Multivariate Analysis of Treatment Outcome in Patients With Esophageal Carcinoma Treated With Definitive Radiotherapy

Takeshi Kodaira, M.D., Nobukazu Fuwa, M.D., Yoshiyuki Itoh, M.D., Minoru Kamata, M.D., Kazuhisa Furutani, M.D., Syunzo Hatooka, M.D., and Masayuki Shinoda, M.D.

To evaluate patient characteristics and treatment factors influencing outcome of patients treated with definitive radiotherapy, we performed retrospective analysis. From 1983 to 2000, 154 patients who were diagnosed as esophageal carcinoma without distant metastasis received definitive radiotherapy with (N = 90) or without (N = 64) systemic chemotherapy. One hundred forty-two males and 12 females were entered in the analysis. Thirty-four patients received an additional boost of intracavitary brachytherapy (ICBT). The median patient age was 68 years (range: 46–86). Disease stage was distributed as stage I, II, III, and IV for 33, 42, 33, and 45 patients, respectively. External beam radiotherapy was prescribed with a median 63 Gy (range: 38–77.8 Gy). The 2- and 5-year overall survival (OAS) and local control (LC) rates were 40.8/18.4% and 48.6/28.9%, respectively. In uni-/multivariate analyses, significant prognostic factors of OAS proved to be advanced T stage, absence of ICBT, and age less than 65 years. As for LC, adverse prognostic factors of uni/multivariate analysis were advanced T stage and poor performance status. The pretreatment T stage showed the most powerful influence on both survival and LC. Combination use of ICBT is proven to refine treatment outcome, although eligible criteria should be decided by a prospective study.

Key Words: Esophageal cancer—Radiotherapy—Chemotherapy—Intracavitary brachytherapy.

Efforts to improve treatment outcome of esophageal cancer have been made, but an encouraging outcome has not been achieved. Cooper et al.[1] demonstrated the superiority of chemoradiotherapy compared to radiotherapy alone. Therefore, the combined modality is now widely accepted as the standard strategy for advanced esophageal carcinoma. However, local failure still remains the chief cause of recurrence.

Intracavitary brachytherapy (ICBT) is expected to improve local tumor control. Hopeful outcomes were cited in several reports,[2–4] although severe morbidity is expected to increase.[5]. The apparent survival benefit with ICBT was not observed in a phase III study from the Japanese Society of Therapeutic Radiology and Oncology study group.[6] Thus, physicians have not yet acquired definite guidelines for ICBT.

In our institute, the treatment strategy toward esophageal cancer changed over the last 2 decades. Development of a staging procedure, including computed tomography (CT) scans and endoscopes, enable us to make an accurate diagnosis in a nonsurgical manner. In addition, efforts to refine chemotherapy have been tried recently. We believe there are various models of radiotherapy for esophageal carcinoma, and thus the optimal treatment should be decided according to patient characteristics and disease severity. In this article, we tried to evaluate the efficacy of a modality within retrospective analysis using multivariate analysis.

MATERIALS AND METHODS

Patient Characteristics

From 1983 to 2000, 154 patients with esophageal cancer who were treated with definitive radiotherapy were entered in the analysis. Patients with distant metastasis were excluded from this analysis. Patients who received radiotherapy chiefly consisted of those who were considered inoperable because of advanced disease or medical complications. In addition, 43 patients had a history of other malignancies. All patients received barium esophogram, esophagoscopy, and cervical, chest, and abdominal CT.

Patient characteristics are summarized in Table 1. One hundred forty-two men and 12 women were entered in the analysis. All but one patient with histology of adenosquamous cell carcinoma had histology of squamous cell carcinoma. The 1997 TNM staging system was used. In this cohort, all M1 disease was limited to disease with nonregional lymph node metastasis.

Radiotherapy

Details of radiotherapy are shown in Table 2. The majority of this cohort received involved field radiation therapy. A radia-

TABLE 1. *Patient characteristics*

Patient characteristics	n (Percentage) Median (range)
Age (y)	68 (46–86)
Sex	
Male	12 (7.8)
Female	142 (92.2)
Performance status	
0–1	133 (86.4)
2–3	21 (13.6)
Histological grade	
Well	22 (14.3)
Moderately	68 (44.2)
Poorly or small	9 (5.8)
Undifferantiated or small cell	3 (1.9)
NA	52 (33.8)
Stage	
I	33 (21.4)
II	42 (27.3)
III	33 (21.4)
IV	45 (29.2)
NA	1 (0.7)
T status	
T1	40 (26.0)
T2	13 (8.4)
T3	77 (50)
T4	24 (15.6)
Location	
Upper thoracic	18 (11.7)
Middle thoracic	112 (72.7)
Lower thoracic	22 (14.3)
NA	2 (1.3)
Tumor length (cm)	6.5 (1–16)
>5	89 (57.8)
≦5	60 (39.0)
NA	5 (3.2)
N status	
Negative	81 (52.6)
Positive	72 (46.8)
NA	1 (0.6)
M status*	
Negative	109 (70.8)
Positive	45 (39.2)

NA, not assessed.
* Only nonregional lymph node metastasis.

TABLE 2. *Treatment modality and content*

Treatment modality	n (Percentage) Median (range)
Radiotherapy	
External beam radiotherapy	
Dose (Gy)	63 (38–77.8)
OTT (days)	49 (14–107)
≦50 days	66 (42.9)
>50 days	88 (57.1)
Intracavitary brachytherapy	
Yes	34 (22.1)
No	127 (77.9)
Dose (Gy)	10 (4–20)
Total dose (Gy)	66 (40–96)
≦66	93 (60.4)
>66	61 (39.6)
Chemotherapy	
Yes	90 (58.4)
No	64 (41.6)
Type of chemotherapy	
Concurrent	69 (76.7)
High-dose	43 (47.8)
Low-dose	26 (28.9)
Others	21 (23.3)

OTT, overall treatment time.

tion field was used to cover the primary lesion with a 3-cm margin longitudinally. In cases with positive lymph node swelling, the radiation field used to cover it was 2 cm with free margins. Eighteen patients received extended field radiation in which cervical, mediastinal, and abdominal regional nodes were included. A daily 1.8 to 2 Gy of external beam radiotherapy (EBRT) was prescribed five times per week with antero-posterior opposing portals. After 36 to 40 Gy, the radiation field was shrunk to the gross tumor with oblique opposing portals. If field length did not exceed 10 cm, a cone-down field was prescribed with conformal dynamic-rotation therapy. The median dose of EBRT was 63 Gy, ranging from 38 to 77.8 Gy.

If excellent local response was achieved after EBRT, another boost via ICBT was considered. In ICBT cases, the dose of EBRT was limited to 50 to 60 Gy. The ICBT session was usually 1 to 2 weeks after the completion of EBRT. Thirty-four patients received ICBT using a radium (n = 12) or iridium source (n = 22). Thirteen patients were treated with ICBT accompanied by intracavitary hyperthermia.[7] A double balloon

type applicator system[2] was used among other patients treated with ICBT. The median dose of ICBT was 10 Gy, ranging from 4 to 20 Gy. The estimated dose was calculated 5 mm beyond the surface of the balloon applicator.

Chemotherapy

Ninety patients received systemic chemotherapy. Sixty-nine patients were prescribed systemic chemotherapy concurrently. In 43 patients, 700 mg/m^2 of 5-fluorouracil (5-FU) (D1–4) and 70 mg/m^2 of cisplatin (D1) were administered intravenously every 28 days. Usually, two cycles were given during the initial treatment course. Elderly or medically complicated patients (N = 26) received protracted low-dose 5-FU (200 $mg/m^2/24$ h) and/or cisplatin (3–6 $mg/m^2/24$ h) during EBRT. For 21 patients, chemotherapy was prescribed in a neoadjuvant or alternative setting. Nine of 21 patients received intravenous 5 days' infusion of 5-FU (D1–5; 3.5 $g/m^2/120$ h) and nedaplatin (D6; 120–140 mg/m^2), alternatively followed by EBRT. In this series, usually two or three courses of chemotherapy were given.

Follow-up

Patients were followed at 1- to 2-month intervals for the first 2 years, and at 3- to 4-month intervals thereafter. Follow-up examinations included physical examinations, blood counts, and chemistry profiles including tumor markers, barium esophogram, esophagoscopy, and cervical, chest, and abdominal CT.

Treatment response was evaluated in 141 patients. Usually, patients received barium esophogram, esophagoscopy, and cervical, chest, and abdominal CT 0 to 1 month after completion of the treatment session. We used the World Health Organization response criteria for measurable diseases. Briefly, a CR was defined as the complete disappearance of all measurable and assessable disease for a minimum of 4 weeks. A partial response (PR) was defined as a greater than or equal to 50%

reduction in the sum of the products of the longest diameter of measurable disease for a minimum of 4 weeks. Stable disease (SD) was defined as the failure to observe a PR, CR, or progressive disease for at least 4 weeks. Progressive disease (PD) was defined as a greater than or equal to 25% increase in the sum of the products of the longest diameter of measurable disease or the appearance of new lesions.

The last follow-up was performed on August 2001. At that time, 22 patients were alive without disease and 26 patients were alive with disease. Eighty-three patients died from disease 1.7 to 85.8 months after the initial treatment (median: 9.8 months). Twenty-three patients died of intercurrent disease without any evidence of recurrent disease 3.6 to 96.2 months after the initial treatment (median: 19.3 months). The follow-up period for the 48 survivors ranged from 6.8 to 239.2 months (median: 18.6 months). For all 154 patients, it ranged from 1.7 to 155.1 months (median: 13.3 months).

Late toxicity derived from treatment sessions was described by the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer toxicity criteria.[8]

Statistical Analysis

Overall survival (OAS) and local control rate (LC) were calculated from the beginning of radiotherapy according to the Kaplan-Meier method.[9] LC was defined with local recurrence or initial response of NC or PD as the event. The log-rank test was used to compare survival curves.[10] The Cox proportional-hazards model was used to estimate the relative risk after adjusting for prognostic factors.[11] The final model considered only those variables that were statistically significant at the 10% level in stepwise regression.

For uni- and multivariate analysis, patient age and radiation dose were divided in two groups at several points. In analysis of performance status (PS), the group was separated in two groups of either score 0 to 1 or 2 to 3. Tumor markers were not analyzed because record omission was observed in almost half of the entire group.

Proportions and means were compared by the chi-square test and the Student t test, respectively.

RESULTS

Results for the Entire Group and Failure Patterns

For all 154 patients, the 2- and 5-year OAS and LC rates were 40.8/13.4% (95% CI 32.4–49.2%/10.4–26.4%) and 48.6/28.9% (95% CI 38.8–58.4%/13.0–44.8%), respectively. Median duration of OAS and LC was 17.0 months (95% CI 11.5–22.5 months) and 22.2 months (95% CI 0.2–44.2 months).

Radiologic CR was acquired in 68 patients (44.2%). For the other 73 patients who could be evaluated after completion of radiotherapy, treatment response was judged as PR, SD, and PD for 58, 13, and 2 patients, respectively. Therefore, the response rate was estimated as 81.8% (126/154).

