Esophageal Squamous Cell Carcinoma

Diagnosis and Treatment

Nobutoshi Ando
Editor

Second Edition

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Preface

Esophageal cancer is the eighth most common cancer worldwide, with 572,000 new cases (3.2% of the total) estimated in 2018, and the sixth most common cause of death from cancer, with 508,000 deaths (5.3% of the total). In recent years there has been an upward trend in the incidence rate of this cancer; however, the background characteristics of esophageal cancer treatment are markedly different between Asian and Western countries. In tumor histology, squamous cell carcinoma associated with smoking and alcohol consumption is overwhelmingly prevalent in Asia, whereas adenocarcinoma associated with Barrett's metaplasia is markedly prevalent in the West. In Asia, especially in Japan, the key persons who play important roles in the management of esophageal cancer patients have been surgeons; in the West those roles have been filled by medical and radiation oncologists as well as surgeons. The concept of esophageal cancer surgery varies with surgeons in different countries. Considering these East–West differences in esophageal cancer treatment, the currently available results of Western evidence should not be considered directly applicable to esophageal cancer in Asia. Asian-originated expertise should be offered to the world.

Five years have passed since publication of the first edition of this title. Much of the original text is still useful; however, many new ideas and developments in diagnosis and treatment of esophageal squamous cell carcinoma (ESCC) have arisen during recent years, especially in minimally invasive surgery, chemotherapy, chemoradiotherapy, and immunotherapy including immune-checkpoint inhibitors and other modalities. In this book the authors present original knowledge and expertise in terms of treatment of ESCC from Japan as well as other Asian countries. As the second edition contains a wide spectrum of current information and addresses topics surrounding treatment of patients with ESCC, it is highly relevant to Asian physicians and researchers as well as to their counterparts in the West.

I would like to express my sincere thanks to the authors for producing their chapters in a timely fashion. Finally, my thanks go to Ms. Saki Kasai, senior editor; Ms. Makie Kambara, senior editorial assistant; and Mr. Rakesh Jotheeswaran, project coordinator; at Springer Nature for their efforts to help me make this book a reality.

Yokohama, Japan — Nobutoshi Ando

Contents

Epidemiology of Esophageal Squamous Cell Carcinoma

1

Taiki Yamaji and Shoichiro Tsugane

Abstract

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer. More than 80% of esophageal cancer cases and deaths occur in developing countries, and approximately 80–90% are squamous cell carcinomas in the high-incidence regions. The incidence rates of esophageal cancer show wide variation internationally. It has been shown to be more common among men than women in general. Of note, it is approximately five times more common among males in Japan. Both incidence and mortality are on the rise in number since 1960 due to the aging of Japanese population, while age-adjusted mortality rates are decreasing in both males and females. Convincing risk factors for esophageal squamous carcinoma include tobacco smoking and alcohol consumption, while suggestive protective factors are fruit and vegetable intake. Likewise, intake of high-temperature beverages and foods show high probability of increasing risk through heat damage in the esophagus. Approximately 88% of male esophageal cancer (52% for females) in Japan is thought to have been avoidable by lifestyle improvements such as refraining from smoking of tobacco and alcohol use, while maintaining sufficient fruit and vegetable intake.

Keywords

Esophageal cancer · Time trend · Risk factor · Tobacco smoking · Alcohol consumption

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1.1 Esophageal Cancer in the World and Japan

1.1.1 Esophageal Cancer in the World: Burden, Geographical Difference, and Trends

1.1.1.1 Global Burden and Geographical Difference (Global Cancer Observatory, https://gco.iarc.fr/)

Esophageal cancer is the eighth most common cancer worldwide, with 572,000 new cases (3.2% of the total) estimated in 2018, and the sixth most common cause of death from cancer with 508,600 deaths (5.3% of the total). These figures encompass both adenocarcinoma and squamous cell carcinoma types. More than 80% of esophageal cancer cases and deaths occur in developing countries.

The incidence rates of esophageal cancer vary internationally more than tenfold in men (Age-standardized incidence rate to the World population (ASR) 17.9 per 100,000 in Eastern Asia compared to 1.6 in Western Africa/ Central America), and almost 15-fold in women (ASR 7.1 per 100,000 in Eastern Africa compared to 0.46 in Central America) (Fig. 1.1). The incidence rate in China is one of the highest, (19.7 in men and 8.2 in women), while also relatively high in Japan (9.3 in men and 1.9 in women).

Esophageal cancer is more common among men than women in general. Of note, it is approximately five times more common among men in Japan and 13 times more common among men in Korea. These differences in sex ratio may suggest different etiologies by region. In Japan and Korea, tobacco smoking and alcohol drinking are assumed to be major causes of esophageal cancer and the predominant incidence rate among males is associated with a much higher prevalence of smoking of tobacco and alcohol use among men versus women. In China and Southern Africa, an important risk factor, in addition to tobacco smoking and alcohol drinking, is thought to be nutrient deficiency such as vitamins and micronutrients, which occurs equally in both men and women. However, the apparent reason for geographic variations is unspecified.

1.1.1.2 Histological Type [1]

In those high-incidence regions that provide information on histological type, approximately 80–90% are squamous cell carcinomas (Fig. 1.2). This is in contrast to some lower-risk populations, such as Caucasian Americans and Europeans, where adenocarcinomas are predominant. For example, in the United States, SEER (Non-Hispanic White) indicated ASR 5.5 in men where 75% of cases are coded as adenocarcinoma as opposed to 17% squamous cell carcinoma. In contrast, Japan, Nagasaki indicated ASR 11.6 in men where only 6% as adenocarcinoma as opposed to 91% squamous cell carcinoma.

1.1.2 Esophageal Cancer in Japan (Cancer Information Service, https://ganjoho.jp)

In 2017, 9580 men and 1988 women died from esophageal cancer, representing 4.3% and 1.3% of total cancer death in men and women, respectively. Mortality

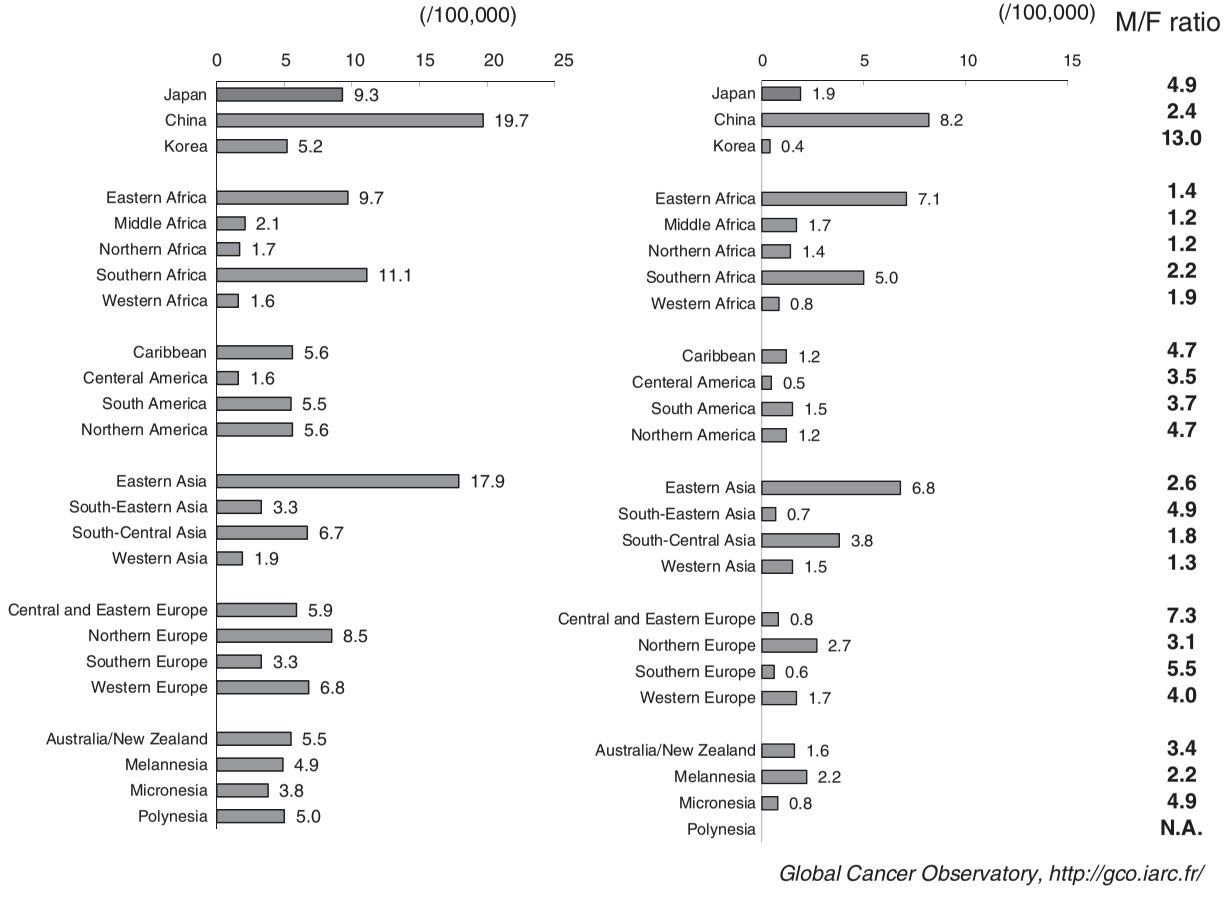
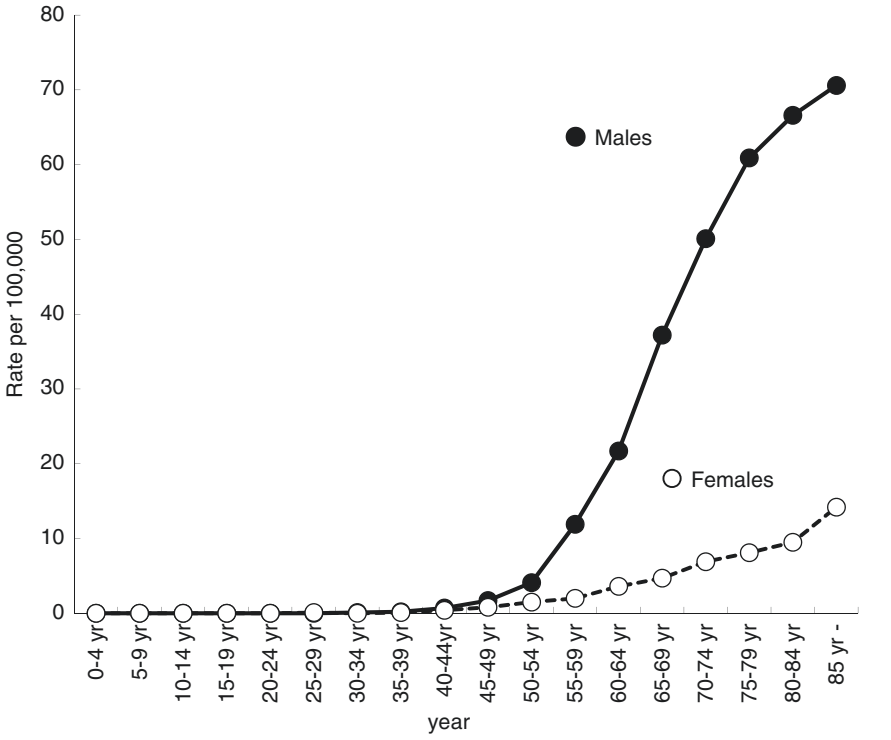


Fig. 1.1 Age-standardized incidence rate (World population) of esophageal cancer in the world (2018)

Fig. 1.2 Esophageal cancer—histological distribution percentage (2008–2012) [1]

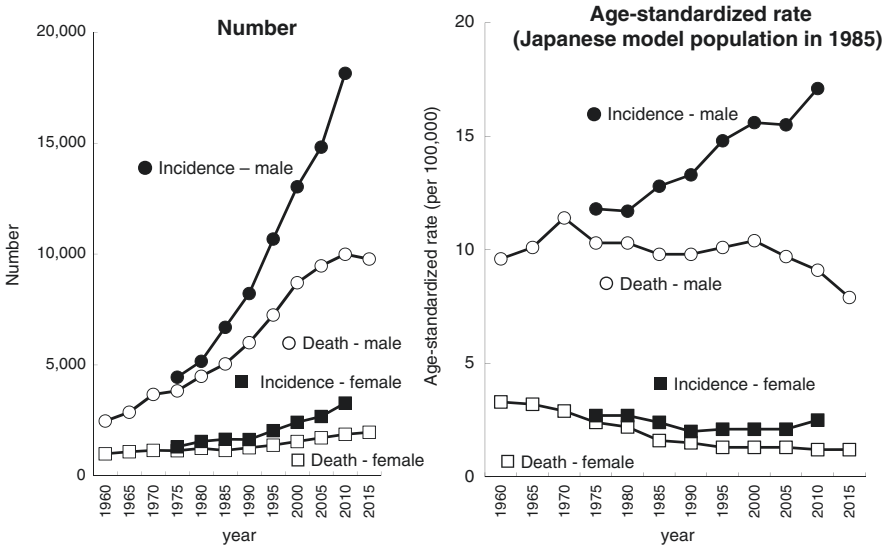
rates increased with age rapidly after 40 years (Fig. 1.3). The mortality rate of esophageal cancer is estimated to be 0.55% in men and 0.09% in women up to 75 years, increasing to 1.06% in men and 0.20% in women over a lifetime. Regarding incidence, 19,233 men and 3551 women were estimated to be diagnosed with esophageal cancer in 2014 and probability of esophageal cancer diagnosis was 1.36% in men and 0.23% in women up to 75 years, increasing to 2.28% in men and 0.46% in women for lifetime. Five-year survival rates were 36.0% in men and 43.9% in women who were diagnosed with esophageal cancer in 2006–2008 based on the population-based cancer registry.

