Guidelines for Diagnosis and Treatment in Japan

7

Yuko Kitagawa and Hiroyuki Kuwano

Abstract

Guidelines for diagnosis and treatment of carcinoma of the esophagus were developed to provide recommendations concerning standard treatments for carcinoma of the esophagus, facilitating the daily clinical practice of esophageal carcinoma management (The Japan Esophageal Society, Guidelines for diagnosis and treatments of esophageal cancer, Kanehara Co. Ltd.: Tokyo, 2012). The third edition of guidelines was published in 2012, covering not only therapeutic issues but also diagnostic aspects. English version of the 3rd edition of guidelines is now under preparation. This chapter was described by summarized and modified the contents of draft version of the 3rd edition of guidelines. Comprehensive evaluation of clinical stage and general condition of the patients are critically important because therapeutic strategies are often greatly influenced by patient-specific factors. There is a significant difference of common histological types of esophageal carcinoma between the East and the West. Therefore, Japanese oncologists could not directly introduce guidelines recommended by western countries based on evidence from clinical studies including adenocarcinoma with different clinicopathological factors.

Although multimodal treatment is now mainstay as a therapeutic strategy for esophageal carcinoma in the whole world, a role and survival impact of surgical treatment among multimodal approach is more obvious and significant in Japan. In the 2012 edition of guidelines, preoperative neoadjuvant chemotherapy with cisplatin and 5-FU is recommended as a standard treatment for resectable stage II or III thoracic esophageal carcinoma (2002 UICC classification) based on

Y. Kitagawa (✉)
Department of Surgery, School of Medicine, Keio University, Tokyo, Japan
e-mail: kitagawa@a3.keio.jp

H. Kuwano
Department of General Surgical Science, Gunma University Graduate School of Medicine, Gunma, Japan

© Springer Japan 2015

N. Ando (ed.), *Esophageal Squamous Cell Carcinoma*,
DOI 10.1007/978-4-431-54977-2_7

the results of randomized controlled trial (RCT) conducted by Japan Clinical Oncology Group (JCOG) which is the largest and the most reliable cooperative study group in Japan. On the other hand, neoadjuvant chemoradiation is the standard approach in the West. As summarized in this chapter, the 2012 edition of guidelines has covered wide range of clinical issues in the management of esophageal carcinoma comprehensively. Utilizing accumulated knowledge in the 2012 edition, we should pay attention to make more clear and concise message for users of the guidelines in the future.

Keywords

Algorithm for treatment strategies • Barrett's carcinoma • Double carcinoma • Esophagogastric junction • Guidelines for diagnosis and treatment • Palliative care • Salvage surgery

7.1 Background and History of Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus

There is a significant difference of common histological types of esophageal carcinoma between the East and the West. Although the incidence of esophageal adenocarcinoma is predominant and still increasing in the western countries, esophageal squamous cell carcinoma is common in eastern Asian countries including Japan. Therefore, Japanese oncologists could not directly introduce guidelines recommended by western countries based on evidence from clinical studies including adenocarcinoma with different clinicopathological factors.

Based on these backgrounds, the Committee to Develop Guidelines for Treatment of Carcinoma of the Esophagus set up in the Japanese Society for Esophageal Diseases (presently the Japan Esophageal Society) has launched the first guidelines for treatment of carcinoma of the esophagus in 2002. In the second edition of the guidelines published in 2007, sections for diagnosis, follow-up observation, and palliative care were added to emphasize the importance of pretreatment comprehensive evaluation of risk factors of patients because of the invasiveness of multimodal treatments for esophageal carcinoma. The third edition with updated evidence was published in 2012 and included new chapters such as epidemiology, handling, and evaluation of resected specimens after endoscopic resection, perioperative management, salvage surgery, diagnosis and treatment of Barrett's esophagus and Barrett's carcinoma, treatment of double carcinoma, and guidelines from western countries [1].

In this chapter we would like to summarize the key contents of the 2012 edition avoiding overlapping with other chapters in this book in detail.

7.2 Principles and Structure of the Guidelines

These guidelines are described to present the standard practice for management of esophageal carcinoma mainly based on currently available evidence. These guidelines provide only guidance and do not restrict or prohibit the use of any treatment deviating from those described herein just same as other clinical guidelines.

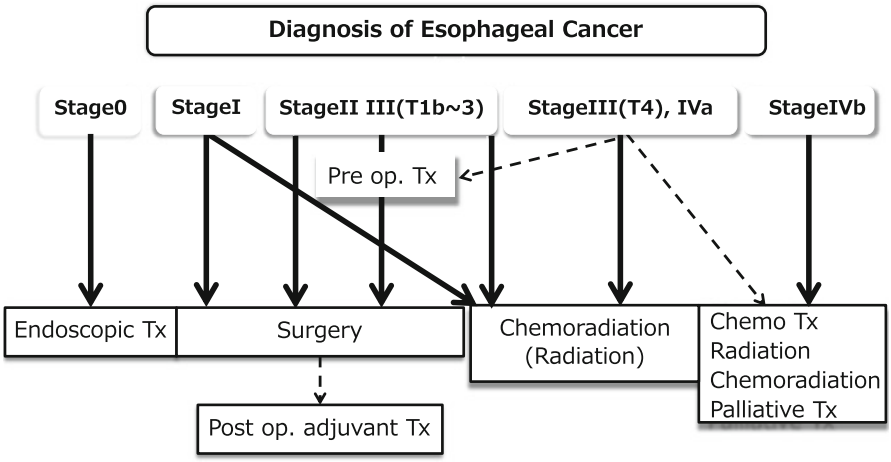

Fig. 7.1 The algorithm for treatment strategies of esophageal carcinoma

In clinical practice, physicians have to explain the details of the treatment, the reasons for indication, possible adverse events, and treatment results to patients to obtain the patients' understanding and informed consent. These guidelines would be helpful to provide current standard for physicians and patients.

