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ORIGINAL PAPER

Scoring System for Predicting Response to Chemoradiotherapy, Including 5-Fluorouracil and Platinum, for Patients with Esophageal Cancer

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Abstract We have retrospectively evaluated clinical data before therapy to enable reliable prediction of the response of esophageal cancer to chemoradiotherapy (CRT). We analyzed 108 patients who received 5-fluorouracil and platinum combined with 60 Gy radiation for esophageal cancer. Factors significantly related to response were extracted by use of logistic regression analysis, and a response score (RS) was prepared by combining these factors. By multivariate analysis, nutritional status, T stage, M stage, and alkaline phosphatase were selected as significant factors that contributed independently to the response of esophageal cancer to CRT ($P < 0.05$). The odds ratios of the four selected factors was approximated and scored. The group with a high RS was found to include patients with complete response with a significantly higher frequency than the group with a low score (72.7% vs. 14.8%, $P < 0.001$). The RS is suggested to be an appropriate scoring system with which to predict response for these patients.

Keywords Esophageal cancer · Chemotherapy · Radiotherapy · Multivariate analysis · Treatment efficacy

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Introduction

Esophageal cancer is a lethal disease, with an estimated 10,548 new cases and 8.48 deaths per 100,000 people from this disease in Japan in 2001. The esophageal cancer of most patients (95%) in Japan histopathologically showed squamous cell carcinoma (SCC), and more than 50% of patients had lesions in the middle third of the thoracic esophagus.

Surgical resection has been widely accepted as the standard treatment for esophageal cancer, with techniques having improved over the decades. However, the prognosis after resection of thoracic esophageal cancer is generally poor, with a five-year survival rate of 20–42.4% [1–4]. The effects of chemotherapy combined with radiotherapy on esophageal cancer have been investigated since the 1980s. Several investigators have reported successful results in cases of local–regional carcinoma [5]. The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) has become a standard regimen, not only because of the clinical outcome but also because of the synergism between the two agents and radiosensitizing effects [6–8]. A recent report on chemoradiotherapy (CRT) indicated that it has a variety of advantages in the treatment of esophageal cancer [9, 10]. In a prospective randomized trial by the Radiation Therapy Oncology Group, which compared CRT with radiotherapy alone, the combined-modality arm demonstrated a significant improvement of survival, with a five-year survival rate of 27%, compared with 0% for radiotherapy alone [11, 12].

At present, a variety of factors regarding the biological state of tumors are reported to be related to the response to CRT [13, 14]. Overexpression of p53 was shown to be the most important factor in response to chemotherapy and radiotherapy [13]. Moreover, a recent report by Nakamura et al. [14] has shown that p21 correlated significantly with

response of esophageal cancer to CRT. However, these factors cannot be measured routinely in the clinic.

We therefore aimed to clarify significant factors associated with the response of esophageal cancer to CRT from various clinical data. Additionally, a response score (RS) was calculated by combining these factors, and its usefulness was analyzed. Predicting response using the RS is expected to be useful for determining the appropriate therapeutic approach for each patient.

Methods

Patients

Between 1995 and 2004, 199 patients with esophageal cancer were admitted to the Showa University Hospital. CRT was performed for 109 patients (54.8%), chemotherapy for 17 (8.5%), and radiotherapy for 30 (15.1%). The 109 patients who underwent CRT were enrolled in this study. One patient who could not complete the first course was excluded.

Diagnosis of esophageal cancer was based on tumor biopsy. Depth of tumor invasion, lymph node metastases, and distant metastasis were evaluated by means of air-contrast barium esophagography, esophagoscopy, neck, chest, and abdominal computed tomography (CT), bronchoscopy, and bone scan. Clinical TNM staging by the International Union against Cancer (UICC) method has been reviewed by radiologists and oncologists [15–18].

Chemotherapy consisted of protracted infusion of 5-FU 400 mg/m^2/day or 5-FU 450 mg/m^2/day on days 1–5 and 8–12, combined with CDDP 40 mg/m^2/day or nedaplatin (CDGP) 45 mg/m^2/day on days 1 and 8. This was repeated twice every five weeks. Concurrent radiotherapy was started on day 1 at 2 Gy/day for five days/week, the total-dose of radiation being 60 Gy, with a two-week break after a dose of 30 Gy. Patients who showed an objective response to the above mentioned treatment received additional chemotherapy consisting of protracted infusion of 5-FU 800 mg/m^2/day or 5-FU 900 mg/m^2/day on days 1–5, combined with CDDP 80 mg/m^2/day or CDGP 90 mg/ m^2/ day on day 1 [19–21].

