Esophageal Cancer Practice Guidelines in Japan

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Abstract

The first edition of the guidelines for esophageal cancer diagnosis and treatment edited by the Japan Esophageal Society was published in 2002. These guidelines were revised every 5 years with the second edition being published in 2007, with additional information on diagnosis, and the third edition in 2012 (Kuwano H, Nishimura Y, Oyama T, Esophagus 12:1–30, 2015). The title of the fourth edition, which was published in 2017, was changed to "Esophageal Cancer Practice Guidelines" and included several modifications (Kitagawa Y, Uno T, Oyama T, Esophagus 16:1–24, 2019a); (Kitagawa Y, Uno T, Oyama T, Esophagus 16:25–43, 2019b). Although the descriptions of diagnosis and treatment options covered in the previous editions were complete, the methodology used to create the guidelines and the evaluation criteria used were not fully presented. Thus, the fourth edition was revised and reorganized to clarify the treatment objectives and the procedures used to develop the guidelines.

The main revisions are as follows:

1. Earlier editions included a single algorithm for treating esophageal cancer; however, the fourth edition includes a detailed algorithm for treating each

The contents of this chapter are based on the two publications "Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1" and "Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 2." The latest information that became available since these guidelines were published has been added to provide an update on this topic.

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stage of the disease in addition to the algorithm that provides a general overview of the diagnosis and treatment of esophageal cancer.
2. Clinical Questions (CQs) relevant to diverse points of the algorithm that require making a decision in clinical practice are extracted from the guidelines and a systematic review was conducted.
3. Emphasis was placed not only on the certainty of evidence for each CQ but also on the balance between benefits and risks presented; the patient's opinion and medical costs were also considered. The expert committee consensus on the recommendation and its strength as well as patient consent rates were also added in the fourth edition. The treatment algorithm includes 41 CQs in total, 15 of which have been described in this chapter.

Keywords

Esophageal cancer · Guidelines · Clinical stage · Clinical question · Algorithm

8.1 Method of Development of the Esophageal Cancer Practice Guidelines [1]

8.1.1 On the Methodology of Preparation of the Guidelines

The guidelines were prepared by referring to the "Guide to Preparation of Guidelines for Diagnosis and Treatment 2014" issued by the Information Division of the Medical Information Network Distribution Service, provided by the Japan Council for Quality Health Care.

8.1.2 Preparation of Clinical Questions and Search of the Literature

The Japan Medical Library Association was entrusted with a systematic research of the literature published from January 1995 through June 2016 using keywords extracted from the clinical questions (CQs). PubMed and the Cochrane Library were used to search for articles in the English language, and the ICHUSHI-Web for articles published in Japanese.

The exact keywords and results of the search of the literature are described in the detailed version of the guidelines (available on the website of the Japan Esophageal Society: https://www.esophagus.jp/).

Moreover, articles that were not retrieved by the systematic search were explicitly searched for as needed based on the information provided by the systematic review team and the Guideline Preparation Committee members.

Table 8.1 Overall evaluation of the collected articles for each outcome and each study design [1]

A	**High-quality evidence (High)**
	We are very confident that the true effect lies close to the estimated effect.
B	**Moderate-quality evidence (moderate)**
	We are moderately confident about the estimated effect.
	The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
C	**Low-quality evidence (low)**
	Our confidence in the estimated effect is limited.
	The true effect may be substantially different from the estimated effect.
D	**Very low-quality evidence (very low)**
	We have very little confidence in the estimated effect.
	The true effect is likely to be substantially different from the estimated effect.

8.1.3 Systematic Review Procedure

For each of the CQs, the outcomes with regard to the balance between the benefits and risks were extracted and the level of importance thereof was presented. Each retrieved article was subjected to a primary and secondary screening, summarized, and assessed for potential bias as well as classification of the study design. For each outcome and the respective benefits and risks, individual papers were summed up and evaluated as "a whole body of evidence." Evaluation of the information as a "whole body of evidence" was carried out by referring to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. The "whole body of evidence for individual outcomes" was then summated to determine and state the quality of evidence as a whole for each CQ (Table 8.1).

8.1.4 Determination of the Strength of Recommendations

The members of the Guideline Preparation Committee prepared a draft of our recommendation statements based on the results of the systematic review, and a consensus conference was held to examine the strength of the recommendations. The strength of each recommendation was examined with regard to the certainty of evidence, benefits and risks, patient preferences, and an evaluation of the costs. To arrive at a consensus, a secret ballot was held with independent voting by 20 members of the Guideline Preparation Committee using an Answer Pad in accordance with the modified Delphi method and nominal group technique. The strength of the recommendation was determined based on a consensus by more than 70% of the members. When a $\geq 70\%$ consensus was not achieved in the first vote, a second vote was called for after consultation. In the case of failure to arrive at a consensus even after the second vote, it was stated that the strength of the recommendation could not be determined.