One hundred nine patients developed treatment failures in this series. Seventy-nine patients had failures at local sites, 21 at lymph nodes, and 15 at distant recurrence sites. All patients who recurred did not receive all imaging examinations, and so lymph node and/or distant failure may have been underestimated in this series.
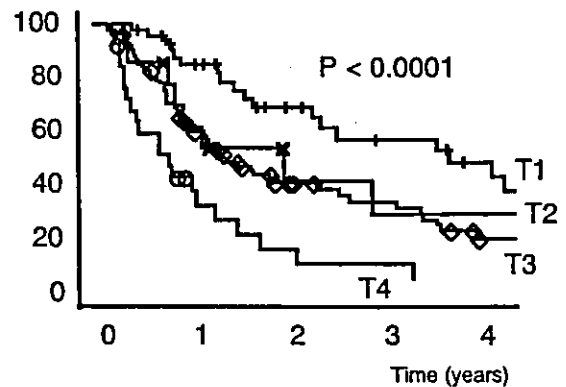

FIG. 1. Overall survival curves defined as T stage.

Forty-nine patients received radiotherapy with (N = 11) or without (N = 38) chemotherapy for salvage. Five patients received ICBT as salvage for superficial type local recurrence. Six patients who developed only local site recurrence received salvage operations and lived a median 17.5 months (range: 5.6–50.5 months) after their interventions.

Overall Survival

Patient age less than or equal to 65 years (p = 0.0013), advanced T status (Fig. 1; p < 0.0001) and disease stage (p < 0.0001), tumor size greater than 5 cm (p = 0.0012), positive regional (N1; p = 0.0302) and nonregional (M1; p = 0.0008) lymph node, overall treatment time (OTT) more than 50 days (p = 0.0324), and absence of ICBT (p < 0.0001) showed significant adverse effects on OAS by univariate analysis. The results are shown in Table 3. Worse PS showed a tendency for an unfavorable OAS factor, although it did not reach a significant level (p = 0.086). Radiation dose and presence or absence of chemotherapy showed no apparent relationship with OAS in this analysis.

After multivariate analysis using Cox's stepwise-regression model, statistically significant factors influencing OAS proved to be patient age (p = 0.0339, relative risk [RR] = 1.595), T status (p = 0.0026, RR = 2.024), and use of ICBT (p = 0.0058, RR = 2.161).

Local Control

As for LC, seven prognostic factors showed a significant influence on LC by univariate analysis (Table 4). These were worse PS (p = 0.0258), advanced T status (p < 0.0001), and disease stage (p = 0.0001), tumor size greater than 5 cm (p < 0.0001), positive regional lymph node (p = 0.0083), OTT greater than 50 days (p = 0.0294), and absence of ICBT (Fig. 2; p = 0.0028). Female patients (p = 0.0519) and positive nonregional lymph nodes (p = 0.0517) showed a tendency for adverse factors of LC, but it did not reach a significance level.

TABLE 3. *Uni- and multivariate analysis according to risk factors influencing overall survival rate*

Factors	Univariate survival rate (2 y)	p value	Multivariate (final model) Relative risk	p value
Age		0.0013		
≤65	24.0		1.595	0.0339
>65	51.0			
Stage		<0.0001		
I	73.9			
II	47.9			
III	29.7			
IV	25.7			
T		<0.0001	2.024*	0.0026
1	66.9			
2	38.1			
3	36.8			
4	5.6			
Size (cm)		0.0012		
>5	30.4			
≤5	53.2			
N		0.0302		
0	45.1			
1	36.7			
M		0.0008		
0	47.0			
1	25.7			
OTT (days)		0.0324		
≤50	47.4			
>50	31.7			
ICBT		<0.0001		
Present	68.6			
Absent	31.9		2.161	0.0058

ICBT, intracavitary brachytherapy; OTT, overall treatment time.
* Relative risk of group with T3–4 lesion compared to that of T1–2 is shown.

TABLE 4. *Uni- and multivariate analysis according to risk factors influencing local control rate*

Factors	Univariate Control rate (2 y)	p value	Multivariate (Final model) Relative Risk	p value
Performance status		0.0258		
0–1	51.8			
1–2	30.3		2.387	0.0082
Stage		0.0001		
I	83.6			
II	45.5			
III	27.9			
IV	22.3			
T		<0.0001	2.667*	0.0013
1	82.9			
2	38.9			
3	36.6			
4	19.3 (17M)			
Size		<0.0001		
>5 cm	36.6			
≤5 cm	67.9			
N		0.0083		
0	58.6			
1	33.9			
OTT		0.0294		
≤50 days	60.6			
>50 days	29.4			
ICBT		0.0028		
Present	71.7			
Absent	40.5			

OTT = overall treatment time, ICBT = intracavitary brachytherapy.
* Relative risk of group with T3–4 lesion compared to that of T1–2 is shown.

In the multivariate analysis, worse performance status ($p = 0.0082$, RR = 2.387) and advanced T status proved to be significantly unfavorable factors of LC.

Intracavitary Brachytherapy

The mean age was greater in the group treated with ICBT compared to the group without ICBT ($p = 0.0099$). Tumor lengths of the group receiving ICBT were significantly shorter than those without ICBT ($p = 0.0148$). Patients receiving ICBT were prescribed significantly higher doses of EBRT ($p < 0.0001$) with smaller OTT ($p = 0.0019$). Distribution was significantly different in terms of disease stage ($p = 0.0001$), T stage ($p = 0.0007$), presence or absence of regional lymph nodes ($p = 0.0064$), and chemotherapy use ($p = 0.0207$). T status of patients treated with ICBT was distributed as 17, 2, and 15 for T1, T2, and T3 disease. Groups treated without ICBT had more advanced disease from the viewpoint of prognostic factors.

Application of ICBT showed a strong favorable effect on OAS, when data were stratified by patient age ($p = 0.0002$), T status (T1–2 vs. T3–4; $p = 0.0006$), N status

($p = 0.001$), M status ($p < 0.0001$), disease stage ($p = 0.005$), and OTT ($p = 0.0001$). The same result was also observed in the case of LC, when data were stratified by several prognostic factors defined by univariate analysis.

Chemotherapy

OAS and LC rates between the group with or without chemotherapy were not significantly different. The 2- and 5-year OAS rates of groups treated with and without chemotherapy were 40.3/17.1% (95% CI 29.1–51.5%/ 6.5–27.7%) and 41.8/20.7 (95% CI 28.7–54.9%/7.6– 33.8%), respectively. As for LC, the 2- and 4-year control rates of groups with and without chemotherapy were 52.7/19.2 (95% CI 38.8–66.6%/–2.2–40.6%) and 42.6/39.6 (95% CI 28.3–56.9/25.1–54.1%), respectively.

By type of chemotherapy, no apparent difference in outcomes existed in this analysis.

The ratio of advanced disease stage ($p < 0.0001$), N1 ($p < 0.0001$), and M1 ($p < 0.0001$) disease was significantly greater in groups with chemotherapy compared to those without chemotherapy. Patients age ($p < 0.0001$) and total radiation dose ($p = 0.0321$) were significantly higher in groups without chemotherapy than those with chemotherapy. On the other hand, tumor length was

Survival rate (%)

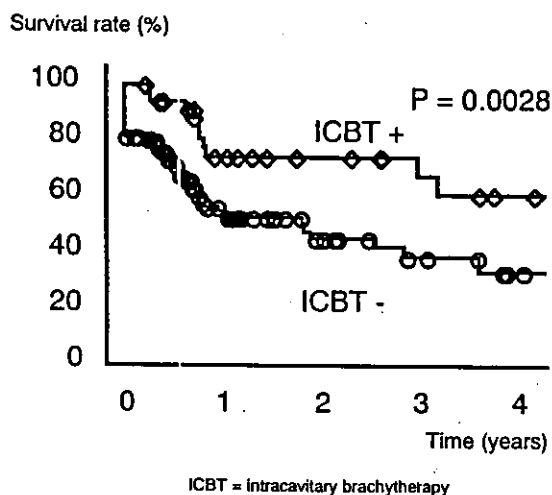ICBT = intracavitary brachytherapy

FIG. 2. Local control curves of group with or without intracavitary brachytherapy.

significantly longer among patients treated with chemotherapy than in patients treated with radiation alone (p = 0.032). Regarding sex, PS, T status, and OTT, we could not observe any significant differences between the two groups.

Toxicity

Acute toxicity with grade III or higher was noted in 15 leukocyte, 6 hemoglobin, and 3 platelets patients. Mild elevation of liver function was noted in four patients, but no medical treatment was needed.

Grade III or higher late toxicity was observed in 7 pulmonary, 17 esophagus, and 1 heart patients. One patient died of acute respiratory distress syndrome immediately after chemoradiotherapy. Eight patients developed esophageal fistula during the follow-up period. They were diagnosed as T1, T3, and T4 lesion for 1, 5, and 2 cases, respectively. One patient with a T1 lesion developed perforation after ICBT, consequently leading to fatal mediastinitis. For another 7 patients, fistula was accompanied with tumor residue and/or local recurrence. Seven of 34 patients (20.6%) treated with ICBT developed grade III or higher toxicity of the esophagus. The esophageal toxicity ratio in groups with ICBT was significantly greater than that of groups with EBRT alone (p = 0.044). On the other hand, the incidence of esophageal morbidity was not significantly different between the groups with or without chemotherapy (p > 0.05).

DISCUSSION

Esophageal carcinoma is thought to be one of the most difficult neoplasms by many physicians. Surgery has played an important role for the majority of patients with esophageal carcinoma. In Western counties, the 5-year survival rates were reported as 6% to 24%,[12] whereas in Japan some institutes reported around 40%.[13–15] In Japan, treatment results were somewhat better than that in

other countries; however, skilled experts in selected institutes can achieve much better outcomes. One explanation is that superficial esophageal cancer is more often diagnosed in Japan, although due to the complicated technique and disappointing outcomes, radiation therapy still remains an essential modality for advanced esophageal cancer.

After results from a phase III study in RTOG 85-01,[16] chemoradiotherapy is generally accepted as the standard treatment for inoperable patients with esophageal cancer. In this trial, four courses of combined fluorouracil and cisplatin plus 50 Gy of radiation therapy was compared to radiation therapy alone with 64 Gy. The median survival was 8.9 and 12.5 months in the radiation alone and combined modality groups, respectively. The trial was stopped because of a significant survival benefit at intermediary analysis. From the results in the Eastern Cooperative Oncology Group phase III trial (EST-1282) with concurrent chemoradiotherapy accompanied by 5-FU and mitomycin C,[17] patients treated with chemoradiation had a longer median survival (14.8 mol/l), compared to patients receiving radiation therapy alone (9.2 mol/l). In the Patterns of Care study,[18] chemoradiotherapy was most commonly used (62.5%) for advanced esophageal cancer.

In this analysis, use of chemotherapy did not show an apparent benefit for either survival or local control. This is chiefly because groups treated with chemoradiotherapy mainly consisted of patients with more advanced stages and bulky disease. In addition, patients treated with radiation alone had somewhat better outcome compared to reported analyses.[1] In this retrospective analysis, the type of chemotherapy varied considerably according to disease severity and patient medical conditions. For eligible patients, we usually prescribed two cycles of concurrent chemotherapy with 70 mg/m² of cisplatin and 2.8 g/m² of 5-FU. An additional boost of chemotherapy was given to only selected patients, mainly nonresponders. Both the amount and length of chemotherapy were relatively smaller than reported data; thus, we suspected that the effect of chemotherapy was insufficient within our cohort. Recently, we have started more intensive systemic chemotherapy using nedaplatin and 5-FU to improve local and/or distant disease control.

