors that were most influential for the development of symptomatic RP. RPA

was used and considered those variables that attained statistical significance in the multivariate analysis. Statistical analyses were performed using the SPSS statistical software package, version 11 (SPSS Inc., Chicago, IL) and R version 2.12.0 (R Project for Statistical Computing, Vienna, Austria). A p -value <0.05 was considered statistically significant.

Results

Patient characteristics

Between November 2006 and June 2009, 165 consecutive oesophageal cancer patients received CRT after 3D treatment planning with DVH analysis. 40 patients were excluded from this analysis for the following reasons: adenocarcinoma ($n=1$), melanoma ($n=1$), total radiation dose <50 Gy ($n=4$), use of intensity-modulated radiotherapy ($n=5$), follow-up <3 months ($n=12$), chemotherapy other than 5-fluorouracil and cisplatin ($n=7$) and missing DVH analysis data ($n=10$). The median follow-up period was 32 months (range, 4–48 months), with 40 patients dead at the time of analysis. The overall survival rate at 1 and 3 years was 84% and 67%, respectively. The local control rate at 1 and 3 years was 81% and 74%, respectively. Patient characteristics are summarised in Table 1. The median total radiation dose for all patients was 60 Gy (range, 50–60 Gy).

Univariate and multivariate analysis

26 (20.8%) of the 125 patients had symptomatic RP greater than or equal to Grade 2. Two patients developed severe RP leading to lethal lung toxicity. Grade 4 RP was not observed. One patient had Grade 3 RP, 23 patients had Grade 2 RP, 54 patients had Grade 1 RP and 45 patients had Grade 0 RP. The median time from the end of radiotherapy to the development of RP was 3.4 months (range, 1–10 months).

Table 2 shows the univariate and multivariate analyses for clinical and dosimetric factors. By univariate analysis, pre-treatment body weight loss in last 6 months, tumour length, Stage IV, response to treatment and all dosimetric factors were significantly associated with the development of RP classified as greater than or equal to Grade 2 ($p<0.05$). By multivariate analysis, Stage IV and all dosimetric factors were independent predictive factors for the development of symptomatic RP ($p<0.05$). DVH parameters, including V5, V10, V15, V20 and MLD, were highly correlated with each other (p -values between 0.733 and 0.974).

Recursive partitioning analysis

Recursive partitioning analysis that includes clinical stage and all dosimetric factors as variables shows that V10 is the initial discriminator of the development of symptomatic RP (Figure 1). RPA indicated that V10 values of 24.8% or more and Stage IV were associated with higher development of RP. All the patients with Grade 3 or 5 RP belonged to this high-risk group.

Table 1. Patient and tumour characteristics

Characteristic	Patients ($n=125$)	%
Age years		
Median	66	
Range	42–84	
Gender		
Male	118	94
Female	7	6
Performance status		
0	8	6
1	117	94
Body weight loss		
No	65	52
Yes	60	48
Smoking history		
Never	18	14
Former or current	107	86
Brinkman index		
Median	800	
Range	0–3200	
Alcohol use		
Never	27	22
Former or current	98	78
Tumour length cm		
Median	5	
Range	1–22	
Tumour site		
Cervical portion	5	4
Upper thoracic portion	20	16
Mid-thoracic portion	69	55
Lower thoracic portion	31	25
T stage ^a		
1	55	44
2	8	6
3	34	27
4	28	22
N stage ^a		
0	63	50
1	62	50
M stage ^a		
0	95	76
1	1	1
1a	9	7
1b	20	16
Stage ^a		
I	42	34
II	20	16
III	33	26
IV	30	24

^aAccording to the sixth edition of the American Joint Committee on Cancer staging system [17].

