



Esophagectomy: Is It Necessary after Chemoradiotherapy for a Locally Advanced T4 Esophageal Cancer? Prospective Nonrandomized Trial Comparing Chemoradiotherapy with Surgery versus without Surgery

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Abstract. The need for surgery after chemoradiotherapy for a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus was evaluated. A series of 53 patients were enrolled in this prospective nonrandomized trial from among 124 patients with an esophageal cancer assessed as T4 in Kurume University Hospital from 1994 to 2002. After the first chemoradiotherapy cycle, which consisted of radiotherapy in a total dosage of 36 Gy and chemotherapy using cisplatin (CDDP) and 5-fluorouracil (5FU), the patients each decided, after being informed of the efficacy of the chemoradiotherapy, whether to undergo surgery. All patients, including those who had undergone surgery and those who had not, later underwent a second chemoradiotherapy cycle consisting of radiotherapy in a total dosage of 24 Gy and chemotherapy using CDDP and 5FU, as far as practicable. Among the responders to the first chemoradiotherapy cycle, there was no significant difference in the long-term (5-year) survival rate between the 18 patients who underwent esophageal surgery and the 13 patients who did not (23% vs. 23%). Among the nonresponders, the 11 patients who underwent surgery showed a tendency toward longer survival than the five patients who had had no surgery. The nonresponders had 1- and 2-year survival rates of 64% and 33%, respectively. The corresponding rates for the 5 nonsurgical patients who completed the two chemoradiotherapy cycle were 20% and 20%, respectively. For a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus, full-dosage chemoradiotherapy (definitive chemoradiotherapy) is preferred for responders to a half-dose of chemoradiotherapy as much as esophagectomy, whereas esophagectomy may be preferred for nonresponders.

The prognosis after surgery alone for patients who have a locally advanced esophageal cancer, in particular a T4 tumor involving the trachea, bronchus, or aorta, has remained dismal. Combined resection of a neighboring organ(s) together with esophagectomy has offered no benefit to the survival rate for such patients despite the high incidence of mortality and morbidity [1]. Palliative (R1 or R2) esophagectomy followed by radiotherapy with or without

chemotherapy has also essentially offered no survival benefit compared with nonsurgical treatment [2].

Many surgeons have considered that chemoradiotherapy followed by surgery (whenever possible) is standard treatment for patients with a locally advanced esophageal cancer (i.e., T3/T4, N-any, M0 clinical stage tumors), whereas chemoradiotherapy alone should be given for nonresectable esophageal cancer or to patients who are medically unfit for surgery [3-5]. These surgeons have believed that only complete (R0) resection of the tumor following chemoradiotherapy can provide a survival benefit for patients with a locally advanced esophageal cancer, and that the volume of chemoradiation should be the minimum required to decrease the otherwise substantial associated postoperative morbidity and mortality (neoadjuvant chemoradiotherapy).

However, the relatively high rate of clinical and pathologic complete response with combined chemoradiotherapy has raised the question of whether surgical resection is necessary after chemoradiotherapy [6]. Radiologists and oncologists have also thought that chemoradiotherapy can offer a survival benefit even for such a tumor, when a complete response is achieved by high-volume chemoradiation (definitive chemoradiotherapy) [7]. They have thought that esophagectomy was necessary, rather, for persistent or recurrent disease after definitive chemoradiotherapy (salvage surgery) [8].

In the prospective nonrandomized trials reported here, long-term results were compared between definitive chemoradiotherapy with and without surgery to evaluate the need for surgery in the multimodal treatment for a T4 esophageal cancer.

Patients and Methods

Population

Among 482 patients with a cancer in the thoracic esophagus referred to the Kurume University Hospital between 1994 and 2002,

the tumor in 124 patients was defined as T4 according to the TNM classification of the International Union Against Cancer (UICC) [9] during the preoperative staging. The criteria for inclusion in this prospective trial were as follows: (1) biopsy-confirmed squamous cell carcinoma in the thoracic esophagus; (2) locally advanced stage clinically defined as a T4 tumor [tumors defined according to the latest UICC classification as M1-Lym because of celiac or supraclavicular nodal involvement were also included in this trial (regional disease), excluding any patient with distant metastasis (M1-Org)]; (3) no previous treatment; (4) WHO performance status 0 to 2; (5) adequate hematologic, hepatic, renal, cardiac, and pulmonary function; the patient must also have a general condition adequate to tolerate esophagectomy or definitive chemoradiotherapy; (6) ≥ 75 years of age; (7) no active double primary cancer; (8) no contraindication to 5-fluorouracil (5FU), cisplatin (CDDP), or extensive irradiation; and (9) the patient must give a written informed consent.