Although a definite advantage of chemoradiotherapy was determined by the phase III study, local failure was considered the major reason for unfavorable outcome. In Japan, ICBT is expected to improve local control of esophageal carcinoma.[2,6] Excellent local control was reported in clinical practice, especially for superficial esophageal carcinoma (SEC).[19,20] On the contrary, ICBT was thought to be an efficacious, but hazardous, technique in Western countries, especially for chemoradiotherapy.[5] RTOG 92-07[5] examined the feasibility of concurrent chemoradiotherapy of 50 Gy of EBRT with 4 courses of cisplatin and 5-FU followed by 10-Gy boost via ICBT. In this report, severe morbidity or mortality was reported in 13 and 4 of 50 eligible patients, respectively. Therefore, they concluded that extreme caution

should be taken when employing ICBT to standard chemoradiotherapy. Indeed, increasing the risk of esophageal ulcer and/or perforation was also reported.[3] We suspected the difference was caused by the type of applicator used[2] and the prescribed fraction size and total dose of ICBT.[19] The double balloon applicator system introduced by Dokiya[3] is widely used in Japan. By using this apparatus, the radiation source can be located in the center of the lumen and the estimated dose can evenly describe the surface of the mucosa. Theoretically, it is safe and a more beneficial method compared to that introduced by RTOG 92-07. Furthermore, Akagi et al.[19] showed that a small fraction size of ICBT could reduce late complications among patients, with SEC.

In our analysis, use of ICBT was a significantly favorable factor of OAS in uni-/multivariate analysis. Although eligible patients for ICBT mainly consisted of groups with low risk factors, this result emphasized the efficacy of ICBT. In this limited outcome, we could not clarify the optimal technique and criteria for ICBT, but we believe it was a useful modality to improve local control of esophageal carcinoma. In the future, a feasible model combined with chemoradiotherapy and ICBT should be determined with a prospective study.

As for other clinical parameters, T stage was revealed to be the most powerful prognostic factor for both OAS and LC. Patients with advanced T-stage disease still had a discouraging prognosis, so more effective chemotherapy is required to improve treatment outcome. ℂ

REFERENCES

1. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623-7.
2. Yorozu A, Dokiya T, Oki Y, et al. Curative radiotherapy with high-dose-rate brachytherapy boost for localized esophageal carcinoma: dose-effect relationship of brachytherapy with the balloon type applicator system. *Radiother Oncol* 1999;51:133-9.
3. Yorozu A, Dokiya T, Oki Y. High-dose-rate brachytherapy boost following concurrent chemoradiotherapy for esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1999;45:271-5.
4. Calais G, Dorval E, Louisot P, et al. Radiotherapy with high dose rate brachytherapy boost and concomitant chemotherapy for stages IIB and III esophageal carcinoma: results of a pilot study. *Int J Radiat Oncol Biol Phys* 1997;38:769-75.
5. Gaspar LE, Winter K, Kocha WI, et al. A phase I/II study of

external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. *Cancer* 2000;88:988-95.
6. Okawa T, Dokiya T, Nishio M, et al. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. *Int J Radiat Oncol Biol Phys* 1999;45:623-8.
7. Fuwa N, Nomoto Y, Shouji K, et al. Therapeutic effects of simultaneous intraluminal irradiation and intraluminal hyperthermia on oesophageal carcinoma. *Br J Radiol* 2001;74:709-14.
8. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341-6.
9. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457-81.
10. Mantle N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; 50:163-70.
11. Cox DR. Regression models and life table. *J R Stat Soc* 1972;34: 197-220.
12. Roth JA, Putnam JB Jr. Surgery for cancer of the esophagus. *Semin Oncol* 1994;21:453-61.
13. Akiyama H, Tsurumaru M, Udagawa H, et al. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994; 220:364-72.
14. Aba M, Aikou T, Yoshinaka H, et al. Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. *Ann Surg* 1994;219:310-6.
15. Fujita H, Kakegawa T, Yamana H, et al. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. *Ann Surg* 1995;222:654-62.
16. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593-8.
17. Smith TJ, Ryan LM, Douglass HO Jr, et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1998;42:269-76.
18. Coia LR, Minsky BD, John MJ, et al. The evaluation and treatment of patients receiving radiation therapy for carcinoma of the esophagus: results of the 1992-1994 Patterns of Care Study. *Cancer* 1999;85:2499-505.
19. Akagi Y, Hirokawa Y, Kagemoto M, et al. Optimum fractionation for high-dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. *Int J Radiat Oncol Biol Phys* 1999;43:525-30.
20. Nishimura Y, Okuno Y, Ono K, et al. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. *Cancer* 1999; 86:220-8.

Cell-Cycle Regulators and the Ki-67 Labeling Index Can Predict the Response to Chemoradiotherapy and the Survival of Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus

Hiroya Takeuchi, MD, Soji Ozawa, MD, Nobutoshi Ando, MD, Yuko Kitagawa, MD, Masakazu Ueda, MD, and Masaki Kitajima, MD

Background: We investigated whether aberrant p53 and p16 expression, the Ki-67 labeling index (LI), and *int-2/cyclin D1* gene amplification predict the response to chemoradiotherapy (CRT) in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: p53 and p16 expression status, the Ki-67 LI, and *int-2/cyclin D1* amplification were assessed by immunohistochemical staining and slot blot analysis in pretreatment endoscopic biopsy specimens of 41 patients with T4 or M1 Lym (distant lymph node metastasis) ESCC. All patients received a course of chemotherapy (5-fluorouracil and cisplatin) with radiotherapy.

Results: The CRT therapeutic response rate was 71%, and resection after CRT was successful in 15 of the cases in which the CRT effect was significant. The cumulative survival rate after CRT in the p53-negative patients was significantly higher than in the p53-positive patients ($P = .037$). The mean Ki-67 LI in the CRT response cases was significantly higher than in the CRT no-response cases ($P = .023$). Multivariate regression analysis revealed high Ki-67 LI to be an independent variable linked to a pathologic complete response to CRT ($P = .033$). The cumulative survival rate after CRT in the group that was p53-negative and *int-2/cyclin D1* amplification-positive was significantly higher than in the other groups ($P = .008$).

Conclusions: Evaluating predictive factors in pretreatment endoscopic biopsy specimens may allow selection of more suitable multimodal treatment for ESCC patients and improve their quality of life.

Key Words: Chemoradiotherapy—Esophageal cancer—p53—p16—Ki-67—*int-2/Cyclin D1* amplification.

Esophageal squamous cell carcinoma (ESCC) has one of the highest malignant potentials of any tumor. The 5-year survival rate of ESCC patients after surgery is low and ranges from 24% to 45%.[1–4] The recent progress in long-term survival can be attributed to technical improvements in the diagnosis of T1 ESCC, extended lymph node dissection, and advances in perioperative

management.[4] Because curative resection is impossible, however, the prognosis of T4 (direct invasion to adjacent organs) and M1 Lym (distant lymph node metastasis) ESCC is still unfavorable, and multimodal treatment is required.[2] We have been performing neoadjuvant chemoradiotherapy (CRT) for patients with T4 or M1 Lym ESCC since 1992.

Recent studies have demonstrated that gene abnormalities of cell-cycle regulators that function in the transition from the G_1 to S phase are associated with clinicopathologic features of ESCC. Amplification of *cyclin D1/ PRAD-1* and cyclin D1 overexpression have been reported as prognostic markers associated with lymph node metastasis and distant organ metastasis of ESCC.[5,6] The *cyclin D1/PRAD-1* gene, which maps to the 11q13 chro-

mosomal region and encodes the cyclin D1 protein, accelerates S phase entry from the G_1 phase by complexing with cyclin-dependent kinase-4 (CDK4) and activating CDK4-mediated phosphorylation of the retinoblastoma (RB) protein.[7,8] The int-2 gene, which belongs to the fibroblast growth factor family, also maps to 11q13, approximately 150 kilobases distant from the cyclin D1/ PRAD-1 gene. We have reported amplification of the int-2 gene as another prognostic marker associated with distant organ metastasis in ESCC.[9] The p16/CDKN2 gene, a tumor-suppressor gene, controls S phase entry by inhibiting CDK4-mediated phosphorylation of the RB protein, and we previously reported that loss of p16 expression is associated with the prognosis of ESCC.[6]

Abnormalities of the p53 gene are associated with oncogenesis and tumor progression in ESCC[10,11]; however, the association between p53 mutation (aberrant p53 expression) and survival remains unclear and is still being assessed.[12–14] DNA-damaging therapy, such as irradiation or chemotherapy, induces wild-type p53 protein, which regulates the cell cycle via p21 expression; this arrests the cell cycle at the G_1 phase. Furthermore, because wild-type p53 protein induces apoptosis in cells with gene abnormalities, some investigations have suggested that p53 gene status is a useful indicator for predicting the radiosensitivity or chemosensitivity of various tumors.[15,16]

The Ki-67 labeling index (LI) has been identified as a parameter of tumor proliferation. ESCC patients with a high Ki-67 LI have lower postoperative survival rates; thus, a high Ki-67 LI is one of the prognostic factors of ESCC.[17,18] Ki-67 is a proliferation-associated nuclear antigen expressed in all cycling cells except resting cells in the G_0 phase, and it reflects cells in the S/G_2+M phase, in particular. The association between Ki-67 LI and response to CRT for ESCC, however, is still unclear.

A response to CRT (cisplatin, 5-fluorouracil, and radiotherapy) cannot be expected with certainty in all patients with T4 or M1 Lym ESCC; thus, CRT is frequently ineffective, valuable time is wasted, and patients experience severe toxicity as a result of CRT.[2] Although no biological factors that predict a response to CRT in patients with locally advanced ESCC have ever been identified, recent investigations of the effects of cytotoxic agents and irradiation on the cell cycle suggest that the response of patients with advanced ESCC to CRT may be associated with dysfunction of cell-cycle regulators and Ki-67 LI.[19] We hypothesized that alterations in genes encoding cell-cycle regulators or the Ki-67 LI in endoscopic biopsy specimens of primary tumors in untreated patients with advanced-stage ESCC predict sensitivity to neoadjuvant CRT and patient survival.

To test this hypothesis, in this study we investigated the status of p53 and p16 expression, int-2/cyclin D1 amplification, and the Ki-67 LI in endoscopic biopsy specimens of untreated ESCC and investigated whether these gene alterations and Ki-67 LI predicted the response to CRT and survival.

MATERIALS AND METHODS

Patients

The subjects of this study were 41 patients (mean age, 61 years) with clinically diagnosed T4 and/or M1a (Lym) thoracic ESCC without distant organ metastasis. The patients were evaluated by esophagography, esophagoscopy, bronchoscopy, computed tomography (CT), and endoscopic ultrasonography, and staging was performed according to the tumor-node-metastasis classification proposed by the International Union Against Cancer. Patients with an esophagobronchial fistula were excluded from the study. The eligibility requirements were that the subjects be < 80 years old, have an Eastern Cooperative Oncology Group performance status of 0 to 2, and have a life expectancy of at least 8 weeks. Patients with serious complications or active carcinoma at another site were also excluded. After signing an informed human subject institutional review board consent form, all patients underwent CRT at Keio University Hospital (Tokyo, Japan) between 1993 and 1997. The clinicopathologic background factors and clinical stage estimates are listed in Table 1. Endoscopic biopsy specimens were obtained from all patients before the start of CRT and were used to detect aberrant p53 and p16 expression, to determine the Ki-67 LI, and to investigate int-2/cyclin D1 gene amplification. Surgical resection (transthoracic esophagectomy) was performed in the patients whose lesions became resectable as a result of a significant effect of CRT.