Both incidence and mortality are observed to have increased in number since 1960 due to the aging of Japanese population (Fig. 1.4, Left), while age-standardized mortality rates tended to have been decreasing in both males and females (Fig. 1.4, Right). Histological distribution trends were analyzed using 8 population-based cancer registries with high level of reliability from 1993 to 2001 [2] and the Miyagi Prefectural Cancer Registry from 2000 to 2010 (Fig. 1.5). Squamous cell carcinoma was the predominant type of esophageal cancer in Japan, and a remarkable increase in adenocarcinoma was not observed until 2010. Disparity in the



Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

Fig. 1.3 Age-specific mortality rate of esophageal cancer in Japan (2017)



Source: Vital statistics and Estimates from the population-based cancer registry

Fig. 1.4 Time trends in the incidence and mortality of esophageal cancer in Japan

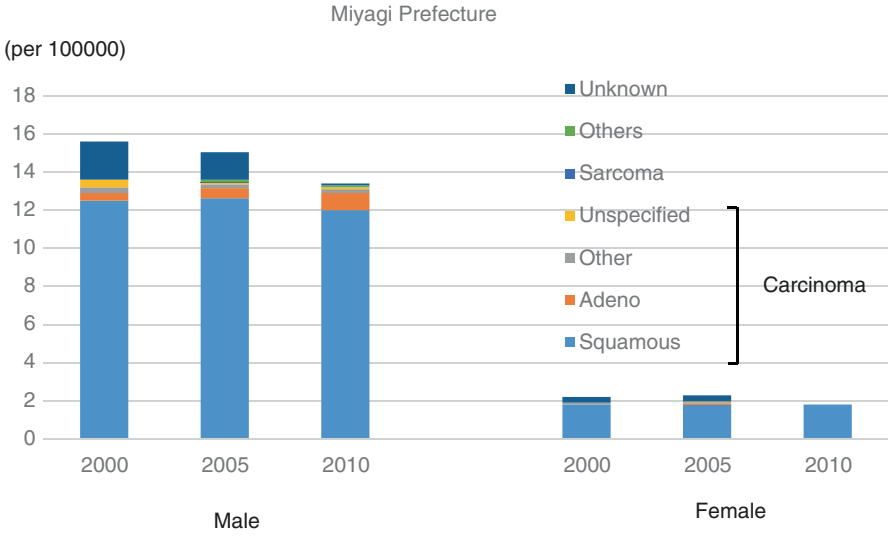


Fig. 1.5 Time trends in the age-standardized (world population) incidence of esophageal cancer by histological subtype in Japan [1]

classification of esophageal and gastric cardia adenocarcinoma may have led to underestimation of esophageal adenocarcinoma incidence.

An increased trend of adenocarcinoma of the esophago–gastric junction was observed among patients who had underwent surgery for advanced gastric adenocarcinoma in the National Cancer Center Hospital in Tokyo, from 2.3% in 1962–1965 to 10.0% in 2001–2005, however, the proportion of Siewert Type I (defined as adenocarcinoma of the distal esophagus) had remained very rare (approximately 1% among adenocarcinoma of the esophago–gastric junction) [3]. Since this finding was confined to operative cases with advanced gastric adenocarcinoma, the proportion of Siewert's type I tumors may have been underestimated.

1.2 Risk Factors

Established risk and protective factors for esophageal cancer are listed according to the level of certainty (Table 1.1). Tobacco smoking and alcohol consumption are convincing risk factors for esophageal cancer, especially squamous cell carcinoma [4–6]. Acetaldehyde associated with the consumption of alcoholic beverages has also been judged as a convincing risk factor for esophageal squamous cell carcinoma [7]. Very hot beverages including, but not limited to, mate, a traditional herbal beverage consumed in parts of South America, has been identified as a probable cause of esophageal squamous cell carcinoma [8]. Physical activity and vegetables may prevent both types of esophageal cancer [6].

Table 1.1 Established risk and protective factors for esophageal cancer

Evidence	Risk factors	Protective factors
Convincing	Tobacco smoking[a] Alcohol consumption[bc](squamous cell carcinoma) Acetaldehyde associated with consumption of alcoholic beverages[d] Body fatness [c](adenocarcinoma)	–
Probable	Mate[c] (squamous cell carcinoma) Very hot beverages including, but not limited to, mate[e](squamous cell carcinoma)	–
Limited suggestive	Processed meat[c] (squamous cell carcinoma)	Physical activity[c] Vegetables[c] Fruit[c] (squamous cell carcinoma)

[a]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 83 (2003) [4]
[b]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 96 (2007) [5]
[c]World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018.
Diet, nutrition, physical activity, and esophageal cancer [6]. Available at dietandcancerreport.org
[d]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 100E (2012) [7]
[e]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 116 (2018) [8]

1.2.1 Tobacco Smoking and Alcohol Consumption

The main risk factors for esophageal squamous cell carcinoma (ESCC) are tobacco smoking and alcohol consumption, which in individual studies have been found to account for 75–90% of cases [9]. The risk of esophageal cancer increases rapidly with the amount of both tobacco smoking and alcohol consumption, with no evidence of any threshold effect for either.

In Japan, four cohort studies and 11 case-control studies tested the association between tobacco smoking and esophageal cancer risk [10]. With the exception of three case-control studies, all cohort studies and eight case-control studies showed strong positive associations and dose–response relationships. Meta-analysis of 12 studies indicated that the summary estimate for current and former smokers relative to lifetime nonsmokers was 3.73 (95% confidence interval (CI), 2.16–6.43) and 2.21 (95% CI, 1.60–3.06), respectively. Similarly, four cohort studies and nine case-control studies tested the association between alcohol consumption and esophageal cancer [11]. With the exception of three case-control studies, all cohort studies and six case-control studies showed strong positive associations and dose–response relationships. Meta-analysis of 12 studies indicated that the summary estimate for ever drinkers relative to never drinkers, was 3.30 (95% CI, 2.30–4.74) and 3.36 (95% CI, 1.66–6.78) across the four studies adjusted for smoking.

We examined the effect of tobacco smoking and alcohol consumption on ESCC in a large-scale population-based cohort study [12] (Fig. 1.6). Forty-four thousand nine hundred seventy middle-aged and older Japanese men were followed up for up to 14 years, and a total of 215 cases of ESCC were newly diagnosed among participants during this time. Regular alcohol consumers of 150–299 and ≥300 g ethanol

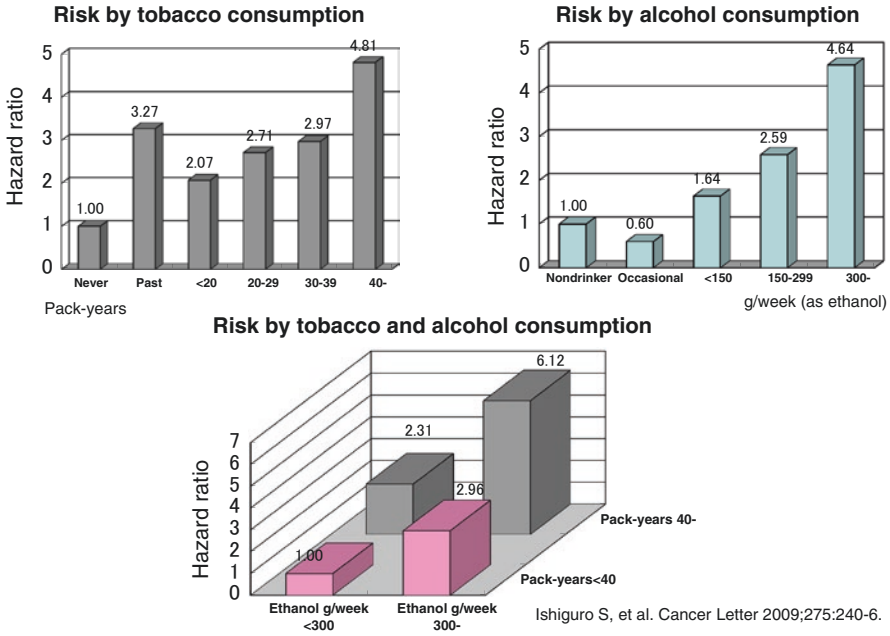


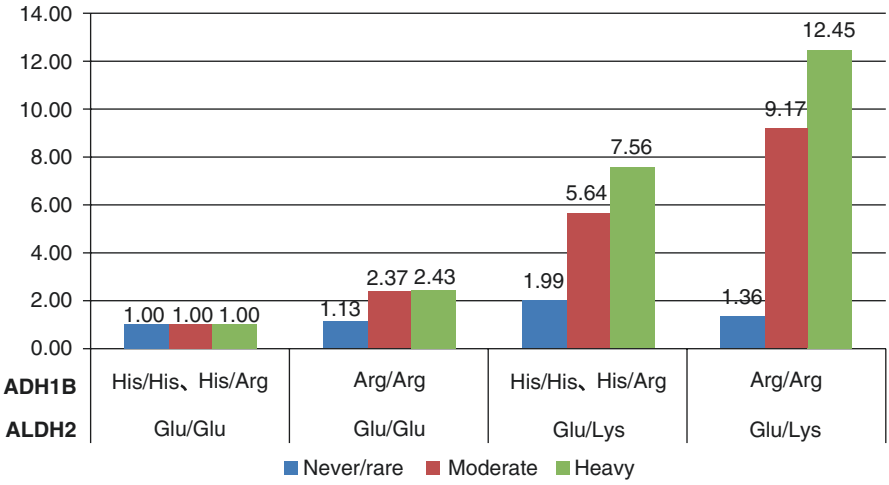
Fig. 1.6 Smoking of tobacco, alcohol consumption, and subsequent risk of esophageal squamous cell carcinoma in men—JPHC Study—[12]

per week had a 2.59—(95% CI, 1.57–4.29) and 4.64-fold (95% CI, 2.88–7.48) higher risk of ESCC than nondrinkers, respectively (p for trend = 0.001). Past smokers, as well as current smokers, had a higher risk than never smokers. Among current smokers, pack-year and cigarettes per day were also associated with the incidence of ESCC, with risk increasing in a dose-dependent manner (p for trend = 0.001). With regard to the interaction of tobacco smoking (pack-years: <40 vs. ≥40) and alcohol consumption (ethanol g/weeks: <300 vs. ≥300), no statistically significant results were identified (p for interaction = 0.70).

1.2.2 Genetic Susceptibility to Tobacco Smoking and Alcohol Drinking

Regarding genetic susceptibility, esophageal cancer does not exhibit any strong familial aggregation and genetic studies of esophageal cancer have instead focused on genes such as cytochrome P 450 (CYP), glutathione-S-transferase (GST), alcohol dehydrogenase (ADH), and acetaldehyde dehydrogenase (ALDH), which metabolize suspected tobacco- and alcohol-derived carcinogens. No consistent findings have emerged for tobacco-derived pathways, although the majority of studies have been limited in sample size.

Conversely, strongly significant effect modifications have been observed with ADH1B and ALDH2 genotype. Among those with ADH1B who have the His allele,



Yang SJ et al. World Journal of Gastroenterology 2010;16:4210-4220.

Fig. 1.7 Risk of esophageal cancer associated with combinations of alcohol dehydrogenase (ADH)-1B and aldehyde dehydrogenase (ALDH)-2 genotypes [13]

approximately 95% of Japanese and 10–20% of Caucasians show a rapid increase of blood acetaldehyde due to the high alcohol metabolizing activity of the ADH1B enzyme, compared with those who have the Arg allele. Among those with ALDH2 Lys allele, approximately 50% of Japanese and <10% of Caucasians, show a higher concentration of blood acetaldehyde after alcohol consumption compared to those who have the ALDH Glu allele, due to the low catalytic activity of ALDH2 enzyme.

A meta-analysis of 19 case-control studies was conducted to evaluate the effect of alcohol consumption modification by ADH1B and ALDH2 polymorphism, to the risk of esophageal cancer [13]. The majority of the studies focused on ESCC and were conducted in Asian populations. A meta-analysis of 13 case-control studies on ADH1B showed that ADH1B∗1/∗1 (Arg/Arg) increased the risk of esophageal cancer among never/rare [odds ratio (OR) = 1.56 (95% CI, 0.93–2.61)], moderate [2.71 (95% CI, 1.37–5.35)], and heavy alcohol consumers [3.22 (95% CI, 2.27–4.57)], compared with ADH1B∗2/∗2 (His/His). Similarly, a meta-analysis of 18 case-control studies on ALDH2 showed that ALDH2∗1/∗2 (Glu/Lys) increased the risk among never/rare [1.28 (95% CI, 0.91–1.80)], moderate [3.12 (95% CI, 1.95–5.01)], and heavy [7.12 (95% CI, 4.67–10.86)] alcohol consumers, compared with ALDH2∗1∗1 (Glu/Glu). The analysis of combined effects of ADH1B and ALDH2 genotypes showed that ADH1B∗1/∗1 plus ALDH2∗1/∗2 was associated with the highest risk of esophageal cancer among heavy drinkers [12.45 (2.9–53.46)] (Fig. 1.7), but no significant increase in risk was seen among never/rare drinkers. Recent large-scale genome-wide gene–alcohol consumption interaction analysis of ESCC in China also showed that drinkers with both of the ADH1B and ALDH2 risk alleles experienced a fourfold increase in risk compared to drinkers without the aforementioned risk alleles, while no increased risk was observed among nondrinkers [14].

Numerous experimental studies have also reported that acetaldehyde has a cytotoxic, genotoxic, mutagenic, and clastogenic potential. In fact, acetaldehyde can cause DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells in vitro. In addition, acetaldehyde can induce DNA–protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents in vivo [5].

Based on sufficient evidence both in humans and in experimental animals for the carcinogenicity of acetaldehyde, the International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans has concluded that acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans and causes cancers of the esophagus [7].

