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Concurrent Chemotherapy (5-Fluorouracil and Cisplatin) and Radiation Therapy Followed by Surgery for T4 Squamous Cell Carcinoma of the Esophagus

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Background and Objectives: Since the prognosis of patients with T4 squamous cell carcinoma (SCC) of the esophagus is extremely poor, an effective multimodal treatment needs to be established.

Methods: Forty-five patients with SCC of the esophagus at the T4 classification of the disease but no hematogenous metastasis were treated with concurrent chemoradiation therapy followed by surgical resection. Twenty-eight patients were treated with a regimen (protocol A) of 5-fluorouracil 750 mg/m^2 on days 1–5 and 22–26, and cisplatin 70 mg/m^2 on days 1 and 22. The remaining 17 patients were treated with a modified regimen (protocol B) of 5-fluorouracil 400 mg/m^2 and cisplatin 10 mg/m^2 on days 1–5, 8–12, 15–19, and 22–26. Radiation was delivered daily for 5 days/week for 4 weeks at the rate of 2 Gy/day to a total dose of 40 Gy in both protocols.

Results: A major clinical response was observed in 29 [3 complete response (CR) and 26 partial response (PR)] patients (64.4%). Twenty-eight patients (62.2%) underwent esophagectomy with no postoperative death. The median survival time of the resected patients (959 days) was significantly longer than that of the non-resected patients (178 days). Protocol B showed significantly higher pathologic effectiveness than protocol A. The pathologic CR rate for the main tumors was 1 (6.3%) of 16 patients for protocol A and 7 (58.3%) of 12 patients for protocol B. The pathologic CR rate for metastasized lymph nodes was 4/11 (36.4%) for protocol A and 5/5 (100%) for protocol B. Good histological response of the main tumors correlated well with long survival. The treatments were well tolerated except for one treatment-related death.

Conclusions: Concurrent chemoradiation therapy followed by surgery is an effective and safe multimodal therapy for patients with primary inoperable T4 SCC of the esophagus.

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KEY WORDS: **inoperable esophageal cancer; squamous cell carcinoma; chemoradiation; neoadjuvant therapy; surgical resection**

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INTRODUCTION

Recent advances in surgical techniques and perioperative management have significantly improved the resectability, long-term survival, and operative mortality of patients with esophageal cancer. However, treatment with surgery alone does not improve the extremely poor prognosis of patients with T4 squamous cell carcinoma (SCC). Iizuka [1] reported that the 2-year survival rate of patients who received non-curative resection was 2% and that of patients who underwent curative resection was 19%. Takagi et al. [2] reported that the 1-year survival rate of patients with T4 esophageal cancer was 17%. To improve the prognosis for patients with locally advanced esophageal cancer, multimodal therapy is needed.

Most investigators have shown that adjuvant treatment with pre- or postoperative radiation may improve locoregional control but does not improve overall survival due to increased incidence of clinically apparent distant organ metastasis during follow-up, suggesting that systemic micrometastasis has been present at the time of diagnosis [3–8]. Nor has adjuvant chemotherapy alone been reported to improve survival [9,10].

Recently, multimodal therapy has been developed to control both local recurrence and distant metastasis of esophageal cancer and to prolong survival. One of the most promising treatments is concurrent chemoradiation therapy given prior to surgical resection. Several phase II studies have indicated that preoperative concurrent chemoradiation therapy resulted in downstaging of the disease to a pathologic complete response (CR) in 17–24% of patients with a median survival period of 12–29 months [11–16]. The rationale behind this preoperative chemoradiation therapy is as follows: (1) preoperative therapy permits higher resectability in subsequent surgery; (2) chemoradiation therapy is more tolerable before surgery than after it; (3) simultaneous treatment with chemotherapy and radiation may control not only local but also occult distant disease; (4) 5-fluorouracil and cisplatin, most frequently used in chemoradiation regimens, both act as radiation sensitizers.

Our previous pilot study demonstrated that the combination of preoperative chemoradiation therapy and surgery was effective for prolonging survival in patients with T4 esophageal cancer compared with our historical control [17]. However, the pathologic CR rate of the previous study was only 8% and not as high as those reported by others because of the advanced stage of the tumors [11–16]. We increased dose intensities and modified the administration schedule of the chemotherapeutic agents (5-fluorouracil and cisplatin) from intermittent administration to a low-dose continuous administration that was completely synchronized with radiation to enhance the action by serving as radiosensitizers.