Chemoradiotherapy

All patients received CRT consisting of continuous 5-fluorouracil administration at a dose of 800 mg/m^2/day days 1 to 4 and 29 to 32, combined with (1) cisplatin administration at a dose of 70 mg/m^2/day day 1 and 29 or 20 mg/m^2/day days 1 to 4 and days 29 to 32 and (2) concomitant radiotherapy (daily dose of 2.0 Gy to a total dose of 50 Gy over 5 weeks).

The responses to CRT were evaluated by three clinicians on the basis of the results of esophagography, esophagoscopy, bronchoscopy, CT, and endoscopic ultrasonography. Effectiveness was classified into four categories according to the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus of

TABLE 1. *Patients and clinicopathologic background factors before chemoradiotherapy entry*

Factors	No. Cases (%)
Age (y)	
≤49	4 (10)
50–59	14 (34)
60–69	16 (39)
≥70	7 (17)
Sex	
Male	39 (95)
Female	2 (5)
Location[a]	
Ut	12 (29)
Mt	24 (59)
Lt	5 (12)
Clinical stage estimation (T4 or M1 Lym[b]**)**	
T4N0	4 (10)
T4N1	26 (63)
T2N1M1 Lym	2 (5)
T3N1M1 Lym	5 (12)
T4N1M1 Lym	4 (10)
T4 organ	
Left bronchus	15 (44)
Trachea	6 (18)
Aorta	5 (15)
Pericardium	2 (6)
Left bronchus + trachea	3 (9)
Left bronchus + aorta	3 (9)
Site of M1 Lym	
Cervical	8 (73)
Abdominal	2 (18)
Cervical + abdominal	1 (9)

[a] According to the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus* of the *Japanese Society for Esophageal Diseases*.[20] Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus.

[b] T4, tumor invades adjacent organs; M1 Lym, distant lymph node metastasis.

the Japanese Society for Esophageal Diseases[20]: complete response (CR), partial response (PR), no change (NC), and progression of disease (PD). CR was defined as 100% regression of all tumors, PR as a ≥50% reduction in the sum of the products of the longest diameter of measurable disease for 4 weeks, NC as <50% reduction of the tumor, and PD as a ≥25% enlargement of the tumor or the appearance of a new tumor. The indications for surgical resection after CRT were judged by the three clinicians, and the only objective was potentially curative resection. If it was concluded that the stage might remain T4 or M1 Lym after CRT, surgery was considered not to be indicated, even if a PR had been achieved. Surgery was performed approximately 4 weeks after the final dose of radiotherapy, and on the basis of the pathologic findings, the resected specimens were classified into three categories by two pathologists according to the following guidelines[20]: grade 3, no viable cancer cells in the resected specimens; grade 2, viable cancer cells account for less than one third of the tumor tissue; grade 1,

viable cancer cells account for more than one third of the tumor tissue; grade 0, no effect of CRT on the cancer cells and tissues. The patients were followed up in outpatient clinics, where diagnostic examinations consisting of chest x-ray, esophagography, endoscopy, CT, and ultrasonography were performed every 3 months to detect recurrence. The longest follow-up period was 57 months, and the median observation period was 28 months.

Immunohistochemistry

Expression of p53, p16, and Ki-67 was assessed by immunohistochemistry. Untreated endoscopic tumor biopsy specimens were fixed in 10% formalin and embedded in paraffin by conventional techniques. Freshly cut 4-μm sections were deparaffinized in xylene, and the slides were subjected to an antigen-retrieval step in Target Unmasking Fluid purchased from PharMingen (San Diego, CA) at 90°C for 10 minutes.[21] The sections were reacted with the monoclonal mouse antihuman p53 antibody DO-7 (DAKO, Glostrup, Denmark) 5 μg/mL at 4°C overnight for p53 staining, with the monoclonal mouse antihuman p16 antibody PMG175-405 (PharMingen) 5 μg/mL at room temperature for 1 hour, and with monoclonal mouse antihuman MIB-1 (Immunotech, Marseille, France) .5 μg/mL at 4°C overnight for Ki-67 staining. Negative control slides were treated with nonspecific mouse immunoglobulin G1 under equivalent conditions. Secondary reagents were included in the DAKO labeled streptavidin-biotin kit. Slides were developed with diaminobenzaminidine and counterstained with hematoxylin.

We used the criteria for assessing the immunohistochemical results as previously described.[6,22–24] p53 staining was considered positive if >10% of the tumor cells showed nuclear staining and negative if <10% of the tumor cells showed nuclear staining. p16 staining was considered positive if >80% of the tumor cells showed nuclear staining.[6] The reliability of the anti-p16 antibody PMG175-405 was confirmed by Western blot analysis in studies on ESCC cell lines.[6] Parabasal cells of the normal esophageal epithelium, inflammatory cells, and the ESCC cell line TE1 were used as a positive control for p16 staining. The Ki-67 LI was calculated as the percentage of Ki-67–positive cancer cells that showed nuclear staining among 1000 cancer cells counted in >3 fields of a specimen. The nuclei of the parabasal cells in normal epithelium were used as positive controls for Ki-67 staining.

Slot Blot Analysis

int-2/Cyclin D1 amplification was assessed by slot blot analysis as previously described.[5,9,25] Untreated endoscopic biopsy specimens of the tumors and adjacent

normal mucosa were frozen at −80°C, and the DNA was extracted by conventional techniques.[5,9,25] DNA concentrations were estimated spectrophotometrically, and DNA (10 μg) was dissolved in .4 N NaOH. The samples were applied to a nylon membrane (Hybond-N; Amersham Life Science, Buckinghamshire, UK) and incubated for 30 minutes at room temperature. The filters were then rinsed in 5× sodium chloride-sodium phosphate-ethylene diamine tetraacetic acid (SSPE) and dried at room temperature. Probes were prepared by multiprime radioactive labeling with [^{32}P]deoxycytidine triphosphate and an oligolabeling kit (Pharmacia, Uppsala, Sweden). Filters were prehybridized in 5× Denhardt's solution, 50% formamide, 5× SSPE, .5% sodium dodecyl sulfate (SDS), and 100 μg of denatured salmon sperm DNA at 42°C for 2 hours and hybridized to the labeled probe at 42°C for 12 hours in the same solution. The probes used were SS6, a .9−kilobase pair *SacI/SacI* fragment of the *int-2* gene provided by the Japanese Cancer Research Bank, and DRD2, a 1.6-kilobase pair *Bam*HI fragment of the dopamine receptor D2 gene obtained from the American Type Culture Collection. The *cyclin D1* probe was the 888−base pair polymerase chain reaction product containing the entire open reading frame region. The primers used for polymerase chain reaction were as follows: upper primer, 5'-ATG GAA CAC CAG CTC CTG TG-3'; and lower primer, 5'-TCA GAT GTC CAC GTC CCG CA-3'.[5] The filters were washed twice at 65°C for 10 minutes in 2× SSPE and .5% SDS, once for 15 minutes in 1× SSPE and .5% SDS, and once for 10 minutes in .1× SSPE and .5% SDS. Autoradiograms were evaluated quantitatively with a bioimage analyzer (BAS 2000; Fujix, Tokyo, Japan). The number of gene copies was calculated as follows[5]:

(tumor:normal tissue ratio of the intensity of the

bands hybridized with the *int-2* or *cyclin D1* probes)/

(tumor:normal tissue ratio of the intensity of

the bands hybridized with the internal

control *DRD2* probes).

Specimens in which more than 2.5-fold the gene copy number of *int-2* or *cyclin D1* was detected were judged to have undergone gene amplification.[5,9,25]

Statistical Analysis

Patient groups were compared by using the χ^2 test, the Fisher exact probability test, and the Mann-Whitney *U*-test. The cumulative survival rates for patient groups were calculated by the Kaplan-Meier method and compared by using the Mantel-Cox test. A multiple regression model was used for multivariate analysis of variables predicting the CRT response. *P* values of <.05 were considered statistically significant.

RESULTS

CRT Response Rate

Of the 41 cases that received CRT, 29 were CR or PR, and the therapeutic response rate (CR + PR) was 71% (CR, 0 cases; PR, 29 cases; NC, 8 cases; PD, 4 cases). Among the 29 cases in which the CRT effect was significant, complete surgical resection after CRT was successful in 15 cases (resectability rate, 37%). A pathologic CR (grade 3) both in the primary lesion and lymph nodes in the resected specimens was achieved in 4 cases. Three cases were grade 2, and eight cases were grade 1. In 6 of the 15 resected cases, including the 3 grade 3 cases, the patients were alive without recurrence of ESCC, with the longest survival being 57 months. One patient among the four with grade 3 resected specimens died of postoperative pyothorax. Postoperative respiratory complications occurred in 4 patients (27%), and the operative mortality rate was 7% (1 in 15). The patients with a CRT response (PR) had a significantly longer survival than the CRT no-response (NC + PD) patients (Fig. 1A). Moreover, the cumulative survival rate among the CRT response patients in whom surgery was subsequently performed was significantly higher than among the CRT response patients who did not undergo resection (Fig. 1A). The cumulative survival rate in the 7 patients with grade 3 or grade 2 resected specimens was significantly higher than that of the other 34 patients (*P* = .005; Fig. 1B).

p53 and p16 Expression

There were no significant differences in the clinicopathologic background factors between the p53-positive and p53-negative (normal expression) groups according to the χ^2 test (Table 1). There were 5 (33%) p53-positive (aberrant expression) cases among the 15 CRT response (PR) cases in which surgery was successfully performed. 10 patients (71%) among the 14 CRT response cases without resection, and 8 (67%) among the 12 CRT no-response cases (NC + PD; *P* = .081; Table 2). Being p53-positive tended to be associated with poorer CRT response, but the association did not reach statistical significance. The cumulative survival rate after CRT in the p53-negative cases was significantly higher than among the p53-positive cases (*P* = .037; Fig. 2A). p16 expression was not correlated with any of the clinicopathologic background factors, the CRT response, or
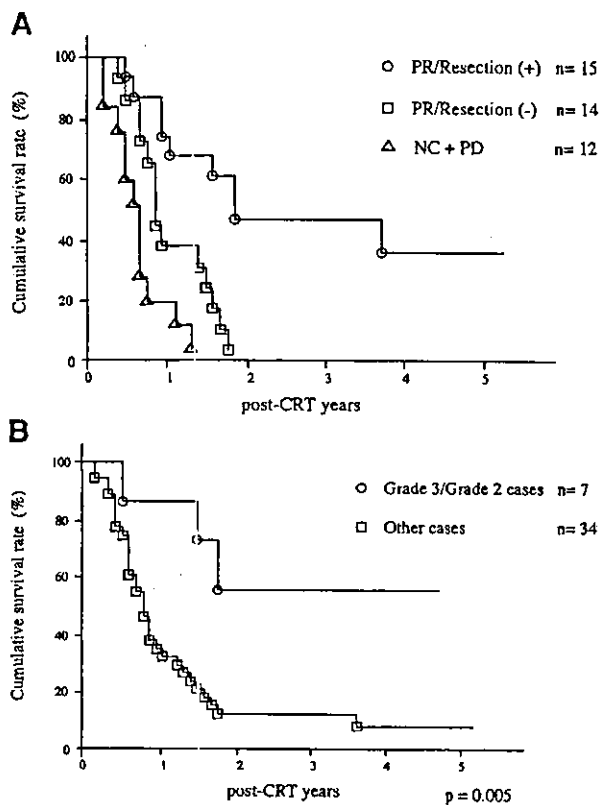
A

B

FIG. 1. Cumulative survival curves after chemoradiotherapy (CRT). (A) CRT response (partial response; PR) cases with or without surgical resection and no response (no change [NC] + progressive disease [PD]). PR with resection versus PR without resection, $P = .001$; PR without resection versus NC + PD, $P = .008$; PR with resection versus NC + PD, $P < .001$. (B) Grade 3 or grade 2 cases versus other cases.

survival (Table 2). However, 8 (67%) of 12 no-response cases were p53 positive and p16 negative (loss of p16 expression), as opposed to only 9 (31%) of the 29 CRT response cases ($P = .096$; Table 2).