The pretreatment staging evaluation consisted of: (1) a general physical examination; (2) chest and abdominal radiography; (3) contrast esophagography; (4) esophagoscopy; (5) cervical and upper abdominal ultrasonography (US); (6) computed tomography (CT) of the neck, chest, and upper abdomen; (7) magnetic resonance of imaging of the neck and chest; and (8) bone scintigraphy; with (9) bronchoscopy performed only for a cancer in the upper or middle thoracic esophagus.

Among the 124 patients with a T4 esophageal cancer referred to our department during the study period, only 53 were included in this trial. The excluded patients were as follows: 2 with adenocarcinoma or small-cell carcinoma; 16 with distant organ metastases; 9 with previous chemotherapy, radiotherapy, or both; 17 with a low performance status index or a contraindication to surgery or chemotherapy; 7 were >75 years old; 1 had an active double primary cancer; and 19 did not give informed consent for this trial. Among the last group, 11 patients chose preceding surgery (palliative esophagectomy), and the other 8 patients chose chemoradiotherapy alone from the beginning.

Treatment

This study was a nonrandomized prospective trial based on the informed decision that patients chose whether to undergo surgery between the first and second chemoradiotherapy cycles (Fig. 1). The first cycle consisted of (1) CDDP 24 mg/m² on days 1 and 8 and 10 mg/day from days 2 to 5 and from days 9 to 12 as a drip intravenous infusion for 2 hours; (2) 5FU 500 mg/day as a continuous intravenous infusion for 24 hours from days 1 to 5 and from days 8 to 12; and (3) radiotherapy delivered in hyperfractions of 1.2 Gy twice a day from days 1 to 5, days 8 to 12 and days 15 to 19, to a total dose of 36 Gy.

The first chemoradiotherapy cycle was evaluated 2 weeks after the end of radiotherapy and consisted of a physical examination, contrast esophagography, esophagoscopy, and CT scan. Patients then each decided whether to undergo surgery after being fully informed of the efficacy of the chemoradiotherapy (informed decision). When patients elected to have surgery, they were subjected to esophagectomy or a bypass operation. On the other hand, when patients elected not to have surgery, they underwent only the second cycle of chemoradiotherapy, which consisted of the same chemotherapy protocol as the first cycle and radio-

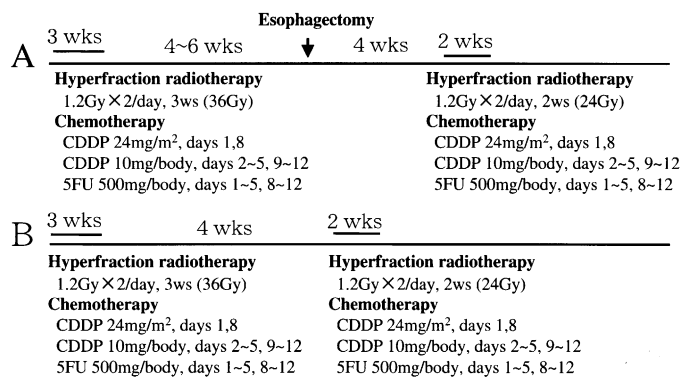


Fig. 1. Our treatment protocol for a locally advanced (T4) esophageal cancer. Arm A: Chemoradiotherapy with surgery. Arm B: Chemoradiotherapy alone. CDDP: cisplatin; 5FU: 5-fluorouracil.

therapy in a total dose of 24 Gy. Patients who did have surgery also underwent a second chemoradiotherapy cycle the same as described above 1 month after surgery.

Radiotherapy was administered using an 10-MV linear accelerator. The visible tumor volume also included 2 cm longitudinal margins and 2 cm lateral margins. In cases of definitive chemoradiotherapy, the radiation fields of the second chemoradiotherapy cycle were the same as those of the first cycle. In the patients with surgery, boost fields, with an oblique field, covered the primary tumor with at least 2 cm margins.

Surgery was scheduled for 1 month after the preoperative treatment. Esophagectomy with systemic lymphadenectomy, including thoracoabdominal two fields or cervicothoracoabdominal three fields, was performed through a right thoracotomy with cervical esophagogastrostomy depending on the tumor location and the macroscopic findings of residual tumor (R classification [9]). For patients who underwent curative (R0) resection of a cancer in the upper or middle thoracic esophagus, three-field dissection was performed, whereas for those who underwent curative (R0) resection of a cancer in the lower thoracic esophagus, two-field dissection (total mediastinal lymphadenectomy) was performed [10]. For patients who underwent macroscopic incomplete (R2) resection of an esophageal cancer in any location, selective lymphadenectomy was performed. When, in the opinion of the surgeon, esophagectomy could not be satisfactorily achieved, a bypass operation was done. In all cases, the stomach was used for the reconstruction.

