Treatment Outcomes and Prognostic Factors for Thoracic Esophageal Cancer with Clinical Evidence of Adjacent Organ Invasion

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Abstract. *Background/Aim: The status of each patient with advanced esophageal cancer varies widely, and the prognosis is generally poor. We aimed to determine which prognostic factors are involved in the management of locally advanced esophageal cancer with adjacent organ invasion. Patients and Methods: We retrospectively investigated the therapeutic outcomes of 74 patients with thoracic esophageal cancer and clinical evidence of adjacent organ invasion but without distant metastasis. The predictive factors for a chemoradiotherapeutic response and survival were evaluated. Results: Definitive chemoradiotherapy (CRT), bypass surgery and CRT, as well as CRT followed by esophagectomy were carried out in 48 (64.9%), 17 (23.0%), and 9 (12.2%) patients, respectively. The median survival time (MST) of patients overall was 11.3 months. The MST of patients after definitive CRT, bypass surgery plus CRT and CRT followed by esophagectomy was 10.4, 11.0 and 16.4 months, respectively; MST did not differ significantly between patients. MST of patients with a complete response (CR), a partial response (PR) and stable (SD)/progressive (PD) disease as clinical outcomes of CRT was 52.6, 11.3 and 6.7 months, respectively; the MST was considerably longer in patients with, than in those without CR (CR vs. SD/PD, p<0.0001; CR vs. PR, p=0.0004). In multivariate analysis, age <60 years [odds ratio (OR)=7.74; 95% confidence interval (CI)=1.85-32.41; p=0.005] and hemoglobin ≥13 g/dl (OR=11.54; 95% CI=1.29-103.21; p=0.03) were independently associated with CR as an outcome of CRT, and serum albumin level ≥3.5 g/dl (OR=2.11; 95% CI=1.09-4.10; p=0.03) was independently associated with prolonged survival. Conclusion: Pre-treatment hemoglobin and albumin levels were valuable predictors of the outcome of CRT and survival, respectively. A better response to CRT as well as improved nutritional status prolonged the survival of patients with advanced esophageal cancer.*

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Key Words: Anemia, chemoradiotherapy, esophageal cancer, nutrition, prognostic factor.

Despite substantial improvements in screening and diagnosis, esophageal cancer is frequently very advanced at the time of presentation (1). The thoracic esophagus lacks serosa, and is closely surrounded by the trachea, bronchus, lung and aorta. Thus, esophageal cancer is more likely to invade these vital organs over time and become unresectable. The reported incidence of esophageal cancer invading adjacent organs is 12-30% (2-7).

Locally advanced esophageal cancer with adjacent organ invasion is generally treated by chemoradiotherapy (CRT) (8-11), and by a multimodal approach comprising of esophagectomy following down-staging and increasing tumor resectability due to induction therapy (2-7, 12-16). Nevertheless, the reported 5-year survival rate of such patients ranges from 0 to 42%, despite aggressive treatment (2-6, 8, 9, 15, 16).

Furthermore, patients with advanced esophageal cancer are frequently malnourished owing to dysphagia caused by esophageal stricture. The status of each patient with invasive thoracic esophageal cancer varies widely owing to variability in tumor extent and the patients' nutritional and general status. Thus, it is important to establish the factors that are involved in therapeutic effectiveness and prognosis for the tailoring of an optimized treatment strategy to suit the needs of individual patients and for further improvement of treatment results.

The present study retrospectively investigated the therapeutic outcomes of patients with thoracic esophageal cancer and clinical evidence of adjacent organ invasion but with no distant metastasis. It also evaluated clinical pre-treatment factors that might affect survival.

Table I. *Patients' characteristics.*

Clinical parameter	No. of patients (%) n=74
Mean age±SD (years)	66.4±10.4
Gender	
Male/female	61 (82.4)/13 (17.6)
Performance status	
0/1/2	58 (78.4)/15 (20.3)/1 (1.4)
Histological type	
Squamous cell carcinoma/others	70 (94.6)/4 (5.4)
Primary tumor location	
Upper third/middle third/lower third	25 (33.8)/39 (52.7)/10 (13.5)
Primary tumor length (mm, mean±SD)	71.2±22.3
Primary tumor depth*,†	
T1/2/3/4	1 (1.4)/1 (1.4)/12 (16.2)/60 (81.1)
Lymph node metastasis*	
N0/1	12 (16.2)/62 (83.8)
M1 lymph node*	
M0/1a/1b	49 (66.2)/12 (16.2)/13 (17.6)
Stage	
III/IVA/IVB	49 (66.2)/12 (16.2)/13 (17.6)
Body-mass index (kg/m^2, mean±SD)	19.9±3.4
Neutrophil to lymphocyte ratio	3.5±2.1
Hemoglobin (g/dl, mean±SD)	13.2±1.8
Albumin (g/dl, mean±SD)	3.9±0.5
Carcinoembryonic antigen (ng/ml, mean±SD)	5.1±8.3

SD, Standard deviation. *TNM grades according to the criteria of the TNM Classification of Malignant Tumors, Sixth edition. †T1-3: Metastatic lymph node invasion of adjacent organs.

Patients and Methods

Patients' characteristics. A total of 96 patients with thoracic esophageal cancer accompanied by clinical invasion of a primary tumor, or lymph node metastasis to adjacent organs, were treated at the Hiroshima University Hospital between January 2000 and August 2011. Among these patients, 74 were selected for the present study based on the following eligibility criteria: Eastern Cooperative Oncology Group performance status, 0-2; no distant organ metastasis; no concomitant advanced cancer; adequate organ function; and CRT as the initial treatment. Patients in poor general health who underwent only palliative radiation therapy without chemotherapy were excluded. Patients with the M1 lymph node within the radiation field were included in the study. We obtained appropriate approval for this study from the Institutional Review Board of Hiroshima University (#eki-728).