"Clinical Questions" are attached to each topic, and the level of recommendation for each topic is indicated according to Minds classification of recommendation grades (A, B, C1, C2, D), together with the recommendation grades of the Committee to Develop Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus.

The algorithm for treatment strategies of esophageal carcinoma is indicated in Fig. 7.1 [1].

7.3 Epidemiology and Current Status of Esophageal Carcinoma in Japan

In Japan, the incidence rate of esophageal carcinoma has been increasing gradually in male, whereas it has been leveling off in female. The mortality has been leveling off in male, but been decreasing in female [2].

The percentage of males is higher with a male-female ratio of about 6:1. Most patients were in their 60s or 70s, accounting for about 68 % of all patients. The most frequent site of primary tumor is the middle thoracic esophagus (51.6 %). Squamous cell carcinoma is the predominant histologic type in Japan [2]. Esophageal carcinoma is also frequently associated with synchronous or metachronous multiple carcinoma.

Alcohol drinking 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. As for 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 in western countries.

The estimated incidence rate in 2004 (crude incidence rate) was 24.4 persons per 100,000 population in male and 4.0 persons per 100,000 population in female [3]. According to a survey of the demographic trends conducted by the Ministry of Health, Labour and Welfare, there were 11.746 deaths from esophageal carcinoma in 2008 (crude mortality rate 9.3 persons per 100,000 population), which accounted for 3.4 % of all deaths from malignant neoplasms [3]. The age-adjusted mortality rate of esophageal carcinoma has been leveling off in men and decreasing in women [3].

7.4 Diagnosis of Esophageal Carcinoma

Clinical stage of esophageal carcinoma is determined by various diagnostic-imaging procedures in terms of the depth of tumor invasion and status of lymph node involvement and distant metastasis. Clinical staging is essential to decide therapeutic strategy for individual patients. Radical esophagectomy with lymph node dissection is one of the most invasive surgical procedures among various types of gastrointestinal surgery. The incidences of postoperative complications after radical esophagectomy and surgery-related mortality still remain higher than those for other procedures [4]. Multimodal approaches including chemoradiotherapy make the invasiveness of treatment much higher and complicated. It should also be noted that elderly patients are more likely to have various comorbidities including hypertension, diabetes mellitus, and hyperlipidemia. Therefore, it is desirable that the functions of vital organs meet certain criteria for implementation of the multimodal therapy.

From these reasons, several tests evaluating performance status, pulmonary function, cardiac function, hepatic function, renal function, glucose tolerance, and central nervous system function are required to decide therapeutic strategy for patients. However, application of therapy based on the patient's general condition should follow comprehensive evaluation [5]. Patients should be informed of the therapeutic strategies based on the assessment of the clinical stage and their general condition.

7.5 Endoscopic Treatment

Endoscopic treatment includes the conventional endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), photodynamic therapy (PDT), argon plasma coagulation therapy, and electromagnetic coagulation therapy.

ESD enable us to perform en bloc resection of an extensive lesion using various types of knives [6].

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 considered as a sufficiently curative treatment for these lesions [7].

Mucosal resection covering 3/4 of the entire circumference is likely to be associated with postoperative stenosis. In cases of superficially spread lesions, deep infiltration may occur in several areas, necessitating careful diagnosis of the depth of invasion.

It is also difficult to accurately determine the depth of invasion of extensive lesions or fragmented specimens. Thus, tissue specimens obtained by en bloc resection are crucial. Handling and pathological evaluation of resected specimens are critical to decide the indication of additional treatments after endoscopic resection. Therefore, precise rules for handling resected specimens are described in the 2012 edition of guidelines [1].

Various complications, including bleeding, esophageal perforation, and serious stenosis, have been reported in association with endoscopic resection. There has been extensive discussion on the need for additional treatments after non-curative endoscopic treatment.

7.6 Surgical Treatment

Although there are various options for therapeutic strategy for esophageal cancer according to the location of the tumor, stage, and general condition of the patient, surgical treatment remains the mainstay of treatment. There are also 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, multimodal treatment including adjuvant therapy, and salvage surgery following definitive chemoradiation.

7.6.1 Surgery for Cervical Esophageal Carcinoma

The anatomical structure and physiological functions of the hypopharynx to the cervical esophagus are complicated. The surgical procedure should be determined carefully because the loss of vocal function by combined laryngectomy largely affects the postoperative QOL of the patient seriously.

7.6.2 Surgery for Thoracic Esophageal Carcinoma

Thoracic esophageal carcinoma is often associated with extensive lymph node involvements in the cervical, thoracic, and abdominal regions. Right thoracotomy

with total extirpation of the thoracoabdominal esophagus and lymph node dissection in all the three regions (cervical, thoracic, and abdominal) is generally carried out in Japan [8, 9]. Intensive lymph node dissection along bilateral recurrent laryngeal nerves is essential and these procedures are the most demanding.

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

Although thoracoscopy- or laparoscopy-assisted esophagectomy and mediastinoscopy- or laparoscopy-assisted transhiatal esophagectomy have been reported as promising surgical procedures, they are still under investigation, in view of the minimal invasiveness and oncological safety. It has been reported that thoracoscopic esophagectomy is comparable to conventional standard thoracotomic surgery in terms of the operating time, amount of blood loss, and number of dissected lymph nodes and is advantageous in terms of providing early recovery from postoperative pain and rapid restoration of vital capacity, as long as it is carried out at institutions with accumulated clinical experience [10, 11].

Although thoracic manipulations were predominantly carried out with the patient in the left lateral decubitus position previously, complete thoracoscopic procedures with the patient in the prone position have been introduced recently in Japan [12].