Criteria for Response and Statistical Analyses

After the first chemoradiotherapy cycle, patients were reevaluated using contrast esophagography, endoscopy, and CT scanning. The response was considered complete (CR) when no radiographic evidence of disease was seen, no residual tumor was found during esophagoscopy, and the biopsy was negative. Otherwise, the response was classified as partial (PR): $>50\%$ regression in the tumor size in square measure on the contrast esophagograms or $>30\%$ regression in the tumor size in its maximal diameter on the CT scan. The final categories were either stable disease (no change, or NC) or progression (progressive disease, or PD) [11, 12]. After resection, a complete histologic response was defined as the absence of residual tumor in the esophagus and in nodal tissue. Toxicity was graded using

the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) [13].

Follow-up using a general physical examination, tumor markers including SCC antigen and carcinoembryonic antigen (CEA), and chest radiographs were performed every month for the first 2 years, every 2 months for 2 to 3 years after treatment, every 3 months for 3 to 5 years after treatment, and every 6 months thereafter. Endoscopy, US of the neck and abdomen, CT scan, and bone scintigraphy were routinely scheduled every year and repeated when any new clinical symptoms appeared or if any of the tumor markers increased to an abnormal level.

The overall survival was estimated according to the Kaplan-Meier method and compared using the generalized Wilcoxon test. The survival rates were calculated as being from the first day of chemoradiotherapy.

Results

Response to Chemoradiotherapy

Fifty-three patients were enrolled in this trial. All patients received the complete dose of the first chemoradiotherapy cycle planned. After the first cycle, there were 32 (60%) patients with a partial response, 16 (30%) patients with no change or stable disease, and 5 (9%) patients with progressive disease. None of the patients had a complete response. Accordingly, the response rate to the first chemoradiotherapy cycle was 60% (32/53). Among the 23 patients who elected not to surgery, the second chemoradiotherapy cycle was completely administered to 18 patients; among them 7 (39%) patients had a complete response, 7 (39%) had a partial response, and 4 (22%) had no change or progressive disease. The other five patients did not undergo the second chemoradiotherapy cycle due to fistulas, tumor progression, or poor general condition. On the other hand, among the 30 patients who elected to undergo surgery, the second chemoradiotherapy cycle was completely administered to 21 patients but not in the other 9 patients due to postoperative complications or the patient's refusal (Fig. 2).

The pathologic response was assessed according to the Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases [11] in the 27 resected specimens: 26 specimens after the first chemoradiotherapy cycle and 1 after the second chemoradiotherapy cycle. A complete pathologic response (pCR)-no cancer was seen in the resected specimen of the esophagus-was found in four (15%) patients. Of these four patients, however, two had metastases in their lymph nodes. Accordingly, only 2 (7%) of 26 patients who underwent esophagectomy after the first chemoradiotherapy cycle in our regimen were cancer-free.

Toxicity

Concurrent chemoradiotherapy was generally well tolerated. The major toxicity was hematologic, with 30% of the patients experiencing grade 3 or 4 leukopenia, 13% with grade 3 or 4 anemia, and 9% with grade 3 or 4 thrombocytopenia during or after the first chemoradiotherapy cycle. Altogether, 2 (6%) of 34 patients experienced grade 3 or 4 leukopenia, and 6% of those experienced grade 3 or 4 anemia during or after the second chemoradiotherapy cycle [13]. There were no death due to hematologic toxicity. Among those with nonhematologic toxicity, fistula formation was

Chemoradiotherapy(CRT) n=53				
Responders n=32 (PR: 32)			Non-responders n=21 (NC: 16, PD: 5)	
Surgery n=19	No-surgery n=13		Surgery n=11	No-surgery n=10
Esophagectomy: 18 R0: 15, R2: 3	2nd CRT cycle: 13 CR: 7 PR: 5 PD: 1		Esophagectomy: 8 R0: 3, R2: 5	1st CRT cycle only: 5 NC: 3 PD: 2
Bypass: 1			Bypass: 3	
1st CRT cycle only: 4 2nd CRT cycle: 15			1st CRT cycle only: 5 2nd CRT cycle: 6	2nd CRT cycle: 5 PR: 2* NC: 2 PD: 1

Fig. 2. Response to chemoradiotherapy and treatment modalities. After being informed of the response to the first chemoradiotherapy cycle, each patient decides whether to undergo surgery (informed decision). PR: partial response; NC: no change; PD: progressive disease; R0: no residual tumor (complete resection); R2: macroscopic residual tumor (incomplete resection).

the most common and serious toxic response, with 6% of the patients developing esophagopulmonary fistula, 6% esophagobronchial fistula, and 2% aortoesophageal fistula during or after the first chemoradiotherapy cycle; 3% of the patients developed an aortoesophageal fistula and 3% an aortobronchial fistula during or after the second chemoradiotherapy cycle. Among the nine patients with fistula formation, five (56%) died of the fistula during hospitalization (Table 1). The overall hospital mortality rate due to chemoradiotherapy associated toxicity was 9% (5/53).