This study examined the effects of preoperative chemoradiation therapy on resectability, pathologic tumor response, lymph node metastasis, survival, and treatment toxicities in patients with primary inoperable T4 esophageal cancer. We also compared the effects of two different schedules of preoperative chemoradiation therapy.

MATERIALS AND METHODS

Patient Eligibility

Between August 1989 and October 1996, a total of 45 patients with biopsy-proven SCC of the esophagus were enrolled in this study. The patients were newly diagnosed and had had no prior treatment. The eligibility for this study was as follows: The patients were 70 years old or younger; showed performance status [Eastern Cooperative Oncology Group (ECOG)] of 3 or less; and were in stage T4 of the disease, as diagnosed by computed tomography (CT), esophagogram, or bronchoscopy. The criteria for T4 in CT images were previously described [18]. Briefly, the fat plane in the triangular space between the esophagus, aorta, and spine was obliterated or a tumor mass shadow was observed between the aorta and spine. Protrusion of the tumor into the lumen of the trachea or bronchus was also considered to be T4. Patients with nodal involvement including regional lymph nodes (N1) and distant lymph nodes (M1LYM) were enrolled in this study. Patients with distant organ metastasis were excluded. The stage was assigned according to the criteria of the American Joint Committee on Cancer [19]. All patients were required to have adequate bone marrow function (white blood cell count of >3,500 cells/ml and platelet count of >100,000 cells/ml), normal renal function (serum creatinine level of <1.2 mg/dl or creatinine clearance of >50 ml/dl), and normal liver function (serum transaminases <2 times the upper limit of normal level). Written informed consent was obtained in all cases.

Treatment Regimen

In the treatment regimen, a single daily fraction of 2 Gy was administered concurrently with either intermittent (protocol A) or completely synchronized (protocol B) administration of cisplatin and 5-fluorouracil. Of the 45 patients, 28 enrolled from August 1989 to March 1994 were treated with protocol A. The remaining 17 patients were treated with protocol B. Prior to initiation of radiation therapy, all patients were subjected to simulation to encompass the primary tumor volume. The width of the radiation field for the mediastinum was 7–8 cm and the lower margin was at least 5 cm caudad from the distal edge of the tumor. Bilateral supraclavicular nodes and the upper mediastinum were also included in the T-shaped field. The radiation technique consisted of parallel-opposed fields using an anterior and posterior portal arrangement. In both protocols, radiation was delivered via a 10 MV X-ray linear accelerator daily for 5 days/week for 4 weeks at a rate of 2 Gy/day to a total dose of 40 Gy. If subsequent surgical resection was not planned,

an additional 20 Gy was administered via two parallel oblique fields or multiple fields to avoid damage to the spinal cord.

In protocol A, 5-fluorouracil was administered intravenously at 750 mg/m^2 on days 1–5 and 22–26. Cisplatin was administered on days 1 and 22 at a dose of 70 mg/m^2 by drip infusion for 2 hr with sufficient pre- and post-hydration to prevent renal toxicity. In protocol B, the administration schedules of 5-fluorouracil and cisplatin were completely synchronized with that of irradiation. 5-Fluorouracil at a dose of 400 mg/m^2 and cisplatin at 10 mg/m^2 were administered by continuous intravenous infusion for 5 days/week for 4 weeks. Antiemetic drugs were given as requested. For hematologic toxicities greater than grade 3 (white blood cell count <2,000 cells/ml or platelet count <30,000 cells/ml), the chemotherapy was withheld until counts recovered beyond the critical level, and then the full dose was resumed. For gastrointestinal toxicity (grade 3: severe diarrhea, nausea and vomiting) and fever (grade 2: 40°C ⩾ 38°C; grade 2 or more: >38°C), chemotherapy was withheld pending improvement. For renal toxicity, the subsequent dose of cisplatin was reduced depending on the degree of toxicity. Two weeks after completing the chemoradiation therapy, the patients were reevaluated for therapeutic responses of the main tumor and metastatic lymph nodes by barium study, tissue biopsy obtained by endoscopy, and chest and abdominal CT scans. The treatment response was categorized using general criteria [20]. CR was defined as 100% regression of the disease. Partial response (PR) was defined as regression of more than 50% in the tumor and metastatic lymph nodes, as confirmed by esophagography and CT scans. Progressive disease (PD) was defined as an increase in the tumor mass or metastatic nodes or the appearance of new lesion(s). Patients who were not classified as CR, PR, or PD were defined as non-responders (NC). If a clinical response was observed and a curative resection was thus considered potentially possible, the patients were scheduled for surgery approximately 4 weeks after the last day of the chemoradiation therapy. The toxicities were assessed according to World Health Organization (WHO) criteria [21].