The clinical study was approved by the Showa University Ethics Committee.

Methods

Host-related Factors

For each patient, we collected data on age, sex, body-mass index (BMI), performance status (PS), nutritional status, past history, family history, body-weight loss, and type of chemotherapy (CDDP or CDGP). The PS of patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) method. Nutritional status was divided into three groups—solid food, liquid food, and intravenous hyperalimentation (IVH) [19]. Nutritional status was determined as the worst intake at any time before treatment. Body-weight loss was defined as the difference between body weight in a healthy condition and that before treatment.

Tumor-related Factors

We collected data on clinical TNM staging, histological subtype (squamous cell carcinoma, or adenocarcinoma) and differentiation (well, moderately, or poorly), location of the tumor (upper, middle, or lower), and length of tumor.

Biochemical Examination

Results of blood tests performed immediately before the CRT for esophageal cancer were collected: white blood cell (WBC), hemoglobin (Hb), albumin (Alb), creatinine (Cr), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyltransferase (γ-GTP), lactate dehydrogenase (LDH), sodium (Na), C-reactive protein (CRP), and SCC antigen as a tumor marker.

Outcome

The patients were divided into a complete response (CR) group and a non-CR group (partial response (PR), stable disease (SD), and progressive disease (PD)). Responses to CRT were assessed using the World Health Organization (WHO) response criteria for measurable lesions. We also adopted the evaluation criteria proposed by the Japanese Society for Esophageal Disease for primary tumors [22]. The response was evaluated by esophagography, esophagoscopy, and neck, chest, and abdominal CT in each course. CR was defined as the complete disappearance of all measurable and assessable tumors for a minimum of 4 weeks. PR was defined as more than 50% reduction in the sum of the products of the longest diameter of a measurable tumor for a period of at least four weeks. PD was defined as a more than a 25% increase in the sum of the products of the longest diameter of measurable disease or the appearance of new lesions. SD was defined as the failure to observe a CR, PR, or PD for at least four weeks.

Statistical Analysis

The continuous variables were divided into two groups based on the median and mean values. Univariate analysis was performed using the χ^2 test between the CR and non-CR groups. Multivariate analysis was performed using logistic regression. Parameters that were significantly different in the univariate analysis between the two groups were entered into the multivariate analysis. Significant independent variables contributing to the response of esophageal cancer to CRT were extracted using stepwise selection methods. The odds ratios of the selected factors were compared and scored as an integer. We defined RS as the sum of scores in each patient. The accuracy of the scoring system was assessed by plotting observed versus predicted outcome. The patients were divided into two groups based on the distribution of their RS. The statistical analysis was performed using SPSS 11.0 J software (SPSS, Tokyo, Japan). P values < 0.05 were considered to be significant.

Results

Characteristics of Patients

Table 1 shows the host-related factors for all patients. Of the 108 patients studied, 97 (89.8%) were men and 11 (10.2%) were women; the mean age was 64.0 ± 8.3 years. Most of the patients had a good PS (PS0 85.2%). The nutritional status before treatment was solid food in 47 patients (43.5%), liquid food in 46 (42.6%), and IVH in 15 (13.9%).

Table 2 shows the tumor-related factors for all patients. The stage of the tumor was T4 in 50 patients (46.3%), N1 in 60 (55.6%), and M1 in 44 (41.1%). Most of the patients had histologically proven SCC (97.2%), and the location of the tumor was the middle in 54 patients (50%).

Table 3 shows the results from blood tests for all patients. Alb was lower than normal and CRP and SCC were higher than normal.