Surgical Results

Chemoradiotherapy followed by esophagectomy resulted in two (8%) hospital mortalities: one 3 days after surgery caused by pulmonary infarction and the other 7 months after surgery caused by a brain abscess. The most common postoperative complications in patients who underwent chemoradiotherapy followed by esophagectomy were recurrent nerve paralysis and aspiration pneumonia, which were the same as those in the patients who underwent surgery alone in our hospital [10]. The most common postoperative complications after chemoradiotherapy followed by bypass operation were anastomotic leak and aspiration pneumonia. The morbidity rates after esophagectomy and after the bypass operation were 85% and 100%, respectively (Table 2).

Survival Outcomes

The median follow-up for the surviving population was 51 months. No patient was lost to follow-up. Altogether, 37 patients died of progressive or recurrent disease: 19 after surgery and 18 after no surgery. Other causes of death were a postoperative complication in one patient (pulmonary embolism), pneumonia without recurrence in one, myocardial infarction in one, and another primary cancer in two (cholangiocellular carcinoma, prostate cancer). For one patient, the precise cause of death and the disease status at the time of death were unknown.

The median survival time for the whole population was 29 months, with 1-, 3-, and 5-year overall survival rates of 60%, 21%, and 16%, respectively. The 1-, 3-, and 5-year survival rates for the 30 patients who elected to undergo surgery (esophagectomy in 26, and bypass in 4) were 73%, 28%, and 17%, respectively. The

Table 1. Toxicity of grade 3 or higher according to the NCI-CTC

First CRTx cycle (n = 53)	
Leukopenia	16 (30%)
Anemia	7 (13%)
Thrombocytopenia	5 (9%)
Esophagopulmonary fistula	3 ^b (6%)
Esophagobronchial fistula	3 ^b (6%)
Sepsis/fever	2 (4%)
Diarrhea	2 (4%)
Pneumonia	2 (4%)
Aortoesophageal fistula	1 ^b (2%)
Renal dysfunction	1 (2%)
DIC	1 (2%)
Second CRTx cycle (n = 39) ^a	
Leukopenia	2 (5%)
Anemia	2 (5%)
Aortoesophageal fistula	1 ^b (3%)
Aortobronchial fistula	1 ^b (3%)
Pneumonitis	1 (3%)

NCI-CTC: National Cancer Institute-Common Toxicity Criteria Version 2.0, January 30, 1998; CRTx: chemoradiotherapy; DIC: disseminated intravascular coagulation:

^aSurgery group 21, no-surgery group 18.

^bHospital death in one cases each.

Table 2. Postoperative complications

Complication	Esophagectomy (n = 26)	Bypass (n = 4)
Recurrent nerve paralysis	13 (50%)	1 (25%)
Aspiration pneumonia	9 (35%)	3 (75%)
Tracheal ischemia (ulcer, erosion)	6 (23%)	0
Pyothorax	6 (23%)	0
Anastomotic leak	5 (19%)	4 (100%)
Ileus	3 (12%)	0
Severe arrhythmia	2 (8%)	0
Pulmonary infarction	1 ^a (4%)	0
MRSA enteritis	1 (4%)	0
Brain abscess	1 ^a (4%)	0
Morbidity	22 (85%)	4 (100%)
Mortality	2 (8%)	0

MRSA: methicillin-resistant *Staphylococcus aureus*.

^aHospital mortality.

corresponding rates for the 23 patients who elected not to undergo surgery (chemoradiotherapy alone in 16, additional esophageal stent in 6, and emergency salvage surgery in 1) were 44%, 13%, and 13%, respectively. There was no significant difference in the survival rate between the surgical patients and the nonsurgical patients ($p = 0.08$) (Fig. 3).

The 1-, 3-, and 5-year survival rate for the 32 responders to the first chemoradiotherapy cycle were 75%, 31%, and 23%, respectively, and for the 21 nonresponders the 1- and 3-year survival rates were 38% and 6%, respectively, with no patient surviving more than 4 years. There was a statistically significant difference in the survival rates between the responders and the nonresponders to chemoradiotherapy ($p = 0.008$) (Fig. 4).