The strength of recommendation was expressed in two directions × two steps as follows:

1. Strong recommendation for conduct or non-conduct.
2. Weak recommendation for conduct or non-conduct.

8.2 Treatment Algorithm for cStage 0 and I Esophageal Cancer (Fig. 8.1) [1]

To select the treatment policy for cStage 0 or I carcinoma of the esophagus, the clinical stage of the disease should first be confirmed via endoscopic examination; computed tomography (CT) scan of the neck, chest, and abdomen; and positron emission tomography (PET). Thereafter, the depth of tumor invasion must be assessed to select which of the following is the most appropriate treatment: endoscopic resection (ER), surgery, and chemoradiotherapy.

Minimally invasive ER should be considered where the physician wavers in his/her assessment of the tumor invasion depth and in patients with a poor general condition. To predict the risk of developing post-ER stenosis, the circumferential extent of the lesion should be assessed in patients with cStage 0 (T1a) who are scheduled to undergo ER. For a lesion involving ≥3/4 of the esophageal circumference, a preventive strategy against stenosis should be considered because lesions are associated with a high risk of developing stenosis after ER.

Post-ER histopathologic assessment is extremely important to determine if any additional treatment is required. In patients with pT1a-epithelium (EP)/lamina propria mucosae (LPM) disease, follow-up should be scheduled. Conversely, in patients diagnosed with pT1a-muscularis mucosae (MM)/pT1b-submucosal (SM) disease, additional treatment with either surgery or chemoradiotherapy should be considered. In patients with cStage I (T1b) disease, either surgery or chemoradiotherapy should be considered after assessing the patient's tolerability for surgery.

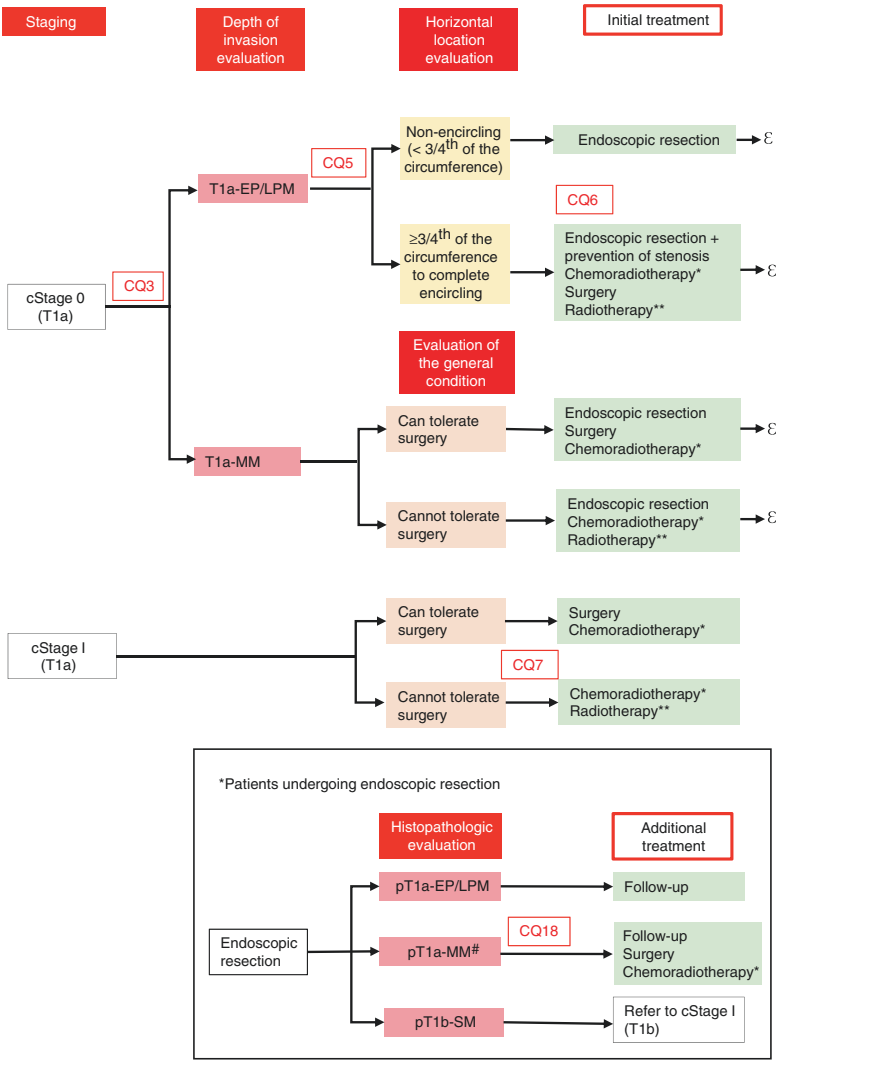
CQ3 What is the recommended method for the clinical diagnostic differentiation between T1a-EP/LPM and T1a-MM disease in patients with superficial cancer of the esophagus?