Statistics

Survival was calculated from the initial date of the treatment to the occurrence of the event or to the date of the most recent follow-up visit. Statistical analysis of survival time was determined by the Kaplan-Meier method, and comparison of the two groups was performed by the log-rank test. $P < 0.05$ was considered significant. Comparison of the histological effectiveness by the two protocols was done by the Mann-Whitney *U*-test. Downstaging by treatment was analyzed by the Wilcoxon signed-rank test.

TABLE I. T4 SCC of the Esophagus: Characteristics and Clinical Responses in 45 Patients

No. of patients (male/female)	45	(41/4)
Age (years)	58.3	(range: 47–70)
Location of tumor		
Cervical	8	
Upper thoracic	9	
Middle thoracic	23	
Lower thoracic	5	
Tumor length (cm)	8.1	(range: 3–14)
Organs invaded		
Aorta	25	
Trachea	27	
Bronchus	2	
Left atrium	1	
Others	8	
Disease stage		
III	37	
T4 N0 M0	16	
T4 N1 M0	21	
IV		
T4 M1(LYM)	8	
Clinical response rate[a]		
CR	3	(6.7%)
PR	26	(57.8%)
NC	10	(22.2%)
PD	5	(11.1%)
Operability	31	(68.9%)
Resectability	28	(62.2%)
Palliative surgery	3	(6.7%)

[a]One patient died of anaphylactic shock during CT examination.

RESULTS

Patient Characteristics and Clinical Response

A total of 45 patients with SCC of the esophagus were enrolled in this study. Patient characteristics are shown in Table I. Forty-one of the 45 patients were male. Mean age of the patients was 58.3 years (ranges 47–70 years). Tumor location was cervical in 8, upper thoracic esophagus in 9, middle thoracic esophagus in 23, and lower thoracic esophagus in 5. Mean tumor size was 8.1 cm in length (range: 3–14 cm). Organs invaded by the primary tumor were aorta in 25 cases, trachea in 27, bronchus in 2, and left atrium in 1. Clinical stage was either stage III (T4 N0 M0 in 16, T4 N1 M0 in 21) or stage IV (T4 N0 or 1 M1(LYM) in 8). After the chemoradiation therapy, all patients were evaluated for their clinical response and toxicities. Thirty-three of 45 patients (73.3%) were given the full dose of their planned chemoradiation therapy, while the remaining 12 received reduced doses due to side effects judging from the criteria described in Materials and Methods. Twenty-nine of 45 patients (64.4%) showed a major response (3 CR and 26 PR) to the treatment. Of the 45 candidates enrolled in this study, 28 patients (62.2%) underwent esophagectomy, while resection could not be done for the remaining 17 patients for the following reasons: no change or progression of the disease in 9 (20%), chemoradiation-related toxicities (1

TABLE II. Pathological Responses in the Resected Specimens Following Chemoradiation

Histological effectiveness	Total	Protocol A	Protocol B	*P**
Main tumors[a]	28	16	12	0.0017
Grade 3	8 (28.6%)	1 (6.3%)	7 (58.3%)	
Grade 2	16 (57.1%)	11 (68.8%)	5 (41.7%)	
Grade 1	4 (14.3%)	4 (25.0%)	0 (0%)	
Grade 0	0 (0%)	0 (0%)	0 (0%)	
Lymph nodes[a]	16	11	5	0.0274
Grade 3	9 (56.3%)	4 (36.4%)	5 (100%)	
Grade 2	2 (12.5%)	2 (18.2%)	0 (0%)	
Grade 1	4 (25.0%)	4 (36.4%)	0 (0%)	
Grade 0	1 (6.3%)	1 (9.1%)	0 (0%)	

[a]Grade 3, complete disappearance of cancer cells; grade 2, more than 2/3 disappearance; grade 1, less than 2/3 disappearance; grade 0, no disappearance.
**P* value was calculated by the Mann-Whitney *U*-test to compare the histological effectiveness in the two protocols.