To analyze the outcome fairly, it seems preferable to compare the surgical patients to the nonsurgical patients according to response to chemoradiotherapy. For the 19 surgical patients among the 31 responders, the 1-, 3-, and 5-year-survival rates were 79%, 37%, and 23%, respectively; the corresponding rates for the 13 nonsurgical patients were 69%, 23%, and 23%, respectively. Among the responders to chemoradiotherapy, there was no dif-

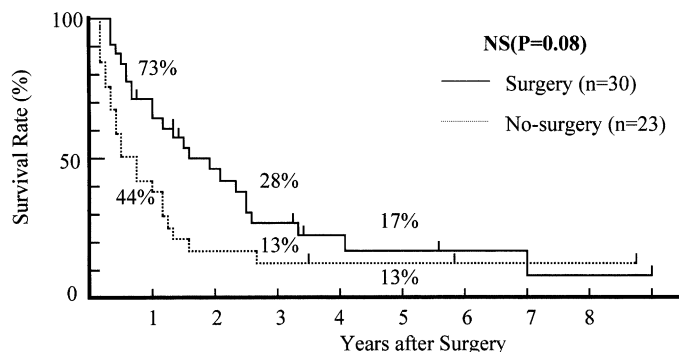


Fig. 3. Survival curves for patients who underwent surgery and those who did not. The survival rate for the surgery group was not different from that for the no-surgery group ($p = 0.08$).

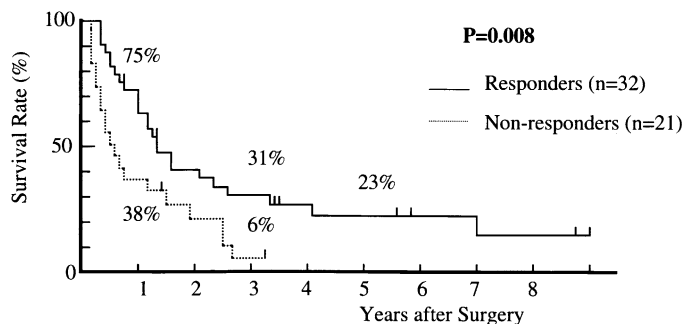


Fig. 4. Survival curves for responders and for nonresponders to chemoradiotherapy. There was a significant difference in the survival rates between the responders and the nonresponders ($p = 0.008$).

ference in the survival rate between the surgical patients and the nonsurgical patients (Fig. 5).

On the other hand, for the 11 surgical patients among the 21 nonresponders, the 1- and 2-year-survival rates were 64% and 33%, respectively; the corresponding rates for the 5 nonsurgical patients who completed both the first and second chemoradiotherapy cycles-definitive chemoradiotherapy-were 20% and 20%, respectively. For the nonresponders to chemoradiotherapy, the surgical patients had a tendency toward longer survival than the nonsurgical patients, although there was no significant difference between them ($p = 0.168$) (Fig. 6). Among five patients classified as nonsurgical patients, one underwent salvage surgery after definitive chemoradiotherapy and survived 32 months, whereas the other four patients died within 1 year. Accordingly, the 1- and 2-year-survival rates of the patients who underwent surgery were 66% and 39%, respectively, whereas the corresponding rates for the patients who did not were 0% and 0%. The difference between them was statistically significant ($p = 0.001$).

Discussion

We have presented the results of a prospective comparative trial of 53 patients with T4N0-1M0 squamous cell carcinomas in the thoracic esophagus treated with chemoradiotherapy and with or without surgery. This trial was not randomized. It was difficult for us to perform a randomized control trial comparing surgery versus no surgery in Japan. Patients themselves chose a treatment arm-surgery versus no surgery-(informed decision) based on

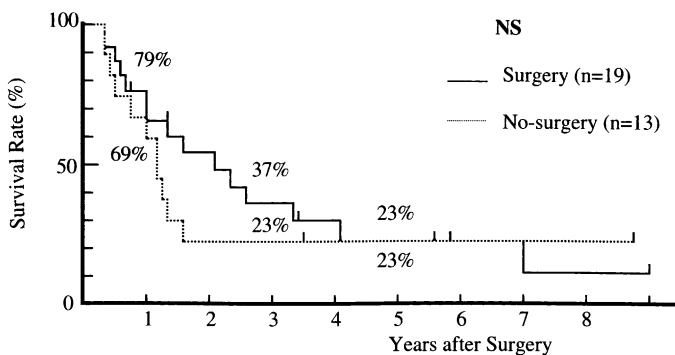


Fig. 5. Survival curves for the responders to chemoradiotherapy. There was no difference in the survival rates between the patients who underwent surgery and those who did not.