Table 1 Characteristics of the patients: host-related factors ($n = 108$)

Variable	Category	n (%) or mean ± SD
Age (years old)		64.0 ± 8.3
Sex	Male	97 (89.8)
	Female	11(10.2)
Body-mass index (kg/m^2)		20.6 ± 2.9
Performance status	0	92 (85.2)
	1	12 (11.1)
	2	4 (3.7)
Nutritional status	Solid food	47 (43.5)
	Liquid food	46 (42.6)
	IVH	15 (13.9)
Past history	+	20 (18.5)
Family history	+	50 (46.3)
Body-weight loss	+	63 (58.3)
Chemotherapy	5-FU/CDDP	72 (66.7)
	5-FU/CDGP	36 (33.3)

SD, standard deviation; IVH, intravenous hyperalimentation; 5-FU, 5-fluorouracil; CDDP, cisplatin; CDGP, nedaplatin

Outcome

The response of esophageal cancer to CRT was CR in 42 patients (39.3%), PR in 40 (37.4%), SD in 20 (18.7%), and PD in 5 (4.7%).

Univariate Analysis

Table 4 shows the results from univariate analysis. The CR group included more patients with a BMI ≥ 22 kg/m^2 than the non-CR group ($P = 0.003$). Regarding nutritional status, more patients were taking solid food ($P < 0.001$) in the CR group. With regard to clinical stage before treatment, patients in the non-CR group had a more advanced disease

Table 2 Characteristics of the patients: tumor-related factors ($n = 108$)

Variable	Category	n (%) or mean ± SD
Clinical TNM staging		
T stage	T1	13 (12.0)
	T2	8 (7.4)
	T3	37 (34.3)
	T4	50 (46.3)
N stage	N0	48 (44.4)
	N1	60 (55.6)
M stage	M0	63 (58.9)
	M1	44 (41.1)
Histological subtype	Squamous cell carcinoma	105 (97.2)
	Adenocarcinoma	3 (2.8)
Differentiation	Well	22 (21.4)
	Moderately	59 (57.3)
	Poorly	22 (21.4)
Location	Upper	16 (14.8)
	Middle	54 (50.0)
	Lower	38 (35.2)
Length (cm)		6.5 ± 2.9

SD, standard deviation

Table 3 Characteristics of the patients: blood tests ($n = 108$)

Variable	Mean ± S.D.
WBC ($\times 10^3/\mu l$)	7.9 ± 3.0
Hb (g/dL)	12.3 ± 1.7
Alb (g/dL)	3.5 ± 0.5
Cr (mg/dL)	0.9 ± 0.7
ALT (IU/L)	27.4 ± 39.7
LDH (IU/L)	357 ± 216
ALP (IU/L)	276 ± 123
Na (mEq/L)	138.9 ± 3.0
CRP (mg/dL)	1.9 ± 3.1
SCC (ng/ml)	3.0 ± 2.4

SD, standard deviation

Table 4 Univariate analysis of predictive factors in the response to chemoradiotherapy ($n = 108$)

Variable	Category	CR $n = 42$ n (%)	non-CR $n = 66$ n (%)	P value
Host-related factors				
Body-mass index (kg/m^2)	≥22	22 (52.4)	16 (24.2)	0.003*
	<22	20 (47.6)	50 (75.8)	
Nutritional status	Solid food	29 (69.0)	18 (27.3)	<0.001*
	Liquid food	11 (26.2)	35 (53.0)	
	IVH	2 (4.8)	13 (19.7)	
Tumor-related factors				
Clinical TNM staging				
T stage	T1–3	34 (81.0)	25 (37.9)	<0.001*
	T4	8 (19.0)	41 (62.1)	
N stage	N1	15 (35.7)	45 (68.2)	0.001*
M stage	M1	8 (19.0)	36 (55.4)	<0.001*
Length (cm)	≥5	22 (53.7)	54 (83.1)	0.002*
	<5	19 (46.3)	11 (16.9)	
Biochemical examination				
Alb (g/dL)	≥3.8	22 (52.4)	17 (25.8)	0.007*
	<3.8	20 (47.6)	49 (74.2)	
ALP (IU/L)	≥250	12 (29.3)	37 (56.9)	0.009*
	<250	29 (70.7)	28 (43.1)	
Na (mEq/L)	≥140	25 (59.5)	18 (27.3)	0.001*
	<140	17 (40.5)	48 (72.7)	
CRP (mg/dL)	≥0.2	22 (52.4)	57 (86.4)	<0.001*
	<0.2	20 (47.6)	9 (13.6)	
SCC (ng/mL)	≥0.8	22 (56.4)	53 (81.5)	0.007*
	<0.8	17 (43.6)	12 (18.5)	