Recommendation statement.

There is weak evidence regarding the use of ultrasound or magnifying endoscopy for the clinical diagnostic differentiation between T1a-EP/LPM and T1a-MM disease in patients with superficial cancer of the esophagus [rate of consensus: 94.7% (18/19), strength of evidence: C].

CQ5 Is assessment of the circumferential extent recommended for patients with esophageal cancer lesions who are eligible for endoscopic treatment based on the depth of invasion?

Recommendation statement.



* Cisplatin 70 mg/m^2 on days 1 and 29; 5-FU 700 mg/m^2 on days 1-4 and 29-32; radiation therapy at 40-60 Gy
** Radiation therapy at 60-66 Gy
# Additional treatment such as surgery or chemoradiotherapy should be considered in cases showing evidence of vascular invasion.

Fig. 8.1 Treatment algorithms for cStage 0, I esophageal cancer

There is strong evidence showing that the circumferential extent of the lesion must be assessed prior to the initiation of treatment in patients with esophageal cancer lesions who are eligible for endoscopic treatment based on the depth of tumor invasion [rate of consensus: 100% (20/20), strength of evidence: A].

CQ6 What is the recommended method for the prevention of postoperative stenosis after endoscopic treatment in patients with esophageal cancer?

Recommendation statement.

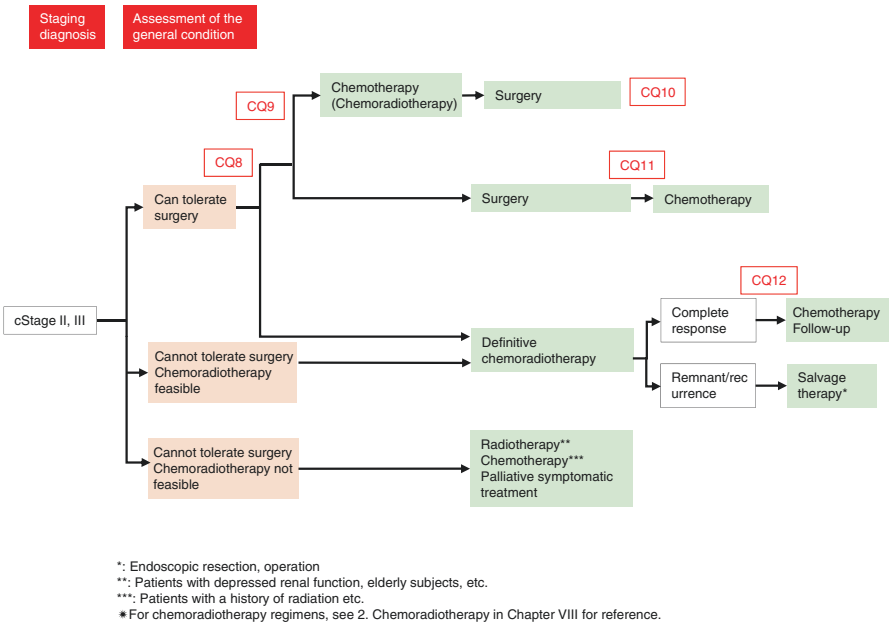


Fig. 8.2 Treatment algorithms for cStage II, III esophageal cancer

There is strong evidence showing that prophylactic balloon dilatation, local steroid injection, or oral steroid administration can be recommended to the patients with esophageal cancer for the prevention of stenosis after endoscopic treatment [rate of consensus: 90% (18/20), strength of evidence: A].

CQ7 Is chemoradiotherapy or radiotherapy recommended for patients with cStage I esophageal cancer who are not eligible for surgical treatment?

Recommendation statement.

There is strong evidence showing that chemoradiotherapy is recommended for patients with cStage I esophageal cancer who are not eligible for endoscopic resection [rate of consensus: 84.2% (16/19), strength of evidence: C].