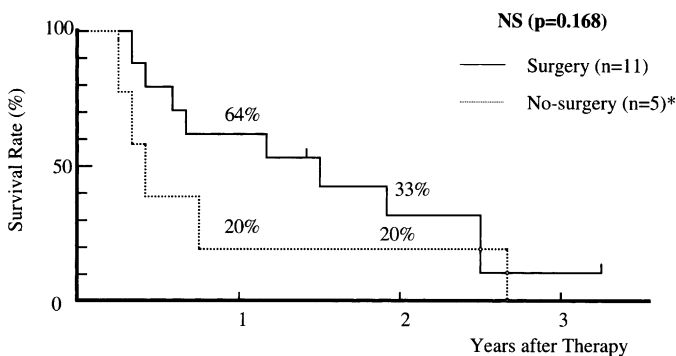


Fig. 6. Survival curves for nonresponders to chemoradiotherapy. *Patients who received both the first and second chemoradiotherapy cycles (i.e., definitive chemoradiotherapy). There was a tendency toward a better survival rate for patients who underwent surgery than for those who did not ($p = 0.168$).

information from both surgeons and radiologists about their response to the first chemoradiotherapy cycle, the method of the next treatment, expected prognosis, and other factors. Because of such a complicated situation, we obtained informed consent using a certain printed form from almost all patients enrolled, whereas for other patients we used hand-written consent forms

A total of 14 patients did not receive the second chemoradiotherapy cycle because of fistulas, postoperative complications, patient's refusal. Moreover, 5 of the 14 patients underwent neither surgery nor the second chemoradiotherapy cycle mainly due to a fistula or poor general condition (or both). When the survival rates were compared in this study, therefore, we included the patients who underwent surgery, regardless of esophagectomy or bypass and regardless of with or without the second chemoradiotherapy cycle; in contrast, we excluded the patients who did not undergo the second chemoradiotherapy cycle from the non-surgical patient group.

In this trial, chemotherapy using (1) CDDP 24 mg/m² on days 1 and 8, and 10 mg/day on days 2 to 5 and days 9 to 12; (2) 5FU 500 mg/days on days 1 to 5 and days 8 to 12; and (3) hyperfraction radiotherapy of 1.2 Gy twice a day on days 1 to 5, days 8 to 12, and days 15 to 19, to a total dosage of 36 Gy were applied as the first cycle. The clinical effect of the first chemoradiotherapy cycle was evaluated after 2 weeks; then more than 1 to 2 weeks was needed to obtain informed consent. Thus the interval between the first

and second cycles of chemoradiotherapy, even in the nonsurgical cases, was about 4 weeks on average. In one-third of patients who underwent chemoradiotherapy according to this regimen, a nadir of grade 3 or higher bone marrow suppression was observed 2 weeks after chemoradiotherapy (Table 1). It was therefore difficult to start the second chemoradiotherapy cycle within 3 weeks after the first chemoradiotherapy cycle. On the other hand, we thought that the first cycle of chemoradiotherapy in our regimen should achieve an effect equal to that of other regimens of neoadjuvant chemoradiotherapy for T4 esophageal cancers [4, 5]. The biologic effect of twice-daily radiotherapy of 2.4 Gy per day, to a total dosage of 36 Gy for 3 weeks, was considered comparable to that of once-daily radiotherapy of 2 Gy per day to a total dosage of 40 Gy for 4 weeks. The area under the curve (AUC) of the CDDP concentration in the blood after administration of CDDP 24 mg/m² on days 1 and 8 and 10 mg on day 2 to 5 and day 9 to 12; that is approximately 150 mg/2 weeks in total, was considered comparable to that after every-day administration of CDDP 10 mg for 4 weeks, that is, 200 mg/4 weeks in total.

The 5-year survival rate in this trial was 16% for the whole population, 23% for the responders, and 0% for the nonresponders. The 5-year survival rate was 17% for the surgical patients and 13% for the nonsurgical patients. Surgery did not seem to have improved the survival for responders to the first chemoradiotherapy cycle: Those patients had a 5-year survival rate of 23% with surgery versus 23% without surgery. On the other hand, surgery seemed to have improved the survival for nonresponders to the first chemoradiotherapy cycle: Those patients had 1- and 2-year survival rates of 64% and 33%, respectively, with surgery versus 20% and 20%, respectively, without surgery. When the patient undergoing salvage surgery was included in the surgical patient group, the 1- and 2-year survival rates for the surgical patients were 66% and 39%, respectively, whereas the corresponding rates for the nonsurgical patients were 0% each. It was concluded that in patients with a T4N0-1M0 esophageal cancer definitive chemoradiotherapy offered a survival similar to that achieved by surgery for responders but not for nonresponders.