* $P < 0.01$

IVH, intravenous hyperalimentation; 5-FU, 5-fluorouracil; CDDP, cisplatin; CDGP, nedaplatin

than those in the CR group (T stage, $P < 0.001$; N stage, $P = 0.001$; M stage, $P < 0.001$). Also, more patients had a tumor of length <5 cm in the CR group ($P = 0.002$). Ratios of patients with values of Alb and Na greater than the median and mean were significantly higher in the CR group than in the non-CR group ($P < 0.01$). On the other hand, ALP, CRP, and SCC were significantly lower in the CR group ($P < 0.01$).

Multivariate Analysis

In the logistic regression analysis, nutritional status, T stage, M stage, and ALP were selected as significant factors that contribute independently to response of esophageal cancer to CRT. Table 5 shows the odds ratio and the 95% confidence interval for each factor. The odds ratios (per unit increase) were 3.116, 3.219, 3.068, and 3.700, respectively ($P < 0.05$).

Scoring System

A simple algorithm was established to calculate the expected response of esophageal cancer to CRT. The integer score derived from odds ratios of four factors was selected by multivariate analysis: T1–3, 1 point; M0, 1 point; ALP < 250 IU/L, 1 point; the taking of solid food, 2 points; the taking of liquid food, 1 point (Table 6). The RS for a given patient was obtained by adding the scores for these four predictive factors. The RS ranged from 0 to 5. For example, a patient with IVH, T2, M0, and ALP ≥ 250 IU/L has a RS of 2.

Clinical Outcome Based on the Scoring System

The RS, the sum of the scores of four factors, was calculated for all patients. Plots of observed and predicted outcomes against RS values for 105 patients, excluding three whose ALP data were missing, are presented in Fig. 1. The patients were divided into two groups based on RS values, a low-score group (RS ≤ 3; $n = 61$) and a high-score group (RS 4, 5; $n = 44$). It was proven that the group with a high score included significantly more patients with CR than did the group with a low score (72.7% vs. 14.8%, $P < 0.001$, Table 7).

Discussion

Nutritional status, T stage, M stage, and ALP were selected as factors that contributed independently to the response

Table 5 Multivariate analysis of predictive factors in the response to chemoradiotherapy ($n = 108$)

Variable	Category	β	Odds ratio	95% Confidence interval	P value
Nutritional status	Solid vs Liquid vs IVH	1.137	3.116	1.278–7.601	0.012*
T stage	T1–3 vs T4	1.169	3.219	1.058–9.797	0.040*
M stage	M0 vs M1	1.121	3.068	1.006–9.358	0.049*
ALP (IU/L)	<250 vs ≥ 250	1.308	3.700	1.310–10.454	0.014*

IVH, intravenous hyperalimentation

If your patient takes solid food and IVH, you select IVH. You should select severe category

* $P < 0.05$

Table 6 Scoring system for response to chemoradiotherapy

Variable		Point[b]
T stage	T1–3	1
	T4	0
M stage	M0	1
	M1	0
ALP	<250 IU/L	1
	≥250 IU/L	0
Nutrition[a]	Solid food	2
	Liquid food	1
	IVH[c]	0

[a] You should chose one of these (solid food/liquid food/IVH) IVH, intravenous hyperalimentation

[b] The total points are 0–5

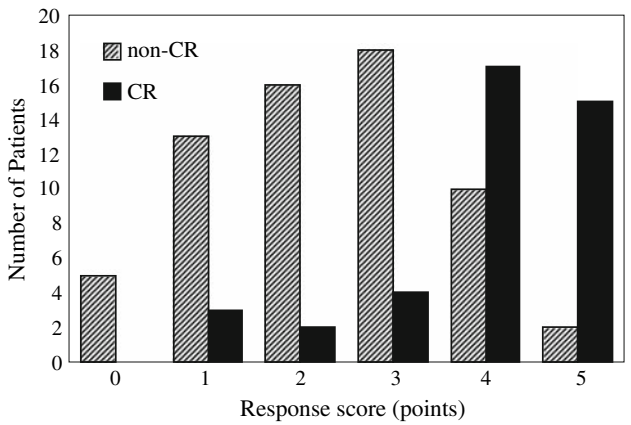

Fig. 1 Distribution of patients according to response score ($n = 105$)

Table 7 Association between patients and response to chemoradiotherapy ($n = 105$)

RS	Total no. of patients	Patients with CR		
		n	%	P value
4–5 points	44	32	72.7	<0.001*
0–3 points	61	9	14.8	

* $P < 0.05$

RS, response score; CR, complete response

after CRT of patients with esophageal cancer. It was found that tumor factor and nutritional status were the most important factors for these patients. In this study, outcome was investigated as a response to CRT. If the response could be predicted on the basis of earlier clinical factors, it could be used for clinical decision-making regarding the continuation of CRT.