Table I shows the clinical characteristics of the patients (61 males and 13 females; mean age, 66.4±10.4 years) enrolled in our study. The clinicopathological profile of each patient was based on the TNM Classification of Malignant Tumors Sixth edition (17).

We also analyzed the body-mass index, neutrophil to lymphocyte ratio, hemoglobin (HB), serum albumin (ALB) and carcinoembryonic antigen levels as pre-treatment clinical parameters that might affect the outcomes of CRT and survival (Table I).

Table II. *Adjacent organs involved with primary tumor or metastatic lymph nodes.*

Organ	n=91* (%)
Trachea and/or bronchus**	45 (49.5)
Aorta	25 (27.5)
Pericardium	5 (5.5)
Pulmonary vein	4 (4.4)
Common carotid artery***	3 (3.3)
Internal jugular vein***	3 (3.3)
Liver***	2 (2.2)
Subclavian artery***	2 (2.2)
Diaphragm***	1 (1.1)
Celiac artery***	1 (1.1)
Number of invaded organs	n=74 (%)
1/2/3	58 (78.4)/15 (20.3)/1 (1.4)

*There are cases with more than one invaded organs. **Six out of 45 cases involved invasion through a metastatic lymph node. ***All cases involved invasion through a metastatic lymph node.

Pre-treatment evaluation. Pre-treatment work-up included a physical examination, standard laboratory tests, chest radiography, upper gastrointestinal endoscopy, esophagography and computed tomography (CT) imaging of the neck, chest and abdomen; and from 2004, systematic positron emission tomography/CT imaging. Patients with suspected tumor invasion of the respiratory tract were also assessed using bronchoscopy.

The clinical diagnosis of tumor invasion to adjacent organs was generally determined from CT images as obvious displacement and deformation of an organ by a tumor, accompanied by the absence of a fat layer between the primary tumor or metastatic lymph node and the adjacent organ. Airway invasion was defined as the displacement, indentation or flattening of the trachea or bronchus by a tumor or by a tumor protruding into the airway on CT images (Figure 1A), or by direct visualization on bronchoscopy. Aortic invasion was defined as direct contact between the tumor and aorta (Picus angle) exceeding 90˚ without a fat layer on CT images (Figure 1B) (18). Radiological evaluations of tumor stage for all patients were reviewed in pre-treatment meetings with radiologists, surgeons and oncologists at our hospital.

When the presence or absence of adjacent organ invasion was uncertain, the lower category (T3) was selected according to the general rule for uncertainty in TNM staging. Therefore, patients were excluded from the present study when there was clinical uncertainty regarding adjacent organ invasion.

Adjacent organs involved with primary tumor or metastatic lymph nodes. Table II describes the invasion into adjacent organs by primary tumors or metastatic lymph nodes. Clinical tumor invasion most frequently involved the trachea and/or bronchus (n=45; 49.5%) and the aorta (n=25; 27.5%). One organ was invaded in the majority of patients at the time of initial diagnosis.

Chemoradiotherapy. Three main CRT regimens were administered during the study. From 2000 to 2002, radiation was combined with low dose-cisplatin and 5-fluorouracil regimens consisting of 5 mg/m^2/day of cisplatin and a continuous infusion of 250 mg/m^2/day of 5-fluorouracil

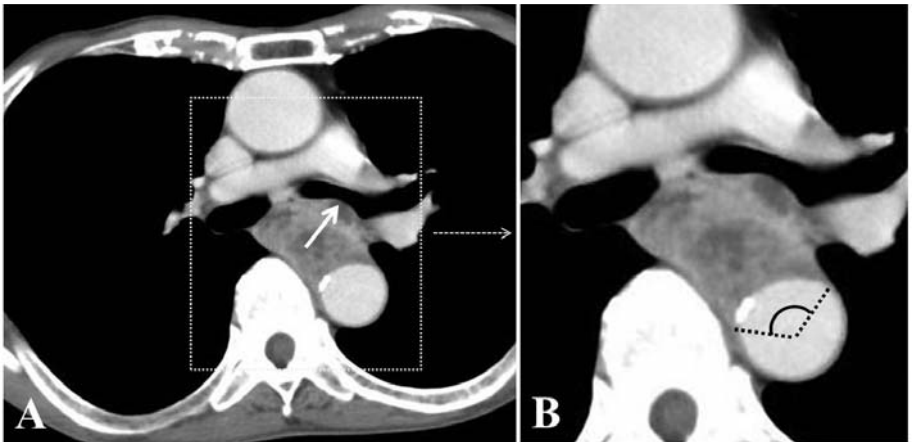

Figure 1. *Chest computed tomography (CT) images of a representative patient with bronchial and aorta invasion. A: Chest CT image showing obvious deformation of the left main bronchus due to esophageal cancer (solid arrow). B: Chest CT image of the same patient showing that the Picus angle exceeded 90˚, without a fat layer between the esophageal cancer and thoracic aorta.*

for the first five days of each week until the end of the course of radiotherapy (RT) (19). Between 2003 and 2007, the regimen comprised of 7.5 mg/m^2/day of docetaxel on days 1, 8, 22 and 29 and a continuous infusion of 250 mg/m2/day of 5-fluorouracil for the first five days each week until the completion of RT (20). The regimen from 2008 consisted of a standard dose of 70 mg/m^2/day of cisplatin on days 1 and 29, and a continuous infusion of 700 mg/m^2/day of 5-fluorouracil on days 1-4 and 29-32 during RT. A few patients with kidney dysfunction were treated with nedaplatin instead of cisplatin, or only with 5-fluorouracil.