1.2.3 Fruit and Vegetable Intake

Although the tobacco smoking and alcohol consumption are the primary lifestyle risk factors for esophageal cancer, dietary factors are also likely to be important [6]. Intake of fruits and vegetables appears to have a protective effect. Although the relationship for particular types of fruits and vegetables is unclear, citrus fruits, and green leafy vegetables appear to possess greater effects than other families of fruits and vegetables.

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan evaluated that fruit and vegetable intake probably prevent esophageal cancer based on a systematic review of epidemiologic evidence among the Japanese population (unpublished data, available at http://epi.ncc.go.jp/can_prev/). Seven studies, two cohort and five case-control studies, tested the association of esophageal cancer prevention with fruit intake and all studies showed a significant protective effect. Eight studies, three cohort and five case-control studies, tested the association with vegetable intake as a whole, and green-yellow or cruciferous vegetables. The majority of studies showed a significant relationship between the intake of such vegetables and esophageal cancer prevention. However, residual confounding by tobacco smoking and alcohol consumption cannot be ruled out even after adjusting for and stratified by these variables. Both of the variables are strong risk factors for esophageal cancer as well as correlate with the amount of fruit and vegetable intake. The casual association between such lifestyle behaviors and esophageal cancer should be investigated further.

We examined the effect of fruit and vegetable intake on ESCC in a large-scale population-based cohort study [15] (Fig. 1.8). An increase in consumption of total fruits and vegetables by 100 grams per day (g/day) was associated with an 11% decrease in the incidence of ESCC (95% CI, 1–21%). In particular, a higher intake of cruciferous vegetables was associated with a significant decrease in risk (hazard ratio per 100 g/day: 0.44; 95% CI, 0.23–0.82). Stratified analyses revealed that the beneficial effect of fruits and vegetables was observed regardless of smoking of tobacco and alcohol use; however, it did not completely offset the harmful effects of smoking of tobacco and alcohol consumption.

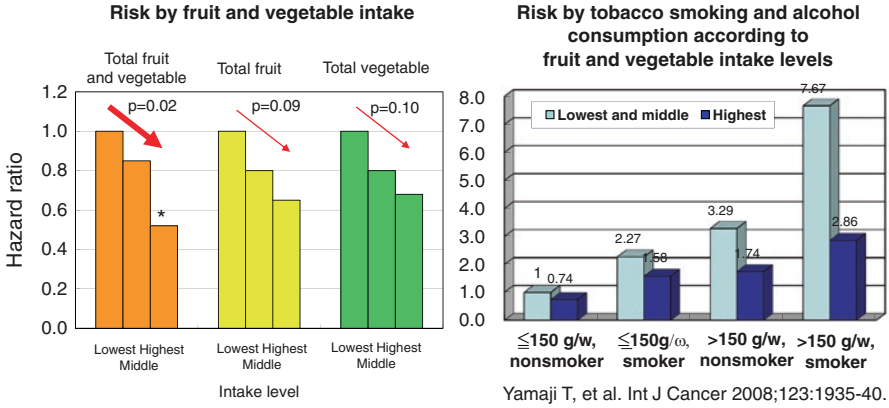


Fig. 1.8 Fruit, vegetable intake, and subsequent risk of esophageal squamous cell carcinoma—JPHC Study—[15]

1.2.4 Mate and Hot Beverages

Regarding the consumption of hot mate, a traditional herbal beverage consumed in parts of Southern Brazil, Argentina, and Uruguay, there appears to be a strong association with consumption of the beverage and development of esophageal squamous cell carcinoma. Meta-analysis of five case-control studies, all adjusted for smoking, showed a summary estimate of 1.16 (95%CI, 1.07–1.25) per cup/day. Mate is typically consumed very hot through a metal straw. This can cause burns in the esophagus and repeated damage of this nature can lead to cancer, although some have proposed that this may also be a result of chemical carcinogenesis from the composition of mate.

In addition to hot mate, there are several studies that show high-temperature drinks and foods are associated with the increased risk of esophageal squamous cell carcinoma, although some studies have not adequately adjusted for tobacco smoking and alcohol consumption. A recent systematic review has reported an overall OR of 2.28 (95% CI, 1.62–3.22) for the association between the consumption of hot beverages (other than mate) or food and risk of squamous cell carcinoma [16]. When the analysis was repeated in 11 studies with adjustment for smoking and alcohol drinking, the OR for all hot beverages (including mate) and food was 2.39 (95% CI, 1.71–3.22). Of interest, there was no statistically significant association with esophageal adenocarcinoma according to the meta-analysis of four studies (OR, 0.78; 95% CI, 0.45–1.35). Based on limited but suggestive evidence not only in humans for the carcinogenicity of drinking very hot beverages but also in experimental animals for the carcinogenicity of very hot water at 65 °C or above, the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans has concluded that drinking very hot beverages at temperatures above 65 °C is probably carcinogenic to humans and may lead to squamous cell carcinoma of the esophagus [8].

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan evaluated that intake of hot tea and food is likely to have increased the risk of esophageal cancer based on the systematic review of epidemiologic evidence (two cohort and three case-control studies) among the Japanese population (unpublished data, available at http://epi.ncc.go.jp/can_prev/). A cohort study showed an increased risk of 1.6 fold (95% CI, 1.2–2.0) for the consumption of hot tea (drinking green tea at high temperatures) in comparison with not-hot tea (drinking green tea at moderate temperatures) [17], while another cohort showed that green tea consumption was significantly associated with an increased risk of esophageal cancer [18].

1.2.5 Causes of Esophageal Cancer in Japan

We estimated the population attributable fractions (PAFs) of esophageal cancer attributable to known risk factors from relative risks derived primarily from Japanese pooled analyses (e.g., tobacco smoking), the JPHC study (e.g., alcohol consumption, fruits, and vegetables), and the prevalence of exposure in the period around 1990 [19]. PAFs of tobacco smoking, alcohol consumption, insufficient intake of vegetables and fruit were estimated to be 58.9%, 53.8%, 10.4%, and 10.9% in men and 14.7%, 28.9%, 10.4%, and 10.9% in women. Thus, 88% of esophageal cancer in men was estimated to be avoidable by lifestyle improvement such as quitting smoking, refraining from too much alcohol consumption, and sufficient intake of fruits and vegetables, after considering combined effect of risk factors. The corresponding statistic for women was estimated at 52%. Therefore, esophageal cancer can be regarded as a lifestyle-related disease.

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Pathology of Esophageal Squamous Cell Carcinoma

2

Yukihiro Nakanishi

Abstract

Superficial esophageal cancers are classified into three major types including type 0-I (superficial and protruding type including type 0-Ip (pedunculated) and type 0-Is (sessile)), type 0-II (superficial and flat type including type 0-IIa (slightly elevated), type 0-IIb (flat) and type 0-IIc (slightly depressed)), and type 0-III (superficial and excavated type)). More protruded (type 0-I) or more depressed (type 0-III) lesions are associated with deeper invasion in the submucosa. All submucosal cancers have a substantial risk of lymph node metastases. Consequently, intraepithelial carcinoma or carcinoma invading the lamina propria is generally treated by endoscopic resection. Advanced esophageal cancers are classified into four types including type 1 (protruding type), type 2 (ulcerative and localized type), type 3 (ulcerative and infiltrative type), and type 4 (diffusely infiltrative type). The two most frequent types are Types 2 and 3. Iodine staining method is useful not only for optimal visualization of esophageal squamous mucosal abnormalities but also for detecting groups at high risk of multicentric cancer in the upper aerodigestive tract. Clinicopathologic prognostic factors include TNM stage, lymph node metastasis, tumor invasion depth, lympho-vascular invasion, intramural metastasis, tumor vascularity, infiltrating growth pattern, inflammatory response, tumor budding, tumor nest configuration, pathologic response to neoadjuvant therapy, completeness of surgical resection, and the patient's general health condition. The subtypes of esophageal squamous cell carcinoma include basaloid squamous cell carcinoma,

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carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma, adenosquamous carcinoma, and verrucous carcinoma.

Keywords

Esophagus · Squamous cell carcinoma · Pathology · Macroscopic features · Microscopic features

2.1 Definitions

According to both the Japanese Classification of Esophageal Cancer [1–3] and the World Health Organization (WHO) Classification of Tumors of the Digestive System [4], esophageal squamous cell carcinoma (ESCC), superficial esophageal cancer, early esophageal cancer, and advanced esophageal cancer are defined as follows: *Squamous cell carcinoma*: A malignant epithelial tumor with squamous cell differentiation, microscopically characterized by keratinocyte-like cells with intercellular bridges and/or keratinization and/or stratified squamous differentiation [1–4]. *Early esophageal cancer*: an esophageal cancer whose invasion is limited to the mucosa irrespective of the presence or absence of lymph node or distant organ metastasis [1–4]. *Superficial esophageal cancer*: An esophageal cancer whose invasion is limited to the mucosa or the submucosa irrespective of the presence or absence of lymph node or distant organ metastasis [1–4]. *Advanced esophageal cancer*: an esophageal cancer whose invasion extends into or beyond the muscularis propria irrespective of the presence or absence of regional lymph node or distant organ metastasis [1–4].

Mucosal cancer and submucosal cancer are subclassified into three categories, respectively, based on the depth of cancer invasion [1–3]: "T1a-*EP (M1)*" for intraepithelial carcinomas/carcinoma in situ, "T1a-*LPM (M2)*" for tumors invading the lamina propria, "T1a-*MM (M3)*" for tumors in contact with or invading the muscularis mucosae, "T1b-*SM1*" for tumors invading the upper third of the submucosa, "T1b-*SM2*" for tumors invading the middle third of the submucosa, and "T1b-*SM3*" for tumors invading the lower third of the submucosa (Fig. 2.1). In the endoscopically resected specimens "T1b-*SM1*" is defined as a carcinoma that infiltrates the submucosa up to 200 μm below the lower border of the muscularis mucosae; and "T1b-*SM2*" is defined as a carcinoma that infiltrates more than a depth of 200 μm in the submucosa [1–3], since the distance of the submucosal layer is unknown in endoscopically resected specimens. Superficial esophageal squamous cell carcinoma is classified into *Tis* (high-grade dysplasia/carcinoma in situ), *T1a* (tumor invades the lamina propria or muscularis mucosae) or *T1b* (tumor invades the submucosa) by the American Joint Committee on Cancer (AJCC) [5] and the Union for International Cancer Control (UICC) TNM Classification [6].

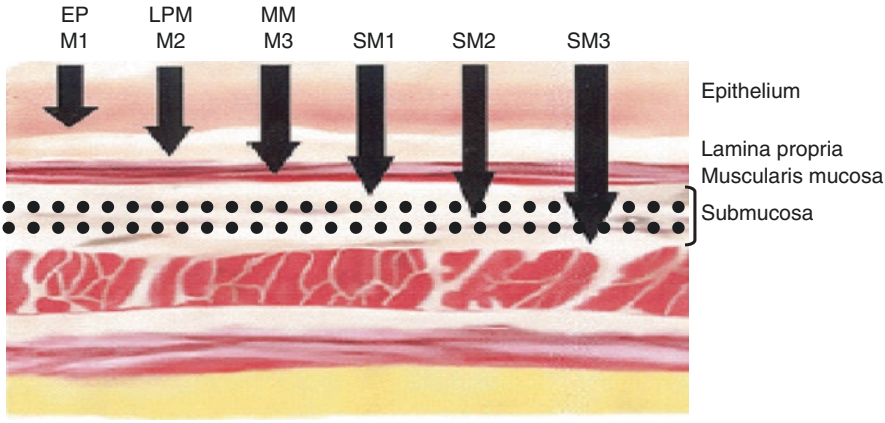

Fig. 2.1 Classification of the depth of invasion

2.2 Macroscopic Features

2.2.1 Handling of Specimens

The proper handling of a specimen by a competent pathologist is the most important step to render an accurate diagnosis and to generate a comprehensive pathology report that will help determine patient management and prognosis. The resected esophagus should be opened along the longitudinal line on the opposite side of the deepest cancer invasion. The specimens should be stretched out to approximate the length to what is in the patient's body, and should be pinned out on a flat board with the mucosal side up before fixation. After applying iodine solution on the esophageal mucosa, superficial esophageal cancers should be sectioned in its entirety [1–3]. The endoscopically resected specimens should be sectioned serially at 2–3 mm intervals parallel to a line that includes the closest part between the margin of the specimen and of the neoplasm, so that both lateral and vertical margins are assessed [1–3] (Fig. 2.2a, b). Spraying the mucosa with iodine solution is the standard method for gross examination of the specimens with abnormal squamous lesions. Iodine staining method significantly improves delineation of abnormal squamous lesions (Fig. 2.3a, b). Glycogen in the normal squamous epithelium interacts with iodine and shows a brown color. Whereas in abnormal squamous mucosa, including areas of squamous intraepithelial neoplasia/dysplasia, squamous cell carcinoma, atrophy, epidermization/epidermal metaplasia, parakeratosis and esophagitis, the squamous epithelium often loses glycogen, and remains partially or totally unstained [7–12]. Glandular mucosa, including normal gastric mucosa, gastric heterotopia, and Barrett's mucosa, also appears unstained [13]. Foci of glycogenic acanthosis appear overstained [8].