Many studies using neoadjuvant chemoradiotherapy followed by esophagectomy to treat locally advanced esophageal cancers have been reported. Most of them used CDDP-based chemotherapy with a radiation dosage between 40 and 45 Gy. The complete histologic response rate in the resected specimens ranged from 28% to 33%. This rate for all patients who had undergone neoadjuvant chemoradiotherapy has ranged from 18% to 28%. They reported the superiority of neoadjuvant chemoradiotherapy followed by surgery over chemoradiotherapy alone or surgery, alone [3-5]. However, some investigators have doubted the need for surgical resection after chemoradiotherapy for a locally advanced esophageal cancer [6]. Phase III studies to determine any significant benefit from neoadjuvant chemoradiotherapy followed by surgery for a locally advanced esophageal cancer compared with chemoradiotherapy alone are rare.

Recently, a French randomized controlled trial on locally advanced but resectable (T3-4N0-1M0) esophageal cancers including squamous cell carcinoma and adenocarcinoma compared chemoradiotherapy followed by surgery to chemoradiotherapy alone. It demonstrated similar 2-year survival rates (34% vs. 40%) for the two treatment modalities in the responders to two-thirds doses of definitive chemoradiotherapy [14]. A German randomized controlled trial also demonstrated no difference in 3-year

survival rates (28% vs. 30%) between preoperative chemoradiotherapy followed by surgery versus chemoradiotherapy alone for a T3-4N0-1M0 squamous cell carcinoma [15]. As reported above, some authors have maintained that surgery is not necessary for responders to chemoradiotherapy.

Another approach has been to explore whether surgical resection after chemoradiotherapy can improve the survival results compared to chemoradiotherapy alone. Murakami et al. [16] reported results from a trial comparing chemoradiotherapy alone to chemoradiotherapy followed by esophagectomy for locally advanced (T3 or T4) esophageal cancers. They divided the patients into two groups. In one group, esophagectomy was performed in nonresponders to chemoradiotherapy but was not performed in responders; in the other group, patients underwent esophagectomy alone. The 5-year survival rate was no different between the two groups (31% vs. 30%). They concluded that surgery was not necessary for responders to chemoradiotherapy. Whether esophagectomy is necessary for those who do not respond to chemoradiotherapy remains controversial. Murakami et al. suggested, similar to our conclusion, that surgery was necessary only for nonresponders to chemoradiotherapy. There are some reasons to support esophagectomy for nonresponders. First, clinical evaluation of the response to chemoradiotherapy does not always correlate with the pathologic response. Therefore, a complete pathologic response in the resected specimen or complete R0 resection of esophageal cancer can be achieved even in patients who were evaluated as being nonresponders. In this trial, 3 (27%) of the 11 nonresponders to the first chemoradiotherapy cycle underwent R0 resection of esophageal cancer (Fig. 2). Second, esophagectomy for nonresponders to the first cycle of chemoradiotherapy and subsequent chemoradiotherapy (the second cycle of chemoradiotherapy) might be comparable to salvage surgery for partial responders to definitive chemoradiotherapy [17].

A consensus is not always obtained regarding the need for esophagectomy in a multimodal treatment regimen for T4 esophageal cancers. Further evaluation using a large-scale prospective randomized study is needed.

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References

1. Ichiyoshi Y, Kawahara H, Taga S, et al. Indications and operative techniques for combined aorto-esophageal resection. *Jpn. J. Thorac. Cardiovasc. Surg.* 1999;47:318–324