Along with these chemotherapy treatments, patients received a total of 50-72 Gy of external-beam irradiation at fractionated doses of 1.8-2.0 Gy/day. Radiation was usually delivered to the primary esophageal lesion and to periesophageal and metastatic lymph nodes.

Surgery. Some patients with tumors that had been reduced and were possibly resectable after receiving a 40 Gy total dose of CRT provided written informed consent to undergo transthoracic esophagectomy with lymphadenectomy. Some patients with poor oral intake and airway invasion with a prediction of esophago-respiratory fistula, or an actual esophago-respiratory fistula, also underwent esophageal bypass surgery before or after CRT.

Clinical assessment of the efficacy of chemoradiotherapy. The efficacy of neoadjuvant CRT was clinically evaluated using CT and endoscopy, with biopsies at 1-2 months after CRT. The clinical outcomes of CRT were judged as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to the guidelines for clinical and pathological studies on carcinoma of the esophagus published by the Japan Esophageal Society (10th edition) (21).

CR at the primary tumor site was defined as the disappearance of the tumor lesion with the endoscopically-proven absence of cancer cells in biopsy specimens. Specimens comprising obvious residual tumor, erosion due to radiation esophagitis and protruding lesions similar to submucosal tumors indicated failure to achieve CR.

With regard to metastatic lymph nodes, CR was evaluated as the disappearance, or a decrease to normal size or below normal size, of all target lesions on CT images. PR was defined as a >30% reduction in the sum of the largest dimensions of measurable target lesions on CT images, and a PD was defined as at least a 20% increase in the sum of largest dimensions of measurable target lesions, or the appearance of new lesion. SD was assessed as the absence of PR or PD.

Overall response was determined based on combinations of primary tumor and metastatic lymph node responses, and the presence or absence of new lesions. When a target lesion was not evident and only non-target lesions such as primary esophageal cancer without lymph node metastasis were present, the overall response was determined exclusively from the responses of the non-target lesions.

Survival and statistical analysis. Outcomes were evaluated in March 2013. Patient survival was calculated from the first day of treatment until the date of death or the most recent follow-up. Survival data were analyzed using Kaplan-Meier curves and compared using the log-rank test. The effects of the various clinicopathological parameters on CRT outcomes were evaluated using univariate analysis; covariates with a p-value of <0.1 in univariate analysis were entered into a multivariate analysis using logistic regression analysis to assess their independent influences. Furthermore, the effects of various clinicopathological parameters on survival were evaluated using univariate analysis; covariates with a p-value of <0.1 were entered into a multivariate Cox proportional hazards analysis to assess their independent influence. Data were statistically analyzed using the StatView software, version 5 (SAS Institute, Cary, NC, USA). Statistical significance was accepted at $p<0.05$.

Results

Treatment of adjacent organ invasion. Table III shows details of the various treatments. All patients underwent either induction or definitive CRT. Definitive CRT, CRT plus esophageal bypass, and CRT plus esophagectomy were carried out in 48 (64.9%), 17 (23.0%) and 9 (12.2%) patients, respectively; esophageal bypass surgery was performed in 12 and 5 patients before and after CRT, respectively. Among 9 patients who

Table III. *Treatments for patients with tumor invasion of an adjacent organ.*

Treatment	n=74 (%)
CRT	48 (64.9)
CRT + esophageal bypass (n=17)	Before CRT: 12 (16.2), After CRT: 5 (6.8)
CRT + esophagectomy	9 (12.2)*
Chemotherapy regimen**	DOC/5FU: 37 (50.0), standard dose CDDP/5FU: 18 (24.3)
	low-dose CDDP/5FU: 16 (21.6), NED/5FU: 2 (2.7), 5FU: 1 (1.4)
Radiation therapy**	61.5 Gy±8.2 Gy (mean±SD, 40-72 Gy)
	<60 Gy: 11 (14.9), ≥60 Gy:63(85.1)
Clinical effect of CRT**	CR: 12 (16.2), PR: 46 (62.2), SD: 6 (8.1), PD: 10 (13.5)

CR, Complete response; CRT, chemoradiotherapy; CDDP, cisplatin; 5FU, 5-fluorouracil; DOC, docetaxel; NED, nedaplatin; PR, partial response; PD, progressive disease; SD, stable disease. *Induction CRT at a total dose of 40 Gy and esophagectomy were performed in eight patients, and salvage esophagectomy after definitive CRT was performed in one. **Eight patients that underwent induction CRT at a total dose of 40 Gy and esophagectomy were included.

underwent esophagectomy, 8 underwent transthoracic esophagectomy with lymphadenectomy to treat tumors that were reduced by CRT at a total dose of 40 Gy and had become potentially resectable, and 1 patient with tumor regrowth after CRT underwent salvage esophagectomy. Resections were complete in 7 (77.8%) patients and partial in 2 (22.2%) owing to residual tumor resulting from primary tumor invasion of the trachea and the pulmonary vein, respectively.