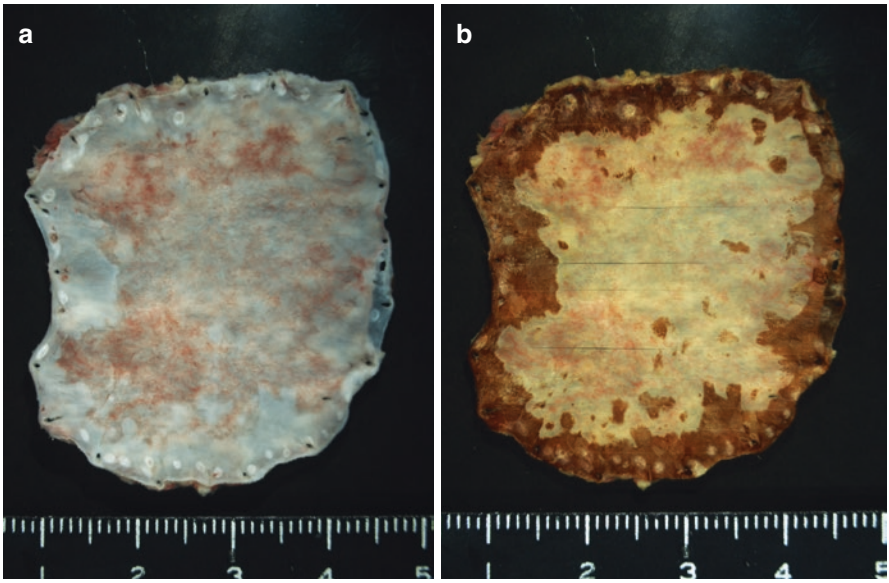

Fig. 2.2 (**a**): A 0-IIc type superficial esophageal carcinoma resected by endoscopic submucosal dissection (ESD). (Courtesy of Dr. Tateishi (Department of Pathology, The University of Tokyo, Tokyo, Japan) and Dr. Hishima (Department of Pathology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan)). (**b**): After fixation and iodine staining, the specimen was sectioned serially at 2–3 mm intervals

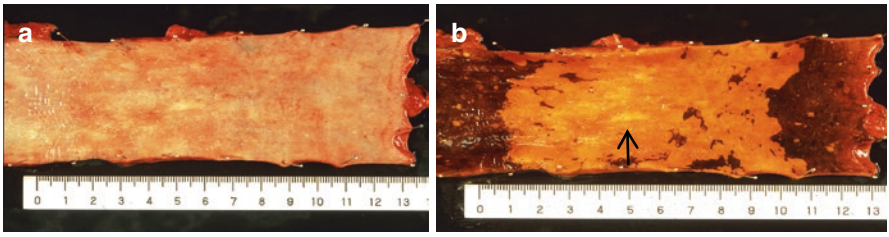

Fig. 2.3 (**a**) A shallow depressed lesion (0-IIc type) resected by esophagectomy. (**b**) Iodine staining clearly revealed an unstained area. This 0-IIc type cancer showed submucosal invasion in the whitish discolored area (arrow). This cancer can be also classified as a superficial spreading type which is defined as a superficial esophageal cancer with more than 5 cm superficial spreading

2.2.2 General Features

Squamous cell carcinoma can occur in any portion of the esophagus but is most common in the middle third [14]. Superficial esophageal cancers appear as pink-tan or gray-white, shallow depressions, plaque-like thickenings, or elevations of mucosa. Advanced esophageal cancers grow into exophytic or ulcerated masses, and obstruct the lumen.

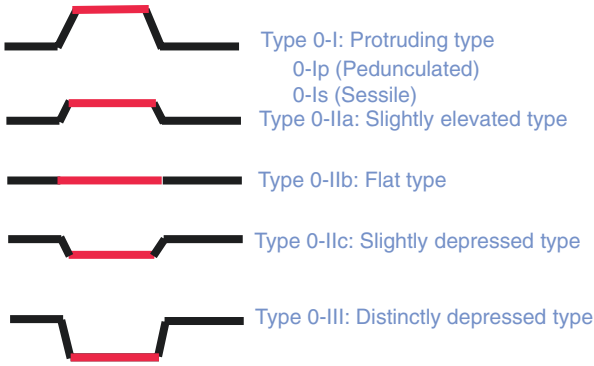

Fig. 2.4 Macroscopic classification of superficial esophageal cancer

2.2.3 Superficial Esophageal Cancer

Superficial esophageal cancers are classified as subtypes of type 0, and further subclassified into three major types including type 0-I, type 0-II, and type 0-III, based on the presence of elevation and depression [1–4] (Fig. 2.4). Type 0-I is a superficial and protruding type, and includes type 0-Ip, which is pedunculated, and type 0-Is, which is sessile. Type 0-II is a superficial and flat type, and is further subclassified into three subtypes, namely, type 0-IIa, which is slightly elevated up to 1 mm in height, type 0-IIb, which is completely flat, and type 0-IIc, which is slightly depressed (Fig. 2.3a, b). Type 0-III is a superficial and excavated type.

A 0-Ip type cancer is most typically seen in esophageal carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma (Fig. 2.5) [15]. A 0-IIc type cancer is most common in superficial esophageal cancers [16, 17]. A 0-IIb type cancer is almost always mucosal cancer, whereas a 0-IIc type cancer consists of squamous cell carcinoma showing a wide range of cancer invasion depth from mucosal to submucosal invasion [17, 18]. More protruded (type 0-I) or more depressed (type 0-III) lesions are associated with deeper invasion in the submucosa [17, 18]. This applies particularly when the lesion has a mixed morphologic pattern. Many superficial esophageal cancers show combined types, e.g., a shallow depression and a sessile protrusion, 0-IIc + "0-Is" (Fig. 2.6). In the combined types, the type occupying the larger area should be described first, followed by the next type according to the Japanese Classification of Esophageal Cancer [1–3]. Double quotation marks (" ") are placed around the macroscopic tumor type that has the deepest tumor invasion.

2.2.4 Advanced Esophageal Cancer

Advanced esophageal cancers are classified into four types [1–4]. A type 1 tumor is defined as a protruding tumor (Fig. 2.7a). A type 2 tumor is defined as an ulcerative and localized tumor characterized by an ulcerated tumor with a sharply demarcated raised border (Fig. 2.7b). A type 3 tumor is defined as an ulcerative and infiltrative tumor characterized also by an ulcerated tumor, but shows infiltration into the

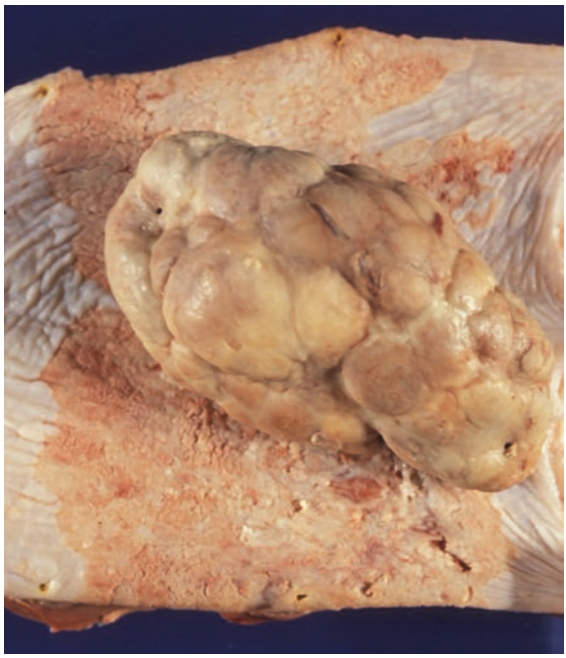

Fig. 2.5 A typical 0-Ip type superficial esophageal cancer (carcinosarcoma), which appears as a large polypoid tumor with a smooth surface and prominent lobulation. The stalk is very small and narrow, and not visible in this picture. Erosive superficial squamous cell carcinoma surrounding the polypoid tumor is also noted

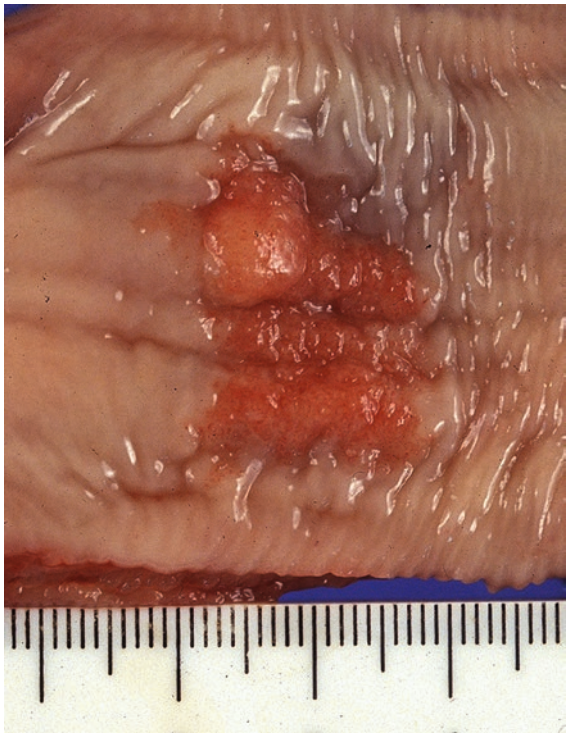

Fig. 2.6 A 0-IIc + "Is" type superficial esophageal cancer. The sessile portion (0-Is type) showed a deepest cancer invasion

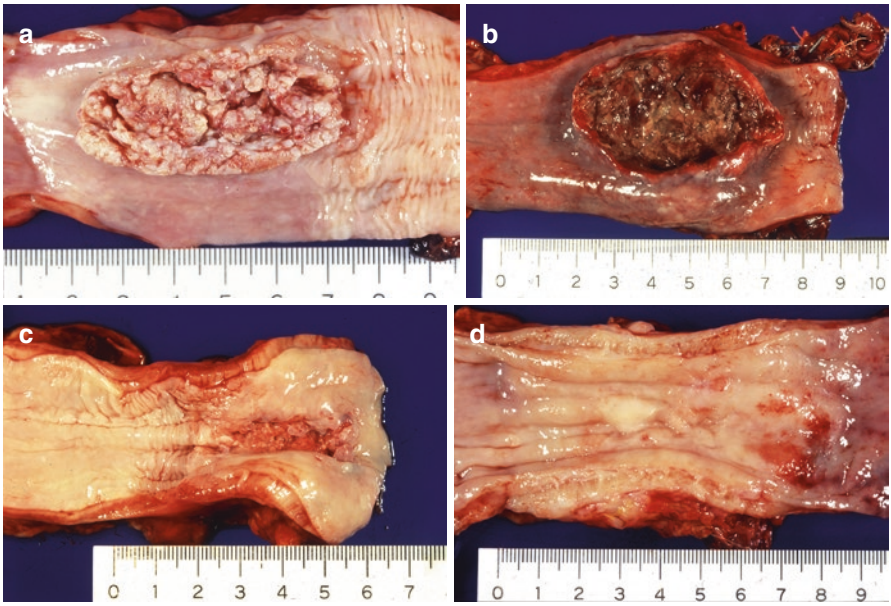

Fig. 2.7 (**a**) A type 1 tumor (a protruding tumor) (**b**) A type 2 tumor (an ulcerated tumor with a sharply demarcated raised border) (**c**): A type 3 tumor (an ulcerated tumor with an unclear border) (**d**): A type 4 tumor (a diffusely infiltrating tumor)

surrounding wall, making the tumor border rather unclear (Fig. 2.7c). A type 4 tumor is defined as a diffusely infiltrating tumor in which ulceration or protrusion is usually not a prominent feature (Fig. 2.7d). A type 5 tumor is defined as a tumor that cannot be classified into any of these types. Superficial esophageal cancer can be found at the periphery of an advanced tumor. When an advanced type is mixed with a superficial type, the advanced type is described first without placing double quotation marks [1–3]. The macroscopic classification of ESCC can be applied to all esophageal adenocarcinomas.

The two most frequent types of advanced cancer are Types 2 and 3 [16]. A protruding type tumor is usually found to be a carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma, squamous cell carcinoma, or malignant melanoma [15]. A protruding type tumor, especially showing a subepithelial growth, is usually composed of a small cell neuroendocrine carcinoma, basaloid squamous cell carcinoma, or lymphoepithelioma-like carcinoma/esophageal carcinoma with lymphoid stroma [19].

2.2.5 Multicentric Squamous Cell Carcinoma (Field Cancerization)

The presence of other cancers synchronously or metachronously associated with esophageal carcinoma is relatively common. According to the Comprehensive

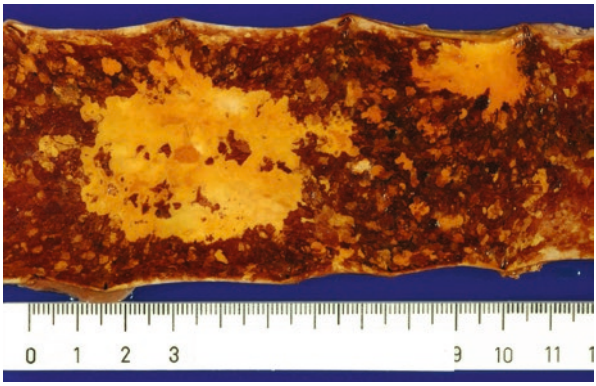

Fig. 2.8 Iodine staining clearly reveals two unstained cancerous areas. In addition to the cancerous areas, there are multiple small iodine-unstained areas in the mucosa surrounding the cancerous lesions

Registry of Esophageal Cancer in Japan, up to 47% of patients with esophageal carcinoma had synchronous or metachronous carcinoma at other sites including the stomach, head and neck, colon/rectum, and lung in this descending order [16]. Up to 20% of patients with ESCC had synchronous or metachronous multiple primary cancers of the esophagus [16]. ESCC, especially multicentric squamous cell carcinoma, is often associated with multiple small areas unstained with Lugol's iodine observed in the mucosa surrounding esophageal carcinomas (Fig. 2.8) [10]. Patients with head and neck squamous cell carcinoma, who have a high risk for ESCC, are also reported to be frequently associated with multiple iodine unstained areas [10, 20, 21]. The incidence of multiple small areas unstained with iodine has been reported to be associated with the development of multiple primary cancers in the upper aerodigestive tract and the patients' tobacco and alcohol consumption [10]. Also, male sex and the presence of aldehyde dehydrogenase type 2 (ALDH2)-2 allele has been reported to be associated with an increased risk for multiple Lugol-voiding lesions of the esophageal mucosa in patients with ESCC [22]. Therefore, iodine staining method is useful not only for optimal visualization of esophageal squamous mucosal abnormalities but also for detecting groups at high risk of multicentric cancer in the upper aerodigestive tract. Although staining the esophageal mucosa with iodine solution has not often been used by endoscopists and pathologists in North America, iodine staining is the sine qua non diagnostic method for ESCC.