Discussion

In oesophageal cancer, there have been two reports investigating the relationship between RP development and DVH parameters. In these two studies, 3D dose calculations were performed using tissue inhomogeneity correction. Wang et al [15] analysed clinical and dosimetric factors ranging from V5 to V60 in lung, and their relationship to the development of greater than or equal to Grade 2 RP by CTCAE v3.0 in oesophageal cancer patients treated with definitive CRT. They reported that dosimetric factors were not associated with the development of symptomatic RP and that induction chemotherapy administered before concurrent CRT significantly increased the development of RP

Table 2. The association of symptomatic radiation pneumonitis and clinical/dosimetric factors with univariate and multivariate analyses

Characteristic	Patients (n=125) %		Univariate analysis			Multivariate analysis		
			Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age years								
<65	51	41	1.00	–	–			
≥65	74	59	0.94	0.39–2.26	0.89			
Gender								
Male	118	94	1.00	–	–			
Female	7	6	0.00	0.0–27 × 10 ¹⁸	0.76			
Performance status								
0	8	6	1.00	–	–			
1	117	94	1.90	0.22–16.15	0.56			
Body weight loss								
No	65	52	1.00	–	–	1.00	–	–
Yes	60	48	2.89	1.15–7.30	0.024	1.62	0.52–5.06	0.41
Brinkman index								
<median	62	50	1.00	–	–			
≥median	63	50	0.81	0.34–1.92	0.63			
Alcohol use								
Never	27	22	1.00	–	–			
Former/current	98	78	0.77	0.27–2.19	0.62			
Total dose								
<median	46	37	1.00	–	–			
≥median	79	63	0.75	0.31–1.80	0.51			
RT field technique								
Conventional fields	61	49	1.00	–	–			
Multiple fields	64	51	0.78	0.33–1.84	0.56			
Tumour length	125	100	1.12	1.01–1.24	0.04	1.02	0.88–1.19	0.81
Tumour site								
Lower thoracic portion	31	25	1.00	–	–			
Cervical portion	5	4	3.47	0.46–26.37	0.23			
Upper thoracic portion	20	16	1.30	0.30–5.57	0.72			
Mid-thoracic portion	69	55	1.44	0.47–4.40	0.52			
Clinical stage ^a								
I	42	34	1.00	–	–	1.00	–	–
II	20	16	3.25	0.65–16.19	0.15	2.21	0.40–12.28	0.37
III	33	26	2.50	0.55–11.37	0.24	1.18	0.20–6.90	0.85
IV	30	24	10.11	2.58–39.64	0.001	6.25	1.15–36.01	0.034
Response to treatment								
Complete response	71	57	1.00	–	–	1.00	–	–
Incomplete response	54	43	2.57	1.06–6.24	0.037	0.70	0.21–2.36	0.56
Dosimetric factors								
MLD cGy	125	100	1.004	1.002–1.006	<0.001	1.003	1.001–1.006	0.005
V20 %	125	100	1.22	1.09–1.36	<0.001	1.21	1.08–1.36	0.001
V15 %	125	100	1.13	1.05–1.22	0.001	1.12	1.03–1.21	0.007
V10 %	125	100	1.10	1.04–1.16	0.001	1.08	1.02–1.15	0.012
V5 %	125	100	1.07	1.02–1.12	0.003	1.06	1.01–1.11	0.032

CI, confidence interval; MLD, mean lung dose; RT, radio therapy; V5, V10, V15, V20, denote volume receiving a particular dose in Gy.

^aAccording to the sixth edition of the American Joint Committee on Cancer staging system [17].

among patients with oesophageal cancer. In their study, chemotherapy regimens were inhomogeneous and quite different from those we used. Furthermore, taxane-based chemotherapy was administered to 96% of their patients who received induction chemotherapy, and it was used in 41% of their patients not receiving induction chemotherapy. Severe or fatal lung toxicity is a well-known toxicity of taxane, even if not combined with radiotherapy [23–25]. Thus, we believe the chemotherapy regimens used in their cohort might have had a greater impact on the development of RP than dosimetric parameters.