2. Fujita H, Kakegawa T, Kawahara H, et al. Questionable resection for carcinoma of the esophagus involving the trachea, bronchus and/or aorta—a comparative and multivariate analysis. *Kurume Med. J.* 1992;39:183–189
3. Stahl M, Wilke H, Fink U, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer: interim analysis of a phase II trial. *J. Clin. Oncol.* 1996;14:829–837
4. Van Raemdonck DVAN, van Cutsem Evan, Menten J, et al. Induction therapy for clinical T4 oesophageal carcinoma: a plea for continued surgical exploration. *Eur. J. Cardiovasc. Surg.* 1997;11:828–837
5. Yano M, Tsujinaka T, Shiozaki H, et al. Concurrent chemotherapy (5-fluorouracil and cisplatin) and radiation therapy followed by surgery for T4 squamous cell carcinoma of the esophagus. *J. Surg. Oncol.* 1999;70:25–32
6. Harrison LE. Is esophageal cancer a surgical disease? *J. Surg. Oncol.* 2000;75:227–231
7. 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;17:2915–2921
8. Urschel JD, Ashiku S, Thurer R, et al. Salvage or planned esophagectomy after chemoradiation therapy for locally advanced esophageal cancer: a review. *Dis. Esophagus* 2003;16:60–65
9. International Union Against Cancer (2002) In: Sobin, LH, Wittekind, CH (editors), *TNM Classification of Malignant Tumours*, 6, Wiley-Liss, New York, pp 1–18; pp 60–64
10. Fujita H, Sueyoshi S, Tanaka T, et al. Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. *World J. Surg.* 2003;27:571–579
11. Japanese Society for Esophageal Diseases Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus 9. Tokyo: Kanehara, 2001, pp 63–83
12. Therasse P, Arbutck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J. Natl. Cancer Inst.* 2000;92:205–216
13. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0, an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int. J. Radiat. Oncol. Phys.* 2000;47:13–47
14. Bedenne L, Michel P, Bouche O, et al. Randomized phase III trial in locally advanced esophageal cancer: radiochemotherapy followed by surgery versus radiochemotherapy alone (FFCD 9102) [abstract]. *Proc. Am. Soc. Clin. Oncol.* 2002;21:130
15. Stahl M, Wilke H, Walz MK, et al. Randomized phase III trial in locally-advanced squamous cell carcinoma (SCC) of the esophagus: chemoradiation with and without surgery [abstract]. *Proc. Am. Soc. Clin. Oncol.* 2003;22:250
16. Murakami M, Kuroda Y, Matsusue S, et al. Treatment results of esophageal carcinoma of clinical T3T4, M0: historical comparison between neoadjuvant chemoradiotherapy followed by surgery or definitive radiotherapy and conventional surgery. *Oncol. Rep.* 2000;7:571–578
17. Hennequin C, Gayet B, Sauvanet A, et al. Impact on survival of surgery after concomitant chemoradiotherapy for locally advanced cancers of the esophagus. *Int. J. Radiat. Oncol. Biol. Phys.* 2001;49:657–664

Invited Commentary (DOI: 10.1007/s00268-004-1081-3)

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The authors performed a prospective nonrandomized trial to evaluate the role of surgery secondary to chemoradiotherapy in patients with T4N0-1M0 esophageal cancer. They found significantly better survival in responders to chemoradiotherapy than in

nonresponders and a better survival rate in the surgery group than in the nonsurgery group. They analyzed whether responders obtained any additional benefit by undergoing surgical resection compared with responders who did not, probably because per-

formance of surgery after chemoradiotherapy was associated with a high rate of serious postoperative complications. They could not detect any benefit of surgical resection following chemoradiotherapy by comparing the survival curves of these two groups, although the 2- and 3-year survival rates were 55% and 37%, respectively, which were higher than the rates of 23% and 23%, respectively, in the nonsurgery group. The same analysis was done for nonresponders and showed no significant difference in survival between the surgery and nonsurgery groups, but the 1- and 2-year survival rates for the surgery group (64% and 33%, respectively) were considerably better than in the no-surgery group (20% and 20%, respectively).

This is an important study for trying to determine the role of surgery in treating of a T4 stage esophageal cancer, which cannot be cured by surgery alone and might be systemic with micrometastases. From a historical point of view, surgery after radiation therapy has not achieved good results for resectable esophageal cancer because of the difficulty performing anatomically precise resection due to severe postradiation fibrosis and various severe postoperative complications. The survival curves in their Figures 4 and 5 show that the 5-year survival rate for responders was 23%

irrespective of surgery, so surgery might provide little if any benefit for T4N0-1M0 cancer in this protocol.

In the discussion, the authors recommended surgery for non-responders, and not for responders. This might be reasonable because surgery did not lead to better survival in responders and a tendency for a better survival rate with the surgery group was noted only in nonresponders. The survival curves of nonresponders in their Figure 6 shows higher survival rates within 2 years for the surgery group compared with the nonsurgery group. We might say that surgery can be recommended for the nonresponders who would like to have a higher probability of living 1 to 2 years longer. In Figure 5, we see a 50% two-year survival rate for the surgery group of responders, although it is only 23% for the no-surgery group, so surgery might also be recommended for responders who want a higher probability of living at least 2 years.

In conclusion, this is an interesting study that showed meaningful efficacy of chemoradiotherapy for T4N0-1M0 esophageal cancer independent of surgery. We would like to see another prospective randomized study by these investigators using another protocol.