Ki-67 LI

The Ki-67 LIs of the 41 patients ranged from 2% to 65% (mean, 29%), and they were not correlated with any of the clinicopathologic background factors assessed. The mean Ki-67 LI in the seven cases in which grade 3 or grade 2 was achieved in the resected specimens was significantly higher than in the CRT no-response (NC + PD) cases ($P = .023$; Table 3). The Ki-67 LI in the grade 3 cases was particularly high (mean, 46.5% $\pm$ 10.2%). The 3-year survival rate after CRT of the 5 patients with a Ki-67 LI >50% was significantly higher than among the 15 patients with a Ki-67 LI <20% (3-year survival, 60% vs. 7%; $P = .032$).

Multivariate regression analysis revealed high Ki-67 LI to be an independent variable linked to a pathologic CR (grade 3) to CRT ($P = .033$; Table 4).

int-2/Cyclin D1 Amplification

int-2/Cyclin D1 amplification was assessed by slot blot analysis in 32 of the 41 cases, after 9 cases were excluded because the amount of DNA in the endoscopic biopsy specimens was insufficient. Amplification of the int-2/cyclin D1 gene was detected in 5 (21%) of the 24 CRT response (PR) cases and in 3 (38%) of the 8 CRT no-response (NC + PD) cases. There were no significant differences in clinicopathologic background factors or CRT response between the group with int-2/cyclin D1 gene amplification and the group without int-2/cyclin D1 gene amplification. The cumulative survival rate after CRT in the patients with int-2/cyclin D1 amplification tended to be higher than in the patients without int-2/cyclin D1 amplification ($P = .062$; Fig. 2B).

Eleven (34%) of the 32 cases were p53-negative and int-2/cyclin D1 amplification-negative, 5 (16%) were p53-negative and int-2/cyclin D1 amplification-positive, 13 (41%) were p53-positive and int-2/cyclin D1 ampli-

TABLE 2. *Association between cell-cycle regulators and CRT response*

Variable	PR/resection (+) (%)	PR/resection (−) (%)	NC⁺ PD (%)	P value
p53 (+)[a]	5 (33)	10 (71)	8 (67)	.081
p53 (−)[b]	10 (67)	4 (29)	4 (33)	
p16 (+)	5 (33)	4 (29)	1 (8)	.29
p16 (−)	10 (67)	10 (71)	11 (92)	
p53 (+)/p16(−)	4 (27)	5 (36)	8 (67)	.096
Others	11 (73)	9 (64)	4 (34)	

CRT, chemoradiotherapy; PR, partial response; NC, no change.
[a] Immunohistochemically positive.
[b] Immunohistochemically negative.

fication-negative, and 3 (9%) were p53-positive and *int-2/cyclin D1* amplification-positive. The cumulative survival rate after CRT in the group that was p53-negative and *int-2/cyclin D1* amplification-positive was significantly higher than in the other groups ($P = .008$; Fig. 2C).
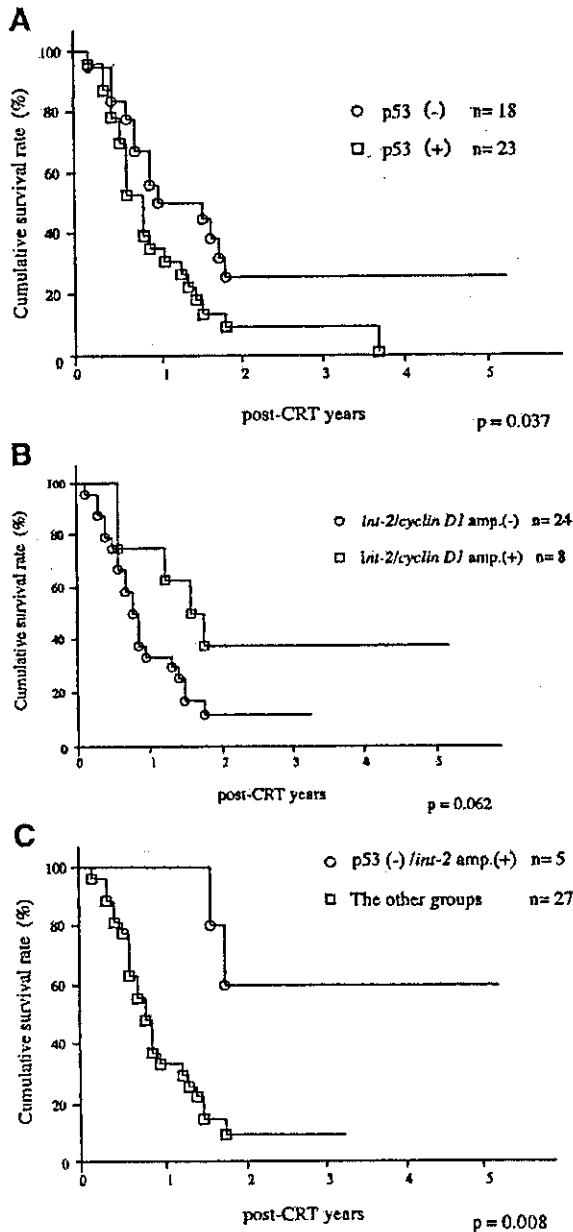
TABLE 3. *Ki-67 labeling index and CRT response*

CRT response	Ki-67 labeling index, % (mean ± SD)
NC + PD (n = 12)	24.6 ± 14.9
PR (n = 29)	30.7 ± 17.8
Grade 3/grade 2 cases (n = 7)	39.1 ± 11.8

CRT, chemoradiotherapy; NC, no change; PD, progressive disease; PR, partial response.

DISCUSSION

In this study, we investigated aberrant p53 and p16 expression, the Ki-67 LI, and *int-2/cyclin D1* amplification by immunohistochemistry and slot blot analysis in endoscopic biopsy specimens of the 41 patients with untreated T4 and M1 Lym ESCC. The cumulative survival rate after CRT in the p53-negative patients was significantly higher than in the p53-positive patients. The mean Ki-67 LI in the CRT response cases (grade 2 and grade 3) was significantly higher than in the CRT no-response cases, and the cumulative survival rate after CRT in the p53-negative and *int-2/cyclin D1* amplification-positive group was significantly higher than in the other groups.

In a preliminary study, we optimized the immunohistochemistry and slot blot assays to detect each molecular marker accurately in the pretreatment endoscopic biopsy specimens, because we needed to determine whether the results for these molecular markers in small biopsy specimens reflected the characteristics of the whole tumor. Because intratumor heterogeneity and technical issues regarding the assays may prevent the results in the biopsy specimens from reflecting those of the whole tumors, we obtained at least five biopsy specimens for immunohistochemistry and another two biopsy specimens for slot blot analysis with a large forceps to obtain an adequate sample of endoscopic biopsy specimens from various sites of the tumor. For the slot blot assay, we verified the absence of necrotic tissues and normal epithelium in the specimens on the basis of endoscopists' observations and hematoxylin and eosin staining. We also compared the molecular markers in endoscopic bi-

FIG. 2. Cumulative survival curves after chemoradiotherapy (CRT). (A) Cases with and without p53 expression. (B) Cases with and without *int-2/cyclin D1* amplification. (C) Cases with p53(−) and *int-2/cyclin D1* amplification (+) versus cases in the other groups.

TABLE 4. *Regression coefficients of variables associated with pathologic complete response (grade 3) on multivariate regression analysis*

Variable	Coefficient	SE	P value
Age (yr)	.004	.005	.448
Tumor length (cm)	.096	.013	.467
p53	−.051	.096	.597
p16	−.042	.110	.707
Ki-67 labeling index (%)	.007	.003	.033

opsy specimens with those in primary ESCC tumors resected without neoadjuvant CRT in a preliminary study. The results of p53 staining of the in-biopsy specimens coincided with the results of staining in the resected tumors in 11 (92%) of the 12 cases, and the results of p16 staining of the biopsy specimens coincided with those in the resected tumors in 9 (75%) of the 12 cases. The Ki-67 LIs in the biopsy specimens showed a trend similar to that in the resected tumors (Spearman correlation coefficient, .705; $P = .02$; data not shown). The int-2/cyclin D1 amplification in the biopsy specimens coincided with that in the tumor resected without CRT in 42 (88%) of 48 cases. We still need to bear in mind the presence of intratumor heterogeneity; however, these preliminary investigations verified the efficacy of the assays and usefulness of pretreatment endoscopic biopsy specimens as a reflection of the tumor as a whole when used in the study.

p53-positive staining tended to correlate with a poorer response to CRT, and the cumulative survival rate after CRT in the p53-negative patients was significantly higher than in the p53-positive patients. Wild-type p53 protein is rapidly degraded and not detected by immunohistochemical staining; however, mutation of the p53 gene results in accumulation of aberrant p53 proteins in ESCC that is identified immunohistochemically as p53-positive staining.[26-28] Sarbia et al.[13] found no correlation between p53 status and survival among patients with surgically treated T1 to T3 ESCC,[14] and our findings suggest that the wild p53 gene (p53-negative expression) may induce cell-cycle arrest and apoptosis in response to CRT in ESCC. CRT in patients with the wild p53 gene allows tumor downstaging and curative resection, which significantly improves survival. In particular, demonstration of a correlation between the p53 status and prognosis after CRT in this study suggests that the wild p53 gene may enhance sensitivity to chemotherapy, which suppresses micrometastasis to distant organs, in addition to enhancing radiosensitivity, which is associated with greater probability of local control. Other investigations have reported that p53 gene insertion enhances chemosensitivity or radiosensitivity in various cell lines, and the wild p53 gene has been found to be associated with a favorable response to CRT in breast cancer.[15,16,29-31] Our results are consistent with these reports.

We immunohistochemically evaluated the other cell-cycle regulator that has been studied as one of the prognostic factors of ESCC: p16.[6,14,32] Loss of p16 expression is unlikely to serve as a clinically useful predictor of CRT response and survival, but the combination of p53 and p16 expression was related to the CRT response. These results suggest that the combination of these two

cell-cycle regulators may enable prediction of the response to CRT.

The Ki-67 LI was significantly correlated with the local response to CRT and the survival of patients with T4/M1 Lym ESCC in this study. The CRT response cases had a high Ki-67 LI, which means a higher population of cycling cells than cases with a low Ki-67 LI. Several studies have demonstrated that cycling cells are more radiosensitive than quiescent cells.[33-35] Okuno et al.[36] have reported results showing a correlation between high Ki-67 LI and radiosensitivity to ESCC similar to our own. Our results indicated that CRT can increase the probability of local control and result in longer survival of patients with a high Ki-67 LI in pretreatment biopsy specimens.