8.3 Treatment Algorithm for cStage II and III Esophageal Cancer (Fig. 8.2) [1]

To select the treatment policy for cStage II or III esophageal carcinoma, the tolerability for surgical intervention should first be confirmed through the evaluation of the patient's general health condition after an accurate diagnosis of the clinical stage via upper gastrointestinal endoscopy, CT scan, and PET. When no problem is identified with respect to the tolerability for surgery, patients should undergo preoperative

chemotherapy followed by radical resection, as the first-line therapy. Radical resection without preoperative treatment or with preoperative chemoradiotherapy may also be selected. In cases of surgery without any preoperative treatments, the administration of adjuvant chemotherapy should be considered in accordance with the histopathologic diagnosis confirmed using the resected specimens, particularly for patients with lymph node metastasis. Definitive chemoradiotherapy (≥50 Gy) should be considered in patients who cannot tolerate surgery or who refuse surgery but can receive chemoradiotherapy. Patients who achieve complete response should be followed-up, and in case of a remnant or recurrent lesion, the practicability of surgical resection as salvage therapy should be explored. In patients who cannot tolerate surgery and who are not eligible for chemoradiotherapy, radiation therapy (e.g., in patients with depressed renal function and elderly patients), chemotherapy (e.g., in patients with a history of radiation), palliative symptomatic treatment, or palliative chemotherapy should be considered.

CQ8 Is therapy primarily consisting of surgery or definitive chemoradiotherapy recommended for patients with cStage II or III esophageal cancer?

Recommendation statement.

There is weak evidence showing that therapy primarily consisting of surgery is recommended for patients with cStage II or III esophageal cancer [rate of consensus: 70% (14/20), strength of evidence: C].

CQ8 Is preoperative chemotherapy, postoperative chemotherapy, or preoperative chemoradiotherapy recommended for patients with cStage II or III esophageal cancer who are scheduled to undergo surgery?

Recommendation statement

1. There is strong evidence showing that preoperative chemotherapy is preferred over postoperative chemotherapy [rate of consensus: 89.5% (17/19), strength of evidence: B].
2. There is weak evidence showing that preoperative chemotherapy is preferred over preoperative chemoradiotherapy [rate of consensus: 100% (18/18), strength of evidence: C].

CQ10 Is postoperative adjuvant therapy recommended in patients with cStage II or III esophageal cancer who have undergone preoperative adjuvant therapy plus surgery?

Recommendation statement.

There is weak evidence showing that patients with cStage II or III thoracic esophageal squamous cell carcinoma who have undergone preoperative adjuvant

therapy plus surgery cannot receive postoperative chemotherapy [rate of consensus: 85% (17/20), strength of evidence: D].

CQ11 *Is postoperative chemotherapy recommended for patients with cStage II or III esophageal cancer who have undergone surgery without preoperative therapy?*

Recommendation statement.

There is weak evidence showing that postoperative chemotherapy should be recommended for patients with cStage II or III esophageal carcinoma who have a pathologically confirmed lymph node metastasis and who have undergone surgery without preoperative therapy [rate of consensus: 85% (17/20); strength of evidence: C].

CQ12 *Is additional chemotherapy recommended for patients with cStage II, III, or IVa esophageal cancer who achieve complete response after chemoradiotherapy?*

Recommendation statement.

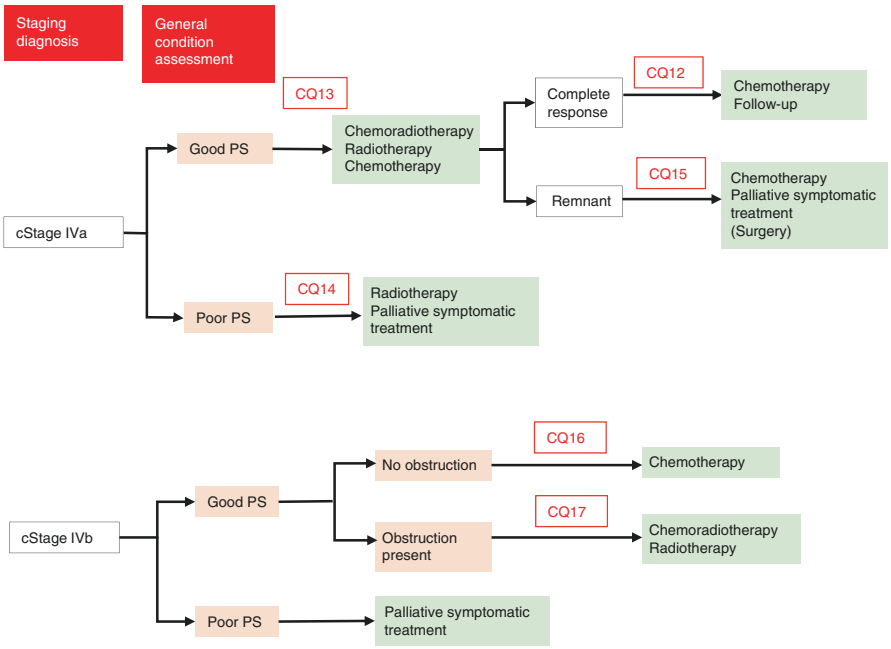
There is weak evidence showing that additional chemotherapy can be recommended for patients with cStage II, III, or IVa esophageal carcinoma who show complete response after radical chemoradiotherapy [rate of consensus: 90% (18/20); evidence level: C].