However, no definitive conclusions have been arrived yet as to the long-term outcomes of this form of minimally invasive esophagectomy as compared with those of conventional standard open esophagectomy with node dissection, and further investigation in randomized controlled trials is required.

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

The 10th edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* defines the esophagogastric junction region as the region within 2 cm above and below the esophagogastric junction and esophagogastric junction carcinoma as carcinoma with its center located within this region [13]. 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 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 gastrectomy via left thoracolaparotomy or serial left thoracoabdominal incisions may be carried out, considering that cervical or upper mediastinal lymph node dissection is of lesser significance. A transhiatal approach to the lower mediastinum without thoracotomy is also reported. In cases of esophagogastric junction carcinoma extending 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 *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*.

7.6.4 Transhiatal Esophagectomy

In transhiatal esophagectomy, the thoracic esophagus is mobilized via the cervical and abdominal approaches without thoracotomy. This technique has been employed mainly in lower thoracic esophageal carcinoma or carcinoma of the esophagogastric junction in western world. RCT conducted in the Netherlands could not show survival benefit of transthoracic esophagectomy for adenocarcinoma on EG junction in comparison with transhiatal esophagectomy [14]. Now, optimal extent of lymph node dissection for carcinoma of the esophagogastric junction is controversial and under investigation.

Currently, the indication of transhiatal esophagectomy has become limited because of the spread of chemoradiotherapy and endoscopic submucosal dissection in Japan.

7.6.5 Perioperative Management and Clinical Path

In recent years, a clinical path for resection and reconstruction of the esophagus has been proposed by various institutions and been applied in clinical practice. However, there have been only limited data from large-scale clinical studies evaluating the usefulness of a clinical path for perioperative management.

Many institutions have introduced nutritional support teams (NST) for perioperative nutritional management of patients with esophageal carcinoma, facilitating early implementation of enteral nutrition [15]. In patients undergoing radical surgery for esophageal carcinoma, it has been considered that early enteral nutrition rather than central venous nutrition is desirable to maintain the postoperative immunity. An enteral feeding tube should be placed during surgery, and a liquid diet should be initiated by 1–3 days after surgery. As an element of perioperative management, steroid administration is useful and recommended in perioperative management [16]. Abstinence from smoking, respiratory physical therapy, and preoperative oral care are generally considered to be important for the prevention of postoperative complications.

7.6.6 Salvage Surgery

The 10th edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* defines salvage surgery as surgery for residual or

recurrent cancer after definitive (chemo)radiotherapy with 50 Gy or more as total irradiation dose [13]. 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 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 [17]. The high incidence of complications and high in-hospital mortality should be taken into account when considering the indications for salvage surgery.

Currently, no treatment other than salvage treatment including endoscopic resection is accepted as curative treatment for residual or recurrent tumor after definitive chemoradiation. However, salvage surgery must be undertaken only with the informed consent of the patients obtained after explaining the risks and long-term outcomes, and thus requires cautious consideration.

7.7 Neoadjuvant Therapy

This is the most significantly updated part in the 2012 edition of guidelines. A number of randomized controlled trials have been conducted in western countries 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 and had been unclear [18]. Therefore, the 2007 edition of guidelines recommended the implementation of adjuvant chemotherapy particularly in patients with positive lymph node metastasis, on the basis of the results of the JCOG (Japan Clinical Oncology Group) 9204 study (1992–1997: postoperative adjuvant chemotherapy with cisplatin + 5-FU vs. surgery alone) [19]. 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 in neoadjuvant group [20]. Based on this finding, neoadjuvant chemotherapy + radical surgery for resectable stage II or III thoracic esophageal carcinoma is recognized as a standard treatment in Japan.

On the other hand, neoadjuvant chemoradiotherapy is a mainstay in the multimodal treatment for esophageal carcinoma in western countries. According to a meta-analysis that addressed surgery preceded by neoadjuvant chemoradiotherapy vs. surgery alone, when the 3-year survival rate was estimated as an endpoint, neoadjuvant chemoradiotherapy (20–45 Gy) in patients with resectable esophageal carcinoma was associated with a significant increase in operation-related mortality within 90 postoperative days, but resulted in a decrease in the local recurrence rate and significant increase of the 3-year survival rate [21].

In meta-analyses carried out so far in the West, the patient population (histologic type, stage, etc.) and chemoradiotherapy protocols have not been consistent. The quality 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 neoadjuvant treatment.

7.8 Postoperative Adjuvant Therapy

7.8.1 Postoperative Chemotherapy

A randomized controlled trial (JCOG9204 study) comparing surgery with and without postoperative chemotherapy (cisplatin + 5-FU, 2 courses) conducted in Japan demonstrated that postoperative chemotherapy resulted in a significant improve in the disease-free survival as compared to surgery alone. However, there was no significant difference in the overall survival [19]. Subgroup analysis 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 recommended only after referring to the results of pathological examination after radical surgery. However, according to the results of the JCOG9907 study, implementation of neoadjuvant chemotherapy has been recognized as a standard treatment as describe above.

7.8.2 Postoperative Radiotherapy

The results of a randomized controlled trial of pre- and postoperative radiotherapy vs. postoperative radiotherapy alone carried out by the JCOG showed that the overall survival rate was significantly higher in postoperative radiotherapy alone group when the analysis was focused only on eligible patients who received treatment according to the protocol. Based on this finding, preventive postoperative irradiation was once in widely used in Japan. On the other hand, in randomized controlled trials in the West 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 been reported to be effective, for 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.