2.2.6 Risk Factors

Risk factors include alcohol [23], tobacco use [23], history of upper aerodigestive tract cancer [23], Achalasia (Fig. 2.9) [23], severe caustic injury [23], frequent consumption of very hot beverages [24], prior radiation therapy to the mediastinum [25], non-epidermolytic palmoplantar keratoderma (tylosis) [23], Plummer-Vinson syndrome [26], nutrition (e.g., nitrosamines in pickled or moldy foods) [27], celiac sprue [28], and lichen planus [29].

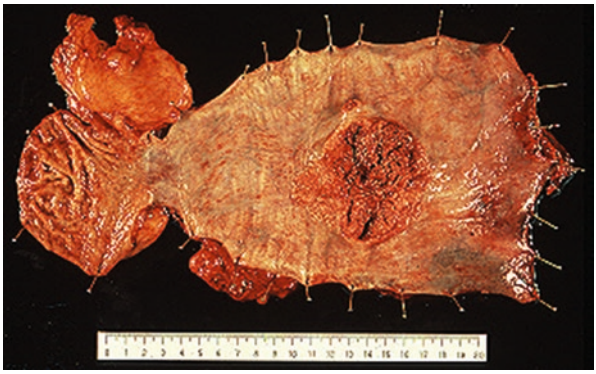

Fig. 2.9 A type 2 advanced esophageal cancer developed in Achalasia

2.3 Microscopic Features

The histology of ESCC is similar to that of squamous cell carcinoma of other sites with enlarged, often vesicular nuclei and eosinophilic opaque cytoplasm. Variable amounts of keratinization with intercellular bridges and stratified squamous differentiation are observed depending on tumor differentiation grade. The neoplastic cells form variably sized irregular tumor nests with variable amount of desmoplastic stromal reaction and inflammatory response [30]. The desmoplastic stromal reaction is one of the histological hallmarks of invasive carcinoma, and is composed of activated fibroblasts with enlarged nuclei, inflammatory cells, and vascular structures. This stromal reaction results from a complex interaction between infiltrating cancer cells and the host. Zonal squamous differentiation with keratinization and vague palisading of basaloid tumor cells in the periphery of tumor nests recapitulate the organization of normal stratified squamous epithelium (Fig. 2.10). According to the Japanese Classification of Esophageal Cancer [1–3], well differentiated squamous cell carcinoma is characterized by extensive keratinization and stratified squamous differentiation, whereas poorly differentiated squamous cell carcinoma shows a nest or sheet-like growth pattern with minimal keratinization. Moderately differentiated squamous cell carcinoma lies between these two (Fig. 2.10). The WHO classification states that grading is based on the degree of cytological atypia, and the presence of keratinization. Both the Japanese and the WHO classifications include no special reference to the ratio of keratinization [1–4]. No widely accepted, well-tested grading system has been established. Although squamous cell carcinoma is classified into three groups based on squamous differentiation; well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3) in both the Japanese and the WHO classifications, the WHO classification recommends a two-tiered system (grade 1–2 vs. grade 3), because the pathological distinction between grade 1 and grade 2 often shows high interobserver variation. Most of ESCCs show a characteristic histomorphology, so that the diagnosis might be unproblematic. The differential diagnosis of squamous cell carcinoma, especially poorly differentiated type, in a biopsy or surgical

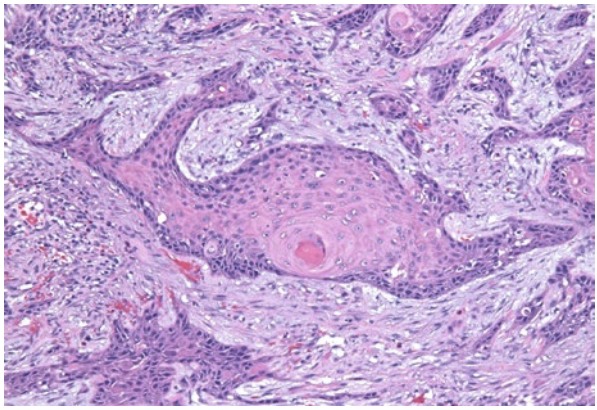

Fig. 2.10 Moderately differentiated squamous cell carcinoma with stratified squamous differentiation and keratinization. The desmoplastic stromal reaction, one of the histological hallmarks of invasive carcinoma, is noted

specimen includes reactive squamous epithelium, undifferentiated carcinoma, neuroendocrine carcinoma, poorly differentiated adenocarcinoma, salivary gland-type carcinoma, pseudoepitheliomatous hyperplasia (e.g., pseudoepitheliomatous hyperplasia associated with granular cell tumor [31]), radiation effect, hyperplastic polyp of the esophagogastric junction [32], malignant melanoma, and metastatic tumor. Immunohistochemistry (e.g., p40, p63, and cytokeratin 5/6) can provide assistance in the differential diagnosis, as well as review of imaging studies. The main differential diagnosis of squamous cell carcinoma in a biopsy specimen is usually a reactive squamous epithelium.

2.4 Tumor Spread

ESCC shows unique patterns of tumor spread including ductal/glandular involvement, diffuse pagetoid spread, and intramural metastasis like those frequently seen in other organs such as uterine cervix and nipple.

2.4.1 Superficial Esophageal Cancer

ESCC begins as an in situ carcinoma, and spreads both horizontally and vertically. Squamous cell carcinoma in situ is characterized by well-demarcated border and a high cellularity with a loss of the basal layer. Initial invasion into the lamina propria is characterized by the proliferation of downward growth of neoplastic squamous epithelium without prominent desmoplastic stromal reaction. It is a distinctive feature of ESCC that lymph node metastasis occurs early in the course of the disease. The abundant lymphatic channels in the lamina propria mucosae and submucosa of the esophagus are responsible for the high frequency of lymph node metastasis [33, 34]. All submucosal tumors have a substantial risk of lymph node metastases [17, 18, 35].

2.4.1.1 Ductal/Glandular Involvement

The esophageal submucosal glands are considered to be a continuation of the minor salivary glands and scattered throughout the entire esophagus. Squamous cell carcinoma in situ can extend into the ducts of the submucosal glands. Ductal/glandular involvement has often been observed in superficial squamous cell carcinoma of the esophagus, with an incidence of 21.3 to 22.3% [36, 37]. Maximum tumor size has been reported to be associated with the presence of ductal/glandular involvement by multivariate analysis, indicating that ductal/glandular involvement develops in association with horizontal tumor growth [37]. According to the Japanese Classification of Esophageal Cancer, tumors with ductal/glandular involvement that extends to the submucosa but does not definitely invade the submucosal stroma should not be classified as submucosal carcinoma [1–3]. However, even in mucosal carcinoma, there exists a possibility of incomplete clearance of the tumor tissue by endoscopic resection due to the presence of ductal/glandular involvement extending to the submucosal layer or reaching the end portions of esophageal glands. Also, it is very important to judge accurately whether a small cancerous nest in the submucosal layer in an endoscopically resected specimen is ductal/glandular involvement, direct tumor invasion, or lympho-vascular invasion in deciding the necessity for additional surgical resection based on the histopathologic findings in endoscopically resected specimens. Immunohistochemistry (e.g., CD31 and D2–40) and elastic stain can be helpful in the differential diagnosis, as well as deeper cut sections.

2.4.1.2 Diffuse Pagetoid Spread

Occasionally, squamous cell carcinoma cells exhibit a pagetoid pattern of growth. However, diffuse pagetoid spreading of squamous cell carcinoma in situ of the esophagus is very rare, and is characterized by the pronounced pagetoid spread of squamous cell carcinoma [38, 39]. Pagetoid spread of squamous cell carcinoma in situ and true Paget's disease are very similar histologically.

2.4.2 Lymph Node Metastasis in Patients with Superficial Esophageal Cancer

The proportion of patients with superficial squamous cell carcinoma of the esophagus and lymph node metastasis has been reported to be 39–54%, whereas the proportion of patients with intraepithelial carcinoma (EP (M1)) or carcinoma invading the lamina propria (LPM (M2)) and lymph node metastasis is only 1.4–4.0% [17, 18, 40, 41]. The risk of lymph node metastases is surprisingly high when it reaches the muscularis mucosae (MM (M3) 5.0–18.0%) or the superficial submucosa (SM1 26.5–53.9%) [17, 18, 40, 41]. Consequently, intraepithelial carcinoma (EP (M1)) or carcinoma invading the lamina propria (LPM (M2)) is generally treated by endoscopic resection [1–3]. Tumors with an estimated depth of invasion of MM (M3) or SM1 without lymph node metastases on diagnostic imaging studies are considered to have a relative indication for endoscopic resection, whereas tumors with an

estimated depth of invasion of SM2 or SM3 have no indication for endoscopic resection [1–3]. However, clinical diagnosis of the depth of invasion is not always accurate. One of the major advantages of endoscopic resection is to recover a specimen for histopathologic analysis, which helps to make a clinical decision for further therapy after endoscopic resection. Previous studies have reported that lymphatic invasion was significantly associated with lymph node metastasis in patients with superficial esophageal carcinoma in a multivariate analysis [40, 41].

2.4.3 Advanced Esophageal Cancer

Advanced esophageal cancers may invade surrounding structures including the trachea, lung, aorta, mediastinum, and pericardium. Distally located tumors often invade the stomach. Metastases to distant organs are frequent, particularly to the liver and lung [16].

2.4.3.1 Intramural Metastasis

Metastasis from an esophageal carcinoma to the esophagus or stomach is termed intramural metastasis. Intramural metastasis has often been found in the resected esophagus, with an incidence of 11–15% [42, 43]. Patients with intramural metastasis have a higher frequency of lymph node metastasis and liver recurrence than those without intramural metastasis, and intramural metastasis is more predictive of a worse prognosis than is local recurrence [42].

2.4.3.2 Prognostic Factors

Clinicopathologic prognostic factors include TNM stage [1–3], lymph node metastasis [44, 45], tumor invasion depth [44, 45], lympho-vascular invasion [44], intramural metastasis [42, 44], tumor vascularity [46], infiltrating growth pattern [47], inflammatory response [47, 48], tumor budding [49], tumor nest configuration [30], extranodal spreading [50], epithelial–mesenchymal transition phenotype [51], pathologic response to neoadjuvant therapy [52], completeness of surgical resection [45], and the patient's general health condition [53]. Most of these studies have shown no significant influence of tumor differentiation grade on survival. Among these clinicopathologic prognostic factors, the number of metastasis-positive lymph nodes is a simple and reliable prognostic factor [52–55]. In patients with tumors limited to within the submucosal layer, even with tumors located in the mid- and lower esophagus, lymph node metastasis was frequent in the upper mediastinum and perigastric area [56]. Isolated distant lymph node involvement from superficial esophageal carcinoma is thus not necessarily a sign of advanced disease [56]. The most predictive factor for the patient's survival is not the area of involved nodes, but the number of involved nodes [57, 58]. Numerous genomic and epigenomic aberrations are involved in the development of ESCC [59–61]. Most of them are involved in signal transduction, regulation of transcription, cell cycle, or cell apoptosis. Such markers may have potential implications in the early detection of tumorigenesis and prediction of metastasis and survival.

2.5 Precursor Lesion (Squamous Dysplasia/ Intraepithelial Neoplasia)

Precursor lesion is named as dysplasia, and also referred to as intraepithelial neoplasia [1–4]. Squamous dysplasia/intraepithelial neoplasia is defined as a neoplastic lesion with architectural and cytological abnormalities [1–4]. Squamous dysplasia/intraepithelial neoplasia is characterized by nuclear atypia and abnormal epithelial maturation with a well-demarcated border (Fig. 2.11). Although the 11th edition of the Japanese Classification of Esophageal Cancer has abolished the previous two-tier subclassification of low grade and high grade, the WHO Classification of Tumors of the Digestive System still maintains the two-tier subclassification [4]. In low-grade intraepithelial neoplasia, the architectural and cytological abnormalities are confined to the lower half of the epithelium. In high-grade squamous dysplasia/intraepithelial neoplasia, the abnormalities involve the upper half of the epithelium. High-grade dysplasia/intraepithelial neoplasia is also diagnosed when severe cytological atypia is present regardless of the extent of epithelial involvement. Full thickness involvement of the squamous epithelium, called squamous cell carcinoma in situ in Japan, is considered synonymous with high-grade intraepithelial neoplasia (high-grade dysplasia) in North America and Europe based on their similar histologic appearance and risk of progression into invasive ESCC [4, 62]. Japanese pathologists diagnose carcinoma solely on the basis of the architectural and cytological changes observed without requiring histological evidence of invasive growth, whereas pathologists in North America and Europe define carcinoma as one that has histological evidence of invasive growth [4, 63, 64].