8.4 Treatment Algorithm for cStage IV Esophageal Cancer (Fig. 8.3) [1]

To determine the treatment policy for cStage IV esophageal cancer, the assessment of performance status (PS) is important, in addition to accurate clinical staging via CT scan, upper gastrointestinal endoscopy, and PET, for patients with other clinical stages of the disease.

In patients with cStage IVa cancer with a good PS, definitive chemoradiotherapy is the treatment of choice, which is believed to be effective. However, the need for salvage surgery for local residual lesions after chemoradiotherapy may increase the risk of surgery-related death; therefore, the situation must be comprehensively assessed with due consideration provided to the benefit–risk balance. Chemotherapy is the mainstay of treatment for patients with cStage IVb esophageal cancer, which represents the progression of cancer beyond local disease and the requirement for systemic treatment; however, palliative radiotherapy may also be considered in patients presenting with the evidence of obstruction.

Conversely, in patients with a poor PS, the main approach is palliative symptomatic treatment. Nevertheless, in cases of cStage IVa esophageal cancer, radiotherapy is effective in improving dysphagia caused by cancer, and improvement in long-term survival has been reported. Although the patients are still at risk of adverse events, it is considered as one of the treatment options.



* For the chemoradiotherapy regimens used, see 2. Chemoradiotherapy in Chapter VIII.

Fig. 8.3 Treatment algorithms for cStage IV esophageal cancer

CQ13 Is chemoradiotherapy recommended for patients with cStage IVa esophageal cancer?

Recommendation statement.

There is weak evidence showing that radical chemoradiotherapy is recommended for the treatment of patients with cStage IVa esophageal cancer [rate of consensus: 85% (17/20); strength of evidence: C].

CQ14 Is radiotherapy recommended for cStage IVa esophageal cancer in patients with a poor PS?

Recommendation statement.

There is weak evidence showing that radiotherapy is recommended for the treatment of patients with cStage IVa esophageal who have a poor PS [rate of consensus: 95% (19/20); strength of evidence: D].

CQ15 Is surgical treatment recommended for patients with cStage IVa esophageal cancer who present with residual disease after chemoradiotherapy?

Recommendation statement.

There is weak evidence showing that surgery is recommended for patients with cStage IVa esophageal cancer who present with residual disease after chemoradiotherapy [rate of consensus: 85% (17/20); strength of evidence: D].

CQ16 Is chemotherapy recommended for the treatment of patients with cStage IVb esophageal cancer?
Recommendation statement.

There is weak evidence showing that chemotherapy is recommended for the treatment of patients with cStage IVb esophageal cancer [rate of consensus: 85% (17/20); strength of evidence: C].

CQ17 Is palliative radiotherapy recommended for the treatment of cStage IVb esophageal cancer in patients presenting with obstruction?
Recommendation statement.

There is weak evidence showing that palliative radiotherapy is recommended for the treatment of cStage IVb esophageal cancer in patients presenting with obstruction [rate of consensus: 100% (20/20); strength of evidence: C].

8.5 Endoscopic Treatment [2]

Endoscopic resection includes endoscopic mucosal resection, wherein the affected mucosal lesion is first lifted or aspirated and then resected with a snare, and endoscopic submucosal dissection, which refers to the *en bloc* resection of an extensive lesion using an insulated-tip knife or hook knife. Other endoscopic treatments include photodynamic therapy, argon plasma coagulation, and electromagnetic coagulation therapy.

CQ18 Is additional treatment recommended in patients diagnosed with a pT1a-MM lesion following endoscopic treatment for superficial esophageal cancer?
Recommendation statement.

There is strong evidence to recommend additional treatment in patients who have a pT1a-MM lesion with vascular invasion after endoscopic treatment. [Rate of consensus: 85% [17/20]; strength of evidence: D].