7.9 Chemotherapy

Chemotherapy in the treatment of potentially resectable esophageal carcinoma is usually combined with surgery or radiotherapy in preoperative or postoperative setting. The application of chemotherapy alone is limited to patients with distant metastasis (M1b) or postoperative distant organ recurrence. Currently, 5-FU + cisplatin is the most commonly used regimen for esophageal squamous cell carcinoma in Japan. However, since there is no definitive evidence of prolongation of the survival period, this therapy is regarded as a palliative treatment.

7.9.1 Proven Effective Monotherapy Drugs

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 survival benefit [22]. 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 with some other drugs and a sensitizing effect when combined with radiotherapy. A few reports of these drugs yielding good results when used in combination in the clinical setting have also been published. These are the reasons for the wide use of these two drugs.

7.9.2 Combination Therapy

Although various combination therapies using cisplatin have been employed since this drug was introduced clinically, the currently most commonly used combination regimen is 5-FU + cisplatin [23]. Recently, regimens containing paclitaxel, irinotecan, or gemcitabine have been tried in the West [24], and regimens using nedaplatin or docetaxel have been tried in Japan; no large-scale phase III trials of these regimens have been carried out. Thus, the survival benefit of these regimens over the standard combination of 5-FU + cisplatin has yet to be demonstrated. Currently in Japan, the combination of 5-FU + cisplatin is commonly used as the first-line treatment, following by docetaxel as a second-line treatment. In any event, the effect of the use of chemotherapy alone, regardless of whether it is combination therapy or monotherapy, is limited, and chemotherapy not combined with other treatment modalities is applied only to patients with unresectable metastatic lesions.

Cisplatin, a chemotherapeutic drug that is in wide use, is classified as a highly pro-emetic drug. Guidelines for appropriate use of antiemetic drugs recommend the triple-drug combination of a 5-HT_3 receptor antagonist, corticosteroid, and aprepitant to prevent emesis while using cisplatin. For other drugs, it is necessary to check the risk of emesis against guidelines for appropriate use of antiemetic drugs and to take appropriate prophylactic measures.

7.10 Radiotherapy

Previously, radiotherapy was primarily used for patients who were not suitable candidates for curative surgery or endoscopic resection. However, in recent years, radiotherapy (particularly, chemoradiotherapy) has been widely used for both superficial carcinoma and locally advanced carcinoma, as radical treatment.

Details of the standard radiotherapy used for esophageal carcinoma are described in the Radiotherapy Planning Guidelines 2008 (ed. by Japanese College of Radiology, Japanese Society for Therapeutic Radiology and Oncology, and Japan Radiological Society) [25].

As compared to radiation alone, concurrent chemoradiotherapy significantly increases the survival rate, although radiotherapy administered sequentially after induction chemotherapy does not [26]. Concurrent chemoradiotherapy is indicated for medically fit patients with T1-4N0-3M0 carcinoma (UICC-TNM classification, 2009 edition) and those with locally advanced carcinoma up to metastasis to the supraclavicular lymph nodes (M1) [27]. However, the risk of serious complications such as fistula formation is high in cases of unresectable locally advanced carcinoma (T4).

Because prolongation of the duration of irradiation decreases the local control rate of radiation monotherapy, it is important to complete irradiation using a radical dose (66–68.4 Gy) within 7 weeks. In radical concurrent chemoradiotherapy, use of at least 50 Gy/25 times/5 weeks by the usual fractionation protocol is necessary. The standard radiation dose for concurrent chemoradiotherapy in the USA is 50.4 Gy/28 times [28]. In contrast, in Japan, the standard radiation dose is 60 Gy/30 times/6–8 weeks for concurrent chemoradiotherapy, and its safety has already been demonstrated [29].

A randomized controlled trial carried out in Japan revealed that combined use of external radiation and intraluminal brachytherapy is effective for patients with T1-2 esophageal carcinoma, a relatively early stage of the disease [30]. However, recently chemoradiotherapy is used commonly, and the available evidence is not sufficient to recommend the addition of intraluminal brachytherapy to chemoradiotherapy.

7.11 Chemoradiotherapy

Randomized controlled trials have demonstrated that chemoradiotherapy has a significantly higher survival rate in comparison to radiation alone in patients with esophageal carcinoma; therefore, this therapeutic modality is regarded as the standard therapy for patients with esophageal carcinoma who are not suitable for surgical treatment [31]. Furthermore, definitive chemoradiotherapy is also indicated for resectable T1-3N0-3M0 cases (UICC-TNM classification, 2009 edition), unresectable T4N0-3M0 cases, and cases with metastasis to lymph nodes other than the regional lymph nodes (M1). There are several reports that have demonstrated the absence of any significant difference in the overall survival and

disease-free survival between patients with resectable lesions treated by definitive chemoradiotherapy or by surgery alone [32]. However, in Japan, neoadjuvant chemotherapy followed by surgery is expected to be superior to chemoradiotherapy in patients with stage IB-III disease (UICC-TNM classification, 2009 edition), while equivalence of chemoradiotherapy and surgery is expected in patients with stage IA disease (T1N0M0, UICC-TNM classification, 2009 edition) [33, 20]. Although the chemo-intensity, irradiation doses, and treatment schedules vary among different clinical trials, the most common protocol employed is combined chemotherapy with 5-FU plus cisplatin and concurrent radiotherapy at a total dose of 50–60 Gy. It is necessary to recognize that any reported treatment results are based on the assumption of adequate chemotherapy and radiotherapy.

7.11.1 An Optimal Dose of Irradiation and Regimen of Chemotherapy

A randomized controlled study (RTOG9405/INT0123) carried out by the RTOG that compared chemoradiotherapy using standard-dose (50.4 Gy) and high-dose (64.8 Gy) radiation in patients with T1-4N0-1M0 esophageal carcinoma (corresponding to UICC-TNM classification, 2002 edition) revealed no superiority of high-dose radiation over standard-dose radiation in terms of the median survival time, the 2-year survival rate, and the local control rate and concluded that the standard radiation dose for chemoradiotherapy using a combination of 5-FU plus cisplatin should be 50.4 Gy (1.8 Gy × 28 times) as described above [28]. On the other hand, a radiation dose of 60 Gy has been used commonly in Japan. Although the standard radiation dose has not yet been established in Japan, change to 1.8 Gy/fraction × 28 times (total dose of 50.4 Gy) is now under clinical investigation.