thrombocytopenia and 1 patient debility) in 2 (4.4%), esophagobronchial fistula in 2 (4.4%), preoperative high-risk factors (1 severe arrhythmia, 1 severe malnutrition due to dysphagia, and 1 liver dysfunction) in 3 (6.7%) and death by anaphylactic shock during CT examination of one patient (2.2%). There was no significant statistical difference in the major response rate and resectability between the two protocols. The major response rates in protocol A and protocol B groups were 17/28 (60.7%) and 12/17 (70.6%), respectively, while the resectability was 16/28 (57.1%) in protocol A and 12/17 (70.6%) in protocol B.

Pathological Responses in the Resected Specimens

Table II summarizes the pathological responses of the surgically resected specimens including primary lesions and dissected lymph nodes. For the primary lesions, grade 3 (complete disappearance of cancer cells) or grade 2 (more than 2/3 disappearance) responses were observed in 8/28 (28.6%) and 16/28 (57.1%), respectively. In 16 resected patients with positive lymph nodes diagnosed by preoperative CT, grade 3 and grade 2 responses for metastasized lymph nodes were found in 9/16 (56.3%) and 2/16 (12.5%), respectively. Of the 8 patients with grade 3 response of the main tumor, 7 showed a grade 3 response in the metastasized lymph nodes, suggesting that chemoradiation was effective not only against the primary lesions but also the metastasized lymph nodes. Comparing the pathologic response of the two protocols, protocol B was significantly more effective than protocol A against both main tumors ($P = 0.0017$) and metastatic lymph nodes ($P = 0.0274$). As shown in Table III, preoperative chemoradiation therapy caused downstaging of the disease in the 28 resected cases. As a result, 20 of the 28 resected cases received R0 resection. The R0 resection rate was significantly higher for the protocol B group ($P = 0.0438$, Mann-Whitney *U*-test). There was a significant difference ($P = 0.040$) of distribution of residual tumor classification (R0, R1, R2) between the two groups. These results suggest that protocol B may be a better preoperative regimen.

TABLE III. Downstaging and Curability of Cancer of the Esophagus Stages III and IV in the 28 Resected Cases After Chemoradiation

	Total	Protocol A	Protocol B
Preoperative stage			
III	25	14	11
IV	3	2	1
Postoperative stage			
0	7	1	6
I	2	0	2
IIA	3	1	2
IIB	6	4	2
III	7	7	0
IV	3	3	0
*P**	0.0002	0.0537	0.0020
Residual tumor classification[a]			
R0 resection	20	9	11
R1 resection	6	5	1
R2 resection	2	2	0
*P***		0.040	

[a]R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.
*Wilcoxon signed-rank test; *P* value-pre- vs. postoperative stage.
**Mann-Whitney *U*-test; *P* value-protocol A vs. B.

TABLE IV. Advanced Cancer of the Esophagus: Major Postoperative Complications

Complications	n = 28
Respiratory	12 (42.9%)
Anastomotic leakage	2 (7.1%)
Cardiovascular	5 (17.9%)
Delirium	7 (25.0%)
Catheter sepsis	3 (10.7%)
Recurrent nerve palsy	6 (21.4%)

Toxicities and Postoperative Complications

Major toxicities equal to or greater than WHO grade 3 were leukopenia in 22 (48.9%), gastrointestinal toxicities in 21 (46.7%), and renal toxicities in 4 (8.9%). Treatment-related death was seen in only 1 patient (2.2%) receiving protocol B, who died of pancytopenia. The frequency of gastrointestinal toxicities was significantly higher in the protocol B group than in the protocol A group (10/28, 35.7% vs. 11/17, 64.7%), while no significant difference was noted for the other toxicities. Among the postoperative complications listed in Table IV, respiratory complication was the most common. There was no postoperative death.