8.6 Surgical Treatment [2]

8.6.1 Surgery for Cervical Esophageal Carcinoma

In the treatment of cervical esophageal carcinoma, simultaneous laryngectomy is often required. Preoperative chemoradiotherapy or definitive chemoradiotherapy may be undertaken in an attempt to conserve the larynx. Larynx-preserving surgery

conserves vocal function, although it is associated with an increased risk of aspiration and pneumonia, necessitating cautious selection of patients for this treatment. Decreased quality of life (QOL) due to the loss of their voice poses a serious problem in patients who have undergone combined laryngectomy. No significant difference in the posttreatment prognosis has been reported so far between cervical esophageal carcinoma patients treated with surgery and radical chemoradiotherapy. Treatment in these patients should be selected with due consideration given to QOL, etc.

8.6.2 Surgery for Thoracic Esophageal Carcinoma

Thoracic esophageal carcinoma is often accompanied by extensive lymph node metastasis in the cervical, thoracic, and abdominal regions. Therefore, it is common practice in T1b-SM 2, 3, and more advanced stages to carry out a right thoracotomy with esophagectomy and lymphadenectomy of the cervical, mediastinal, and upper abdominal regions. According to the revision of the Japanese Classification of Esophageal Cancer, supraclavicular lymph nodes [#104] are classified as Group 2 to ensure that a three-field lymphadenectomy for D2 resection is performed in the surgical treatment of middle thoracic esophageal carcinoma.

In thoracoscopic surgery, thoracic manipulations are starting to be carried out with the patient in the prone position, whilst previously, thoracic manipulations were predominantly undertaken with the patient in the left lateral decubitus position. This is still at the stage of clinical research. A randomized comparative study to compare the long-term outcomes of thoracoscopic surgery vs. conventional surgery with thoracotomy has been started (JCOG1409 Study), and the results are awaited [3].

8.6.3 Surgery for Carcinoma of the Esophagogastric Junction (Abdominal Esophageal Carcinoma)

There is no consensus on the best treatment and surgical procedures for carcinoma of the esophagogastric junction, particularly for an adenocarcinoma according to Nishi's classification or a Siewert type II carcinoma. Based on a retrospective analysis, the Japanese Gastric Cancer Association–Japan Esophageal Society Joint Working Group proposed the optimal extent of lymph node resection for esophagogastric junction carcinomas measuring ≤4 cm in diameter. Prospective clinical studies to determine the optimal extent of lymph node resection for more advanced tumors are currently in progress.

8.7 Perioperative Management and Clinical Path [2]

Various improvements have been made to the clinical pathway for esophageal cancer at facilities overseas and in Japan in an effort to implement safe perioperative management and reduce complications. However, convincing evidence of their

effect is yet to be presented. The clinical significance of a new concept of perioperative management introduced in recent years, the Enhanced Recovery after Surgery or fast-track surgery, in the surgical resection of the esophagus, has drawn increasing attention.

8.8 Chemotherapy for Unresectable Advanced or Recurrent Esophageal Cancer [2]

Chemotherapy is used as the only systemic therapy modality under various settings in the treatment of esophageal cancer. Chemoradiotherapy and preoperative chemotherapy are used for cStage I to stage IV local esophageal cancer, and also for unresectable advanced or recurrent esophageal cancer. Combination therapy with cisplatin + fluorouracil (5-FU) is used for unresectable advanced and recurrent esophageal cancer, although there is no clear evidence of its ability to prolong survival. Taxanes and other drugs are used as second-line therapy in patients who become refractory to the first-line therapies, but these have only been reported in phase II studies involving a small number of patients, and consequently, should be used carefully.

8.9 Radiotherapy [2]

For definitive radiotherapy, concurrent chemoradiotherapy is recommended. The potential usefulness of preoperative chemoradiotherapy for resectable advanced cancer is being investigated in an ongoing clinical study [4]. Chemoradiotherapy or radiotherapy alone is indicated for patients with unresectable cancer according to the PS. Palliative radiotherapy is considered for cStage IVb esophageal cancer patients presenting with obstruction. A total dose of 60 or 50.4 Gy is often prescribed for chemoradiotherapy, and it is considered that unnecessary prolongation of treatment should be avoided.

