FIG. 1 a, b Overall survival and progression-free survival curves of 151 patients with unresectable gastric cancer after initial chemotherapy between those who underwent chemotherapy plus surgery and those who underwent chemotherapy alone. c Overall survival curves between the S-1 plus cisplatin and the S-1 plus paclitaxel groups
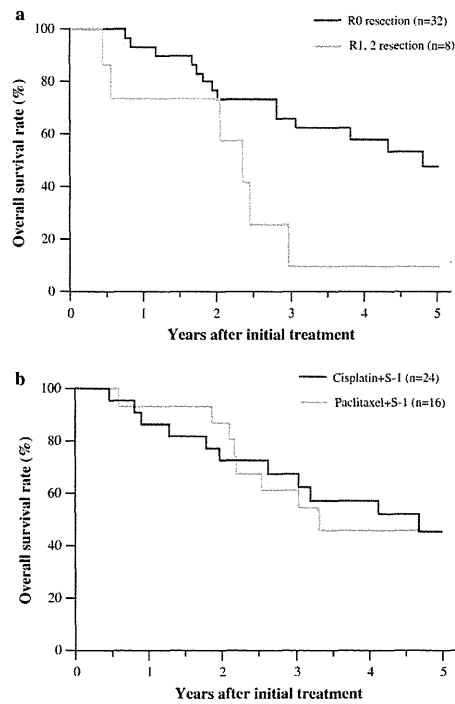

FIG. 2 a Overall survival curves of 40 patients treated with conversion surgery after initial chemotherapy between R1 and R1, R2 resection. R0 complete resection with no residual tumor. R1, 2 microscopic or gross residual tumor. b Overall survival curves between the S-1 plus cisplatin and the S-1 plus paclitaxel groups

patients treated with chemotherapy plus surgery, the 5-year OS rate was 43 % (median time, 53 months) (Fig. 1a) and the 5-year PFS rate was 36 % (median time, 30 months) (Fig. 1b). Among the 111 patients treated with chemotherapy alone, the 5-year OS rate was 1 % (median time, 14 months) (Fig. 1a) and the 5-year PFS rate was

0 % (median time, 6 months) (Fig. 1b). Patients treated with chemotherapy plus surgery had significantly longer OS and PFS times than those treated with chemotherapy alone ($P < 0.01$) (Fig. 1a, b). The median OS did not differ significantly between the S-1 plus cisplatin group (17 months) and the S-1 plus paclitaxel group (16 months; $P = 0.95$) (Fig. 1c).

Among the 40 patients treated with surgery, the 32 patients (80 %) who underwent R0 resection exhibited a 5-year OS rate of 49 % (median time, 62 months), and the eight patients who underwent R1 and R2 resection exhibited a 5-year OS rate of 15 % (median time, 30 months) (Fig. 2a). Patients who underwent R0 resection had a significantly longer OS than did those who underwent R1 and R2 resection ($P = 0.03$). Among these patients, there was no significant difference in the median OS between the S-1 plus cisplatin group (56 months) and the S-1 plus paclitaxel group (40 months; $P = 0.74$) (Fig. 2b).

TABLE 3 Univariate and multivariate predictors of overall survival 40 patients who underwent conversion surgery

Variable	Univariate analysis		Multivariate analysis	
	n (%)	P	OR (95 % CI)	P
Macroscopic type		<0.01		0.77
2, 3	11 (49.3)		0.90 (0.47–1.80)	
4	19 (0)		1	
Histologic grade		0.03		0.08
G1, G2	20 (59.1)		0.60 (0.33–1.07)	
G3	20 (26.8)		1	
Noncurative factors		<0.01		0.02
1	33 (50.5)		0.49 (0.28–0.88)	
2	7 (0)		1	
Residual tumor		0.03		0.03
R0	33 (49.0)		0.52 (0.28–0.95)	
R1, 2	7 (15.0)		1	

OR odds ratio, CI confidence interval

We selected the following 21 variables in addition to residual tumor (R0 vs. R1, R2) and chemotherapy (S-1 plus cisplatin vs. S-1 plus paclitaxel) for Kaplan–Meier analysis: age (<65 vs. ≥65 years), sex (male vs. female), PS (0 vs. 1), location (U vs. M, L) macroscopic type (type 2, 3 vs. 4), histologic grade (G1, G2 vs. G3), tumor depth (T2–4a vs. T4b), nodal stage (N0–2 vs. N3), P1 (yes vs. no), H1 (yes vs. no), M1 (yes vs. no), CY1 (positive vs. negative), number of noncurative factors (1 vs. 2), cycles of chemotherapy (< 4 vs. ≥4), toxicity grade (grade 1, 2 vs. 3, 4), response (partial response vs. stable disease), type of gastrectomy (distal vs. total), pathologic grade (grade 0–1 vs. 2) and second-line chemotherapy (yes vs. no).

According to the log rank test, the following four variables were significantly associated with a better OS: non–type 4 ($P < 0.01$), histologic grade of G1 or G2 ($P = 0.05$), and one noncurative factor ($P < 0.01$) with R0 resection. In multivariate Cox regression analysis, one noncurative factor (odds ratio 0.49; 95 % CI, 0.28–0.88; $P = 0.02$) and R0 resection (odds ratio 0.52; 95 % CI, 0.28–0.95; $P = 0.03$) were significant independent predictors of a favorable OS (Table 3).

DISCUSSION

Patients with unresectable gastric cancer usually have a poor prognosis and are first considered to receive systemic chemotherapy, but not surgery. The exception to this is patients who require palliation of symptoms such as bleeding or obstruction.[15] Systemic chemotherapy results in long-term survival in some patients. Conversion surgery may result in further long-term survival in selected patients. Our data indicate that patients undergoing conversion surgery have longer survival than do those receiving chemotherapy alone, similar to previous studies.[8-12] Our data also show that among patients undergoing conversion surgery, one noncurative factor before surgery and R0 resection are predictors of a favorable OS. When chemotherapy has produced a transient response and curative surgery can be accomplished, conversion surgery is occasionally associated with prolonged survival in selected patients. However, conversion surgery must be carefully performed in patients other than those with one initial noncurative factor.

Neoadjuvant chemotherapy has been evaluated for patients with advanced gastric cancer. Its rationale is based on the difficulty of performing R0 resection in patients with locally advanced gastric cancer without organ metastasis and the high risk of micrometastasis in these patients. Neoadjuvant chemotherapy aims to downstage the primary tumor, resulting in a higher R0 resection rate, and simultaneously treat micrometastases at an early stage.[16-18] However, conversion surgery is performed with a curative aim after a response to chemotherapy has been achieved in patients with initially unresectable gastric cancer.[12] The difference between neoadjuvant chemotherapy and conversion surgery is their respective indications.

Combination chemotherapy occasionally allows for conversion of unresectable gastric cancer to resectable cancer, similar to previous studies.[11,12] In the present study, the regimen of either S-1 plus cisplatin or paclitaxel was selected as initial combination chemotherapy.[7] However, the survival rates did not differ significantly between the two treatment groups among patients with unresectable gastric cancer treated with initial chemotherapy or conversion surgery. Although the currently performed treatment in such patients is combination chemotherapy, it is sufficient for survival.[19] Additionally, conversion surgery is preferred for patients with a favorable response to combination chemotherapy on the basis of our survival data.

Even when patients respond to a novel regimen with long-term survival, many require treatment changes because of drug resistance or adverse events.[12,19] Such patients are required to change to another regimen. Therefore, the timing of conversion surgery may occur at the point at which the tumor is reduced but before the appearance of drug resistance. In the present study, the median number of cycles between the two treatment groups was four, both in patients treated with initial chemotherapy and in those treated with conversion surgery. Because the median treatment time of S-1 plus cisplatin and S-1 plus paclitaxel was 5 and 4 months, respectively, and the median PFS of all patients was 8 months, the appreciate timing of conversion surgery seems to be within 4–8 months after initial chemotherapy.

This study evaluated the prognostic role of conversion surgery for unresectable gastric cancer. Patients with one initial noncurative factor can obtain a survival benefit from chemotherapy and subsequent curative surgery. In a previous study, P1 disease was associated with poor survival.[12] In the present study, however, the number of noncurative factors such as T4b, P1, H1, M1, and CY1, but not individual factors, was associated with poor survival.

Although unresectable gastric cancer still has a poor prognosis, the current results provide a practical treatment plan for affected patients. Large-scale, multicenter randomized trials will help to further determine the best treatment strategy for these patients and thus elucidate the prognostic role of conversion surgery. Numerous obstacles remain to be overcome regarding the selection of initial combination chemotherapy, the timing of conversion surgery, and the postoperative chemotherapy regimen.

DISCLOSURE The authors declare no conflict of interest.

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SPECIAL ARTICLE

Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society

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Introduction

Purpose

These guidelines are intended for doctors who are engaged in the diagnosis and treatment of esophageal carcinoma, for the following purposes: (1) to present the standard practice for the diagnosis and treatment of esophageal carcinoma with a high regard for the principles of evidence-based medicine (EBM); (2) to improve the safety and results of treatment, thereby reducing the difference in treatment results among different institutions; (3) to reduce unnecessary costs and efforts; (4) help enable people to undergo treatment without anxiety.

These guidelines provide only guidance on the indications for treatment and do not restrict or prohibit the use of any treatment deviating from those described herein.