Among all patients who received definitive or induction CRT, chemotherapy regimens with docetaxel/5-fluorouracil, standard dose cisplatin/5-fluorouracil, and low dose cisplatin/5-fluorouracil comprised the main treatment approach for 37 (50.0%), 18 (24.3%) and 16 (21.6%) patients, respectively. Only 1 (1.4%) and 2 (2.7%) patients were treated with 5-fluorouracil alone and nedaplatin/5-fluorouracil, respectively, owing to kidney dysfunction. Radiation therapy was delivered at a total dose of 61.5±8.2 (mean±SD; range=40-72) Gy.

Effects of chemoradiotherapy. Table III also shows the clinical effects of CRT including definitive and induction therapy. The clinical outcome of CRT was CR in 12 (16.2 %) patients, PR in 46 (62.2%), SD in six (8.1%) and PD in 10 (13.5%). Among 10 patients with PD, one had a progressive primary tumor, one had metastatic lymph nodes and eight developed lymph node metastasis outside the radiation field, or distant metastasis during or after CRT.

Survival of patients with thoracic esophageal cancer and adjacent organ invasion. Seven patients remained alive at the time of the outcome analysis, and 59 and 4 patients had died of esophageal cancer and unrelated causes, respectively. Four patients were lost to follow-up after referral for palliative/hospice care. The median overall survival time (MST) of all patients was 11.3 months, and the 1-, 3- and 5-year overall survival rates were 47.4%, 17.9% and 12.7%, respectively (Figure 2).

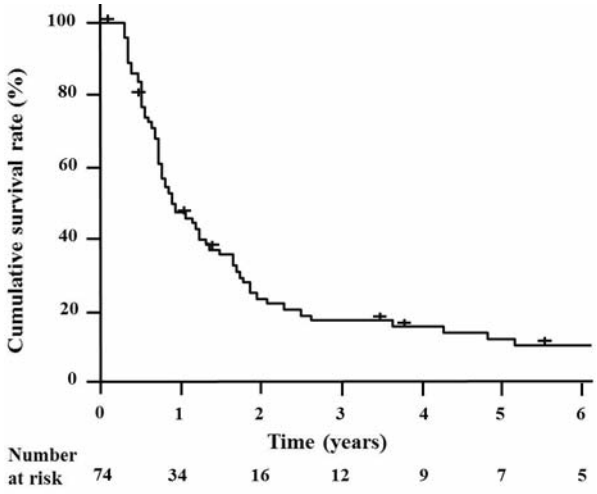

Figure 2. *Overall survival time of all patients with adjacent organ invasion.*

The MST of the patients only undergoing definitive CRT, esophageal bypass plus CRT and esophagectomy after CRT was 10.4, 11.0 and 16.4 months, respectively. Overall survival did not significantly differ between patients who underwent esophagectomy (p=0.26) or esophageal bypass (p=0.33) and those treated only with CRT (Figure 3).

All patients underwent induction or definitive CRT. Therefore, we also assessed survival with respect to the clinical effects of CRT. The MST of patients with CR, PR and SD/PD was 52.6, 11.3 and 6.7 months, respectively. The 1-, 3- and 5-year overall survival rates of patients with CR were 91.7%, 66.7% and 48.6%, respectively, and the 1-, 3- and 5-year overall survival rates of patients with PR were 46.7%, 10.1% and 6.7%, respectively. The 1- and 3-year overall survival rates of patients with SD/PD were 14.1% and 0%, respectively. Overall survival significantly differed

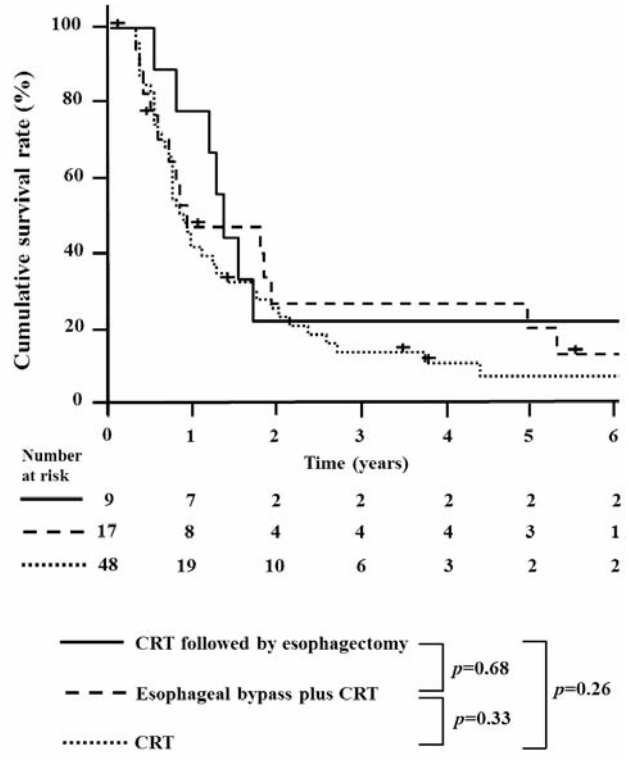

Figure 3. *Overall survival times of patients undergoing only definitive chemoradiotherapy (CRT), esophageal bypass plus CRT and esophagectomy after CRT.*