8.10 Multidisciplinary Treatment [2]

8.10.1 Pre- and Postoperative Adjuvant Therapy

At present, the standard treatment for cStage II and III thoracic esophageal cancer in Japan is preoperative chemotherapy with cisplatin +5-FU, followed by surgery. In Europe and North America, the standard treatment is preoperative chemoradiotherapy followed by surgery. A randomized comparative study to confirm the superiority of preoperative docetaxel + cisplatin +5-FU (DCF) therapy and that of preoperative chemoradiotherapy (cisplatin +5-FU, radiotherapy at 41.4 Gy) over the currently used preoperative regimen of cisplatin +5-FU (JCOG1109 Study) is ongoing [4].

8.10.2 Chemoradiotherapy

Chemoradiotherapy has been demonstrated to prolongate survival more than radiotherapy alone in patients with locally advanced esophageal cancer. It is considered the standard of care in nonsurgical treatment, and chemoradiotherapy aimed at a complete cure is indicated for cStage 0 to IVa cancer. Although a study comparing chemoradiotherapy and surgery alone in resectable cancer reported that chemoradiotherapy can be expected to have an efficacy equivalent to surgery, no studies have directly compared the two, and it has been surmised that the standard treatment, namely, preoperative chemotherapy + surgical treatment, would achieve better results in patients with cStage II and III cancer. Therefore, chemoradiotherapy is considered as one option in patients who are intolerant to surgery or refuse surgery. It is important to select the appropriate radiation dose, irradiation area, and chemotherapy regimen to develop an optimal treatment strategy, along with considering salvage treatments for residual and recurrent lesions after chemoradiotherapy (Table 8.2).

Table 8.2 Summary of prospective clinical studies of chemoradiotherapy [2]

Study name	Histological type studied	Regimen	Radiation dose (Gy)	Complete response rate (%)	Survival (%)
JCOG9708	cStage Ib SCC	Cisplatin 75 mg/m^2 on days 1 and 29 5-FU 1000 mg/m^2 on days 14 and 29–32	60	87.5	4-year survival 80.5
RTOG85-01	cStage I, II, III SCC, AC	Radiotherapy alone	64	NA	5-year survival 0
		Cisplatin 75 mg/m^2 on days 1 and 29 5-FU 1000 mg/m^2 on days 1–4 and 29–32	50	NA	5-year survival 26
RTOG94-05	cStage I, II, III SCC, AC	Cisplatin 75 mg/m^2 on days 1 and 29 5-FU 1000 mg/m^2 on days 1–4 and 29–32	50.4	NA	2-year survival 31
		Cisplatin 75 mg/m^2 on days 1 and 29 5-FU 1000 mg/m^2 on days 1–4 and 29–32	64.8	NA	2-year survival 40
JCOG9906	cStage II, III SCC	Cisplatin 40 mg/m^2 on days 1, 8, 36 and 43 5-FU 400 mg/m^2 on days 1–5, 8–12, 36–40 and 43–47	60	52.2	3-year survival 44.7
mRTOG	cStage II, III SCC	Cisplatin 75 mg/m^2 on days 1 and 29 5-FU 1000 mg/m^2 on days 1–4 and 29–32	50.4	70.6	3-year survival 63.8

(continued)

Table 8.2 (continued)

Study name	Histological type studied	Regimen	Radiation dose (Gy)	Complete response rate (%)	Survival (%)
JCOG9516	Unresectable local SCC	Cisplatin 70 mg/m^2 on days 1 and 29 5-FU 700 mg/m^2 on days 1–4 and 29–32	60	15	2-year survival 31.5
JCOG0303	Unresectable local SCC	Cisplatin 70 mg/m^2 on days 1 and 29 5-FU 700 mg/m^2 on days 1–4 and 29–32	60	0	2-year survival 25.9
		Cisplatin 4 mg/m^2/5 doses weekly for 6 weeks 5-FU 200 mg/m^2/5 doses weekly for 6 weeks	60	1.4	2-year survival 25.7
KROSG0101/ JROSG021	cStage II, IVA Local SCC	Cisplatin 70 mg/m^2 on days 1 and 29 5-FU 700 mg/m^2 on days 1–5 and 29–33	60	NA	2-year survival 46
		Cisplatin 7 mg/m^2 on days 1–5, 8–12, 29–33 and 36–40 5-FU 250 mg/m^2 on days 1–14 and 29–42	60	NA	2-year survival 44
KDOG0501	Unresectable local SCC	Cisplatin 40 mg/m^2 on days 1, 15, 29 and 43 5-FU 400 mg/m^2 on days 1–5, 15–19, 29–33 and 43–47 Docetaxel 20–40 mg/m^2 on days 1, 15, 29 and 43	61.2	42.1	1-year survival 63.2

SCC squamous cell carcinoma, *AC* adenocarcinoma, *5-FU* 5-fluorouracil, *NA* Not available

8.11 Follow-Up after Treatment of Esophageal Cancer [2]

The purpose of follow-up after treatment of esophageal cancer is (1) to detect and treat recurrence early, and (2) to detect and treat multiple/double cancers early. Furthermore, follow-up is important from the standpoint of systemic management and establishing QOL of the patients after treatment.