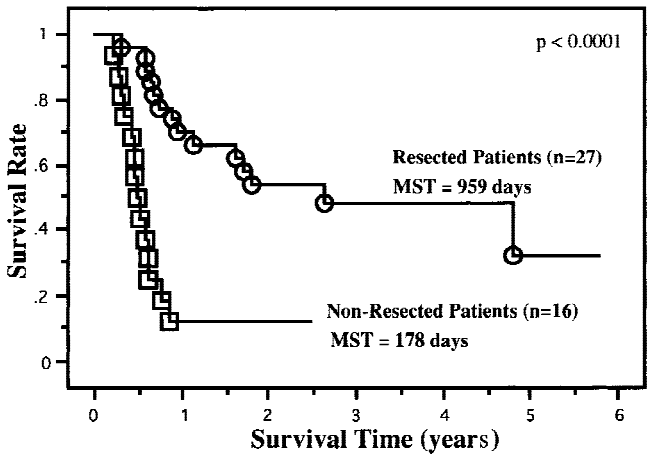

Fig. 1. Comparison of survival rates between 27 resected and 16 non-resected patients after chemoradiation therapy. MST, median survival time.

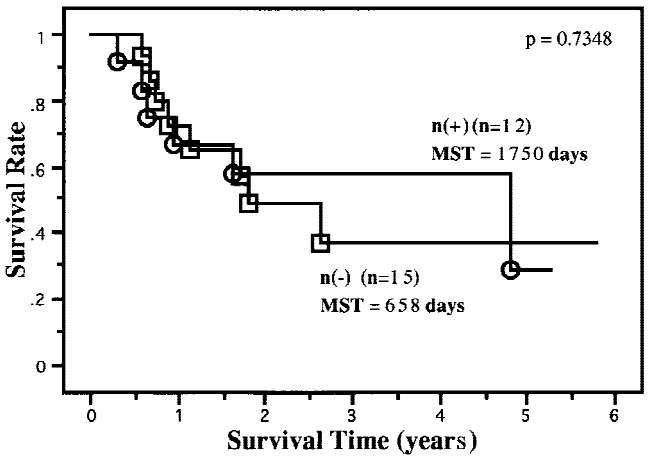

Fig. 3. Relationship between survival rates and histological lymph nodal status. MST, median survival time.

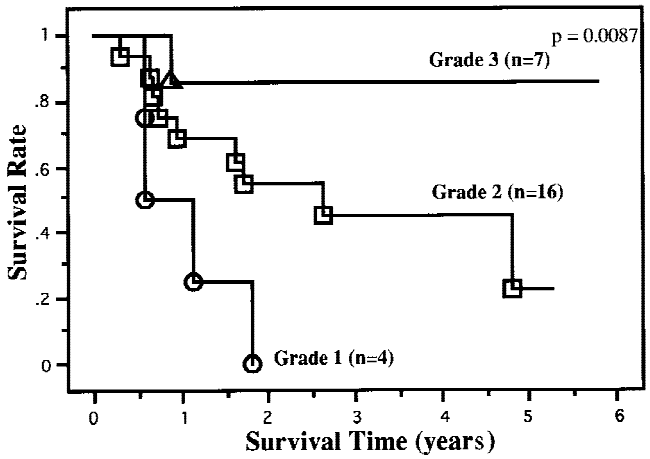

Fig. 2. Relationship between survival rates and histological effectiveness of the main tumors. Histological effectiveness was defined as follows: grade 3, complete disappearance of cancer cells; grade 2, more than 2/3 disappearance; grade 1, less than 2/3 disappearance. (One of 8 grade 3 patients was lost to follow-up.)

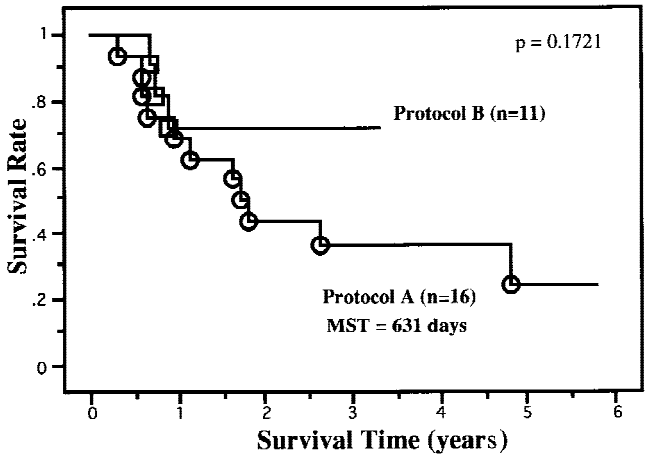

Fig. 4. Comparison of survival between patients receiving protocol A and protocol B. MST, median survival time.