Responsibilities

The Japan Esophageal Society assumes responsibility for the content described in these guidelines.

However, responsibility for the treatment results should be borne by the doctor providing the treatment and shall not rest with the Japan Esophageal Society.

Basic principles adopted for the preparation of these guidelines

These guidelines only present indications for the treatment procedures and do not address the technical problems of each treatment modality. The principles of presenting adequate treatment procedures include the following:

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This article does not contain any studies with human or animal subjects performed by any author(s). This paper consists of summary and text of Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited without references and clinical questions and answers and grade of recommendation.

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(1) treatments are introduced in relation to the progression of carcinoma, without excess or deficiency; (2) the therapeutic efficacy is evaluated by evidence-based approaches; (3) the final evaluation of treatment procedures is based on the survival period, but remission of symptoms, reduction of tumor, and improvement of quality of life (QOL) are also taken into account; (4) evaluation is carried out depending on the location of the lesion. We propose to revise these guidelines continually along with advances in medical science.

Choice of treatment and patients' consent

When choosing a treatment, regardless of whether it is made based on these guidelines or not, it is necessary that the doctors explain the details of the treatment, the reasons for choosing it, possible complications, treatment results, etc., to patients to obtain the patients' understanding and informed consent.

Level of recommendation

"Clinical Questions" are attached to each item, and the levels of evidence/strength of recommendation for each item is indicated according to Minds (Medical Information Network Distribution System: http://minds.jcqhc.or.jp/n/) classification of recommendation grades (A, B, C1, C2, D), together with the recommendation grades of the Committee

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to Develop Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus.

Algorithm for treatment of esophageal carcinoma (Fig. 1)

Epidemiology, present status, and risk factors

Summary

With regard to the dynamic trends of esophageal carcinoma in Japan, the incidence rate[1] has been increasing slowly in men, whereas it has been leveling off in women. The mortality has been leveling off in men, but has been decreasing in women.

Currently, among patients with esophageal carcinoma, the percentage of males is higher, and the percentage of patients in their 60s to 70s is high. The carcinoma is most frequently located in the middle thoracic esophagus. Squamous cell carcinoma is the predominant histologic type. Esophageal carcinoma is frequently associated with synchronous or metachronous multiple carcinoma.

The cited risk factors include smoking and alcohol drinking in the case of squamous cell carcinoma. In regard to the risk factors for adenocarcinoma, Barrett's epithelium derived from persistent inflammation of the lower esophagus due to gastroesophageal reflux disease (GERD) has been reported to serve as the background mucosa for esophageal carcinoma in Europe and North America. In Japan, however, the risk associated with this factor remains unclear because of the scarcity of patients.

Morbidity and mortality

According to statistics issued by the Center for Cancer Control and Information, National Cancer Center based on cancer morbidity data derived from the Population-Based Cancer Registry, the estimated incidence rate in 2004 (crude incidence rate) was 24.4 persons per 100,000 population in men and 4.0 persons per 100,000 population in women. The age-adjusted incidence rate[2] has been showing

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[1] *Incidence rate* The number of cases detected in a certain population during a certain period of time divided by the number of individuals in the population. The data shown are those provided by the Center for Cancer Control and Information Services, National Cancer Center, on the basis of the national statistics of cancer morbidity data derived from the Population-Based Cancer Registry (1975–2005).

[2] *Age-adjusted incidence rate* The incidence rate that would have been observed if the composition of the population was the same as the base population.
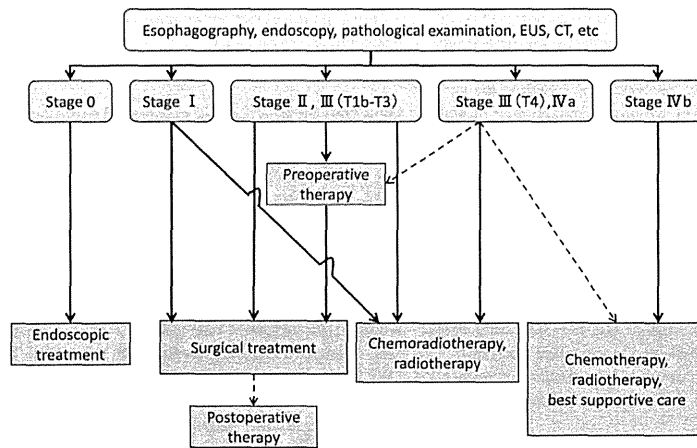
Stage is based on the 10th edition of the Japanese Classification of Esophageal Cancer.

Fig. 1 Algorithm for treatment of esophageal carcinoma

an upward trend in men, whereas there has been no particular pattern of increase or decrease recently in women.

According to the vital statistics compiled by the Ministry of Health, Labour and Welfare, there were 11,746 deaths from esophageal carcinoma in 2008 (the crude mortality rate[3] 9.3 persons per 100,000), which accounted for 3.4 % of all deaths from malignant neoplasms. The crude mortality rate associated with esophageal carcinoma was 16.3 persons per 100,000 population in men, ranking after cancers of the lung, stomach, large intestine, liver, and pancreas. The corresponding rate was 2.7 persons per 100,000 population in women, ranking below the 10th place. The age-adjusted mortality rate[4] of esophageal carcinoma has been leveling off in men and decreasing in women.

Cancer mortality data from vital statistics and various graphs based on this data are available at the Center

for Cancer Control and Information Services, National Cancer Center (http://ganjoho.jp/professional/statistics/index.html).

Present status of esophageal carcinoma in Japan

With regard to the present status of esophageal carcinoma in Japan, a nationwide survey conducted by the Japan Esophageal Society (2002) revealed that male patients outnumbered female patients, with a male–female ratio of about 6:1. Most patients were in their 60s or 70s, accounting for about 68 % of the patients overall. The carcinomas were predominantly located in the middle thoracic esophagus (51.6 %), followed in frequency by the lower thoracic esophagus (24.2 %), upper thoracic esophagus (13.4 %), abdominal esophagus (4.5 %), and cervical esophagus (4.0 %). Squamous cell carcinoma was the overwhelmingly frequent histologic type, accounting for 92.9 % of all cases, followed in frequency by adenocarcinoma (2.4 %). A family history of malignant tumor was found in 22.7 % of patients. A family history of esophageal carcinoma was present in 17 % of all cases with a family history of malignant tumor, although gastric cancer was the most frequent at 28.9 %. About 20 % of patients with esophageal carcinoma have synchronous or metachronous multiple cancer, which was the most frequently observed gastric cancer, followed by pharyngeal cancer, representing an important issue in the clinical diagnosis and treatment of

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[3] Crude mortality rate: The number of deaths occurring during a certain period of time divided by the population during the period.

[4] *Age-adjusted mortality rate* The mortality rate that would have been observed if the composition of the population was the same as the base population. Because the cancer mortality rate increases as the age advances, the crude mortality rate increases in a population containing a greater proportion of elderly people than in one containing a smaller proportion of elderly people. Therefore, the mortality rate in a population as a whole is obtained in a way adjusted for the age composition of a population used as the base (base population). The 1985 model population (virtual population model based on Japan's population in 1985) is the base population used in Japan.

esophageal carcinoma (see "Diagnosis and treatment of double carcinoma").

Risk factors

The risk factors for esophageal carcinoma are alcohol drinking and smoking.

Alcohol and smoking are important risk factors for squamous cell carcinoma, serving as risk factors in more than 90 % of all cases of esophageal carcinoma in Japan. It is known that the risk of developing esophageal carcinoma is increased by concomitant use of tobacco and alcohol. In October 2009, a working group of the World Health Organization prescribed that acetaldehyde associated with alcoholic beverages is a Group 1 carcinogen. In addition, in relation to dietary factors, poor nutritional status and vitamin deficiency due to inadequate intake of fruits and vegetables are also reported as risk factors. By contrast, intake of green and yellow vegetables and fruits are reported as preventive factors.

Although adenocarcinoma accounts for only a small percentage of patients with esophageal carcinoma, the percentage is increasing in Europe and North America, accounting for about more than half of all the cases of esophageal carcinoma. Barrett's epithelium caused by persistent inflammation of the lower esophagus due to gastroesophageal reflux disease (GERD) is known to serve as the background mucosa of the disease in Europe and America. GERD, high BMI, which serves as a risk factor for GERD, and smoking are involved in the development of the disease. In Japan, no clear evidence has been established because of the scarcity of cases.

Diagnosis of esophageal carcinoma

Diagnosis of the stage of carcinoma

Summary

The clinical stage of esophageal carcinoma is determined by various diagnostic imaging procedures in terms of the depth of tumor invasion, and presence/absence of lymph node metastasis and distant metastasis. Patients should be informed of the therapeutic strategies based on the assessment of the characteristic features of the lesion (grade of malignancy) and their general condition. Therapeutic strategies should be decided after explaining the basis for and process of diagnosis to patients, and obtaining their understanding, will, and consent (Fig. 2).