The methods of follow-up after esophageal cancer treatment vary depending on the type of initial treatment and on the stage of cancer at the time of the initial treatment. During follow-up, it is important to keep in mind that early detection and treatment of recurrence may allow long-term survival, and pay attention to the potential occurrence of metachronous multiple esophageal cancers and metachronous double cancers in other organs, particularly common cancers, such as gastric and head and neck cancer. A consensus-based follow-up system has to be established and its effectiveness must be verified.

8.12 Treatment of Recurrent Esophageal Cancer [2]

Since there is a variety of initial treatments for esophageal cancer, such as endoscopic treatment, radical surgery, and definitive chemoradiotherapy, treatment for recurrent esophageal cancer needs to be considered individually and according to the type of the initial treatment. Furthermore, treatment varies depending on whether the pattern of recurrence is lymph node recurrence, local recurrence, distant organ recurrence, or mixed recurrence. The general condition of the patient at the time of recurrence also affects the choice of treatment. It is difficult to conduct large-scale clinical studies of the treatment of recurrent esophageal cancer, and there is currently little evidence of the effectiveness of any type of treatment used. While cure may be achieved depending on the type of recurrence, for example, by salvage therapy after radical chemoradiotherapy, treatment is also often used to suppress tumor exacerbation or improve QOL.

8.13 Palliative Care [2]

Palliative care should be provided for cancer at any location. In esophageal cancer patients, dysphagia, malnutrition, and cough due to fistula formation with the airways, and other symptoms often decrease the QOL. Treatment to relieve these symptoms and maintain, or, whenever possible, improve the QOL of the patient, should be considered from the early stages of cancer treatment. However, the method of palliation adopted is mostly determined by the prevailing practice at individual institutions, and further evaluation is required. All medical professionals need to master the knowledge and skills needed to provide effective palliative care.

8.14 Diagnosis and Treatment of Barrett's Esophagus and Barrett's Carcinoma [2]

An esophagus lined with Barrett's mucosa is called Barrett's esophagus [5]. Barrett's mucosa refers to endoscopically recognizable columnar epithelium extending from the stomach to the esophagus and does not require histological confirmation of specific columnar epithelial metaplasia [6–10]. However, identification of the esophagogastric junction is required for the diagnosis of Barrett's mucosa. In principle, it is defined as the endoscopically identifiable distal end of the lower esophageal palisade vessels. Barrett's mucosa is characterized by at least one of the following histological findings: (1) esophageal gland ducts in the mucosa beneath the columnar epithelium or esophageal glands proper in the submucosa; (2) squamous islands within the columnar epithelium; and (3) double muscularis mucosae beneath the columnar epithelium. Barrett's carcinoma is defined as an adenocarcinoma arising from Barrett's mucosa. Early, superficial, and advanced cancers are generally defined in the same manner as for esophageal squamous cell carcinoma, but the deep muscularis mucosae is regarded as the genuine muscularis mucosae. Barrett's

carcinoma is treated in accordance with the treatment principles for esophageal squamous cell carcinoma. Endoscopic resection is currently indicated for lesions extending down to the lamina propria (EP: within the epithelium, noninvasive lesion; SMM [superficial muscularis mucosae]: remaining in the superficial muscularis mucosae; LPM [lamina propria mucosae]: not reaching the deep muscularis mucosae). However, larger numbers of patients need to be diagnosed, treated, and followed-up in order to establish the optimal treatment for these tumors.

8.15 Future Perspectives

Two randomized comparative studies conducted by JCOG are designed to establish new standard treatments for esophageal cancer in the future. One is JCOG 1109, which is a randomized comparative study performed to confirm the superiority of preoperative DCF therapy and that of preoperative chemoradiotherapy (cisplatin +5-FU, radiotherapy of 41.4 Gy) over the currently used preoperative regimen of cisplatin +5-FU [9]. The second study is JCOG 1409, which is a randomized comparative study to assess the long-term outcomes of video-assisted thoracoscopic surgery as compared to conventional standard surgery with thoracotomy [3].

Esophageal cancer is more common in the elderly than in the younger population. The guidelines for selecting treatment based on the patient's condition are only intended for reference. In clinical practice, it is important to make the most effective use of the guidelines while carefully tailoring the treatment to the individual patient.

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