The standard chemotherapy regimen for concurrent chemoradiation is 5-FU + cisplatin. In the RTOG9405/INT0123 study, a course of 4-day continuous intravenous infusion of 5-FU at 1,000 mg/m^2/day plus intravenous cisplatin at 75 mg/m^2 on day 1 was repeated every 4 weeks up to a total of 4 courses (concurrent radiation was used in the initial 2 courses) [28]. In Japan, although use of the 5-FU + cisplatin regimen is variable, a phase II clinical study (JCOG9708) of chemoradiotherapy (5-FU + cisplatin + irradiation of 60 Gy) for cases of stage I esophageal carcinoma (T1N0M0, UICC-TNM classification, 1997 edition [*corresponding to stage IA: T1N0M0 in the 2009 edition]) conducted by JCOG used 2 courses of 4-day continuous intravenous drip infusion of 5-FU at 700 mg/m^2/day plus intravenous drip infusion of cisplatin at 70 mg/m^2 on day 1 repeated every 4 weeks. In the JCOG9708 study, the complete response rate was 87.5 %, the 4-year survival rate was 80.5 %, and the 4-year progression-free survival rate was 68 %, suggesting equivalent results to those of surgery [33]. Currently, a phase III clinical study (JCOG0502) comparing definitive chemoradiotherapy with surgery alone is under investigation. In another phase II JCOG study (JCOG9906) of chemoradiotherapy (5-FU + cisplatin + irradiation of 60 Gy) performed in cases of resectable stage II–III

esophageal carcinoma, a course of 5-day continuous intravenous infusion of 5-FU at 400 mg/m^2/day for 2 weeks plus intravenous cisplatin at 40 mg/m^2 on days 1 and 8 was repeated every 5 weeks for a total of 4 courses (the initial 2 courses were combined with concurrent irradiation) [34]. On the other hand, the introduction of chemotherapy according to the RTOG regimen is now under investigation in Japan.

7.11.2 Adverse Events after Chemoradiotherapy

Major early adverse events associated with chemoradiotherapy include nausea, vomiting, myelosuppression, esophagitis, stomatitis, diarrhea, constipation, and radiation pneumonitis. In particular, radiation pneumonitis may be fatal, and it is desirable to identify factors that may predict the development of this condition. In this regard, it has been suggested that dose-volume histogram (DVH) parameters of irradiation may be useful [35]. On the other hand, late adverse events include radiation epicarditis, radiation pleuritis, pleural effusion, and pericardial effusion. Hypothyroidism may occur in patients who have received radiation in the cervical area, which may also be accompanied by pleural effusion or pericardial effusion, necessitating caution. Although rare, the occurrence of thoracic vertebral compression fracture or radiation myelitis has also been reported. In regard to the late toxic effects, it is considered that the radiation dose to organs at risk such as the lung and heart is important [36]. Use of a 3-dimensional radiation planning technique based on CT images aimed at reducing the toxic effects is now common [37].

As other possible adverse events, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) attributable to cisplatin and leukoencephalopathy attributable to 5-FU have been reported [38]. Early detection and treatment is essential after prompt discontinuation of medication.

7.11.3 Follow-up and Salvage Treatments after Chemoradiotherapy

Contrast-enhanced CT and endoscopic examination are generally used for follow-up observation after radical chemoradiotherapy. Although there is no definitive evidence for the appropriate timing of the efficacy evaluation and follow-up observation, patients are usually examined 3–4 weeks after the end of chemoradiotherapy and at the end of each course of additional chemotherapy, and subsequently every 3 months during the first year and every 4–6 months thereafter.

Salvage treatment using endoscopy or surgery has recently been tried for the treatment of local remnant or recurrent lesions after definitive chemoradiotherapy. As for salvage endoscopic treatment, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and photodynamic therapy (PDT) have been tried, and favorable long-term results have been reported without any serious risk [39]. However, the indications for these treatments and selection of the appropriate treatment method have not yet been adequately evaluated.

7.12 Diagnosis and Treatment of Barrett's Esophagus and Barrett's Carcinoma

Barrett's mucosa refers to columnar epithelial metaplasia that extends from the stomach to the esophagus in a continuous fashion and can be confirmed by endoscopy. Histological confirmation of specific columnar epithelial metaplasia is not required [40]. Histologically, Barrett's mucosa exhibits one of the following features: (1) proper esophageal glands in the columnar epithelial mucosal region; (2) squamous epithelial islets in the columnar epithelium; and (3) double structure of the lamina muscularis mucosae. Barrett's carcinoma is defined as adenocarcinoma arising from Barrett's mucosa. Although the definitions of early, superficial, and advanced carcinomas are the same as those of esophageal carcinoma, the deep-seated lamina muscularis mucosae is handled as the original lamina muscularis mucosae. Treatment of Barrett's carcinoma is in accordance with the treatment of squamous cell carcinoma of the esophagus at the same location in the esophagus [16]. Endoscopic resection is indicated for lesions confined to the lamina propria mucosae (EP, SMM, and LPM). Relative indications are currently under investigation.