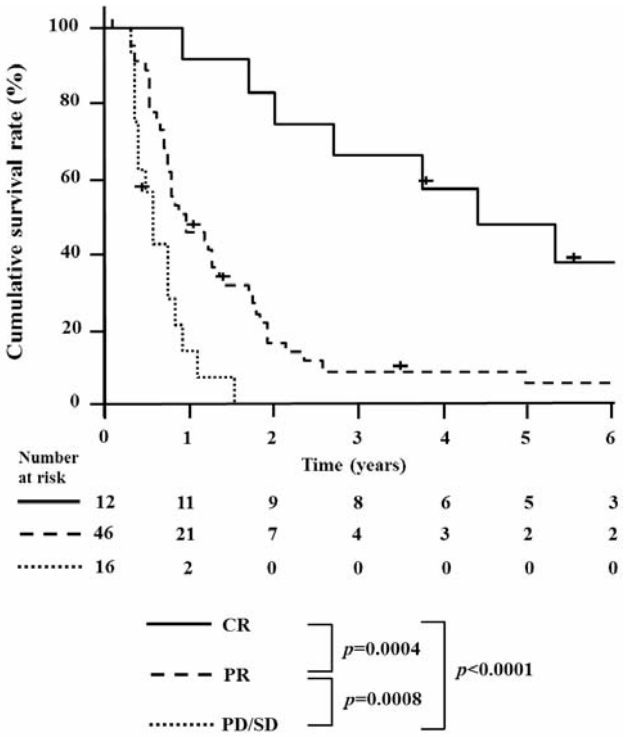

Figure 4. *Overall survival times with respect to complete response (CR), partial response (PR) and progressive disease (PD)/stable disease (SD) after chemoradiotherapy (CRT).*

between patients with CR ($p<0.0001$) or PR ($p=0.0008$) and those with SD/PD, and between those with CR and PR ($p=0.0004$; Figure 4).

Predictors of response to CRT. The prognosis was clearly better for patients with thoracic esophageal cancer and adjacent organ invasion, where the clinical outcome of CRT was CR. We therefore assessed the pre-treatment clinical factors that might predict CR to CRT (Table IV) using univariate analysis. We found that only age <60 years ($p=0.007$) and HB ≥13 g/dl ($p=0.04$) significantly correlated with CR to CRT. Only these covariates had a *p*-value of <0.1 and were subsequently entered into a multivariate analysis. Multivariate analysis also identified these factors as being independent predictors [age <60 years, odds ratio (OR)=7.74; 95% confidence interval (CI)=1.85-32.41, $p=0.005$; HB ≥13 g/dl, OR=11.54, 95% CI=1.29-103.21, $p=0.03$].

Prognostic factors for thoracic esophageal cancer with adjacent organ invasion. Table V shows the possible pre-treatment clinical factors that affect survival in thoracic esophageal cancer with adjacent organ invasion evaluated using a Cox regression model. Univariate analysis of prognostic factors showed that a neutrophil-to-lymphocyte ratio of <5 ($p=0.047$), HB ≥13 g/dl ($p=0.02$) and ALB level of ≥3.5 g/dl ($p=0.003$) significantly correlated with prolonged survival. The covariates with a *p*-value of <0.1 in the univariate analysis were included in the COX regression multivariate analysis, which identified the levels of ALB (≥3.5 g/dl; OR=2.11, 95% CI=1.09-4.10, $p=0.03$) as being independent prognostic factors for esophageal cancer with adjacent organ invasion. The performance status (0; OR=1.77, 95% CI=0.96-3.27, $p=0.07$) and HB (≥13 g/dl; OR=1.70, 95% CI=0.99-2.92, $p=0.06$) were marginally significant for prolonged survival.

Discussion

We have described the treatment outcomes and factors that could predict responses to CRT, as well as the survival of patients with thoracic esophageal cancer and clinical evidence of adjacent organ invasion. We show that patients with CR to CRT survived much longer than those without CR, regardless of treatment strategies such as definitive CRT, bypass surgery and esophagectomy. Furthermore, the pre-treatment clinical factors of age <60 years and a HB level of ≥13 g/dl were independently associated with CR to CRT, and a serum ALB level of ≥3.5 g/dl was independently associated with prolonged survival.

Table IV. *Univariate and multivariate analysis of predictive factors of chemoradiotherapy response.*

Clinical parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age: <60 *vs.* ≥60 years	6.27	1.65-23.8	0.007	7.74	1.85-32.41	0.005
Sex: Male *vs.* female	1.08	0.21-5.63	0.93	–	–	–
Performance status: 0 *vs.* 1, 2	1.02	0.56-6.76	0.30	–	–	–
Body-mass index: <18 *vs.* ≥18 kg/m^2	1.13	0.30-4.22	0.85	–	–	–
Neutrophil to lymphocyte ratio: <5 *vs.* ≥5	1.08	0.21-5.62	0.93	–	–	–
Hemoglobin: <13 *vs.* ≥13 g/dl	9.06	1.10-74.54	0.04	11.54	1.29-103.21	0.03
Albumin: <3.5 *vs.* ≥3.5 g/dl	3.51	0.42-29.49	0.25	–	–	–
Carcinoembryonic antigen: <5 *vs.* ≥5 ng/ml	1.13	0.27-4.69	0.86	–	–	–
Tumor location: Upper *vs.* middle and lower	1.50	0.42-5.32	0.53	–	–	–
Tumor length: <70 *vs.* ≥70 mm	1.39	0.40-4.78	0.61	–	–	–
Tumor depth: T1-3 *vs.* T4	1.55	0.36-6.67	0.56	–	–	–
Number of metastatic lymph nodes: 0-2 *vs.* ≥3	1.30	0.37-4.58	0.68	–	–	–
cStage: III *vs.* IV	1.65	0.40-6.76	0.49	–	–	–
Invasion to airway: No *vs.* yes	1.26	0.34-4.65	0.73	–	–	–
Invasion to aorta: No *vs.* yes	1.65	0.40-6.74	0.49	–	–	–
Number of invaded organs: 1 *vs.* 2, 3	3.83	0.46-32.26	0.22	–	–	–

CI, Confidence interval; OR, odds ratio. Univariate and multivariate analyses were performed using the logistic regression model.