Evaluation of the general condition

Radical surgery for esophageal carcinoma, particularly surgery accompanied by thoracolaparotomy, is the most invasive among various types of surgery for gastrointestinal carcinomas. Recent advances in surgical techniques, anesthetic procedures, postoperative management, etc., have led it to safer and more radical treatment for esophageal carcinoma. However, the incidences of postoperative complications and surgery-related mortality still remain higher than those for other diseases. It should also be noted that esophageal carcinoma occurs predominantly in people of advanced age, i.e., 65–70 years of age, and that people of this age group are more likely to have various lifestyle-related diseases (hypertension, diabetes mellitus, hyperlipidemia, etc.). Therefore, it is desirable that application of

Fig. 2 Algorithm for deciding the therapeutic strategies for esophageal carcinoma
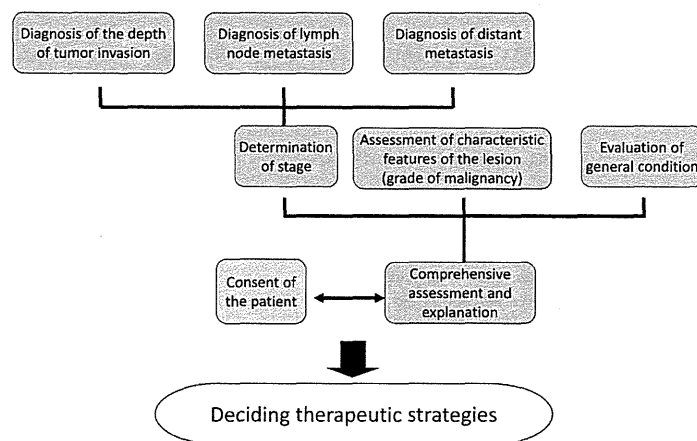
radical surgery be decided with due caution after evaluation of vital organ function. When applying chemotherapy, radiotherapy or chemoradiotherapy, it is desirable that the functions of vital organs meet certain criteria for implementation of the therapy.

In this connection, several tests that are required for evaluating the general condition and function of major organs are described below, in addition to rough guides for judging the test results. However, therapy based on the patient's general condition should follow comprehensive evaluation and it is not easy to establish accurate numerical standards.

Performance status (PS)

Performance status is a simple and useful index commonly used for comprehensive evaluation of the patient's general condition (Table 1). Esophageal carcinoma patients with PS scores of 0–2, as described below, are generally considered as suitable candidates for radical surgery, chemotherapy, or radiotherapy.

Pulmonary function tests

Aging and smoking history are risk factors in patients with carcinoma of the esophagus, and the prevalence of chronic obstructive lung disease is relatively high among these patients. Pulmonary function test results are important indices for deciding the advisability of thoracotomy. Whether or not thoracotomy is indicated should be judged comprehensively, taking into account the results of spirometry (%VC, FEV1.0 %, %RV/TLC), arterial blood gas analysis, chest radiography findings, CT findings, smoking history, and past medical history. Thoracotomy should be considered carefully if the values of %VC is 40 % or less, FEV1.0 % is 50 % or less, FEV1.0 is less than 1.5 L, and %RV/TLC is 56 % or more, respectively, and the arterial oxygen tension is 60 Torr or less.

Table 1 Eastern Cooperative Oncology Group (ECOG) activity score

PS 0	Fully active and able to carry out all pre-disease activities without restriction
PS 1	Restricted in physically strenuous activities, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework and office work
PS 2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 % of waking hours
PS 3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Cardiac function tests

In principle, surgery is not indicated in patients with heart failure due to valvular disease or cardiomyopathy, severe arrhythmia, or myocardial infarction within 3 months prior to the onset. A resting or exercise electrocardiography (ECG) is carried out as a rule. If any abnormality is found, the patient should be subjected to Holter ECG monitoring, echocardiography, cardiac catheterization, or exercise stress perfusion imaging.

It is desirable to consult with a cardiovascular internist if the patient has cardiac function abnormalities or has been on antiplatelet therapy or anticoagulant therapy before surgery.

Hepatic function tests

Surgical treatment is basically not indicated for severe hepatitis or fulminant hepatitis. In cases of chronic hepatitis or hepatic cirrhosis, surgical treatment should be considered based on a comprehensive evaluation of blood counts and the results of blood coagulation tests, blood biochemistry tests, ICG stress test (15 min), and hepatitis screening. Excluding special conditions, surgery is basically not performed in patients who have an ICG retention rate of 40 % or more at 15 min due to hepatic dysfunction. If the value is 20–40 %, application of minimally invasive surgery including reduction of operative radicality may be considered with due caution.

It has been pointed out that systemic chemotherapy may cause reactivation of hepatitis B virus in HBs antigen-positive patients. Chemotherapy may also cause fulminant hepatitis in patients who have a history of hepatitis B virus infection (negative for HBs antigen and positive for HBc antibody or HBs antibody). Therefore, it is desirable to consult a hepatologist beforehand.

Renal function tests

Evaluation of renal function includes general urinalysis, serum creatinine, BUN, electrolytes, and creatinine clearance (Ccr). Although it is relatively rare for surgery to be ruled out only because of renal function deterioration, it is desirable to explain to the patient the possible need for dialysis therapy if the serum Cr level is 2.0 mg/dL or more and the Ccr is 30 % or less.

Glucose tolerance test

Perioperative blood glucose control should be implemented strictly in patients with diabetes or decreased glucose tolerance. Measurement of fasting blood glucose levels, the oral
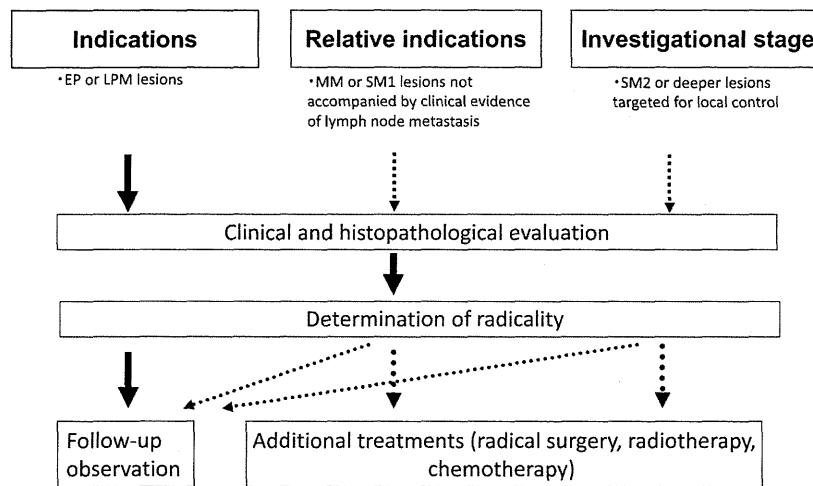
Indications	Relative indications	Investigational stage
• EP or LPM lesions	• MM or SM1 lesions not accompanied by clinical evidence of lymph node metastasis	• SM2 or deeper lesions targeted for local control

Clinical and histopathological evaluation

Determination of radicality

Follow-up observation

Additional treatments (radical surgery, radiotherapy, chemotherapy)

Fig. 3 Indications for endoscopic resection

75 g glucose tolerance test, measurement of HbA1c levels, quantitative urinary glucose measurement, and urinary ketone testing should be performed. Preoperative control is targeted at a fasting blood glucose of <140 mg/dl, daily urinary glucose excretion of ≤10 g, and negative test for urinary ketones.

Other considerations

Central nervous system function, including the presence/absence of mental disorders, should be evaluated comprehensively. In general, radical surgery is not indicated for patients with carcinoma of the esophagus when there is a concomitant acute-phase cerebrovascular disorder. It is desirable that patients with depression, anxiety, delirium, or dementia be referred for professional evaluation by a psychiatrist.

Endoscopic treatment

Summary

The mainstay of endoscopic treatment is endoscopic resection (ER).

Endoscopic resection includes conventional endoscopic mucosal resection (EMR), in which the affected mucosa is held or aspirated and resected with a snare, and endoscopic submucosal dissection (ESD), which refers to en bloc resection of an extensive lesion using an IT knife or a hook

knife. Other available endoscopic treatments include photodynamic therapy (PDT),[5] argon plasma coagulation therapy,[6] and electromagnetic coagulation therapy.

Indications for endoscopic resection (Fig. 3) Among lesions that do not exceed the mucosal layer (T1a), those remaining within the mucosal epithelium (EP) or the lamina propria mucosae (LPM) are extremely rarely associated with lymph node metastasis; therefore, endoscopic resection is a sufficiently radical treatment for these lesions. Lesions reaching the muscularis mucosae or slightly infiltrating the submucosa (up to 200 μm, T1b-SM1) are amenable to mucosal resection, but may have a risk of lymph node metastasis. Therefore, these cases represent relative indications. Furthermore, 50 % of lesions invading deeper (more than 200 μm) into the submucosa (T1b-SM2) are associated with metastasis, and even superficial carcinomas

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[5] *Photodynamic therapy (PDT)* In this treatment modality, the oncotropic, light-sensitive substance porfimer sodium (Photofrin) is injected intravenously, and tumor tissue is necrotized by applying 630 nm red light to the light-sensitive substance selectively incorporated into the tumor. Use of this treatment for early carcinomas of the lung, stomach, and uterus and superficial esophageal carcinoma has been covered by the national health insurance in Japan since October 1994. The reported local control rate in cases of superficial esophageal carcinoma is 90 %. PDT is reported to be effective for unresectable cases by ER and remnant lesions after ER, radiation therapy, or chemoradiation therapy.

[6] *Argon plasma coagulation (APC)* This is an endoscopic treatment method in which argon gas is applied, and tissue is cauterized by thermocoagulation using high-frequency currents.

should be treated in the same manner as advanced carcinomas (carcinomas exceeding the muscularis propria).