7.13 Diagnosis and Treatment of Double Carcinoma (Head and Neck, Stomach)

Patients with esophageal carcinoma are well known to develop carcinoma of other organs, particularly of the upper aerodigestive tract, including head and neck carcinoma, gastric carcinoma, and lung carcinoma [41]. Preoperative examination and postoperative follow-up should be carried out paying attention for the possible presence of double/multiple carcinomas. Therapeutic strategies vary widely according to the type, stage, and time of onset of the double carcinoma. It is important to select the invasive therapeutic procedures in a well-balanced manner, taking into consideration the general condition of the patient, and the prognosis of the esophageal carcinoma and second primary carcinoma.

7.14 Follow-Up Observation After Treatment of Esophageal Carcinoma

The purposes of follow-up observation after treatment of esophageal carcinoma are (1) early detection and early treatment of recurrent disease and (2) early detection and early treatment of metachronous esophageal carcinomas and double carcinomas in other organs. In addition, follow-up observation is important from the point of view of general management of the patient including QOL. The methods used for follow-up observation after treatment of esophageal carcinoma depend on the initial treatment employed and the stage of the disease at the time of the initial treatment. It is important to follow the patient for possible recurrence,

bearing in mind the fact that early detection and early treatment of recurrence may allow prolongation of life. It is also important to exercise caution for the development of metachronous multiple esophageal carcinoma or metachronous multiple carcinoma of another organ, such as commonly seen in cases of gastric carcinoma or head and neck carcinoma. Establishment of an effective follow-up protocol based on consensus and verification of its efficacy is required.

7.15 Treatment of Recurrent Esophageal Carcinoma

The initial treatment for esophageal carcinoma is selected from a wide variety of options, including endoscopic treatment, radical surgery, and definitive chemoradiotherapy. Therefore, treatment of recurrent esophageal carcinoma should be determined individually according to the modality selected for the initial treatment. In addition, treatment of recurrent carcinoma varies according to the type of recurrence. The general condition of the patient at the time of recurrence also should be considered to decide therapeutic strategy for recurrent diseases. Recurrence is not rare even in patients in whom the initial treatment has been successfully and curatively implemented. Large-scale clinical trials to clarify issues related to treatment of recurrence are difficult to conduct. Recurrent carcinoma may be curable depending on the type of recurrence, and aggressive treatment may be desirable. Treatment, however, is often aimed at suppression of tumor progression and improvement of the QOL.

Although local recurrence after endoscopic mucosal resection most often occurs within 1 year after the initial treatment, it may even occur after 2–3 years in some cases. In recent years, the indications for endoscopic resection for local recurrence after initial endoscopic treatment have been extended from the aspect of clinical research [42].

The survival rate of patients with recurrence after radical esophagectomy is extremely poor, with the median survival time from the diagnosis of recurrence reported to be 5–10 months. However, long-surviving cases with complete response by aggressive treatment have been reported [43].

Treatment strategy of recurrence after radical esophagectomy is selected on the basis of the site, type, and extent of recurrence. Treatment also depends on the general condition of the patient at the time of recurrence, whether the recurrence is within or outside the scope of surgical manipulation and whether or not the patient has received radiation pre- or postoperatively. Therefore, there are few data on the treatment results from a large number of patients with various clinical conditions.

7.16 Palliative Care

Although palliative care should be provided commonly in all fields of cancer care, a decrease of the patient's QOL is particularly common and serious in patients with esophageal carcinoma, caused by the difficulty in swallowing, malnutrition, and/or

cough due to fistula formation, and consideration of procedures for symptom relief and maintenance and improvement of the QOL is required from the initial phase of treatment. However, selection of therapeutic strategies currently depends on the physician's preference. Further assessment of these issues would be required in the future. All medical staffs should acquire the knowledge and skills involved in the field of palliative care.

Palliative care requires a team approach that includes not only the physicians in charge and nurses but also psycho-oncologists, pharmacists, social workers, and physical therapists. It has been pointed out that in particular, the role of a specialist nurse as a team leader is important in the palliative care of patients with esophageal carcinoma [44].

Because the patients and their families have to live with the fear of sudden death or sudden change of the clinical condition, provision of psychological support and mental care to both is indispensable. To treat carcinoma-related pain, procedures described in the *Clinical Guideline for Pharmacological Management of Cancer Pain* issued by the Japanese Society for Palliative Medicine are recommended.

7.17 Therapeutic Outcomes and Recommended Guidelines in the West

In western countries, adenocarcinoma originating in the lower thoracic esophagus is predominant [45]. Therefore, it is not so simple to compare the therapeutic strategies and their outcomes in the West to those in Japan.

A simple comparison of endoscopic treatments in Japan and western countries is precluded by differences in the indication criteria. There are no well-established guidelines for endoscopic treatment in the West.

As for the surgical procedures, transhiatal esophagectomy is relatively common in the West, reflecting the increase in the frequency of lower thoracic esophageal adenocarcinoma. The extent of lymph node dissection is often restricted to the middle and lower mediastinal area. Although there are no significant differences between Japan and the West in terms of the surgical indications in relation to the disease stage, the surgical outcomes are relatively poor in the West. A summary of randomized controlled trials of surgical treatment for esophageal carcinoma from western countries and the Japanese national registry data was indicated in Table 7.1.

The clinical significance of neoadjuvant chemotherapy is controversial in western countries [18]. US Guidelines recommend neoadjuvant chemotherapy only to carcinomas of the lower esophagus and the esophagogastric junction and recommend neoadjuvant chemoradiotherapy for others. In the UK and Scotland, guidelines recommend 2 courses of neoadjuvant chemotherapy for cases with resectable esophageal carcinoma, but do not recommend neoadjuvant chemoradiotherapy.