Table V. *Univariate and multivariate analysis of survival time of patients with tumor invasion of adjacent organ.*

Clinical parameters	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age: <60 *vs.* ≥60	1.26	0.73-2.17	0.41	–	–	–
Sex: Male *vs.* Female	1.02	0.54-1.92	0.95	–	–	–
Performance status: 0 *vs.* 1, 2	1.70	0.93-3.12	0.08	1.77	0.96-3.27	0.07
Body-mass index: <18 *vs.* ≥18	1.40	0.83-2.37	0.20	–	–	–
Neutrophil to lymphocyte ratio: <5 *vs.* ≥5	1.91	1.01-3.62	0.047	1.68	0.84-3.36	0.14
Hemoglobin: <13 *vs.* ≥13	1.85	1.10-3.10	0.02	1.70	0.99-2.92	0.06
Albumin: <3.5 *vs.* ≥3.5	2.56	1.38-4.77	0.003	2.11	1.09-4.10	0.03
Carcinoembryonic antigen: <5 *vs.* ≥5	1.04	0.59-1.84	0.90	–	–	–
Tumor location: Upper *vs.* Middle and Lower	1.04	0.62-1.74	0.89	–	–	–
Tumor length: <70 *vs.* ≥70	1.56	0.94-2.58	0.08	1.33	0.78–2.27	0.29
Tumor depth: T1-3 *vs.* T4	1.05	0.55-2.02	0.90	–	–	–
Number of metastatic lymph nodes: 0-2 *vs.* 3–	1.34	0.80-2.24	0.26	–	–	–
cStage: III *vs.* IV	1.20	0.71-2.02	0.50	–	–	–
Invasion to airway: – *vs.* +	1.18	0.71-1.95	0.53	–	–	–
Invasion to aorta: – *vs.* +	1.00	0.60-1.68	0.99	–	–	–
Number of invaded organs: 1 *vs.* 2,3	1.32	0.72-2.42	0.37	–	–	–

CI, Confidence interval; OR, odds ratio. Univariate and multivariate analyses were performed using the Cox regression model.

Although obvious infiltration of adjacent structures by esophageal cancer is clearly evident on CT, magnetic resonance imaging (MRI), endoscopic ultrasonographic and bronchoscopic images, the correct identification of a slight invasion is difficult. The reported ranges of diagnostic accuracy of adjacent organ invasion are 77%-87.5% for endoscopic ultrasonography (22, 23), 43.8%-80% for CT (18, 23) and 87% for MRI (24). The diagnosis of adjacent organ invasion varies somewhat owing to the diagnostic modality and criteria, and thus tumor staging and therapeutic strategies might be altered according to the different diagnoses. Furthermore, a pre-treatment diagnosis might be associated with differences in the reported prognoses of patients with thoracic esophageal cancer who are clinically diagnosed with adjacent organ invasion (2-6, 8, 9, 15, 16).

The reported treatment strategies for these diseases include induction therapy followed by surgery (2-7, 12-17) and definitive CRT (8-11). Although definitive CRT is generally applied to treat esophageal cancer with obvious adjacent organ invasion, multimodal therapy with surgery might be effective for some patients whose tumors were reduced in size and potentially resectable after induction therapy. However, determination as to whether or not surgical resection should be indicated, or whether or not subsequent CRT should be provided at a definitive dose, is difficult for patients with a good response to induction therapy.

In the present study, the prognosis did not differ significantly between patients who underwent CRT and esophagectomy, and those treated only by definitive CRT; the prognosis was more obviously favorable for patients with a clinical CR after CRT than for those with SD and PD, and with PR. Previous studies involving esophageal cancer with adjacent organ invasion have also reported that there was no difference in the survival rate between patients who underwent esophagectomy and those who did not, among the responders to induction CRT; the prognosis of these patients was not influenced by esophagectomy but by the response to CRT (5, 16). Thus, the prognosis of such patients might be most influenced by the response to CRT, and a more effective CRT regimen should be developed to improve the prognosis of locally advanced esophageal cancer with adjacent organ invasion.

We also investigated pre-treatment clinical parameters that might influence the outcome of CRT, and the pre-treatment HB level was found to be significantly associated with the efficacy of CRT. Furthermore, the HB levels were marginally significant for prolonged survival. Similarly, the HB levels have been reported to be associated with sensitivity (25), locoregional control (26, 27) and survival (26, 28-30) after radiation therapy for esophageal cancer with or without chemotherapy. Tumor-associated and therapy-induced anemia are major pathogenetic mechanisms that are involved in the development of tumor hypoxia, which can cause patients to become refractory to radiation and some forms of chemotherapy (31). Therefore, anemia is an extremely important factor associated with the therapeutic effect.

Furthermore, in the present study, the analysis of prognostic factors demonstrated that pre-treatment serum ALB levels were significantly associated with prolonged survival. However, tumor size, lymph node metastasis and clinical stage were not significant factors for prognosis. Because our patients were limited to those who already had extremely advanced esophageal cancer with adjacent organ invasion and a poor prognosis, the factors indicating locoregional extent might not have influenced prognosis.