We investigated the nutritional status and body weight of the patients before treatment. Nutritional disorders occur in most patients with advanced esophageal cancer, resulting in a poor quality of life. Patients with advanced esophageal cancer often show decreases in body weight, serum albumin levels, the proportion of lymphocytes, and immunologic function, due to poor nutritional conditions mainly resulting from dysphagia [23–26]. In this study, nutritional status was significantly better for the CR group than non-CR group. Moreover, BMI, Alb, and Na, which are also indices of nutritional status, were selected by the univariate analysis. Therefore, nutritional status before treatment is suggested to affect strongly the response after CRT for esophageal cancer.

T stage and M stage show the progress of cancer. In this study it was found that ratio of patients with CR was higher in the early stage than in the progressive stage (Stage I, 100%; Stage II, 57.7%; Stage III, 37.0%; Stage IV, 15.9%). It is reported that the stage before treatment is related to the prognosis after CRT [27]. In this study, using the factors T, N, and M separately in stage classification, we clarified which factors contributed to the response after CRT. As a result, factor T which indicates the extent of cancer, was selected as a factor relating to CR. It was suggested that the smaller the tumor, the greater the effect of CRT for esophageal cancer. Moreover, factor T was reported to be related to disease-free survival after combined 5-FU and radiation [28] and also after neoadjuvant CRT for esophageal cancer [29], Therefore, factor T is suggested to affect strongly the response after CRT for esophageal cancer.

Patients with distant organ metastasis are classified into Stage IV. Treatment for these patients has included palliative resection and CRT. Recently, concurrent CRT was potentially curative even in cases with locally advanced

esophageal cancer (i.e. T4 and/or M1 lymph node metastasis disease) [20, 30]. This study obtained similar results. CR was found in 15.9% of patients with Stage IV. However, patients with M1 did not achieve CR more easily than patients with M0. Therefore, factor M is suggested to affect strongly the response to CRT for esophageal cancer.

ALP is an enzyme distributed in all tissues, and an increase in this enzyme's activity indicates impairment of the tissue. In addition, the frequency of raised ALP IV in patients with malignant neoplasm is known to be high [21]. In this study, the isozyme of ALP was not measured in most patients. However, the ratio of patients with CR was significantly higher among patients with low ALP levels than among those with high ALP levels. Moreover, the ALP level is known to be related to prognosis after treatment including CDDP [31]. Therefore, ALP is expected to be an index for the progress of tumor which can be easily monitored.

The RS of each patient was calculated using four factors selected by the multivariate analysis, and the patients were divided into two groups according to the RS. As a result, the group with a high RS was found to include patients with CR with a significantly higher frequency than the group with a low score. Therefore, RS is suggested to be an appropriate scoring system to predict the response after CRT for esophageal cancer. In another study, a prognostic index consisting of CRP, body weight change, and clinical TNM staging has been reported to be useful for predicting the prognosis of patients with esophageal cancer [32]. Prediction of the response to CRT using the RS was thought to be more reliable than that using an individual factor.

In some studies the involvement of biological factors such as oncogenes, tumor suppressor genes, and growth factors in response to chemotherapy and radiotherapy has been studied [13, 14]. In these studies, overexpression of p51, p21, and vascular endothelial growth factor has been identified as related to response [13, 14]. However, these factors cannot be routinely investigated. On the other hand, the four factors selected in our study can be measured routinely in the clinic and predicting response using the RS is expected to be useful for determining the appropriate therapeutic approach for each patient. Furthermore, using such a scoring system, medical staff can obtain a common understanding about the response of the patients, leading to the appropriate medical care and instruction, important to a patient's quality of life.

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