Mucosal resection covering 3/4 of the entire circumference is likely to be associated with postoperative cicatricial stenosis. Therefore, sufficient explanation should be given to the patient prior to the operation and preventive measures must be taken. In cases of superficially spreading carcinoma, deep infiltration may occur in several areas, necessitating careful diagnosis of the depth of invasion.

Diagnosis of resected tissue specimens There are limitations to all modes of diagnosis of the depth of tumor invasion. It is also difficult to accurately determine the depth of invasion of extensive lesions. Thus, tissue specimens obtained by en bloc resection are necessary.

Treatment of lesions not amenable to ER Elevation of the mucosa may pose difficulty in additional ER of lesions remaining marginally after ER or ER after radiotherapy or chemoradiotherapy. These cases and cases with a bleeding tendency are not amenable to ER, and consideration of other treatment options such as photodynamic therapy (PDT) and argon plasma coagulation (APC) is required.

Superiority of en bloc resection En bloc resection is desirable for histologic diagnosis of resected specimens. Endoscopic submucosal dissection (ESD) enables en bloc resection of lesions which formerly were subjected to fractional resection. Further development of equipment and spread of improved techniques are anticipated.

Complications Various complications, including bleeding, esophageal perforation, and cicatricial stenosis have been reported in association with ER, including ESD. The need for prevention, prophylactic measures, and treatment of these complications should be well recognized. There has been extensive discussion on the need for additional treatment after diagnosis of resected tissue.

Indications for endoscopic resection

Handling of resected specimens and evaluation of the integrity of treatment

The rules for the handling of endoscopically resected specimens and the procedures for histopathological examination to help determine therapeutic strategies are as follows:

1. Only specimens obtained by en bloc resection should be used for histopathological evaluation of the adequacy of resection.
2. The following procedures should be undertaken when handling specimens, in accordance with the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus, 10th edition.

- EMR and ESD specimens should be stretched out so that they are approximately the same size as in vivo, and the proximal and distal ends should be identified. Specimens should then be promptly fixed.
- Iodine staining is recommended before sectioning, to identify the iodine-unstained area.
- Specimens should be sectioned in a direction that allows accurate assessment of the resection margins. When the specimen has adequate resection margins, it should be sectioned transversely (perpendicular to the long axis) to obtain as much information as possible. When the specimen has small resection margins, it should be sectioned perpendicular to the tangent line at the smallest margin. The entire specimen should be continuously sectioned at 2–3 mm intervals. The cut surface should include the full thickness of the epithelium and the muscularis mucosae (Fig. 4).
3. The histopathological diagnosis should be made by examination of all the sections obtained by the above process.
4. The objective of performing histopathological diagnosis of endoscopically resected specimens is to determine whether any additional treatment is necessary. The depth of invasion, presence/absence of lymphovascular invasion, and status of the resection margin should therefore be specified to determine whether the lesion has been completely removed and to assess the likelihood of metastasis.

Surgical treatment

Summary

Therapeutic strategies vary according to factors such as the location of the esophageal lesion, extent of the lesion, depth of invasion, presence/absence of metastasis, general condition of the patient, and the institution that provides the treatment. There are many treatment options available. Some treatments are already formulated and used commonly in daily clinical practice. Some other treatments are in the clinical research phase and in the process of expanded use, although lacking in solid supportive evidence.

With regard to surgical treatment, there are various options depending on the institution as to the width of the resection margin, extent of lymph node dissection, the organ and route used for reconstruction, multimodality therapy including adjuvant therapy, and salvage surgery following definitive (chemo-) radiotherapy. Therefore, it is difficult to choose the currently most appropriate standard therapy based on evidence.

The esophagus extends anatomically from the cervical through the thoracic region into the abdominal region. It

1. When the specimen has adequate resection margins, it should be sectioned transversely.
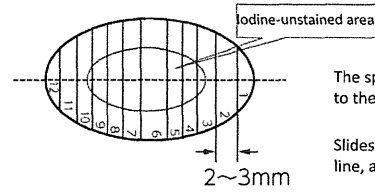
Iodine-unstained area

The specimen should be sectioned transversely (perpendicular to the long axis) to obtain as much information as possible.

Slides are prepared from sections cut below each numbered line, and are viewed under a microscope.

2~3mm

2. When the resection margin is small, the specimen should be sectioned perpendicular to the tangent line at the closest margin.
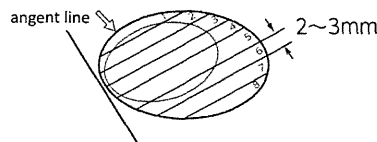
Tangent line

2~3mm

Slides are prepared from sections cut below each numbered line, and are viewed under a microscope.

When section No. 1 includes part of the lesion, it should be inverted (⇨) so that slides are prepared from above the numbered line to evaluate the edge of the lesion.

Fig. 4 Sectioning of specimens obtained by endoscopic resection. The specimen should be cut after the iodine-unstained area is identified by the staining

is surrounded by various organs according to its location. Although therapeutic strategies vary widely according to the location of the tumor, stage, and general condition of the patient, surgery remains the mainstay of treatment. In general, absolute indications for endoscopic treatment are carcinomas with a depth of invasion classified as EP or LPM. However, esophagectomy and reconstruction not accompanied by lymph node dissection may be indicated as a comprehensive judgment for extensive early carcinomas without clinical lymph node metastasis. For lesions reaching up to the muscularis mucosa, the frequency of lymph node metastasis is about 9.3 %. This percentage increases as the depth of invasion increases. For lesions invading deeper into the submucosal tissue, the rate of metastasis is about 50 %. In general, if there is reasonable ground for suspecting lymph node metastasis, lymph node dissection should be carried out even for superficial lesions in the treatment of T2 or deeper carcinomas. Surgery may be considered in patients with T4 lesions, only when curative resection is judged to be applicable. Basically, surgery is not chosen as the initial treatment when there is metastasis to distant lymph nodes or other organs.

At present, efforts are focused on the establishment of surgical treatments by the formulation and standardization of surgical techniques represented by three-field lymph node dissection (cervical, thoracic, and abdominal) for cases of thoracic esophageal carcinoma, as well as the introduction and promotion of endoscopic surgery (video-assisted surgery) based on established surgical treatments and minimization of surgical invasion through the use of

limited surgery. However, supportive evidence to promote these actions still remains inadequate.

Surgery for cervical esophageal carcinoma

Summary The anatomical structure and physiological functions of the hypopharynx to the cervical esophagus are complicated. Because the loss of vocal function by combined laryngectomy greatly affects the postoperative QOL of the patient, the surgical procedure should be determined carefully, after due consideration given to the balance between the radicality of the treatment and the QOL.

Resection

Carcinoma of the cervical esophagus is often advanced at diagnosis, with a high incidence of lymph node metastasis and infiltration into other organs. However, lymph node metastasis is mainly restricted to the cervical region, and radical surgery is often applicable. Patients who have extensive distant metastases and metastasis to a number of superior mediastinal lymph nodes are usually not suitable candidates for radical resection.

Larynx-conserving surgery

This operation is indicated for patients in whom the tumor has not invaded the larynx or trachea and in whom the proximal end of the tumor remains inferior to the esophageal orifice.

Larynx-conserving surgery is divided into larynx-conserving cervical esophagectomy and larynx-conserving total esophagectomy according to the necessity for thoracic esophagectomy. Concomitant resection of the thoracic

esophagus may be performed when the tumor has invaded the thoracic esophagus, when there are multiple lesions not amenable to endoscopic resection, or when it is difficult to perform reconstruction requiring microvascular anastomosis. This surgery may be indicated for patients in whom preoperative therapy results in tumor shrinkage.

Laryngopharyngoesophagectomy (combined laryngectomy)

Laryngopharyngoesophagectomy is indicated for patients with tumors invading the larynx, trachea, and hypopharynx, or those in whom sufficient preservation of the cervical esophagus to perform anastomosis is difficult.

This type of surgery is divided into laryngopharyngectomy plus cervical esophagectomy and laryngopharyngectomy plus total esophagectomy according to the necessity for thoracic esophagectomy. Resection of the thoracic esophagus may be combined when the tumor has invaded the thoracic esophagus, when there are multiple lesions not suitable for endoscopic resection, or when it is difficult to perform reconstruction requiring microvascular anastomosis.

Lymph node dissection

According to the 10th edition of the Japanese Classification of Esophageal Cancer, cervical lymph nodes include superficial cervical nodes of the neck [100], cervical paraesophageal lymph nodes [101], deep cervical lymph nodes [102], peripharyngeal lymph nodes [103], and supraclavicular lymph nodes [104]. The major thoracic lymph nodes are the recurrent laryngeal nerve lymph nodes [106-rec] and upper thoracic paraesophageal lymph nodes [105].

Among these, [101] and [106-rec] lymph nodes belong to group 1, and [102], [104] and [105] lymph nodes belong to group 2 in cases of cervical esophageal carcinoma. It is preferable to remove them.

Method of reconstruction

Although reconstruction using a free intestinal graft is common when the operation involves cervical manipulation alone, gastric tube reconstruction may be employed in some cases. Myocutaneous flaps or skin rolls may also be used for reconstruction. When concomitant thoracic esophagectomy is performed, the stomach or colon is used for reconstruction as in cases of usual reconstruction following resection of the thoracic esophageal carcinoma. However, a free jejunal graft may be added if the length of the organ prepared for reconstruction is not sufficient.