The differentiation of squamous dysplasia/intraepithelial neoplasia from reactive change is sometimes challenging. The abrupt transition of the normal squamous cells to atypical squamous cells may serve as a diagnostic indicator for squamous

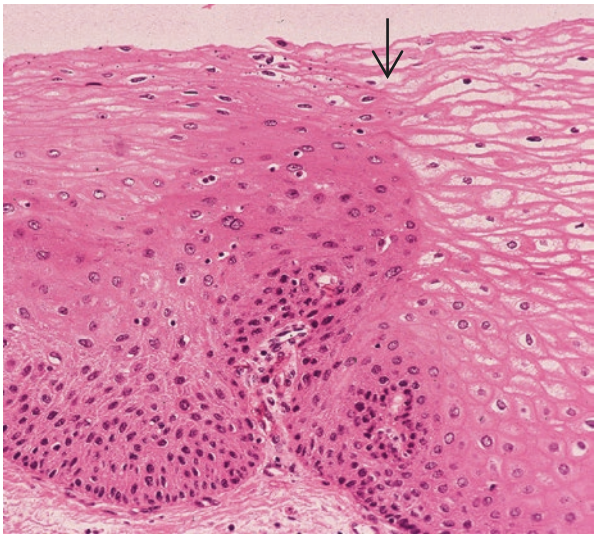

Fig. 2.11 Increased cellularity, mild nuclear atypia, and hyperchromasia are evident, which can be regarded as dysplasia (low-grade intraepithelial neoplasia). The abrupt transition of squamous cells (right) to atypical squamous cells (left) is noted. Arrow indicates the border between normal squamous epithelium and dysplastic squamous epithelium

dysplasia/intraepithelial neoplasia (Fig. 2.11). Immunohistochemistry for Ki-67 and p53 is also adjunctively available in the diagnosis of squamous dysplasia/intraepithelial neoplasia [65].

2.6 Tumor Response to Neoadjuvant Therapy

Tumor response to neoadjuvant therapy has been identified as an important prognostic factor [52]. Histopathologic changes induced by neoadjuvant therapy include nuclear enlargement or shrinkage, nuclear vacuolation, apoptosis, necrosis, free keratin pearls/debris, foreign body giant cell reaction, dystrophic calcification, and fibrosis [4]. The extent of tumor regression is graded based on histologic examination by subjectively comparing the amount of residual tumor with the amount of therapy-induced fibrosis [1–4, 66].

2.7 Variants

The subtypes of ESCC include basaloid squamous cell carcinoma, carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma, adenosquamous carcinoma, and verrucous carcinoma.

2.7.1 Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma is an uncommon variant of squamous cell carcinoma with a male predominance, accounting for approximately 2–5% of primary esophageal malignancies [4, 14, 67–69]. It is histopathologically distinct from squamous cell carcinoma, and is characterized by a poor degree of differentiation and high proliferative activity [67]. Histologically, typical basaloid squamous cell carcinomas are composed of relatively uniform, small, round-to-oval cells with scant cytoplasm forming a large solid tumor nest with comedo-like necrosis (Fig. 2.12). The tumor nest contains eosinophilic hyaline material, suggesting a basement membrane-like substance. Basaloid squamous cell carcinoma has been reported to have a wide variation of histological features including solid nest, cribriform pattern, microcyst, trabecular nest, and ductal differentiation [68]. Basaloid squamous cell carcinoma with salivary-type differentiation, mimicking the histologic features of epithelial–myoepithelial carcinoma of the salivary gland, has also been reported [70]. Areas of squamous intraepithelial neoplasia or invasive squamous cell carcinoma are often observed [69, 71]. Biopsy specimens are taken from superficial areas of a tumor. Therefore, many cases of basaloid squamous cell carcinoma of the esophagus are reportedly diagnosed as squamous cell carcinoma preoperatively. Basaloid squamous cell carcinoma could be mistakenly diagnosed as adenocarcinoma, adenoid cystic carcinoma, undifferentiated carcinoma, or neuroendocrine carcinoma if a biopsy sample contains only components of ductal differentiation, cribriform pattern, sold nest or trabecular nest, respectively.

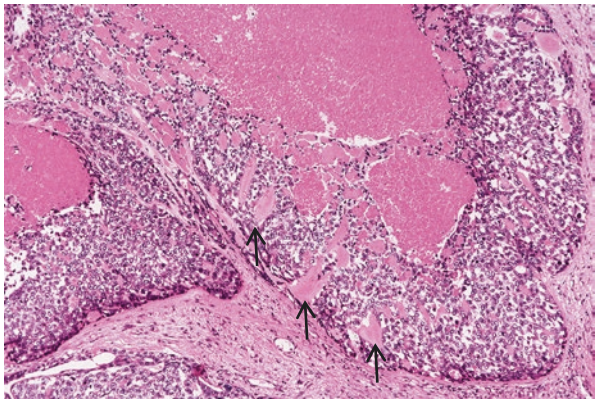

Fig. 2.12 Typical histologic features of basaloid squamous cell carcinoma. Relatively uniform neoplastic cells with scant cytoplasm form a large solid tumor nest with comedo-like necrosis. The tumor nest contains eosinophilic hyaline material, suggesting a basement membrane-like substance (arrows)

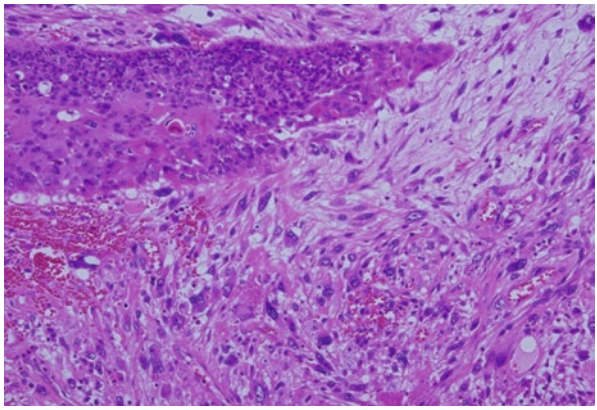

Fig. 2.13 Carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma with biphasic differentiation composed of both spindle-shaped sarcomatous tumor cells and squamous cell carcinoma forming tumor nests

2.7.2 Carcinosarcoma/Spindle Cell Squamous Cell Carcinoma/ Sarcomatoid Carcinoma

Carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma is a rare variant of squamous cell carcinoma, and accounts for approximately 1.0% of primary esophageal malignancies [14]. Histologically, carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma is composed of a proliferation of spindle-shaped sarcomatous tumor cells and squamous cell carcinoma forming tumor nests (Fig. 2.13) [4]. The spindle cell component may show osseous, cartilaginous, and skeletal-muscle differentiation. Therefore, this tumor can be regarded as carcinosarcoma with biphasic differentiation. Immunohistochemically, spindle-shaped sarcomatous tumor cells may display varying degrees of epithelial differentiation. Almost all reported cases of esophageal carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma have been macroscopically polypoid, and rarely show an ulcerated appearance [15]. Grossly, esophageal carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma shows a typical 0-Ip type superficial esophageal carcinoma, which appears as a large polypoid tumor with a smooth surface and prominent lobulation (Fig. 2.5). The stalk is

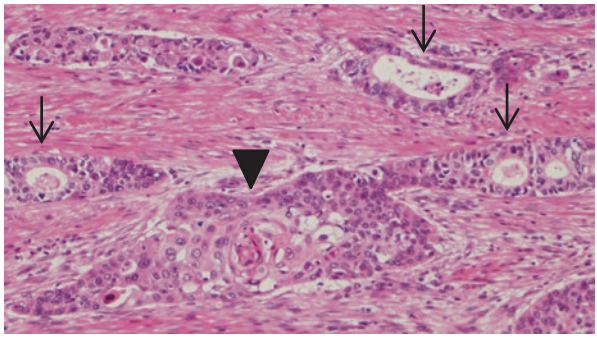

Fig. 2.14 Adenosquamous carcinoma containing coexisting elements of infiltrating squamous cell carcinoma (arrowhead) and adenocarcinoma (arrows)

usually very small and narrow. This tumor shows such characteristic macroscopic features that one can easily recognize its histologic type. Superficial-type squamous cell carcinoma is often found in the mucosa surrounding a polypoid carcinosarcoma/spindle cell squamous cell carcinoma/sarcomatoid carcinoma (Fig. 2.5).

2.7.3 Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare variant of squamous cell carcinoma. According to the previous reports, approximately 1.0% of resected esophageal cancers are diagnosed pathologically as adenosquamous carcinoma [14, 72, 73]. Microscopically, it consists of coexisting elements of infiltrating squamous cell carcinoma and adenocarcinoma (Fig. 2.14). According to the Japanese Classification of Esophageal Cancer, adenosquamous carcinoma of the esophagus is defined as having at least 20% of each of squamous cell carcinoma and adenocarcinoma elements on routine microscopic examination, using hematoxylin and eosin staining [1–3]. The WHO classification, however, states simply that adenosquamous carcinoma has a significant squamous carcinomatous component that is intermingled with tubular adenocarcinoma elements, with no special reference to the ratio of these two components [4]. Although some previous reports of esophageal adenosquamous carcinoma have indicated that these tumors show highly aggressive biological behavior [74–77], other previous reports showed that such patients had a significantly better outcome or had no significant difference in survival time compared with patients with squamous cell carcinomas or adenocarcinomas [72, 73]. The median age at presentation, the location, and macroscopic features of adenosquamous carcinomas were similar to those of squamous cell carcinomas [72, 73, 77].

2.7.4 Verrucous Carcinoma

Verrucous carcinoma is an extremely rare, highly differentiated variant of squamous cell carcinoma. Verrucous carcinoma grows slowly and locally, and only rarely metastasizes [1–3, 78, 79]. It is generally an exophytic and warty in appearance, and

demonstrates blunt papillary projections of highly differentiated squamous cells with a pushing margin. Therefore, the diagnosis of verrucous carcinoma may be particularly challenging due to its bland histologic features. A superficial biopsy is usually not sufficient to make a definitive diagnosis.

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Diagnostic Imaging of the Esophageal Cancer

3

Hiroya Ojiri

Abstract

Diagnostic imaging can play an important role in detecting and staging esophageal cancer. Current diagnostic workup consists of barium esophagography, endoscopy/endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). CT, EUS, MRI, and PET should be considered complementary modalities. In combination, they are crucial to determine the most appropriate treatment for patients with esophageal cancer.

This chapter describes the diagnostic imaging, mainly of CT and MRI, and relevant anatomy of the esophagus for clinical decision-making with regard to esophageal cancers. EUS precisely shows tumor invasion mainly localized in the esophageal wall (defined as T1–3). On the other hand, cross-sectional imaging such as CT and MRI are useful to detect tumor invasion to the adjacent structures beyond the adventitia (defined as T4). Currently, regional lymph node metastases are evaluated using EUS, CT, and/or FDG-PET. Detection of metastatic lymphadenopathies on CT depends primarily on nodal size (size criteria) although size is known to be an insensitive parameter. MRI's role to assess regional nodal metastasis is limited so far. CT is currently the best diagnostic method to detect metastases.

Keywords

CT · Esophageal cancer · Imaging · MRI

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3.1 Introduction

Patients with esophageal cancer have a poor prognosis because it is usually detected at an advanced stage. Accurate preoperative staging is crucial in determining the most appropriate therapeutic strategy for each patient. Surgical resection is currently the best curative treatment for esophageal cancers without locoregionally advanced invasion or distant metastases. Inappropriate attempts of surgery must be avoided.

The radiologist can play an important role in detecting and staging esophageal cancer. Current diagnostic workup consists of barium esophagography, endoscopy/endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). In combination, they are crucial to determine the most appropriate treatment for patients with esophageal cancer. CT, EUS, MRI, and PET should be considered complementary modalities. The main purpose of imaging studies in patients with esophageal cancer is to stage the disease as accurately as possible and to determine which patients may be suitable candidates for surgery. The accurate assessment requires knowledge of the advantages and limitations of each modality, an anatomy of the esophagus and spread patterns of esophageal cancer.

Squamous cell carcinoma (SCC) that is the most prevalent esophageal cancer worldwide mostly arises from the upper portion of the esophagus whereas adenocarcinoma primarily involves the lower portion and esophagogastric junction (EGJ). Hence, importance of a direct invasion to the tracheobronchial tree and metastatic adenopathy in the superior mediastinum should be emphasized in the imaging diagnosis of esophageal SCC.

This chapter describes the diagnostic imaging, mainly of CT and MRI, and relevant anatomy of the esophagus for clinical decision-making with regard to esophageal cancers.

3.2 Anatomy of the Esophagus

3.2.1 Divisions of the Esophagus

The esophagus is a tubular structure between the esophageal verge and esophagogastric junction (EGJ), clinically divided into four segments [1]: cervical esophagus, upper thoracic esophagus, middle thoracic esophagus, and lower thoracic esophagus/EGJ. The cervical esophagus begins at the level of the inferior border of the cricoid cartilage and ends at the thoracic inlet. The upper thoracic esophagus begins at the thoracic inlet and ends at the level of the lower border of the azygos vein. The middle thoracic esophagus is bordered superiorly by the lower border of the azygos vein and inferiorly by the inferior pulmonary vein. The lower thoracic esophagus is bordered superiorly by the inferior pulmonary vein and inferiorly by the stomach. The lower end of the lower esophagus includes the EGJ.