We previously reported that the cumulative survival rate of T1 to T3 ESCC patients with int-2/cyclin D1 amplification was significantly lower than that of patients without int-2/cyclin D1 amplification.[5,6,9] In this study, however, after CRT, the survival of the T4/M1 Lym patients with int-2/cyclin D1 amplification was better than that of the patients without int-2/cyclin D1 amplification, and the p53-negative and int-2/cyclin D1 amplification–positive group, in particular, had a significantly longer survival. These results may indicate that the survival of the T4/M1 Lym patients with int-2/cyclin D1 amplification was improved by the CRT. The mechanism linking the int-2/cyclin D1 gene abnormality and chemo- or radiosensitivity has not yet been defined. Some investigations have shown that cyclin D1 overexpression is related to resistance to cisplatin or methotrexate in vitro.[37,38] Martin et al.,[39] however, found that cyclin D1 overexpression enhanced radiation-induced apoptosis and radiosensitivity in a breast cancer cell line. In their study and others, radiation treatment resulted in a rapid increase in p53 and p21 and induced apoptosis in the cyclin D1–overexpression cells,[39-41] and those findings are consistent with our results showing better survival in the p53-negative (wild-type p53) and int-2/cyclin D1 amplification–positive group. Cyclin D1 gene amplification and overexpression is thought to accelerate the cell cycle, and this is correlated with an increased cell proliferative index in ESCC.[42,43] Chemotherapy and radiotherapy are generally effective against tumor cells that have a high proliferative index (including Ki-67 LI).[33-36,39,44] Recent reports have demonstrated a correlation between cyclin D1 overexpression and both increased tumor chemo-/radiosensitivity and better survival in patients with squamous cell carcinoma of the head and neck, similar to our own results.[45-48]

To verify our results, we should observe changes in response to CRT by the insertion of missing molecular

markers or the antisense oligonucleotide into ESCC in vivo, and a randomized study based on information about molecular markers is needed to verify the clinical significance of molecular markers obtained from pretreatment biopsy specimens in ESCC patients treated with neoadjuvant CRT. Although no randomized studies have confirmed the clinical benefits of neoadjuvant CRT for patients with ESCC,[49–51] the subjects of our neoadjuvant CRT were limited to T4 and/or M1 Lym ESCC patients, and its purpose was downstaging and improving the resectability of the whole tumor. The patients in this study whose tumors became surgically resectable after CRT had a significantly better survival than the patients with inoperable (unresectable) tumors after CRT. Long-term survival was achieved after surgery, particularly in the pathologic CR (grade 3) cases.[51–55] The pathologic response to CRT has been determined only on the basis of the microscopic findings in the resected specimens. However, grade 3 patients may not require surgery, because esophagectomy after CRT often results in failure, along with various postoperative complications and mortality.[51,56,57] However, the patients in whom CRT was ineffective also experienced severe toxicity because of the CRT, such as nausea, esophagitis, and leukopenia,[51] and these issues make it very important to be able to predict the response of ESCC patients to CRT.

This study showed a significant correlation between high Ki-67 LI and local response to CRT, and wild $p53$ (p53-negative) expression predicted a good prognosis in patients treated with CRT. CRT may be useful for ESCC with $int-2/cyclin$ $D1$ amplification, and the p53-negative and $int-2/cyclin$ $D1$ amplification–positive group, in particular, showed a significantly longer survival. Larger multicentric randomized studies are needed to confirm the predictive values of these factors; however, evaluating these predictive factors in endoscopic biopsy specimens may allow the selection of more suitable multimodal therapy for ESCC patients and improve their quality of life.

ACKNOWLEDGMENTS

REFERENCES

1. Iizuka T, Isono K, Kakegawa T, Watanabe H. Parameter linked to ten-year survival in Japan of resected esophageal carcinoma. *Chest* 1989;96:1005–11.
2. Ohtsu A, Boku N, Muro K, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999;17:2915–21.
3. Ide H, Nakamura T, Hayashi K, et al. Esophageal squamous cell carcinoma: pathology and prognosis. *World J Surg* 1994;18:321–30.
4. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 2000;232:225–32.
5. Shinozaki H, Ozawa S, Ando N, et al. *Cyclin D1* amplification as a new predictive classification for squamous cell carcinoma of the esophagus, adding gene information. *Clin Cancer Res* 1996;2:1155–61.
6. Takeuchi H, Ozawa S, Ando N, et al. Altered *p16/MTS1/CDKN2* and *cyclin D1/PRAD-1* gene expression is associated with the prognosis of squamous cell carcinoma of the esophagus. *Clin Cancer Res* 1997;3:2229–36.
7. Matsushime H, Roussel MF, Ashmun RA, Sherr CJ. Colony-stimulating factor 1 regulates novel cyclins during the G1 phase of the cell cycle. *Cell* 1991;65:701–13.
8. Motokura T, Bloom T, Kim HG, et al. A novel cyclin encoded by a *bcl1*-linked candidate oncogene. *Nature (Lond)* 1991;350:512–5.
9. Kitagawa Y, Ueda M, Ando N, Shinozawa Y, Shimizu N, Abe O. Significance of *int-2/hst-1* coamplification as a prognostic factors in patients with esophageal squamous cell carcinoma. *Cancer Res* 1991;51:1504–8.
10. Wagata T, Shibagaki I, Imamura M, et al. Loss of 17p, mutation of the *p53* gene, and overexpression of p53 protein in esophageal squamous cell carcinomas. *Cancer Res* 1993;53:846–50.
11. Gao H, Wang LD, Zhou Q, Hong JY, Huang TY, Yang CS. *p53* tumor suppressor gene mutation in early esophageal precancerous lesions and carcinoma among high-risk populations in Henan, China. *Cancer Res* 1994;54:4342–6.
12. Shimaya K, Shiozaki H, Inoue M, et al. Significance of *p53* expression as a prognostic factor in esophageal squamous cell carcinoma. *Virchows Arch A Pathol Anat Histopathol* 1993;422:271–6.
13. Sarbia M, Porschen R, Borchard F, Horstmann O, Willers R, Gabbert HE. p53 protein expression and prognosis in squamous cell carcinoma of the esophagus. *Cancer* 1994;74:2218–23.
14. Sturm I, Petrowsky H, Volz R, et al. Analysis of p53/BAX/p16$^{ink4a/CDKN2}$ in esophageal squamous cell carcinoma: high BAX and p16$^{ink4a/CDKN2}$ identifies patients with good prognosis. *J Clin Oncol* 2001;19:2272–81.
15. Spitz FR, Giacco GG, Hess K, et al. p53 immunohistochemical staining predicts residual disease after chemoradiotherapy in patients with high-risk rectal cancer. *Clin Cancer Res* 1997;3:1685–90.
16. Bergh J, Norberg T, Sjogren S, Lindgren A, Holmberg L. Complete sequencing of the p53 gene provides prognostic information in breast-cancer patients, particularly in relation to adjuvant systemic therapy and radiotherapy. *Nat Med* 1995;1:1029–34.
17. Youssef EM, Matsuda T, Takada N, et al. Prognostic significance of the MIB-1 proliferative index for patients with squamous cell carcinoma of the esophagus. *Cancer* 1995;76:358–66.
18. Lam KY, Law SYK, So MKP, Fok M, Ma LT, Wong J. Prognostic implication of proliferative markers MIB-1 and PC10 in esophageal squamous cell carcinoma. *Cancer* 1996;77:7–13.
19. Deisseroth AB, DeVita VT Jr. The cell cycle. Probing new molecular determinants of resistance and sensitivity to cytotoxic agents. *Cancer J* 1995;1:15–21.
20. Japanese Society for Esophageal Diseases. *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus.* 9th ed. Tokyo: Kanehara Public Co, 1999.
21. van den Berg FM, Baas IO, Polak MM, Offerhaus GJA. Detection of p53 overexpression in routinely paraffin-embedded tissue of human carcinomas using a novel target unmasking fluid. *Am J Pathol* 1993;142:381–5.
22. Casey G, Lopez ME, Ramos JC, et al. DNA sequence analysis of exon 2 through 11 and immunohistochemical staining are required to detect all known p53 alterations in human malignancies. *Oncogene* 1996;13:1971–81.