Surgery for thoracic esophageal carcinoma

Summary Thoracic esophageal carcinoma is often accompanied by extensive lymph node metastasis in the cervical, thoracic, and abdominal regions. A right thoracotomy with total extirpation of the thoracoabdominal esophagus and lymph node dissection is generally carried out. The width of the resection margin of the tumor should be decided bearing in mind

both the possibility of persistent carcinoma in the remaining esophageal wall and the extent of lymph node dissection.

In cases of thoracic esophageal carcinoma, the extent of lymph node dissection should be determined after preoperative evaluation of the location, size, and depth of invasion of the carcinoma by imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and PET.

Three routes of reconstruction, i.e., antethoracic, retrosternal, and posterior mediastinal are available. Although each of these routes has its own advantages and disadvantages, the posterior mediastinal route has been most frequently employed recently. The stomach is the most common organ used for reconstruction.

Resection

Thoracic esophageal carcinoma is often accompanied by extensive lymph node metastasis in the cervical, thoracic, and abdominal regions. A right thoracotomy with total extirpation of the thoracoabdominal esophagus, and lymph node dissection of the lymph nodes in all the three regions (cervical, thoracic, and abdominal) is generally carried out.

The width of the margin of resection of the tumor should be decided bearing in mind both the possibility of persistent carcinoma in the remaining esophageal wall and the extent of lymph node dissection. Persistent carcinoma in the esophageal wall may result from intramural spread, intraepithelial spread, vascular invasion, or intramural metastasis. Submucosal spread increases according to the tumor depth, reportedly reaching 30 mm in cases of T2 carcinoma. There is no standard extent of resection established for all of the above cases, and a sufficient margin may not be available at the proximal end of the resection according to the location of the tumor. Thus, the extent of resection should be decided on the basis of the findings on preoperative esophagography and endoscopy, intraoperative rapid frozen-section diagnosis, and intraoperative macroscopic evaluation including close observation of the mucosal surface (and iodine application) under intraoperative esophagotomy.

Endoscopic esophagectomy and reconstruction

Thoracoscopy- or laparoscopy-assisted esophagectomy with esophageal reconstruction and mediastinoscopy- or laparoscopy-assisted transhiatal esophagectomy have been reported as promising surgical procedures, although they are still in the investigational stages, in view of the minimal invasiveness, radicality, and the long-term results. In Japan, endoscopic esophagectomy is almost always performed as a radical surgery which includes sufficient lymph node dissection comparable to open surgery. Indications for this operation vary among institutions and it is used for T3 cancer in some institutions. It has been reported that endoscopic esophagectomy is comparable to conventional standard surgery with open thoracotomy

in terms of the operating time, amount of blood loss, and number of dissected lymph nodes, and is advantageous in terms of providing early relief from postoperative pain and rapid restoration of vital capacity, as long as it is carried out at institutions with accumulated clinical experience. On the negative side, recurrent laryngeal nerve paralysis is reported to occur more frequently after this procedure than after standard surgery via thoracotomy.

Some techniques have been suggested for performing carrying out implementing safe endoscopic surgery with reduced operating time and improved accuracy of node dissection. These techniques include for direct manipulations, via a minor thoracotomy, video-assisted thoracoscopic surgery (VATS) with minor thoracotomy and hand-assisted laparoscopic surgery (HALS), involving manipulation with one hand on the abdomen. Although thoracic manipulations have been predominantly carried out with the patient in the left lateral decubitus position, complete endoscopic thoracic manipulations with the patient in the prone position is becoming more and more frequent recently. Transhiatal esophagectomy with mediastinal dissection using a mediastinoscope inserted via a cervical incision or with mediastinal dissection via laparotomy has also been proposed. It is reported that endoscopic surgery allows node dissection with improved accuracy because of the higher-power visualization that allows observation of microanatomy. However, no definitive conclusions have been reached yet as to the long-term outcomes of this form of surgery as compared to those of conventional standard surgery with open thoracotomy and node dissection, and further investigation in randomized controlled trials is awaited.

Lymph node dissection

Thoracic esophageal carcinoma is commonly accompanied by lymph node metastasis in extensive areas from the cervical to the abdominal region. However, because the distribution and incidence of lymph node metastasis vary according to the location, size, and depth of invasion of the tumor, preoperative evaluation of individual patients by CT, US, MRI, and PET is important to determine the extent of lymph node dissection.

Radical surgery for thoracic esophageal carcinoma is accomplished ordinarily as a combination of three approaches, i.e., the cervical, thoracic, or abdominal approaches. The mediastinal approach has also been proposed as an alternative to the cervical approach for dissection of the cervical paraesophageal lymph nodes [101].

Upper thoracic esophageal carcinoma (Ut)

Patients with this type of lesion usually present with lymph node metastasis, mainly in the cervical to upper mediastinal region; thus, lymph node dissection should include the cervical region. Addition of median sternotomy or manubriotomy has also been suggested to allow a

better field of view of the cervicothoracic junction region. Although metastasis to the lower mediastinal or abdominal lymph nodes occurs less frequently in cases of Ut, dissection should ordinarily cover all the three regions, i.e., cervical, thoracic, and abdominal regions, including the left gastric artery lymph nodes.

Middle thoracic esophageal carcinoma (Mt)

In general, metastatic lymph nodes in cases of Mt are relatively evenly distributed over the cervical to upper, middle, and lower mediastinal and abdominal regions. Because the involvement of cervical lymph nodes other than the cervical paraesophageal lymph nodes [101] is relatively rare, lymph node dissection via the intrathoracic approach instead of the cervical approach has also been proposed.

When the thoracic approach is judged to be inadequate based on the preoperative diagnosis of metastasis, it is important to add a cervical approach to dissect the lymph nodes surrounding the bilateral recurrent laryngeal nerve up to the inferior pole of the thyroid. In particular, the lymph nodes of 101L are difficult to be dissected thoroughly by thoracic manipulations alone, and additional dissection via a cervical incision is necessary. In addition, supraclavicular lymph nodes [104] cannot be dissected by thoracic manipulations, and a cervical approach is necessary for secure lymph node dissection in this region.

Lower thoracic esophageal carcinoma (Lt)

In cases of Lt, while lymph node metastasis mainly occurs in the mediastinal and abdominal regions, metastasis to the cervical lymph nodes may also occur, albeit at a lower frequency. The optimal approach for lymph node dissection remains under discussion; while some propose adding the cervical approach, similar to the case for Mt, others regard the thoracic approach as being superior. Because metastasis to the upper mediastinal lymph nodes is less frequent in cases of superficial carcinoma of the lower thoracic esophagus, there is a view that the extent of lymph node dissection could be minimized and that cervical lymph node dissection could be omitted altogether in some cases.

Method of reconstruction (Table 2)

Route of reconstruction

Three routes, i.e., the antethoracic, retrosternal, and posterior mediastinal (including intrathoracic) routes, are available for reconstruction. The route employed varies according to the case, and each route has its own advantages and disadvantages. Recently, the posterior mediastinal route is the most frequently used for reconstruction when high intrathoracic anastomosis is included. Because surgery for second primary cancer in the gastric tube is difficult after reconstruction via the posterior mediastinal route, the risk of carcinoma occurring in the gastric tube should be considered particularly when long survival is expected.

Table 2 Advantages and disadvantages of each route of reconstruction

Route	Antethoracic	Retrosternal	Posterior mediastinal
Advantages	1. Proximal esophagectomy at a higher level is possible	1. Proximal esophagectomy at a higher level is possible	1. This route is the most original anatomic location
	2. The anastomotic technique is simple	2. Reconstruction length is shorter than in the antethoracic route	2. The surgical stress is less
	3. Treatment of anastomotic leakage is simple and safe	3. The procedure for treatment of anastomotic leakage, if any, is easier than in the case of intrathoracic anastomosis	3. The frequency of anastomotic leakage is low
	4. Treatment of carcinoma occurring in the reconstructed organ is easy	4. Treatment of carcinoma occurring in the reconstructed organ is relatively easy	
Disadvantages	1. The reconstruction length is long	1. The reconstructed organ may compress the heart	1. Anastomotic leakage may become critical (particularly, in cases of intrathoracic anastomosis)
	2. The frequency of anastomotic leakage is high	2. If the sternoclavicular joint part is narrow, pressure necrosis of the reconstructed organ may occur	2. There may be restrictions to proximal esophagectomy
	3. The reconstructed organ is likely to be bent		3. Regurgitation occurs frequently
	4. There are esthetic issues		4. Perforation or severe ulcers may occur
	5. Blockage due to bending is apt to occur		5. Surgery for recurrent carcinoma in the reconstructed organ is difficult
			6. Radiotherapy for recurrent disease may be difficult

Organs used for reconstruction

Reconstruction using the stomach is the most common method. In patients with past history of gastrectomy, those with a concomitant gastric carcinoma, and those in whom the stomach needs to be preserved, colic and ileocolic or jejunal grafts may be used.