The cricoid cartilage is an easy-to-recognize structure to identify the transition between the hypopharynx and the cervical esophagus (Fig. 3.1). The esophageal verge is at the lower margin of the cricopharyngeus muscle at the level of C6. The cricopharyngeus muscle is actually a specialized functional zone of inferior constrictor muscle that identifies this physiologic boundary. Cross-sectional images clearly depict such

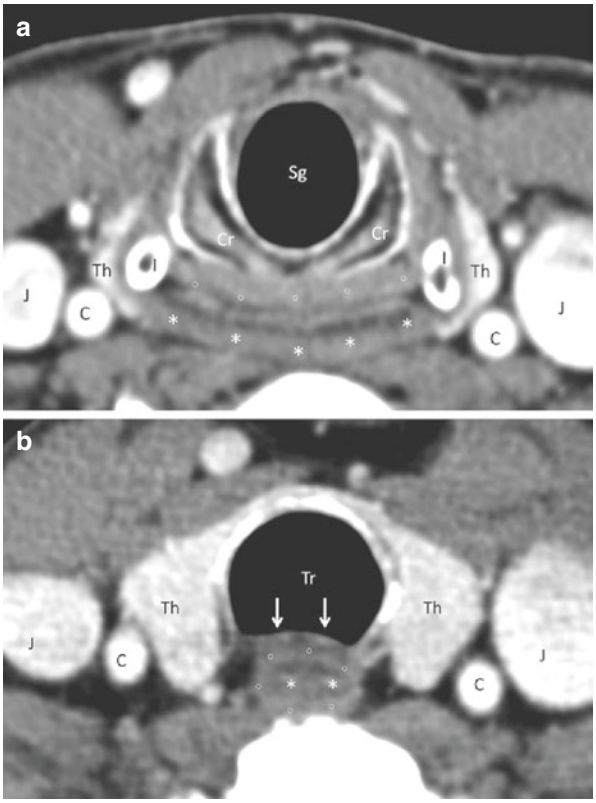

Fig. 3.1 Normal CT anatomy of the hypopharynx and cervical esophagus. (**a**) Contrast-enhanced axial CT image obtained at the level of the hypopharynx. The ossified cricoid cartilage (Cr) is identified as a "U-shaped" structure at this level because the anterior arch is lower than the posterior lamina of cricoid cartilage. A posterior aspect of the subglottic laryngeal airway (Sg) is convex along the internal surface of the lamina of cricoid cartilage. The hypopharynx is a flattened ellipsoid structure on axial image as the inferior pharyngeal constrictor partly arises from the inferior cornu (*I*) of thyroid cartilage on both sides. The hypopharynx at this level consists of anterior "postcricoid portion (*open circle*)" and "posterior pharyngeal wall (*asterisk*)." *C* common carotid artery, *J* internal jugular vein, *Th* (superior pole of) thyroid gland. (**b**) Contrast-enhanced axial CT image of the cervical esophagus. The cervical esophagus identified as an oval structure posterior to the trachea (*Tr*) shows a circumferential zonal anatomy. It seemingly consists of three layers: an inner enhancing layer representing the mucosa (*asterisk*), outer soft tissue attenuation layer (*open circle*) representing the muscularis propria, and low-attenuation submucosal fat between them. A posterior aspect of the trachea is concave because of indentation of the cervical esophagus upon the membranous portion (*arrows*) of the trachea. *C* common carotid artery, *J* internal jugular vein, *Th* thyroid gland

transition [2]; the hypopharynx is a flattened soft tissue ellipsoid structure attached to the posterolateral margin of the thyroid lamina and inferior cornu (Fig. 3.1a). On the other hand, the cervical esophagus creates an oval structure posterior to the trachea as the muscular wall loses its attachment to the thyroid cartilages (Fig. 3.1b). The trachea normally stays in the midline from the lower neck to the thoracic inlet, while the esophagus will often deviate to the left at this level (Fig. 3.2) [2].

3.2.2 Zonal Anatomy of the Esophageal Wall

The esophageal wall consists of mucosa, muscularis mucosae, submucosa, muscularis propria, and adventitia. EUS can differentiate such layers to determine the depth of tumor invasion into the esophageal wall (Fig. 3.3) [3]. Mucosal enhancement may be visible on contrast-enhanced CT (Figs. 3.1b and 3.2) and contrast-enhanced MRI.

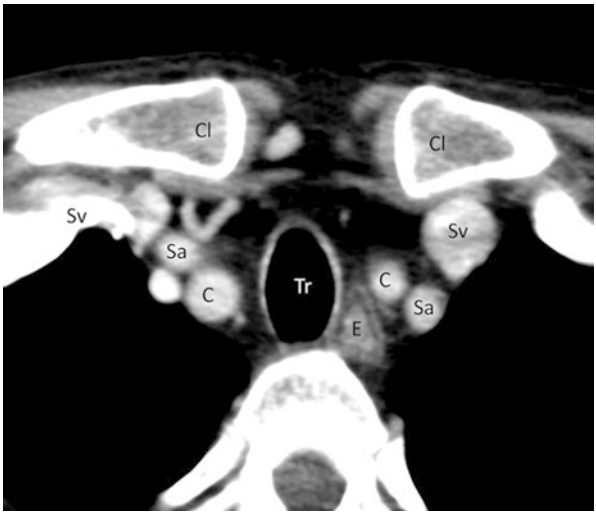

Fig. 3.2 Normal CT anatomy of the thoracic inlet. Contrast-enhanced axial CT image. The esophagus (E) deviates to the *left,* whereas the trachea (Tr) stays in the *middle. C* common carotid artery, *Cl* clavicle (sternal end), *Sa* subclavian artery, *Sv* subclavian vein

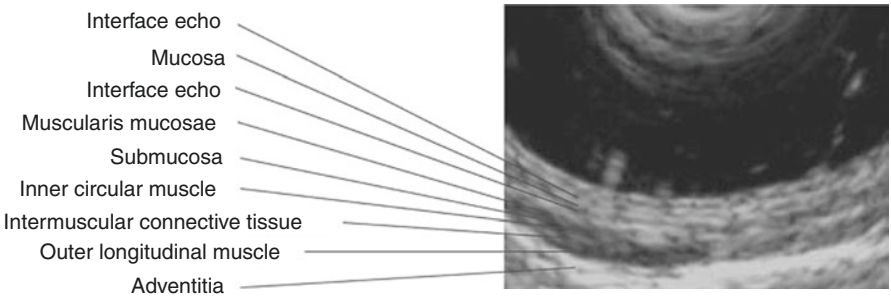

Fig. 3.3 EUS of the normal esophagus (by courtesy of Dr. Gohda, Department of Endoscopy, The Jikei University School of Medicine). EUS differentiates nine layers of the esophageal wall

3.3 T Staging by Imaging

T staging of the esophageal cancer is principally defined by depth of invasion. Because the esophagus lacks a serosa, there is no anatomic barrier to prevent rapid local invasion of the tumor into the mediastinum. As a result, esophageal cancer can easily spread to adjacent structures in the neck or thorax, including the trachea, thyroid gland, larynx, bronchi, aorta, lung, pericardium, and diaphragm [4]. Involvement of the adjacent structures in the mediastinum is classified as T4 disease which is further divided into two: resectable disease (T4a) and unresectable disease (T4b) [1].

An important goal of clinical T staging is the identification of tumor invasion of mediastinal structures, since affected patients may not be suitable candidates for surgical resection [5]. Depth of tumor invasion is one of the criteria used to select multimodality therapy instead of primary surgery [5].

Imaging modalities should be complementary to stage the primary lesion; EUS precisely shows tumor invasion mainly localized in the esophageal wall (defined as T1–3). On the other hand, cross-sectional imaging such as CT and MRI are useful to detect tumor invasion to the adjacent structures beyond the adventitia (defined as T4). This chapter mainly focuses on CT and MRI.

3.3.1 Barium Esophagography

Barium esophagography is commonly performed as an initial examination to evaluate patients with dysphagia/odynophagia which may be the first manifestation of esophageal cancer.

Single-contrast technique is suitable to assess passage and wall rigidity and characterize strictures. Double-contrast technique allows the assessment of mucosal irregularity such as elevated and ulcerative lesions although double-contrast images of good quality may not be obtained distal to high-grade obstructive disease.

Barium esophagography is very helpful to determine longitudinal extent and location of the disease relative to anatomical landmarks such as the tracheal bifurcation; to which esophageal division does the lesion belong? This is necessary to set an appropriate field of radiotherapy (RT).

On esophagograms, early esophageal cancers manifest as small polypoid or plaque-like lesions or superficial spreading lesions, whereas advanced esophageal cancers manifest as infiltrating, polypoid, ulcerative, or varicoid lesions (Figs. 3.4 and 3.5) [6]. Typical findings of advanced diseases include an irregular stricture (Figs. 3.4, 3.5, and 3.6a), mass-like filling defect (Fig. 3.7a), or ulcer (Fig. 3.4) on single-contrast images, and an abrupt change in caliber and contour (Fig. 3.6b) or irregularly shaped mass on double-contrast images. The Japan Esophageal Society uses a classification system based on the macroscopic appearance of esophageal cancer [7].

Double-contrast esophagography has a sensitivity of greater than 95% in the detection of esophageal cancer [8]. When malignancy suggested on barium esophagogram, a positive predictive value is approximately 40%. And endoscopically proven esophageal cancers were found on barium esophagogram in 98% [8, 9].

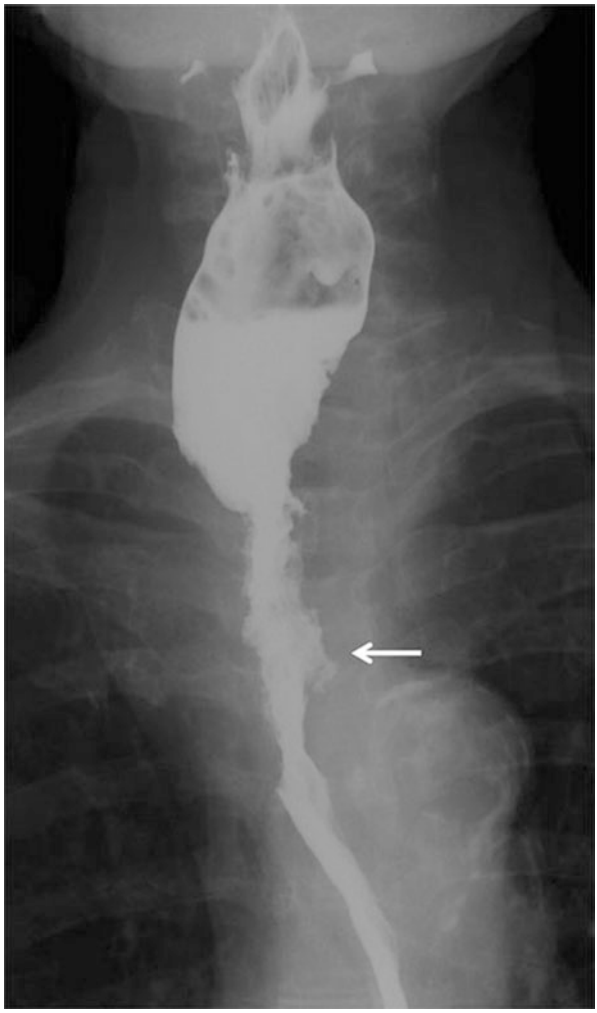

Fig. 3.4 Esophageal cancer (upper thoracic esophagus). On single-contrast barium esophagography there is an irregular stricture of the esophagus (Ut) associated with ulceration (*arrow*)

The synchronous second primary lesion must be carefully inspected. Tracheoesophageal fistula may be demonstrated when resulting from the tumor invasion (Fig. 3.8a).

3.3.2 EUS

EUS allowing visualization of the distinct layers of the esophageal wall (Fig. 3.3) can accurately demonstrate the depth of tumor invasion. It is useful in distinguishing T1 and T2 lesions.

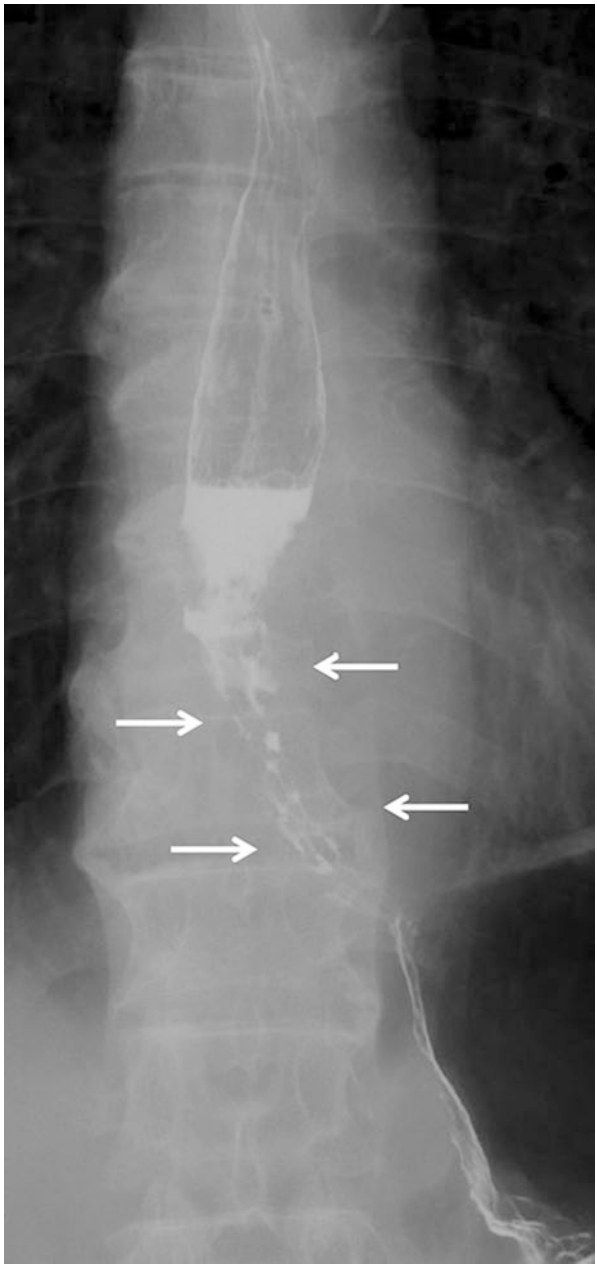

Fig. 3.5 Esophageal cancer (lower thoracic esophagus). Barium esophagography shows an irregular stenosis and varicoid appearance of the lower thoracic esophagus (*arrows*)