Table 7.1 Summary of randomized controlled trials of surgical treatment for esophageal carcinoma and the Japanese national registry data

Author	Year	Target[a]	Treatment[b]	No. of cases	Histologic type S/A/O[c]	Resected cases	Treatment-related deaths	2-year survival (%)	3-year survival (%)	5-year survival (%)	MST (month)[d]
Bosset	1989–1995	Stage I–III, excluding T3N1	S	139	134/0/5	137	5 (3.6 %)	About 42	About 35	About 25	18.6
			CR + S	143	139/0/4	138	17 + 1 (12.6 %)	About 48	About 35	About 25	18.6
Kelsen	1990–1995	Stage I–III	S	234	110/124	217	13 (5.6 %)	35	19	7	16.1
			C + S	233	103/120	171	5 + 10 (6.4 %)	31	18	6	14.9
MRCOCWP	1992–1998	Resectable cases	S	402	124/268/10	386	40 (10 %)	34	About 25	About 15	13.3
			C + S	400	123/265/12	361	36 + 8 (11 %)	43	About 32	About 25	16.8
Bedenne	1993–2000	T3N0-1M0 (Stage II–III) ditto CR cases	CR + S	129	115/14	107	12 (9.3 %)	39.9			16.4
			CR + C	130	115/15	1	1 (0.8 %)	35.4			14.9
Burmiester	1994–2000	Stage I–III, excluding T4	S	128	50/78/0	110	6 (5.4 %)	39.8	28.1	14.8	19.3
			CR + S	128	45/80/3	105	5 (4.7 %)	45.3	32.8	16.4	22.2
Stahl	1994–2001	T3-4N0-1M0	S	86	86/0	51	11 (12.8 %)	39.9	31.3		16.4
			CR + S	86	86/0	0	3 (3.5 %)	35.4	24.4		14.9

(continued)

Table 7.1 (continued)

Author	Year	Target[a]	Treatment[b]	No. of cases	Histologic type S/A/O[c]	Resected cases	Treatment-related deaths	2-year survival (%)	3-year survival (%)	5-year survival (%)	MST (month)[d]
Japan Esophageal Society	2002	All resected cases	S + α			1518	41 (4.5 %)[e]	62.2	53.6	44.1	About 44
		Stage I	S + α			361		88.5	82.7	71.2	About 53
		Stage IIA	S + α			290		66.6	60.7	49.2	About 46
		Stage IIB	S + α			211		64.9	55.7	42.8	About 20
		Stage III	S + α			494		44.4	33.7	27.7	

[a]Clinical TNM classification
[b]*S* Surgery, *C* Chemotherapy, *R* Radiotherapy, *+α* Regardless of whether or not adjuvant therapy was given
[c]*S* Squamous cell carcinoma, *A* Adenocarcinoma, *O* Other histologic type
[d]*MST* Median survival time
[e]In-hospital mortality (including direct surgical death and death from recurrence)

In regard to nonsurgical treatment, as chemoradiotherapy has been shown to yield better results than radiation monotherapy, guidelines published from Europe and North America also recommend chemoradiotherapy. The protocol recommended by the Radiation Therapy Oncology Group that is commonly employed in Europe and North America consists of irradiation using the multiple field technique at a total dose of 50.4 Gy administered in 28 fractions, with the exposure field covering the region within 5 cm above and below the tumor. This regimen is based on the results of a randomized controlled trial that found no difference in the survival period between standard-dose (50.4 Gy) and high-dose (64.8 Gy) chemoradiotherapy, and reached a negative conclusion about the usefulness of increasing the total radiation dose. The NCCN guidelines specify that the radiation dose should be 50–50.4 Gy.

7.18 Future Perspective

In the 2012 edition of guidelines, neoadjuvant chemotherapy + radical surgery for resectable stage II or III thoracic esophageal carcinoma is recommended as a standard treatment in Japan based on JCOG 9907 study. This is the representative achievement by well-organized clinical trial in Japan to establish novel standard treatment for esophageal carcinoma. However, the subgroup analysis of this study has shown survival benefit in stage III to be insufficient. Therefore, development of more effective preoperative treatment is required. Now, JCOG is conducting a 3-arm randomized controlled trial comparing preoperative chemoradiation therapy with cisplatin plus 5-fluorouracil and preoperative chemotherapy with docetaxel in addition to cisplatin and 5-fluorouracil (DCF) to standard preoperative treatment with cisplatin plus 5-fluorouracil (JCOG1109). This study should be a significant milestone for surgical oncology in examining the possible additive efficacy and safety of preoperative chemoradiation which is the current standard in the West.

Although an evidence-based approach to describe clinical guidelines is ideal and required, it takes long period with sufficient patient population. In Japan, the National Clinical Database (NCD) has been established since 2011 and clinical information of surgically treated patients was accumulated. In the next version of guidelines, analyzed data from NCD would contribute to make recommendations at least in a part.

As summarized in this chapter, the 2012 edition of guidelines has covered a wide range of clinical issues in the management of esophageal carcinoma comprehensively. Utilizing accumulated knowledge in the 2012 edition, we should pay attention to make more clear and concise message for users of the guidelines in the future.