Anastomosis

Anastomosis may be divided into cervical and intrathoracic depending on the site of anastomosis. This site of anastomosis is chosen according to the location of the tumor, the organ used for reconstruction, and the route of reconstruction. Intrathoracic anastomosis is associated with a high risk of serious complications in the event of anastomotic leakage. The anastomosis techniques include manual suture and mechanical suture. For intrathoracic anastomosis, mechanical suture using a circular stapler is frequently employed. Because anastomotic leakage and stricture exert a strong influence on the postoperative course and QOL of the patient, it is important to use appropriate anastomotic techniques tailored to individual patients.

Surgery for carcinoma of the esophagogastric junction (abdominal esophageal carcinoma)

Summary Similar to the case for surgical treatment of thoracic esophageal carcinoma, various techniques are available for the surgical treatment of carcinoma of the esophagogastric junction (E, EG). These include a right thoracotomy with dissection including the upper mediastinal lymph nodes and reconstruction using a gastric tube, lower esophagectomy with proximal gastrectomy or lower esophagectomy with total gastrectomy via left thoracolaparotomy or serial left thoracic and abdominal incisions, and a transhiatal approach to the lower mediastinum without thoracotomy. Metastasis involving the lower paraesophageal to upper abdominal lymph nodes is frequent in these cases. The most commonly employed technique is intrathoracic anastomosis using a gastric tube or the jejunum.

Resection and lymph node dissection

The 10th edition of the Japanese Classification of Esophageal Cancer defines the esophagogastric junction region as the region within 2 cm above and below the esophagogastric junction, and esophagogastric junction carcinoma as that with its center located within this region. According to this definition, abdominal esophageal carcinoma is included in this category. In cases of esophagogastric junction carcinoma extending more to the esophageal side than to the gastric side (E, EG), right thoracotomy with dissection including the upper mediastinal lymph nodes and reconstruction using a gastric tube are frequently performed in the same manner as for cases of thoracic esophageal carcinoma. In some cases, lower esophagectomy with proximal gastrectomy or lower esophagectomy with total

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gastrectomy via left thoracolaparotomy or serial left tho-racic and abdominal incisions may be carried out, consider-ing that cervical or upper mediastinal lymph node dissec-tion is of lesser significance. A transabdominal approach to the lower mediastinum via dilated esophageal hiatus with-out thoracotomy is also reported. Metastasis to the lower thoracic paraesophageal lymph nodes [110], cardiac lymph nodes [1] [2], lesser curvature lymph nodes [3], left gastric artery lymph nodes [7], and celiac artery lymph nodes [9] is frequent.

In cases of esophagogastric junction carcinoma extend-ing more to the gastric side than to the esophageal side (G, GE), metastasis to the mediastinal lymph nodes is less frequent; thus dissection of these lymph nodes is of lesser consequence. Therefore, these lymph nodes are classified as group 3 in the 10th edition of the Japanese Classification of Esophageal Cancer.

Method of reconstruction

Intrathoracic anastomosis using a gastric tube, jejunal interposition by elevation of the jejunum, and intratho-racic anastomosis by the Roux-en-Y style are available. In cases of esophagogastric anastomosis following lower esophagectomy with proximal gastrectomy, postoperative reflux esophagitis is a potential problem and may require prophylactic measures.

Other surgical treatments

Summary Although radical surgery for esophageal carci-noma basically consists of resection, lymph node dissec-tion, and reconstruction, other treatments may be carried out if it is difficult or unnecessary to complete these pro-cedures because of various factors such as the stage and malignancy grade of the carcinoma and the general con-dition of the patient. Transhiatal esophagectomy has been performed as a radical operation for mucosal carcinoma or abdominal esophageal carcinoma that is difficult to treat with an endoscopic procedure and that presumably requires no mediastinal lymph node dissection. This has also been used as a palliative operation for patients who are not suit-able candidates for thoracotomy and mediastinal lymph node dissection because of poor pulmonary function or other reasons. However, indications for this procedure have recently become limited because of the expanding applica-tion of endoscopic treatment as esophagus-preserving ther-apy and the spread of multidisciplinary therapy including chemoradiotherapy.

Bypass surgery may be performed as a palliative treat-ment for patients who have difficulty in oral intake because of esophageal stenosis due to esophageal carcinoma or changes after treatment for esophageal carcinoma. How-ever, the indications for bypass surgery have become lim-ited because of the spread of esophageal stenting.

Transhiatal esophagectomy

In this method, the thoracic esophagus is detached and removed via the cervical and abdominal approaches with-out thoracotomy. This technique was first reported by Turner in 1933. Akiyama et al. introduced this method in Japan in 1971, and it has since come to be used widely in clinical practice in this country. This technique has been employed for resection and reconstruction in patients with cervical esophageal carcinoma, patients with thoracic or abdominal esophageal carcinoma who are not suitable can-didates for thoracotomy because of severe pleural adhe-sions or poor pulmonary function, patients of advanced age, and patients with mucosal carcinoma not requiring lymph node dissection. Although this technique allows dis-section of the abdominal to lower mediastinal lymph nodes to some extent, upper to middle mediastinal dissection is difficult.

Currently, the use of transhiatal esophagectomy has become rare because of the spread of chemoradiotherapy and endoscopic submucosal dissection.

Treatments for unresectable cases

Advanced esophageal carcinomas that are unresectable because of infiltration into other organs or distant metas-tasis are initially treated by radiotherapy, chemotherapy, or chemoradiotherapy. However, patients with esophageal stenosis or trachea–esophageal fistula not responding to these treatments suffer from difficulty in oral intake, result-ing in a marked decrease in QOL. Bypass surgery is a pal-liative treatment used to achieve oral feeding in these cases of malignant esophageal stenosis or obstruction. Currently, indications for bypass surgery have become rare because of the spread of covered esophageal stent placement.

In bypass surgery, the thoracic esophagus is excluded from the continuity of the digestive tract and a new route of oral intake is made. The route of bypass is antethoracic or retrosternal. Because most patients have advanced car-cinoma and a poor nutritional status, anastomotic leakage occurs frequently, necessitating caution. In recent years, this procedure has been also employed as a palliative oper-ation in patients in whom major lesions are judged to be unresectable during salvage surgery following definitive chemoradiotherapy.

Perioperative management and clinical path

Summary It was previously considered that introduction of the clinical path method would be difficult for periop-erative management of esophageal carcinoma, because of the pathological features of this carcinoma and the diver-sity of surgical techniques available. In recent years, how-ever, a clinical path for resection and reconstruction of the esophagus has been proposed by various institutions and has been applied in clinical practice. However, there has

been only limited data from large-scale clinical studies evaluating the usefulness of a clinical path for perioperative management.

In recent years, an increasing number of institutions have included nutritional support teams (NST) for perioperative nutritional management of patients with esophageal carcinoma, facilitating early implementation of enteral nutrition. As an element of perioperative management, steroid administration is useful and recommended in postoperative management. Abstinence from smoking, respiratory physical therapy, and preoperative oral care are generally considered to be important for the prevention of postoperative complications.

Introduction of a clinical path in perioperative management of esophageal carcinoma

Clinical path is a treatment plan prepared to facilitate provision of safe team-approached medical care involving health-care professionals from multiple medical fields, including doctors, nurses, pharmacists, nutritionists, and physical therapists, with the aim of improving the quality of care through standardization of health care. In the USA, along with the introduction of the diagnosis-related group/prospective payment system (DRG/PPS) in 1983, the fixed charge system, replacing the fee-for-service system, came to be employed for inpatient hospital care and a clinical path was introduced mainly for the purpose of reducing the length of stay in the hospital of patients and to reduce health-care costs. In Japan, around the time of the introduction of the diagnosis procedure combination (DPC) system, clinical paths were introduced for the treatment of various diseases in the 1990s. The use of clinical paths has recently come to be considered to be important not only for improvement of the quality of health care and medical education to provide safe team health care, but also for enhancement of patient-centered health care, including promotion of obtainment of informed consent.

In patients with esophageal carcinoma, the general condition is greatly affected by the disease state and surgery. Perioperative management techniques in these patients, including the treatment of concomitant diseases, are diverse, with large differences among institutions. Therefore, preparation of a simple clinical path has been considered to be difficult, as reflected by the scarcity of reports documenting the clinical usefulness of a clinical path. The various clinical paths for esophageal carcinoma reported to date are those developed by institutions to achieve safe perioperative management of patients undergoing resection and reconstruction of the esophagus. It is currently difficult to find evidence comparing the usefulness of clinical paths.

Clinical paths for diagnosis and treatment involving EMR and ESD, endoscopic treatment procedures for early esophageal carcinoma have already been developed and are

in clinical use in many institutions. Clinical paths have also been introduced for thoracoscopy- or laparoscopy-assisted esophagectomy with reconstruction, which are used in high-volume centers treating a large number of patients.

Perioperative nutritional management of esophageal carcinoma

Nishi et al. have reported that spontaneous healing of anastomotic leakage after surgery for esophageal carcinoma requires a caloric intake of at least 45 kcal/kg/day, and that the serum albumin concentration must be maintained at 3.5 g/dL or more. It has been reported that enteral nutrition in the perioperative period is associated with a lower incidence of perioperative complications, due to reduced production of endotoxins and inflammatory cytokines, as compared to parenteral nutrition. In cases of radical surgery for esophageal carcinoma, perioperative management by aggressive use of enteral nutrition has been reported to be helpful.