The serum ALB levels can serve as a useful prognostic factor regarding the outcome of patients with esophageal cancer treated using induction CRT and surgery (32), RT (33) and definitive CRT (34). Furthermore, ALB levels of >3.5 g/dl is the only independent predictive factor of CR to CRT (35). Almost all patients with advanced esophageal cancer have poor nutritional status due to dysphagia caused by esophageal stricture. Pre-treatment nutritional status might be involved in the general condition of a patient, their response to CRT and the achievement of CR, and could eventually influence the survival of patients with advanced esophageal cancer. Therefore, in order to improve outcomes, more aggressive administration of oral nutritional supplements and nutritional intervention, by means of nasogastric or gastrostomy feeding, might be required before and during CRT in order to correct malnutrition.

In conclusion, the therapeutic outcome of patients with thoracic esophageal cancer and adjacent organ invasion was influenced by anemia and serum albumin. Our results indicate that not only the outcome of CRT, but also improved nutritional status prolong the survival of patients with locally advanced esophageal cancer accompanied by adjacent organ invasion.

Disclosures

The Authors have no conflicts of interest or financial ties to disclose.

References

1 Enzinger PC and Mayer RJ: Esophageal cancer. N Engl J Med *349*: 2241-2252, 2003.

2 Miyata H, Yamasaki M, Kurokawa Y, Takiguchi S, Nakajima K, Fujiwara Y, Mori M and Doki Y: Clinical relevance of induction triplet chemotherapy for esophageal cancer invading adjacent organs. J Surg Oncol *106*: 441-447, 2012.

3 Noguchi T, Moriyama H, Wada S, Takeno S, Wakisaka M, Mori H and Uchida Y: Resection surgery with neoadjuvant chemoradiotherapy improves outcomes of patients with T4 esophageal carcinoma. Dis Esophagus *16*: 94-98, 2003.

4 Ikeda K, Ishida K, Sato N, Koeda K, Aoki K, Kimura Y, Iwaya T, Ogasawara S, Iijima S, Nakamura R, Uesugi N, Maesawa C and Saito K: Chemoradiotherapy followed by surgery for thoracic esophageal cancer potentially or actually involving adjacent organs. Dis Esophagus *14*: 197-201, 2001.

5 Fujita H, Sueyoshi S, Tanaka T, Tanaka Y, Sasahara H, Shirouzu K, Suzuki G, Hayabuchi N and Inutsuka H: Prospective non-randomized trial comparing esophagectomy followed by chemoradiotherapy *versus* chemoradiotherapy followed by esophagectomy for T4 esophageal cancers. J Surg Oncol *90*: 209-219, 2005.

6 de Manzoni G, Pedrazzani C, Pasini F, Bernini M, Minicozzi AM and Giacopuzzi S: Chemoradiotherapy followed by surgery for squamous cell carcinoma of the thoracic esophagus with clinical evidence of adjacent organ invasion. J Surg Oncol *95*: 261-266, 2007.

7 Tachibana M, Dhar DK, Kinugasa S, Yoshimura H, Shibakita M, Ohno S, Ueda S, Fujii T, Kohno H and Nagasue N: Surgical treatment for locally advanced (T4) squamous cell carcinoma of the thoracic esophagus. Dysphagia *17*: 255-261, 2002.

8 Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Ishikura S, Ogino T, Miyata Y, Seki S, Kaneko K and Nakamura A: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol *17*: 2915-2921, 1999.

9 Crosby TD, Brewster AE, Borley A, Perschky L, Kehagioglou P, Court J and Maughan TS: Definitive chemoradiation in patients with inoperable oesophagus carcinoma. Br J Cancer *90*: 70-75, 2004.

10 Nishimura Y, Suzuki M, Nakamatsu K, Kanamori S, Yagyu Y and Shigeoka H: Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys *53*: 134-139, 2002.

11 Itoh Y, Fuwa N, Matsumoto A, Asano A and Morita K: Outcomes of radiotherapy for inoperable locally advanced (T4) esophageal cancer-retrospective analysis. Radiat Med *19*: 231-235, 2001.

12 Makino T and Doki Y: Treatment of T4 esophageal cancer. Definitive chemo-radiotherapy *vs*. chemo-radiotherapy followed by surgery. Ann Thorac Cardiovasc Surg *17*: 221-228, 2011.

13 Ancona E, Ruol A, Castoro C, Chiarion-Sileni V, Merigliano S, Santi S, Bonavina L and Peracchia A: First-line chemotherapy improves the resection rate and long-term survival of locally advanced (T4, any N, M0) squamous cell carcinoma of the thoracic esophagus. Ann Surg *226*: 714-724, 1997.

14 Malaisrie SC, Untch B, Aranha GV, Mohideen N, Hantel A and Pickleman J: Neoadjuvant chemoradiotherapy for locally advanced esophageal cancer. Arch Surg *139*: 532-539, 2004.

15 Morita M, Toh Y, Saeki H, Sugiyama M, Ohgaki K, Maehara S, Minami K, Ikeda Y, Sakaguchi Y, Okamura T, Uehara S and Maehara Y: Clinical Significance of Chemoradiotherapy and Surgical Resection for cT4 Esophageal Cancer. Anticancer Res *32*: 3275-3282, 2012.

16 Fujita H, Sueyoshi S, Tanaka T, Tanaka Y, Matono S, Mori N, Shirouzu K, Yamana H, Suzuki G, Hayabuchi N and Matsui M: Esophagectomy: Is it necessary after chemoradiotherapy for a locally advanced T4 esophageal cancer? Prospective nonrandomized trial comparing chemoradiotherapy with surgery *versus* without surgery. World J Surg *29*: 25-31, 2005.