Survival

Two of the 45 patients were excluded from the analysis of survival: one was lost during follow-up and the other died of anaphylactic shock during preoperative CT examination. The median survival time of 43 patients was 349 days. Figure 1 compares the survival between resected and non-resected patients. The median survival durations of the resected and non-resected patients were 959 days and 178 days, respectively, with the difference being significant at $P < 0.0001$. Figure 2 demonstrates the effects of the histological response of the main tumors on the survival of 27 surgically resected cases. Seven patients with grade 3 response showed significantly higher $P = 0.0483$ by log-rank test cumulative survival than those showing grade 2 or less response (1 of 8 grade 3 patients was lost to follow-up). The results may reflect a difference in the surgical curability among patients with different pathologic responses. Among 4 patients with grade 1 response, 2 underwent R2 resection and the other 2 underwent R1 resection, while all 8 patients with grade 3 response underwent R0 resection.

We also examined the effects of nodal sterilization by chemoradiation on prognosis. Figure 3 shows that no significant difference was observed in survival between n(+) and n(−) groups ($P = 0.7348$). To examine the effects of chemoradiation schedules on prognosis, survival was compared in the surgically resected patients receiving protocol A and protocol B. Patients in the protocol B group showed higher 2-year (72%) and 3-year (72%) survival rates compared with those in the protocol A group (43% and 36%), although the difference was not significant at $P = 0.1721$ (Fig. 4). Because the present study was retrospective and the follow-up periods of the

TABLE V. Patterns of Failure Following Chemoradiation and Surgery for Advanced Cancer of the Esophagus

Failure pattern	n = 27[a]	Death after[b]
Local failure	8 (29.6%)	9 m, 9 m, 10 m, 1 y, 1 y 1 m, 1 y 3 m, 1 y 10 m, 2 y 9 m
Distant metastasis	6 (22.2%)	10 m, 10 m, 1 y 9 m, 1 y 11 m, 3 y 2 m, 3 y 4 m
Local plus distant	2 (7.4%)	6 m, 1 y 11 m
Uncertain	1 (3.7%)	3 y 2 m
Other disease	3 (11.1%)	2 y 8 m, 3 y 9 m, 5 y 11 m
Disease-free survivor	7 (25.9%)	1 y 1 m, 1 y 8 m, 2 y 5 m, 2 y 9 m, 2 y 11 m, 3 y 5 m, 3 y 11

[a]One of 28 patients was lost to follow-up.
[b]m, month; y, year.

two protocols were different, the conclusions on survival require longer follow-up.

Patterns of Failure

As shown in Table V, 17 patients (63.0%) showed recurrence in 27 curatively resected cases: 8 (29.6%) local, 6 (22.2%) distant, 2 (7.4%) local plus distant, and 1 (3.7%) cancer death of unknown recurrence pattern. Three of 27 (11.1%) died of other diseases: 2 of pneumonia and 1 of unknown cause. Seven patients (25.9%) are presently alive with no sign of recurrence.

DISCUSSION

Recently, many studies have been conducted concerning neoadjuvant combined chemoradiation therapy for esophageal cancer. However, most trials have been conducted on potentially resectable tumors, and a few studies have dealth with primary inoperable and locoregionally far advanced esophageal cancer. In this study, primary inoperable esophageal cancer of T4 classification with or without lymph node metastatis, corresponding to stage 3 or 4 of the disease, was treated using 5-fluorouracil, cisplatin and radiation. Coia et al. [22] reported the median survival time of esophageal cancer patients with stage 3 or 4 disease to be 9 and 7 months, respectively, using 5-fluorouracil, mitomycin C, and radiation. Seitz et al. [23] reported that the median survival time of inoperable non-metastatic esophageal cancer patients in stage 3 is 11 months on treatment with 5-fluorouracil, cisplatin, and radiation. Izquierdo et al. [24] reported the median survival time of patients with unresectable non-metastatic SCC of the esophagus to be 8 months using sequential chemotherapy (cisplatin and bleomycin) and radiation therapy. The median survival time of all 43 patients in our analysis was 349 days, which was comparable to or even better than those of other reports. In addition, our resected cases showed a significantly longer median survival time than the non-resected cases (959 vs. 178 days). The prognosis of the resected cases after chemoradiation was better than that of our historical controls with histological T4 tumors who had undergone non-curative or relatively non-curative resection without any preoperative therapy. The median survival time of these controls was 281 days, and there were no 5-year survivors [25].