In patients undergoing radical surgery for esophageal carcinoma, the digestive and absorptive capability of the small intestine is often maintained in a normal condition. Therefore, it has been considered that early enteral nutrition rather than central venous nutrition is desirable to enhance postoperative immunity, etc. An enteral feeding tube should be placed during surgery, and a liquid diet should be initiated by 1–3 days after surgery.

Salvage surgery

Summary The definition of salvage surgery is often debated. In the narrow sense, salvage surgery is aimed at curative resection of residual or recurrent tumor after definitive chemoradiotherapy. In Japan, the experience of salvage surgery began to be reported in the early 2000s. Although its indication and role have not yet been established, salvage surgery is recognized to pose a greater risk than general surgery for esophageal carcinoma. It is also known that the frequency of noncurative resection is high, resulting in a poor prognosis. In contrast, cases of curative resection are accompanied by an improved prognosis. Currently, no treatment other than salvage surgery (including endoscopic resection) is accepted as curative treatment for residual or recurrent tumor. Salvage surgery must be implemented only with the informed consent of the patients obtained after explaining the risks and long-term outcomes, and thus requires cautious consideration.

Definition

The 10th edition of the Japanese Classification of Esophageal Cancer defines salvage surgery as that for residual or recurrent cancer after definitive (chemo-) radiotherapy. The variety of surgeries include resection of the esophagus, removal of lymph nodes (dissection), and endoscopic resection (for salvage endoscopic treatment, see

XI. Chemoradiotherapy). Additional resection of residual or recurrent tumor after endoscopic treatment may also be referred to as salvage surgery, but this is not included in these guidelines.

The standard radiation dose for definitive chemoradiotherapy is 50.4 Gy in Europe and North America, on the basis of the results of the INT0123 study. However, in Japan, many institutions use 60 Gy or more as the radiation dose for definitive chemoradiotherapy. The Japan Esophageal Society defines surgery following irradiation of 50 Gy or more as salvage surgery. Although salvage surgery is aimed at achieving curative resection, it ends up in non-curative resection at times because of its nature as a rescue treatment. Therefore, curativity (i.e., R0 resection or not) is not included in its definition.

Indications

The indication for salvage surgery is determined by both tumor factors and patient factors. Tumor factors include the feasibility of radical resection and the long-term prognosis, whereas patient factors include the patient's general ability to tolerate surgery, especially the functions of important organs such as the heart and lung.

The incidence of complications is higher in cases of salvage surgery than in patients treated by surgery alone or surgery combined with preoperative chemoradiotherapy (radiation dose less than 50 Gy). The reported incidence of respiratory complications such as pneumonia is 9–62 %, while that of anastomotic leakage is 14–39 %. In particular, it is of great concern that the incidence of serious complications due to tissue ischemia, such as tracheal necrosis, perforation, and necrosis of the reconstructed gastric tube, is higher after salvage surgery than that after usual surgery. The reported in-hospital mortality after salvage surgery is 7–22 %, indicating that this type of surgery is associated with a higher surgical risk than usual surgery. The high incidence of complications and high in-hospital mortality should be taken into account when considering the indications for salvage surgery.

With regard to the postoperative survival rate, the reported 5-year survival rate is 25–35 %. Long-term survival can be expected in patients only when curative resection is achieved. However, the rate of non-curative resection is high in salvage surgery, reported to be in the range of 12–50 %. Because the prognosis of patients with non-curative resection is extremely poor, careful judgment is required when determining the indications for salvage surgery.

Neoadjuvant therapy

Summary

Neoadjuvant therapy (preoperative adjuvant therapy) has been compared with surgery alone or postoperative adjuvant therapy in cases of resectable Stage II or III thoracic esophageal carcinoma. The significance of neoadjuvant therapy for Stage I esophageal carcinoma has yet to be evaluated.

Neoadjuvant chemotherapy The randomized controlled trial (JCOG9907 study) that compared neoadjuvant chemotherapy and postoperative chemotherapy with cisplatin + 5-FU in patients with resectable Stage II or III thoracic esophageal carcinoma (2002 UICC classification) revealed a significant improvement in the overall survival time in the patients given neoadjuvant chemotherapy. Based on this finding, neoadjuvant chemotherapy + radical surgery for resectable Stage II or III thoracic esophageal carcinoma was positioned as a standard treatment in Japan.

Neoadjuvant chemoradiotherapy The results of a meta-analysis of randomized controlled trials performed in Europe and North America have indicated that neoadjuvant chemoradiotherapy combined with surgery has the potential to improve the long-term survival in patients undergoing surgical resection for esophageal carcinoma as compared to surgery alone. In Japan, this combination therapy is administered to patients with locally advanced carcinoma in some institutions, although, currently, there is no firm basis for its recommendation.

An expected advantage of neoadjuvant therapy over postoperative adjuvant therapy is that it is easier to complete the protocol treatment when applied as neoadjuvant therapy. Neoadjuvant therapy is expected to improve the resection rate and long-term follow-up results by reducing the size of the primary lesion and controlling lymph node metastasis and micrometastasis. It is possible that neoadjuvant therapy allows assessment of the patients' response to chemotherapy and radiotherapy to some extent by allowing histopathologic studies of the resected specimens. However, issues of concern include the following: drug resistance may be induced; local control may be delayed in ineffective cases, resulting in facilitation of metastatic spread of the disease; preoperative radiotherapy may make surgical manipulations more difficult and increase the postoperative risk.

The multicenter clinical study JCOG9907 carried out by the Esophageal Oncology Group of the Japan Clinical Oncology Group (JCOG) deserves special mention in the present revision of the guidelines, because its results provided the rationale for neoadjuvant chemotherapy to be established as the standard treatment for patients with no particular impediments to this treatment.

Neoadjuvant chemotherapy

A number of randomized controlled trials have been conducted in Europe and America addressing the possible beneficial effects of neoadjuvant chemotherapy on the survival rates of patients with esophageal carcinoma. According

to the results of a meta-analysis of these randomized controlled trials, the effects of neoadjuvant chemotherapy on the survival of the patients varied according to the set end points. Therefore, the effects of neoadjuvant chemotherapy in resectable cases have not yet been established (T1-3N0, 1M0, UICC Classification, the 2002 edition).

The 2007 Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus recommended the implementation of neoadjuvant chemotherapy particularly in patients with positive lymph node metastasis, on the basis of the results of the JCOG9204 study (1992–1997: postoperative adjuvant chemotherapy with cisplatin + 5-FU vs. surgery alone). At the time of revising the guidelines, the timing of adjuvant chemotherapy with cisplatin + 5-FU was examined in the JCOG9907 study (1999–2006), and it was found that neoadjuvant chemotherapy yielded significantly improved overall survival in comparison to postoperative chemotherapy. Therefore, in Japan, neoadjuvant chemotherapy with cisplatin + 5-FU followed by radical surgery is now regarded as the standard treatment for resectable Stage II or III thoracic esophageal carcinoma.

Neoadjuvant chemoradiotherapy

Neoadjuvant chemoradiotherapy is a treatment strategy premised on planned surgery and is distinguished from rescue treatment for residual or recurrent carcinoma following chemoradiotherapy aimed at radical cure. In recent years, this type of treatment is recognized as a tri-modality therapy involving a combination of chemotherapy, radiotherapy, and surgery rather than as neoadjuvant chemoradiotherapy. In some cases, a radiation dose of 50.4 Gy, which is the standard dose for definitive chemoradiotherapy, is used.

In Europe and North America, a number of randomized controlled trials that verified the usefulness of neoadjuvant chemoradiotherapy have been reported since the latter half of the 1980s, because of the limitations of local control by surgery. Although neoadjuvant chemoradiotherapy did not contribute to overall survival in most of these studies, the pCR rate was generally higher in patients given neoadjuvant chemoradiotherapy. In addition, in a study of esophageal adenocarcinoma reported by Walsh et al. and in the CALGB9781 study, the postoperative survival rate was significantly higher in patients given neoadjuvant chemoradiotherapy than in those undergoing surgery alone. In a randomized controlled trial conducted by Bosset et al. in patients with squamous cell carcinoma, neoadjuvant chemoradiotherapy significantly improved the recurrence-free survival period, although there was no prolongation of overall survival. Many other randomized controlled trials have demonstrated prolongation

of survival in patients receiving neoadjuvant chemoradiotherapy, although there was no significant influence in the overall survival rate.

According to a meta-analysis that addressed surgery preceded by neoadjuvant chemoradiotherapy vs. surgery alone, when the 3-year survival rate was used as an end point, neoadjuvant chemoradiotherapy (20–45 Gy) in patients with resectable carcinoma was associated with a significant increase in operation-related mortality within 90 postoperative days. However, it resulted in a decrease in the local recurrence rate and significant increase of the 3-year survival rate.

In meta-analyses carried out so far in Europe and North America, the patient characteristics (histologic type, stage, etc.) and chemoradiotherapy protocols have not been consistent. The radicality of surgery has been suggested to greatly influence the outcome. No randomized controlled trials of neoadjuvant chemoradiotherapy have been carried out to date in Japan, and thus at present there is no satisfactory rationale for recommending this therapy as effective preoperative therapy.

Postoperative adjuvant therapy

Summary

Surgery combined with postoperative adjuvant therapy has been compared to surgery with or without preoperative adjuvant therapy in resectable cases or cases of Stage II or Stage III thoracic esophageal carcinoma judged as candidates for curative resection. However, to date, the value of postoperative adjuvant therapy for patients with Stage I esophageal carcinoma has not yet been studied.