References

1. The Japan Esophageal Society (eds) (2012) Guidelines for diagnosis and treatments of esophageal cancer, 3rd edn. Kanehara Co. Ltd., Tokyo. (Japanese)
2. Ozawa S, Tachimori Y, Baba H et al (2010) Comprehensive registry of esophageal cancer in Japan, 2002. Esophagus 7(1):7–22
3. Center for Cancer Control and Information Services, National Cancer Center, Japan (2013) http://ganjoho.jp/professional/statistics/index.html. (Japanese)
4. Birkmeyer JD, Stukel TA, Siewers AE et al (2003) Surgeon volume and operative mortality in the United States. N Engl J Med 349(22):2117–2127
5. Haga Y, Beppu T, Doi K et al (1997) Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. Crit Care Med 25(12):1994–2000
6. Oyama T, Tomori A, Hotta K et al (2005) Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 3(7 Suppl 1):S67–S70
7. Shimizu Y, Tsukagoshi H, Fujita M et al (2002) Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. Gastrointest Endosc 56(3):387–390
8. Akiyama H, Tsurumaru M, Udagawa H et al (1994) Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 220(3):364–372, discussion 372–373
9. Ando N, Ozawa S, Kitagawa Y et al (2000) Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg 232 (2):225–232
10. Luketich JD, Alvelo-Rivera M, Buenaventura PO et al (2003) Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 238(4):486–494, discussion 494–495
11. Osugi H, Takemura M, Higashino M et al (2003) A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. Br J Surg 90(1):108–113
12. Palanivelu C, Prakash A, Senthilkumar R et al (2006) Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position–experience of 130 patients. J Am Coll Surg 203(1):7–16
13. Japanese Society for Esophageal Disease (eds) (2008) Japanese classification of esophageal cancer, 10th edn. Kanehara Co. Ltd., Tokyo. (Japanese)
14. Hulscher JB, van Sandick JW, de Boer AG et al (2002) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347(21):1662–1669
15. Aiko S, Yoshizumi Y, Tsuwano S et al (2005) The effects of immediate enteral feeding with a formula containing high levels of omega-3 fatty acids in patients after surgery for esophageal cancer. JPEN J Parenter Enteral Nutr 29(3):141–147
16. Sato N, Koeda K, Ikeda K et al (2002) Randomized study of the benefits of preoperative corticosteroid administration on the postoperative morbidity and cytokine response in patients undergoing surgery for esophageal cancer. Ann Surg 236(2):184–190
17. Nakamura T, Hayashi K, Ota M et al (2004) Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. Am J Surg 188(3):261–266
18. Malthaner RA, Wong RK, Rumble RB et al (2004) Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and metaanalysis. BMC Med 2:35
19. Ando N, Iizuka T, Ide H et al (2003) Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study–JCOG9204. J Clin Oncol 21(24):4592–4596
20. Ando N, Kato H, Igaki H et al (2012) A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 19(1):68–74

21. Gebski V, Burmeister B, Smithers BM et al (2007) Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8(3):226–234
22. Ajani JA (1994) Contributions of chemotherapy in the treatment of carcinoma of the esophagus: results and commentary. Semin Oncol 21(4):474–482
23. Iizuka T, Kakegawa T, Ide H et al (1992) Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 22(3):172–176
24. Ilson DH, Ajani J, Bhalla K et al (1998) Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16(5):1826–1834
25. Nemoto K et al (2008) Esophageal cancer. In: Japanese College of Radiology, Japanese Society Therapeutic radiology and Oncology, Japan Radiological Society (eds) Guidelines for clinical radiotherapy treatment planning. Medical Kyoiku Kenkyusha, Tokyo, pp 157–163. Japanese. http://www.kkr-smc.com/rad/guideline/2008/
26. Wong RK, Malthaner RA, Zuraw L et al (2003) Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. Int J Radiat Oncol Biol Phys 55(4):930–942
27. Nishimura Y, Suzuki M, Nakamatsu K et al (2002) Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys 53(1):134–139
28. Minsky BD, Pajak TF, Ginsberg RJ et al (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20(5):1167–1174
29. Ishida K, Ando N, Yamamoto S et al (2004) Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol 34(10):615–619
30. Okawa T, Tanaka M, Kita-Okawa M et al (1995) Superficial esophageal cancer: multicenter analysis of results of definitive radiation therapy in Japan. Radiology 196(1):271–274
31. Herskovic A, Martz K, Al-Sarraf M et al (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326 (24):1593–1598
32. Ariga H, Nemoto K, Miyazaki S et al (2009) Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 75(2):348–356
33. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 39(10):638–643
34. Kato K, Muro K, Minashi K et al (2011) Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys 81(3):684–690
35. Asakura H, Hashimoto T, Zenda S et al (2010) Analysis of dose-volume histogram parameters for radiation pneumonitis after definitive concurrent chemoradiotherapy for esophageal cancer. Radiother Oncol 95(2):240–244
36. Kumekawa Y, Kaneko K, Ito H et al (2006) Late toxicity in complete response cases after definitive chemoradiotherapy for esophageal squamous cell carcinoma. J Gastroenterol 41 (5):425–432
37. Morota M, Gomi K, Kozuka T et al (2009) Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys 75 (1):122–128
38. Otsuka F, Hayashi Y, Ogura T et al (1996) Syndrome of inappropriate secretion of antidiuretic hormone following intra-thoracic cisplatin. Intern Med 35(4):290–294

39. Yano T, Muto M, Hattori S et al (2008) Long-term results of salvage endoscopic mucosal resection in patients with local failure after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Endoscopy 40(9):717–721
40. Sharma P, Dent J, Armstrong D et al (2006) The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 131 (5):1392–1399
41. Muto M, Nakane M, Hitomi Y et al (2002) Association between aldehyde dehydrogenase gene polymorphisms and the phenomenon of field cancerization in patients with head and neck cancer. Carcinogenesis 23(10):1759–1765
42. Katada C, Muto M, Momma K et al (2007) Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae–a multicenter retrospective cohort study. Endoscopy 39(9):779–783
43. Toh Y, Oki E, Minami K et al (2010) Follow-up and recurrence after a curative esophagectomy for patients with esophageal cancer: the first indicators for recurrence and their prognostic values. Esophagus 7:37–43
44. Viklund P, Wengström Y, Lagergren J (2006) Supportive care for patients with oesophageal and other upper gastrointestinal cancers: The role of a specialist nurse in the team. Eur J Oncol Nurs 10(5):353–363
45. Trivers KF, Sabatino SA, Stewart SL (2008) Trends in esophageal cancer incidence by histology, United States, 1998-2003. Int J Cancer 123(6):1422–1428