23. Sgambato A, Migaldi M, Leocata P, et al. Loss of p27^{kip1} expression is a strong independent prognostic factor of reduced survival in N0 gastric carcinomas. *Cancer* 2000;89:2247–57.
24. Takeuchi H, Ozawa S, Ando N, et al. Further evidence that altered *p16/CDKN2* gene expression is associated with lymph node metastasis in squamous cell carcinoma of the esophagus. *Oncol Rep* 2001;8:627–32.
25. Ikeda Y, Ozawa S, Ando N, Kitagawa Y, Ueda M, Kitajima M. Meanings of c-*erb* B and *int-2* amplification in superficial esophageal squamous cell carcinomas. *Ann Thorac Surg* 1996;62:835–8.
26. Levine AJ, Momand J, Finlay CA. The p53 tumor suppressor gene. *Nature* 1991;351:453–6.
27. Finlay CA, Hinds PW, Tan TH, Eliyahu D, Oren M, Levine AJ. Activating mutations for transformation by p53 produce a gene product that forms an hsc70-p53 complex with an altered half life. *Mol Cell Biol* 1988;8:531–9.
28. Scott N, Sagar P, Stewart J, Blair GE, Dixon MF, Quirke P. p53 in colorectal cancer: clinicopathological correlation and prognostic significance. *Br J Cancer* 1991;63:317–9.
29. Lowe SW, Ruley HE, Jacks T, Housman DE. p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. *Cell* 1993;74:957–67.
30. McIlwrath AJ, Vasey PA, Ross GM, Brown R. Cell cycle arrests and radiosensitivity of human tumor cell lines: dependent on wild-type p53 for radiosensitivity. *Cancer Res* 1994;54:3718–72.
31. Fujiwara T, Grimm EA, Mukhopadhyay T, Zhang WW, Owen-Schaub LB, Roth JA. Induction of chemosensitivity in human lung cancer cells *in vivo* by adenovirus-mediated transfer of the wild-type *p53* gene. *Cancer Res* 1994;54:2287–91.
32. Maesawa C, Tamura G, Nishizuka S, et al. Inactivation of the *CDKN2* gene by homozygous deletion and *de novo* methylation is associated with advanced stage esophageal squamous cell carcinoma. *Cancer Res* 1996;56:3875–8.
33. Mendonca MS, Rodriguez A, Alpen EL. Quiescence in pL cells and correlation with radiosensitivity and PLD repair. *Radiat Res* 1989;117:433–47.
34. Masunaga S, Ono K, Abe M. A method for the selective measurement of the radiosensitivity of quiescent cells in solid tumors—combination of immunofluorescence staining to BrdU and micronucleus assay. *Radiat Res* 1991;125:243–7.
35. Nakano T, Oka K. Differentiation values of Ki-67 index and mitotic index of proliferating cell population, an assessment of cell cycle and prognosis in radiation therapy for cervical cancer. *Cancer* 1993;72:2401–8.
36. Okuno Y, Nishimura Y, Kashu I, Ono K, Hiraoka M. Prognostic values of proliferating cell nuclear antigen (PCNA) and Ki-67 for radiotherapy of oesophageal squamous cell carcinomas. *Br J Cancer* 1999;80:387–95.
37. Warenius HM, Seabra LA, Maw P. Sensitivity to cis-diamminedichloroplatinum in human cancer cells is related to expression of cyclin D1 but not c-raf-1 protein. *Int J Cancer* 1996;67:224–31.
38. Hochhauser D, Schmieders B, Ercikan-Abali E, et al. Effect of cyclin D1 overexpression on drug sensitivity in a human fibrosarcoma cell line. *J Natl Cancer Inst* 1996;88:1269–75.
39. Martin JMC, Balkenende A, Verschoor T, Lallemand F, Michalides R. Cyclin D1 overexpression enhances radiation-induced apoptosis and radiosensitivity in a breast tumor cell line. *Cancer Res* 1999;59:1134–40.
40. Kranenburg O, van der Eb AJ, Zantema A. Cyclin D1 is an essential mediator of apoptotic neuronal cell death. *EMBO J* 1996;15:46–54.
41. Sofer-Levi Y, Resnitzky D. Apoptosis induced by ectopic expression of cyclin D1 but not cyclin E. *Oncogene* 1996;13:2431–7.
42. Shamma A, Doki Y, Shiozaki H. et al. Effect of cyclin D1 and associated proteins on proliferation of esophageal squamous cell carcinoma. *Int J Oncol* 1998;13:455–60.
43. Musgrove EA, Lee CS, Buckley MF, Sutherland RL. Cyclin D1 induction in breast cancer cell lines shortens G1 and is sufficient for cells arrested in G1 to complete the cell cycle. *Proc Natl Acad Sci U S A* 1994;91:8022–6.
44. Konishi T, Hiraishi M, Mafune K, et al. The therapeutic efficacy and toxicity of sequential methotrexate and 5-fluorouracil in gastric cancer. *Anticancer Res* 1994;14:1277–9.
45. Shintani S, Mihara M, Ueyama Y, Matsumura T, Wong DTW. Cyclin D1 overexpression associates with radiosensitivity in oral squamous cell carcinoma. *Int J Cancer* 2001;96:159–65.
46. Yoo SS, Carter D, Turner BC, et al. Prognostic significance of cyclin D1 protein levels in early-stage larynx cancer treated with primary radiation. *Int J Cancer* 2000;90:22–8.
47. Akervall J, Brun E, Dictor M, Wennerberg J. Cyclin D1 overexpression versus response to induction chemotherapy in squamous cell carcinoma of the head and neck—preliminary report. *Acta Oncol* 2001;40:505–11.
48. Hwang CF, Cho CL, Huang CC, et al. Loss of cyclin D1 and p16 expression correlates with local recurrence in nasopharyngeal carcinoma following radiotherapy. *Ann Oncol* 2002;13:1246–51.
49. Ajani JA. Preoperative therapy for patients with resectable squamous cell carcinoma of the esophagus: are we still confused? *Ann Surg Oncol* 2002;9:605–6.
50. Chan ACW, Lee DWH, Griffith JF, et al. The clinical efficacy of neoadjuvant chemotherapy in squamous esophageal cancer: a prospective nonrandomized study of pulse and continuous-infusion regimens with cisplatin and 5-fluorouracil. *Ann Surg Oncol* 2002; 9:617–24.
51. Geh JI, Crellin AM, Glynne-Jones R. Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer. *Br J Surg* 2001;88: 338–56.
52. Jones DR, Detterbeck FC, Egan TM, Parker LA Jr, Bernard SA, Tepper JE. Induction chemoradiotherapy followed by esophagectomy in patients with carcinoma of the esophagus. *Ann Thorac Surg* 1997;64:185–92.
53. Ancona E, Ruol A, Santi S, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. *Cancer* 2001;91: 2165–74.
54. Lew JI, Gooding WE, Ribeiro U Jr, Safatle-Ribeiro AV, Posner MC. Long-term survival following induction chemoradiotherapy and esophagectomy for esophageal carcinoma. *Arch Surg* 2001; 136:737–42.
55. Heath EI, Burtness BA, Heitmiller RF, et al. Phase II evaluation of preoperative chemoradiation and postoperative adjuvant chemotherapy for squamous cell and adenocarcinoma of the esophagus. *J Clin Oncol* 2000;18:868–76.
56. Slater MS, Holland J, Faigel DO, Sheppard BC, Deveney CW. Does neoadjuvant chemoradiation downstage esophageal carcinoma? *Am J Surg* 2001;181:440–4.
57. Ikeda K, Ishida K, Sato N, et al. Chemoradiotherapy followed by surgery for thoracic esophageal cancer potentially or actually involving adjacent organs. *Dis Esophagus* 2001;14:197–201.

特集 食道癌治療―最近の話題

5 食道癌に対する根治的な放射線化学療法

室　　　圭* 新井　達広* 宇良　　敬* 後藤　　歩*
安井　久晃* 濱口　哲弥* 山田　康秀* 島田　安博*
白尾　国昭* 井垣　弘康** 日月　裕司** 加藤　抱一**
伊藤　芳紀*3 今井　　敦*3 加賀美芳和*3

Key words : 放射線化学療法, clinical stage, Japan Clinical Oncology Group(JCOG), 晩期毒性, salvage surgery

――要旨――

　近年，食道癌に対する放射線化学療法の良好な成績が報告されるようになり，その有用性が明らかになってきた．当センターを中心に各ステージで行ってきた本療法の生存成績を，historical control として同じ clinical stage の外科手術成績と比較してみると，ほぼ同等の結果が得られることがわかってきた．食道温存が得られる点も考慮すれば，きわめて魅力的な治療法であることは間違いない．しかし，症例数や長期成績が不十分であり，単一施設の retrospective の成績では説得力に欠けること，晩期毒性に対する一般の認識は不十分であることなど問題点も多い．時に致死的となる晩期毒性を未然に防ぐことや起きた場合に適切に対処すること，さらに遺残・再発例に対して EMR を含む salvage surgery を確立させることが，今後，本療法の治療成績向上のための課題であると考える．

　今後，食道癌治療に携わる多くの医師が，臨床実地のなかで本療法の経験を積み，そして prospective な臨床試験を積み上げていくことで，本療法の意義・位置づけを明確化させていくことが必要である．

はじめに

　本邦における食道癌治療は，外科的切除術が根治的治療としてもっとも確実な治療法と考えられ，第一選択とされている．全国食道がん登録調査報告[1),2)]によれば，食道癌治療を行った全登録症例(内視鏡的粘膜切除術，化学療法，放射線療法，手術療法など)における手術療法の占める割合は，1983年〜1987年が72.4%(4,407/6,090)，1998年が66.2%(1,981/2,991)，1999年が64.7%(1,882/2,907)であった．近年，若干減少傾向にあるものの，依然手術療法が食道癌治療の大部分を占めている．根治目的の食道癌治療において，手術をしないということは考えられない状況である．

　一方欧米では，従来，術前化学療法や術前放射線化学療法などの集学的治療や根治的放射線化学療法が広く行われており，本邦の状況とは異なっている．

　近年，本邦でも食道癌に対する非手術放射

*国立がんセンター中央病院内科　**同 食道外科
*3同 放射線科
（〒104-0045 東京都中央区築地5-1-1）

線化学療法の治療成績が報告されるようにな
り，各ステージで従来の手術成績に匹敵する
良好な結果[3]~[5]が明らかになりつつある．手
術を行わずに（食道が温存されて）根治が得ら
れ，かつ手術に匹敵する治療成績が得られる
という点で，本邦での今までの食道癌治療に
対する考え方を大きく変える状況になってき
ている．

本稿では，当センターを中心に行ってきた
食道癌に対する根治的放射線化学療法の治療
成績を述べ，有望な将来性と現状の問題点を
明らかにし，最後に今後の食道癌治療の展望
について論じたい．

I. 本邦における食道癌手術成績

5年生存割合は近年向上し，国際的にも
トップクラスの治療成績をおさめているが，
これは表在癌症例の割合の増加に加え，術前
に行う各種検査法の高い精度，手術手技や術
後管理のレベルの高さなどに起因していると
考えられる．さらに，従来の2領域郭清に頸
部上縦隔拡大郭清を加えた頸胸腹3領域拡大
郭清が1980年代後半から導入されたことが，
かかる遠隔成績の向上をもたらしたとする向
きもある[6]~[12]が，解析法に問題点も多く，3
領域郭清の意義は未だ不明瞭と言わざるをえ
ない[13]．このように，郭清の程度の差異が予
後にどの程度影響を及ぼすかは不明瞭である
が，ただ，十分に郭清を行う本邦の食道癌の
手術成績（生存割合）が，十分には郭清を行わ
ない非開胸食道抜去術が主体の欧米に比し，
一般に良好である．この相異は術式や術後管
理だけではなく，本邦と欧米の疾患背景や患
者背景の相異に起因している可能性も考えら
れる．このためか，本邦と欧米で食道癌治療
に対する考え方や集学的治療の内容，展開は

異なっている．つまり，本邦では手術療法が
主体であるのに比し，欧米では術前治療に力
点を置いた集学的治療や非手術の放射線化学
療法が主体である．

本邦の食道癌手術成績が良好であるとはい
え，3領域郭清が一般に導入されるように
なった1988年～1997年の全手術例(11,642
例)の5年生存割合は36.1%[2]と低く，食道
癌はほかの消化器癌と比較して，依然として
治癒困難な予後不良の癌といえる．日本臨床
試験グループ(Japan Clinical Oncology
Group；JCOG)食道がんグループの調査に
よれば1989年～1998年の10年間の手術直
接死亡率1.8%，全体の在院死亡率5.4%と，
近年死亡率は低下してきているが，ほかの消
化器癌外科手術と比較しても依然高い数値で
ある．また，各施設で概ね60～70%の高い
術後合併症率が報告されている．3領域郭清
をはじめとする拡大郭清の患者に及ぼす手術
侵襲は許容限界に近く，外科手術単独ではこ
れ以上の予後の改善は望めない現状にある．
また，食道切除による術後QOLの低下も無
視できない問題である．もっと侵襲の少ない
新たな治療法の開発が急務であり，現在のと
ころ放射線化学療法がその最右翼である．

以下，各ステージにおける放射線化学療法
の治療成績を述べる．ここで述べるステージ
とは，臨床病期(clinical stage)のことであ
る．通常，外科手術成績は病理学的病期
(pathological stage)で治療成績を公表して
いることがほとんどであるが，非手術の治療
では当然のことながら手術標本を使った病理
学的な検討は不可能である．放射線化学療法
の治療成績を手術成績との比較で検討する場
合，両者をclinical stageで統一させ，同じ
土俵の上で比較しなければ決して正しい評価
はできない．この点は非常に重要なポイント

週	1	2	3	4	5	6	7	8	9	10
5FU 400mg/m²/d	■	■				■	■			
CDDP 40mg/m²	■	■				■	■			
RT 2Gy/dx 30d(60Gy)	■	■	■			■	■	■		

for responders	11	12	13	14	15	16	17	18
5FU 800mg/m²/d	■				■			
CDDP 80mg/m²	■				■			
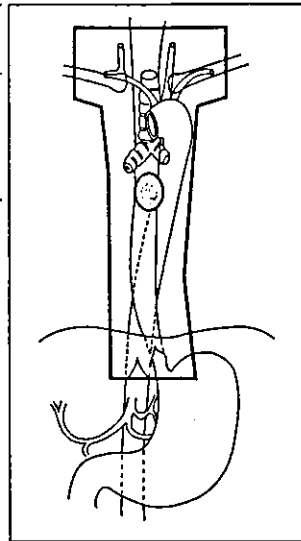
Schema of initial RT port

including elective nodal irradiation up to 40 Gy
booster dose of 20 Gy to the gross tumor

図1 治療スケジュール(for T 4/M 1 LYM, clinical stage II, III)

であることを強く認識すべきである.