17 Sobin LH and Wittekind C: TNM Classification of Malignant Tumours, Sixth edn. Wiley, New York: John & Sons, 2002.

18 Picus D, Balfe DM, Koehler RE, Roper CL and Owen JW: Computed tomography in the staging of esophageal carcinoma. Radiology *146*: 433-438, 1983.

19 Shimizu K, Hihara J, Yoshida K and Toge T: Clinical evaluation of low-dose cisplatin and 5-fluorouracil as adjuvant chemoradiotherapy for advanced squamous cell carcinoma of the esophagus. Hiroshima J Med Sci *54*: 67-71, 2005.

20 Hihara J, Yoshida K, Hamai Y, Emi M, Yamaguchi Y and Wadasaki K: Phase I study of docetaxel (TXT) and 5-fluorouracil (5FU) with concurrent radiotherapy in patients with advanced esophageal cance. Anticancer Res *27*: 2597-2603, 2007.

21 Japan Esophageal Society: Japanese Classification of Esophageal Cancer, tenth edition: parts II and III. Esophagus *6*: 71-94, 2009.

22 Gheorghe C, Stanescu C, Gheorghe L, Bancila I, Herlea V, Becheanu G, Voinea D, Iacob R, Lupescu I, Anghel R, Croitoru A and Popescu I: Preoperative noninvasive EUS evaluation in patients with esophageal cancer considered for esophagectomy. J Gastrointestin Liver Dis *15*: 137-141, 2006.

23 Chak A, Canto M, Gerdes H, Lightdale CJ, Hawes RH, Wiersema MJ, Kallimanis G, Tio TL, Rice TW and Boyce HW Jr: Prognosis of esophageal cancers preoperatively staged to be locally invasive (T4) by endoscopic ultrasound (EUS): a multicenter retrospective cohort study. Gastrointest Endosc *42*: 501-506, 1995.

24 Takashima S, Takeuchi N, Shiozaki H, Kobayashi K, Morimoto S, Ikezoe J, Tomiyama N, Harada K, Shogen K and Kozuka T: Carcinoma of the esophagus: CT *vs*. MR imaging in determining resectability. Am J Roentgenol *156*: 297-302, 1991.

25 Yi Y, Li B, Sun H, Zhang Z, Gong H, Li H, Huang W and Wang Z: Predictors of sensitivity to chemoradiotherapy of esophageal squamous cell carcinoma. Tumour Biol *31*: 333-340, 2010.

26 Zhao KL, Liu G, Jiang GL, Wang Y, Zhong LJ, Wang Y, Yao WQ, Guo XM, Wu GD, Zhu LX and Shi XH: Association of haemoglobin level with morbidity and mortality of patients with locally advanced oesophageal carcinoma undergoing radiotherapy – a secondary analysis of three consecutive clinical phase III trials. Clin Oncol *18*: 621-627, 2006.

27 Rades D, Golke H, Schild SE and Kilic E: The impact of tumor expression of erythropoietin receptors and erythropoietin on clinical outcome of esophageal cancer patients treated with chemoradiation. Int J Radiat Oncol Biol Phys *71*: 152-159, 2008.

28 Zenda S, Hironaka S, Boku N, Yamazaki K, Yasui H, Fukutomi A, Yoshino T, Onozawa Y and Nishimura T: Impact of hemoglobin level on survival in definitive chemoradiotherapy for T4/M1 lymph node esophageal cancer. Dis Esophagus *21*: 195-200, 2008.

29 Zhang HQ, Wang RB, Yan HJ, Zhao W, Zhu KL, Jiang SM, Hu XG and Yu JM: Prognostic significance of CYFRA21-1, CEA and hemoglobin in patients with esophageal squamous cancer undergoing concurrent chemoradiotherapy. Asian Pac J Cancer Prev *13*: 199-203, 2012.

30 Valencia Julve J, Alonso Orduña V, Escó Barón R, López-Mata M and Méndez Villamón A: Influence of hemoglobin levels on survival after radical treatment of esophageal carcinoma with radiotherapy Clin Transl Oncol *8*: 22-30, 2006.

31 Vaupel P, Thews O and Hoeckel M: Treatment resistance of solid tumors: role of hypoxia and anemia. Med Oncol *18*: 243-259, 2001.

32 Zemanova M, Novak F, Vitek P, Pazdro A, Smejkal M, Pazdrova G and Petruzelka L: Outcomes of patients with oesophageal cancer treated with preoperative chemoradiotherapy, followed by tumor resection: Influence of nutritional factors. J BUON *17*: 310-316, 2012.

33 Wang CY, Hsieh MJ, Chiu YC, Li SH, Huang HW, Fang FM and Huang YJ: Higher serum C-reactive protein concentration and hypoalbuminemia are poor prognostic indicators in patients with esophageal cancer undergoing radiotherapy. Radiother Oncol *92*: 270-275, 2009.

34 Cincibuch J, Neoral C, Aujeský R, Srámek V, Schneiderka P, Studentová H, Melichar B, Kohoutek M, Stráznická J, Vrba R, Juránová J, Flodr P, Machácek J and Cwiertha K: Prognostic factors in patients with esophageal carcinoma treated with chemoradiation: single center experience. Hepatogastroenterology *57*: 1145-1149, 2010.

35 Di Fiore F, Lecleire S, Pop D, Rigal O, Hamidou H, Paillot B, Ducrotté P, Lerebours E and Michel P: Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. Am J Gastroenterol *102*: 2557-2563, 2007.

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