Asakura et al [16] also reported that all DVH parameters were apparently correlated with the development of symptomatic RP in oesophageal cancer patients, and

they used V20 as representative of these parameters. Their methods and results appear to be similar to ours. They reported that 35.1% of patients developed greater than or equal to Grade 2 RP, which is slightly higher than seen in our patients (20.8%). The mean MLD and V20 of the RP group in their study were 1659 ± 389 cGy and $34.8 \pm 9.0\%$, respectively, whereas in our study these were 954 ± 363 cGy and $18.2 \pm 4.0\%$, respectively. The differences were assumed to be because the ratio of their patients with advanced disease (Stage III–IV; 65%) was slightly higher than in our study (50%). In addition, they used a prophylactic regional radiation field up to 40 Gy, resulting in higher lung dosimetric parameters compared with parameters in our study. They reported that V20 cut-off values $\geq 37\%$ resulted in RP development more

Group	n	G0	G1	G2	G3	G5
I	15	13	2	0	0	0
II	55	21	29	5	0	0
III	36	10	17	9	0	0
IV	19	1	6	9	1	2

Group
Events/n
Odds ratio

Figure 1. Recursive partitioning analysis using stage and all dosimetric factors as variables. In each terminal node, the upper row shows group number, the middle row shows the number of events (the development of symptomatic radiation pneumonitis) and patients and the bottom row shows the odds ratio with reference to all patients. MLD, mean lung dose.

frequently compared with patient subgroups with V20 <37%. On the other hand, in our analysis, the V10 cut-off value of 24.8% or more was significant for predicting the development of symptomatic RP. The DVH parameters were important predictors of symptomatic RP; however, a reliable cut-off value for V20 remains controversial. Further studies are needed to determine which cut-off value is appropriate.

In our study, the intent of treatment planning was to reduce the V20 values of the lung (V20<30%), and the treatment resulted in lower V20 values in enrolled patients (median, 15.1%; range, 2.0–25.2%) compared with those reported previously. Almost all patients treated in this study satisfied the recommendation value of V20 established in previous reports (*i.e.* V20<25–30%). Nevertheless, severe RP could not be completely prevented in patients with relatively lower DVH parameters of the lung. By the use of 3D conformal radiotherapy to provide a minimal radiation field, we emphasise that three patients (2%) developed greater than or equal to Grade 3 RP. Our result indicated that Stage IV is also an important predictive factor for symptomatic RP, regardless of adjustment by DVH parameters. Among higher dosimetric parameters, according to RPA, patients with non-Stage IV were relatively lower risk (OR 1.27) in comparison with patients with stage IV (OR 6.53). In contrast, only 2 patients (18.2%) with Stage IV and lower dosimetric parameters developed symptomatic RP. Thus, we speculated that both higher dosimetric parameters and Stage IV rather than either alone may be associated with RP.

Because the Asakura et al [16] study had strict inclusion criteria, only 37 (28.7%) out of 129 consecutive patients were included in their study. We suppose that considerable selection bias regarding patient characteristics and type of treatment were present in their study, which would affect clinical outcomes. In the present

study, we analysed a relatively larger proportion of 165 consecutive patients (75.8%); therefore, we believe that our clinical results are more meaningful.

The late toxicity in other organs such as the heart, after definitive radiotherapy for oesophageal cancer patients, is thought to have become a more significant problem. Although heart toxicity in oesophageal cancer patients treated with definitive CRT has been reported [6], DVH analysis of the heart regarding development of adverse events has not been reported until now. We have not assessed late adverse events for the heart in the present study because of insufficient follow-up periods. In the future we are going to evaluate heart DVH parameters to predict late-occurring heart damage, including pericarditis, in oesophageal cancer patients treated with definitive CRT.

In conclusion, our study demonstrated that severe RP was also developed in patients treated with the minimal radiation field. Stage IV and the dosimetric factors were identified as an independent predictive factor for symptomatic RP in oesophageal cancer patients treated with CRT without prophylactic nodal irradiation.

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