Postoperative chemotherapy: A randomized controlled trial (JCOG9204 study) comparing surgery with and without postoperative chemotherapy (cisplatin + 5-FU, 2 courses) carried out in Japan demonstrated that postoperative chemotherapy resulted in a significant increase in the disease-free survival rate as compared to surgery alone, although there was no significant difference in the overall survival rate. Analysis of subgroups from the JCOG9204 study demonstrated that the recurrence-preventive effect of 2 courses of cisplatin + 5-FU therapy administered postoperatively was observed only in patients with positive lymph node metastasis. Therefore, in clinical practice, postoperative adjuvant chemotherapy has been considered only after carefully considering the pathological diagnosis after radical surgery. However, in view of the results of the aforementioned JCOG9907 study, implementation of neoadjuvant chemotherapy has been positioned as a standard treatment after taking into account the general condition of the patient.

Postoperative radiotherapy: The results of a randomized controlled trial of pre- and postoperative radiotherapy vs. postoperative radiotherapy alone carried out by the Esophageal Oncology Group of the JCOG showed that the overall survival rate was significantly higher in patients given postoperative radiotherapy alone when the analysis was focused only on eligible patients who received treatment according to the protocol. Based on this finding, preventive postoperative irradiation was formerly in wide use in Japan. However, in overseas randomized controlled trials that compared surgery with and without postoperative irradiation (usual fractionation; 45–60 Gy), postoperative irradiation was associated with a decrease in the local recurrence in the irradiated area, but without a significant increase in the survival rate. Therefore, there is little evidence for recommending postoperative irradiation after curative resection as a standard treatment. At present, the significance of postoperative (chemo-) radiotherapy is unclear. (Chemo-) radiotherapy has been employed in clinical practice and also reported to be effective in cases of non-curative resection or postoperative local recurrence. Although there is insufficient evidence, some local therapy may be necessary for patients who have undergone non-curative resection and who have macroscopic residual tumor without distant metastasis. (Chemo-) radiotherapy seems to be a useful treatment option for such patients.

The rationale for implementing postoperative adjuvant therapy is its potential to control local residual tumor after surgical resection, lymph node metastasis outside the dissection area, and distant micrometastasis, and thereby to lead to improvement in long-term outcomes. The advantage of postoperative adjuvant therapy is that it is possible to implement treatment suited to the disease stage as determined at surgery. However, its disadvantages are that the absence of evaluable lesions makes it difficult to determine its efficacy and postoperative adjuvant therapy may be associated with a lower rate of completion of therapy than preoperative adjuvant therapy.

The 2007 Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus stated that radical resection followed by postoperative chemotherapy was the most commonly employed treatment strategy in Japan. However, preoperative chemotherapy (neoadjuvant chemotherapy) is now regarded as a standard treatment on the basis of the results of the aforementioned JCOG9907 study (1999–2006: neoadjuvant chemotherapy vs. postoperative chemotherapy).

Postoperative chemotherapy

In a randomized controlled trial (JCOG8806) in patients with squamous cell carcinoma carried out by the Esophageal Oncology Group of the JCOG (comparison between surgery plus 2 courses of postoperative cisplatin + vindesine and surgery alone), addition of postoperative chemotherapy did not have any beneficial effect on survival and yielded no significant difference in the 5-year survival rate. Subsequently, another randomized controlled trial carried out in patients with esophageal squamous cell carcinoma using a different chemotherapy regimen (JCOG9204: comparison between surgery plus 2 courses of postoperative cisplatin + 5-FU and surgery alone) showed no clear intergroup difference in the overall survival rate. However, the disease-free survival time was significantly longer in patients given postoperative chemotherapy than in those treated by surgery alone. Thus, postoperative chemotherapy appeared to have a recurrence-preventive effect, particularly in patients with lymph node metastasis. By contrast, no such beneficial effect of postoperative adjuvant therapy was noted in patients without lymph node metastasis.

A randomized controlled trial carried out in France comparing surgery with and without 6–8 courses of postoperative cisplatin + 5-FU included patients undergoing palliative resection who accounted for about half of all the subjects. There was no significant difference in the median survival time between the two groups, and the researchers concluded that postoperative adjuvant chemotherapy with cisplatin and 5-FU exerted no beneficial effect. A meta-analysis of these randomized controlled trials also showed no beneficial effect of adjuvant chemotherapy on the survival rate.

The results of surgery with and even without adjuvant therapy obtained from all previous JCOG clinical studies were much better than the results of surgery plus postoperative adjuvant therapy reported by clinical studies conducted in Europe and North America. This may reflect the differences in the policy and accuracy of lymph node dissection between Japan and Western countries. This should be borne in mind when comparing the results of clinical studies carried out in Japan and those conducted in Europe and North America.

Thus, there is not enough evidence to show that adjuvant chemotherapy improves the overall survival rate of patients undergoing curative resection. However, a Japanese randomized controlled study (JCOG9204) demonstrated a significant increase in the disease-free survival rate after adjuvant chemotherapy, showing the recurrence-preventive effect of this therapy, particularly in patients with lymph node metastasis. Considering the fact that the accuracy of lymph node dissection is characteristically high in Japan and placing weight on the evidence obtained from this country, adjuvant chemotherapy (cisplatin + 5-FU, 2 courses) seems to have a role in the prevention of postoperative recurrence in patients with lymph node metastasis in whom curative resection has been achieved without any preoperative therapy.

Adjuvant radiotherapy

Preoperative irradiation has long been considered a standard treatment in Japan. However, since there is no report definitively documenting that preoperative irradiation improves the survival rate, the Esophageal Oncology Group of the JCOG performed a randomized controlled trial from 1981 to 1984 to compare the outcomes of preoperative (30 Gy/15 fractions) plus postoperative (24 Gy/12 fractions) irradiation with postoperative irradiation alone (50 Gy/25 fractions). Since a number of cases were excluded from the analysis in this study because of non-curative resection or surgical complications, the results may be somewhat unreliable. However, when the analysis was confined to the eligible patients who received treatment as per protocol, the overall survival rate was significantly higher in the group administered postoperative irradiation alone. Based on this finding, prophylactic postoperative irradiation came to be used commonly in Japan.

By contrast, 4 overseas randomized controlled trials comparing surgery with and without postoperative irradiation (usual fractionation, 45–60 Gy) demonstrated no significant increase in the survival rate, although the rate of local recurrence in the irradiated areas decreased in the group given postoperative irradiation. A meta-analysis based on these controlled studies also showed no increase in the survival rate in the group treated by postoperative irradiation. Therefore, there is little evidence for recommending postoperative radiotherapy following curative resection as a standard treatment. However, a subset analysis in a large-scale randomized controlled trial performed in China showed that postoperative radiotherapy led to a significant increase in the survival rate in Stage III patients alone. Therefore, postoperative radiotherapy may be of clinical value for selected patients.

Chemotherapy

Summary

Chemotherapy in the treatment of esophageal carcinoma is usually combined with surgery or radiotherapy in the form of preoperative or postoperative adjuvant chemotherapy or chemoradiotherapy. The use of chemotherapy not combined with other modalities is limited to patients with distant metastasis (M1b) or postoperative distant recurrence. Currently, 5-FU + cisplatin is the most commonly used combination regimen for chemotherapy. However, since there is no definitive evidence of prolongation of the survival time, this therapy is regarded as a palliative treatment.

Proven effective monotherapy drugs

Many chemotherapeutic drugs, such as 5-FU, cisplatin, mitomycin C, bleomycin, vindesine, adriamycin, paclitaxel, docetaxel, vinorelbine, nedaplatin, irinotecan, and gemcitabine are known to be effective in the treatment of esophageal carcinoma (Table 3). However, while 15–44 % of patients have been estimated to respond to monotherapy, cases of complete response (CR) are rare and no monotherapy has been shown to have a survival-prolonging effect. At present, the most commonly used drugs are 5-FU and cisplatin. Basic studies have demonstrated that these two drugs are effective when used as monotherapy, and exert a synergistic effect when combined and a sensitizing effect when combined with radiotherapy. In clinical, many reports were published about good results of these drags combination therapy. These are the reasons for the wide use of these two drugs. At present (as of February 2012), the use of paclitaxel is not yet covered by the national health insurance in Japan, although public knowledge-based application of this drug has been approved. The use of vinorelbine, irinotecan, and gemcitabine for the treatment of esophageal carcinoma is also not covered by the national health insurance in Japan.

Efficacy in combination therapy

Although various combination therapies using cisplatin have been employed since this drug was introduced clinically (Table 4), the currently most commonly used

Table 3 Efficacy of major monochemotherapeutic agents against carcinoma of the esophagus (drugs covered by the national health insurance in Japan)

Drug	Dose and schedule	No. of cases	Response rate (%)
5-FU	500 mg/m^2/day × 5 days	26	15
Mitomycin C	20 mg/m^2 every 4–6 weeks	24	42
Cisplatin	50 mg/m^2 every 3 weeks	24	25
Vindesine	3–4.5 mg/m^2 every week	23	18
Docetaxel	70 mg/m^2 every 3 weeks	48	21
Nedaplatin	100 mg/m^2 every 4 weeks	29	52
Paclitaxel[a]	100 mg/m^2 every week × 6, 2-week withdrawal	52	44

[a] This drug is approved through public knowledge-based application (as of February 2012)

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