II. 局所高度進行型(T 4/M 1 LYM)食道癌に対する放射線化学療法

　国立がんセンター東病院を中心とした数施設において, 局所高度進行型食道癌であるT 4 または照射範囲内の M 1 LYM を対象にした放射線化学療法が行われ, その結果が報告されている[14]. 治療スケジュールを図1に示す. 5 FU(5-fluorouracil)＋CDDP(シスプラチン)療法と同時に放射線照射を行い, 計2コースの5 FU＋CDDP 療法と総線量60 Gy の放射線治療を施行, さらに奏効例では5 FU＋CDDP の化学療法を2コース(計4コース)行うものである. 治療前診断(clinical stage)T 4/M 1 LYM で手術をせずに放射線化学療法を行った 54 例において, 全体の CR(完全腫瘍消失)率が 33%(18/54)と高い抗腫瘍効果を認め, 毒性に関しては grade 3 以上の白血球減少 42%, 食道炎 21%で, 対象の進行度を考慮すれば十分許容範囲内で耐用可能と考えられた. 生存期間に関しては, MST 9 カ月, 1 年 41%, 2 年 34%, 3 年生存割合 23%と良好な治療成績が得られている. 最近の追跡調査の結果によれば5年

＜放射線化学療法症例＞
n=54
MST：9ヵ月
CR rate：33%
2年生存割合：34%

N.S.

CRT(n=54)

Surgery(n=64)

Surgery：1985-1993, 国立がんセンター中央病院
CRT：1992-1997 国立がんセンター東病院 他
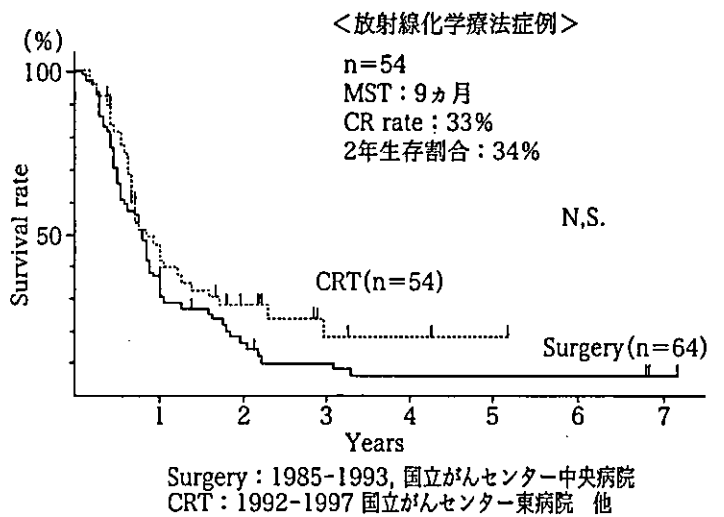
図2 他臓器浸潤(T 4), 遠隔リンパ節転移(M 1 LYM)
症例の生存比較(手術 vs 放射線化学療法)

生存割合が 17%[15]であり, このような局所高度進行型でも根治の得られる可能性が示唆された.

　図2は, 上記 54 例の生存曲線(1992 年～1997 年)と術前診断 T 4/M 1 LYM で手術を行った国立がんセンター中央病院の 64 例の生存曲線(1985 年～1993 年)を同一グラフ内に示したものである. より予後の悪い T 4 症例と比較的予後の良い M 1 LYM 症例の分布は両群間に偏りはないが, 治療時期が両群間で異なること, 手術群では手術単独もあれば術後種々の補助療法が施行されている症
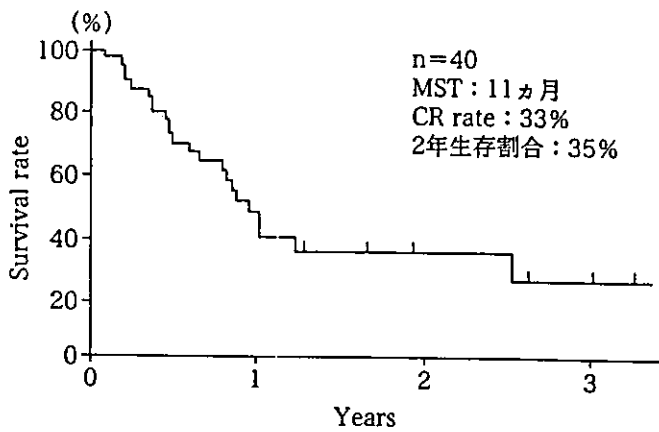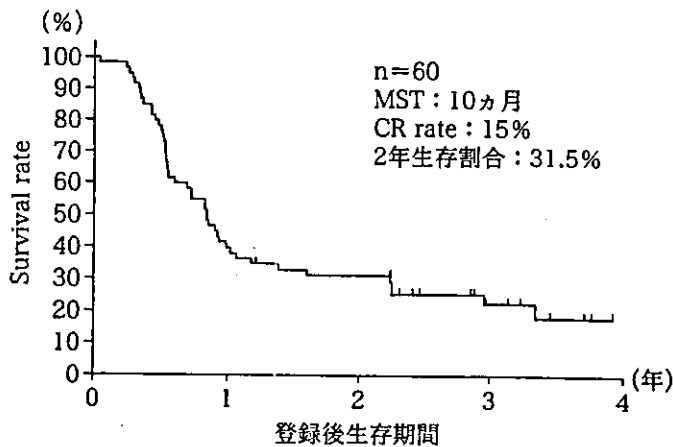
図3　T4/M1LYM 食道癌に対する放射線化学療法
（国立がんセンター中央病院 1997〜2000 年）

図4　T4/M1LYM 食道癌に対する放射線化学療法
JCOG 9516（JCOG 食道がんグループ多施設共同研究）March, 1996〜April, 1998

例もあり単一治療群ではないこと，無作為化比較試験ではなく retrospective な検討であることなどから，両者を単純に比較することはできない．しかし，T4/M1LYM 食道癌における根治的放射線化学療法の治療成績が手術療法を凌駕しえる可能性を支持するものといえる．

　図3 は，同じ対象の国立がんセンター中央病院における放射線化学療法の治療成績であり，図4 は，同様の対象症例に対して JCOG 食道がんグループが多施設共同研究として行った臨床第 II 相試験の治療成績結果である．いずれにおいても生存成績に差異を認めず，再現性のある良好な治療成績の結果が確認された．
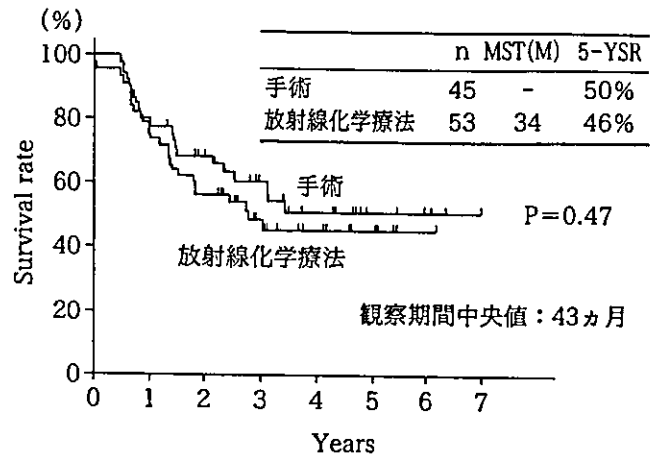
　T4/M1LYM 食道癌に対しては，手術成

図5　T4 を除く Clinical Stage II，III症例の
生存比較（手術 vs 放射線化学療法）
（国立がんセンター東病院 1992 年〜1999 年）

績が悪く術死や術後合併症の頻度も高いこともあり，現在は大多数の施設で放射線化学療法を中心とした非外科的治療が中心となっている．

III．Clinical stage II，III（T4 を除く）食道癌に対する放射線化学療法

　図5 は，国立がんセンター東病院における clinical stage II，III の放射線化学療法の生存成績と，ほぼ同時期に術前 clinical stage II，III と診断されて手術された外科的切除術単独の生存成績とを比較したものである．図2 同様，無作為化比較試験の結果ではないので，その取り扱いには十分慎重を期する必要があるが，放射線化学療法では，同じ clinical stage II，III の外科手術成績とほぼ同等の良好な生存成績結果が得られた．この外科的切除術の治療成績は本邦の食道癌手術成績として標準的なものである．また，治療の侵襲度や治療後の摂食状況，体重変化を調査すると，放射線化学療法では手術に比べいずれも良好な結果が得られ，QOL の点で優れている結果が確認された．以上より，T4 を除く stage II，III食道癌に対しても，放射線化学療法が標準的治療になりえる可能性が示唆

	d 1	4, 5	8	12	15	19
CDDP(70 mg/m²)	■					
5 FU(700 mg/m²/d)	■■					
Radiation(2 Gy/d)	■■■		■■	■■		■■

Every 4 weeks×2 courses, total radiation dose：60 Gy

図6　治療スケジュール(for clinical stage Ⅰ)

された.

この結果を受けて2000年4月から,JCOG消化器がん内科グループにおいて,clinical stage Ⅱ, Ⅲ食道癌に対する根治的放射線化学療法の多施設共同臨床第Ⅱ相試験(JCOG 9906；研究代表者：大津　敦,研究事務局：室　　圭)の登録が開始された.2002年3月に全76症例の登録が終了し,現在追跡中である.現時点で本試験の生存成績等はまだ公表の段階ではない.中間解析時点でのOverall CR例は, 37適格例中24例(CR rate＝65%)とまずまずの抗腫瘍効果であった.治療開始からCRと判定されるまでに半年間近く要する症例もあるかと思えば,CRに入らず短期間で原発巣増悪が進行する症例もあるので,画像で評価する際には綿密で注意深い観察が必要である.

今まで,手術可能対象例での根治的放射線化学療法の抗腫瘍効果や生存成績は,単施設のretrospectiveな結果しか存在せず,その評価は不十分であると言わざるをえなかった.しかし,本試験(JCOG 9906)の治療成績が明らかとなれば,手術可能症例に対する根治的放射線化学療法の意義や位置づけ,そして問題点が明確になるであろう.本試験の最終的な成績の結果解析が待たれる.

Ⅳ. Clinical stage Ⅰ食道癌に対する放射線化学療法

clinical stage Ⅰ食道癌において, m癌であれば通常,内視鏡的粘膜切除術(EMR)を

考慮するが, EMR不適の表層拡大型のm癌や大多数のsm癌では標準的治療は外科的切除術である.進行癌同様, このステージでの放射線化学療法のパワーは未知のものであった.しかし,今まで述べてきた進行食道癌での放射線化学療法の良好な治療成績結果から, かかるステージにおいても本治療の可能性が期待できる.この章では,国立がんセンター中央病院においてEMR適応外と判断されたclinical stage Ⅰ食道癌に対する放射線化学療法の治療成績結果[4],[16]を述べる.1997年6月〜2002年5月までの5年間に,国立がんセンター中央病院で放射線化学療法を行ったclinical stage Ⅰ食道癌73例について検討した.検討対象の抽出条件として以下のすべての項目を満たすものとした.

1）内視鏡生検にて食道扁平上皮癌と診断された症例.

2）EMR適応外と判断されたclinical stage Ⅰ(T1N0M0)食道癌症例.

3）同部位の食道癌に対していかなる前治療(例：EMR後の遺残症例など)のない症例.

4）合併症の有無は問わないが,主要臓器機能が保たれている症例.

5）治療前に活動性の重複癌のない症例.

6）根治目的に同一レジメン(図6)の放射線化学療法を施行した症例.

73例の中にm癌を3例含んでいるが, いずれも表層拡大型や多発病巣のため, EMRによる根治的治療が不可能と判断された症例である.