The prognosis of non-curative cases with macro- or microscopic residual tumors after surgery is extremely poor regardless of postoperative adjuvant treatments. Therefore, accurate preoperative diagnosis of T4 tumor is important for the choice of treatment modality. Our criteria for T4 tumor using CT had a positive predictive value of 67% and a negative predictive value of 75% [18]. Deviation of the esophageal axis on the esophagogram was also adopted as an additional criteria for T4 diagnosis in this study, and bronchoscopy was employed in case of tracheal or bronchial invasion. However, endoscopic ultrasonography was not performed because the endoscope could not pass through the lumen because of the tumors in most cases.

One of the interesting findings in this study was the metastasized lymph nodes diagnosed by CT responded equally or even more to the chemoradiation therapy than the main tumors. Thus, neoadjuvant chemoradiation therapy may increase the curability not only for resection of main tumors but also for lymph node dissection. However, in contrast to the close association of the response of the main tumor with prognosis, the nodal status in the resected specimens did not reflect the prognosis of the resected cases. There are two possible explanations for these results. One is that other factors such as T or M rather than N may be important prognostic factors in T4 tumor. The other possibility is that lymph node dissection might have improved the survival of the patients with positive lymph node metastasis. In this study, we performed esophagectomy with radical nodal dissection as a salvage operation for R0 resection. However, the role of nodal dissection remains to be clarified.

This study also showed that the histological response in the resected specimen correlated well with the prognosis. The patients with a higher histological response showed significantly better survival than those with lower histological response. Histological grade 3 (pathologic CR) was found in 8 (28.6%) of 28 surgical specimens in this study, which is comparable to other studies

(17–27%) [12–16]. Most of the long-term survivors, i.e., those who survived more than 5 years, were seen in the grade 3 group. The median survival time of the patients with grade 2 was 895 days and there were a few 5-year survivors. Forastiere et al. [16] reported that pathological CR patients had a median survival duration of 70 months and 60% were alive at 5 years, while those with residual tumors in the resected specimen had a median survival duration of 26 months and 32% were alive at 5 years, demonstrating a significantly better prognosis in patients with pathological CR than in those with microscopically residual tumors in the resected esophagus. For long-term survival of patients with T4 esophageal cancer, preoperative chemoradiation therapy should give a high pathological CR rate.

In this study, two different schedules of chemoradiation protocols, with the same chemotherapeutic drugs (5-fluorouracil and cisplatin), were employed. Protocol A was converted to protocol B because the radiosensitizing action of 5-fluorouracil and cisplatin was enhanced by complete synchronization with the irradiation schedule and the dose intensity could be increased with comparable toxicities. As expected, protocol B gave a significantly higher pathologic CR rate and led to more effective downstaging of the disease than protocol A. In the short-term survival of up to 3 years, protocol B gave a better survival rate than protocol A, although the difference was not significant. Possible reasons for this may be that the follow-up duration in the protocol B group was too short to obtain a significant difference or that protocol B was not strong enough for complete local control and/or prevention of distant metastasis in T4 tumors, since the major failure patterns were local and distant ones in this study. In future trials, the addition of new drugs such as paclitaxel to the present combination would be interesting to obtain a higher CR rate and better prognosis in the treatment of T4 esophageal cancer.

Pathologic CR does not always mean complete disappearance of the tumor cells. A surgical specimen showing pathological CR might contain a trace amount of viable tumor cells, because the sensitivity of the routine histological examination is limited. Preoperative examinations by CT scan and endoscopy could not correctly evaluate pathological CR or underestimated the response, since we were able to diagnose only 3 cases as clinical CR. As is well known, there is no way to predict pathological CR. Surgical resection is considered basically necessary for all responders of T4 tumors after chemoradiation therapy. Our experiences in this study proved that preoperative chemoradiation does not increase the risk for surgery, although substantial toxicities of WHO grade 3 or more were seen in nearly half of the patients during the treatment.

Although this was a retrospective and non-randomized study, our results suggest that preoperative chemoradiation results in clinical and pathologic downstaging of the disease and increases survival in responders, especially in those with pathological CR. Concurrent chemoradiation therapy followed by surgery is, therefore, an effective and safe multimodal therapy in the treatment of primary inoperable T4 SCC of the esophagus, which has long been considered incurable.

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