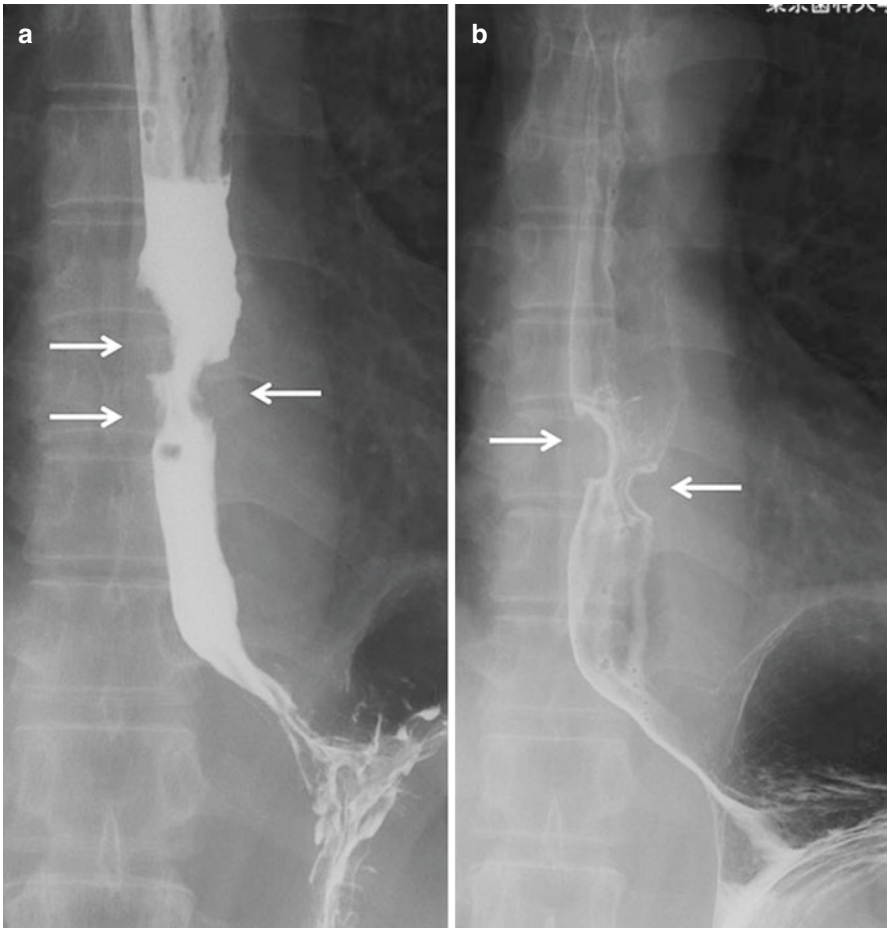

Fig. 3.6 Esophageal cancer (middle thoracic esophagus). Single-contrast image (**a**) and double contrast image (**b**) of barium esophagography reveal an irregular stricture and abrupt caliber change of the middle thoracic esophagus (*arrows*)

However, EUS has several limitations in T staging: one is that the accuracy is highly operator dependent and another is evaluation of non-traversable, stenotic tumors. There is a known failure rate of 14–25% because of stenotic lesions that prevent the passage of the endoscope [10, 11]. EUS and CT should be used as complementary methods for TNM staging of esophageal cancer [12].

EUS is also useful to determine regional lymph node involvement. Combined use of fine-needle aspiration and EUS can improve assessment of lymph node involvement [5].

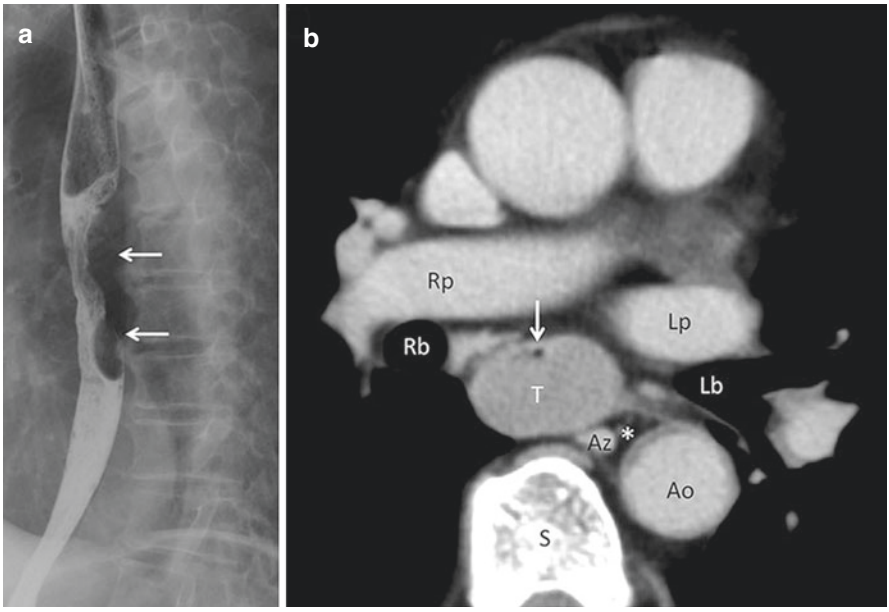

Fig. 3.7 Esophageal cancer (middle thoracic esophagus). (**a**) Barium esophagography shows an irregularly shaped, mass-like filling defect (*arrows*) in the lower thoracic esophagus. (**b**) Contrast-enhanced axial CT image at the level of the middle thoracic esophagus. Asymmetrical wall thickening forms a soft tissue mass (*T*) in the distended middle thoracic esophagus. Narrowing esophageal lumen is identified as an eccentric area of air density (*arrow*). A fat plane around the esophagus is entirely preserved, and a triangular fat space (*asterisk*) among the esophagus, aorta (*Ao*), and spine (*S*) is also maintained. Such findings exclude T4 disease with high degree of confidence. *Az* azygos vein, *Lb* left main bronchus, *Lp* left pulmonary artery, *Rb* right main bronchus, *Rp* right pulmonary artery

3.3.3 CT

Patients with esophageal cancer are best staged by CT, despite recognizing difficulties in determining local irresectability and mediastinal node involvement [13–15]. With the advent of multi-detector CT, it allows more accurate staging of the disease [5]. CT has been the mainstay for staging newly diagnosed esophageal cancer. The increasing use of EUS and PET has improved the staging algorithm for it. Currently, combined use of CT, EUS, and PET is advocated to determine whether a patient should be treated with surgery, chemotherapy, or a chemoradiation therapy [5].

In practice, CT is recommended for initial imaging following confirmation of esophageal cancer at pathologic analysis. The N and M status can be evaluated by CT at the same time.

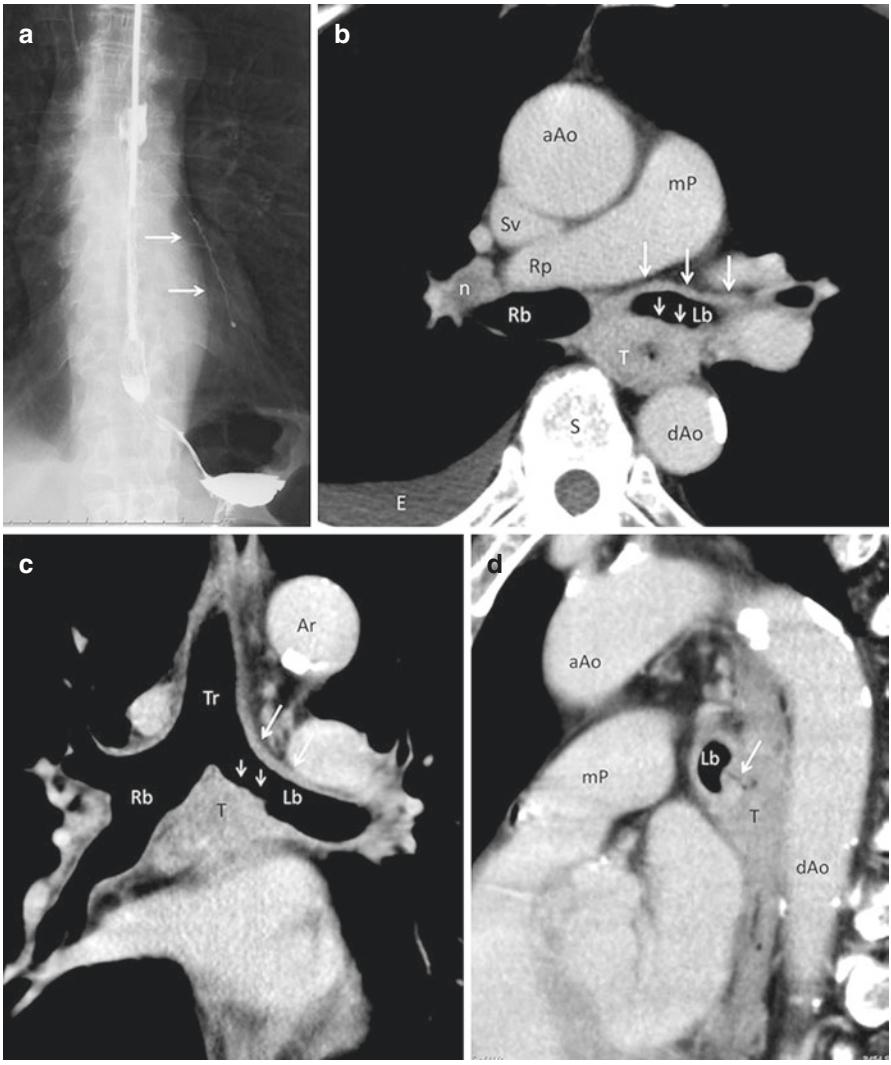

Fig. 3.8 Esophageal cancer (middle thoracic esophagus). Esophagography (**a**) shows contrast material leaking into the left main bronchus and lower lobe bronchi (*arrows*). Contrast-enhanced axial CT image at the level just below the tracheal bifurcation (**b**) and coronal image at the level of the tracheal bifurcation (**c**) show an irregular and circumferential wall thickening of the esophagus representing esophageal cancer (*T*). An irregular interface (*small arrows*) between the tumor (*T*) and air density within the left main bronchus (*Lb*) and diffusely infiltrative change (*large arrows*) along the left main bronchus strongly suggest bronchial invasion. Metastatic hilar adenopathy (*n*) and right pleural effusion (*E*) are also noted (**b**). Reformatted sagittal image (**d**) well depicts a fistula (*arrow*) between the tumor (*T*) and a posterior aspect of left main bronchus (*Lb*). *aAo* ascending aorta, *Ar* aortic arch, *dAo* descending aorta, *mP* main pulmonary artery, *Rb* right main bronchus, *Rp* right pulmonary artery, *S* spine, *Sv* superior vena cava

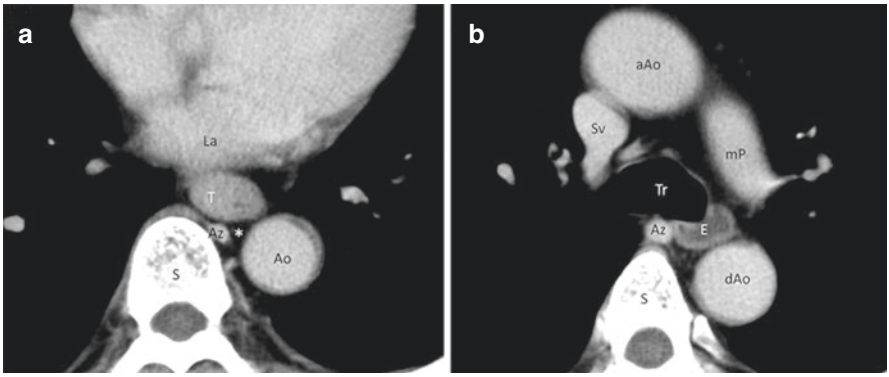

Fig. 3.9 Esophageal cancer (lower thoracic esophagus). (**a**) Contrast-enhanced axial CT image at the level of Lt shows asymmetrical wall thickening of the lower thoracic esophagus (*T*). Integrity both of an entire fat plane around the esophagus and of a triangular fat space (*asterisk*) among the esophagus, aorta (*Ao*), and spine (*S*) is maintained, excluding T4 disease. Az azygos vein, *La* left atrium. (**b**) Contrast-enhanced axial CT image at the level of the tracheal bifurcation. The esophagus (*E*) proximal to the esophageal cancer (**a**) is distended with fluid attenuation. The esophagus at this level has even thin wall measuring approximately 2 mm. *aAo* ascending aorta, *Az* azygos vein, *dAo* descending aorta, *mP* main pulmonary artery, *S* spine, *Sv* superior vena cava, *Tr* trachea

CT is limited in determining the exact depth of tumor infiltration of the esophageal wall and considered to be unable to adequately help differentiate between T1, T2, and T3 disease. However, CT is useful to distinguish between T3 and T4 lesions and to rule out unresectable (T4a) or distant metastatic disease (Figs. 3.7b and 3.9a).

3.3.3.1 CT Study Protocol and Optimal Phase for the Evaluation

CT examination should be inclusive from the neck through the entire upper abdomen to evaluate T, N, and M factors. Intravenous administration of contrast material is necessary. Optimal timing of image acquisition is a little bit controversial, depending on what should be evaluated by CT. Pre-contrast and post-contrast of delayed phase images are sufficient to evaluate N and M factors. On the other hand, some investigators recommend an arterial phase (on dynamic study) to detect the primary lesion (T factor) which may be better evaluated by EUS.

Umeoka et al. reported that the second arterial phase of dynamic CT (35 second after attenuation of 200HU was obtained at the descending aorta) is the optimal phase for visualization of esophageal cancer [16]. In their other report early esophageal rim enhancement on arterial phase of dynamic CT that was identified only in T3/T4 diseases could improve preoperative differentiation between T1/T2 and T3/T4 diseases [17].

Holsher et al. reported that the sensitivity values of the T staging in the arterial phase were 0% in T1a, 71.4% in T1b, 12.5% in T2, 89.5% in T3, and 100% in T4. The sensitivity values in the venous phase were 0% in T1a, 14.3% in T1b, 0% inT2, 94.7% in T3, and 100% in T4 [12].

Venous phase images are necessary to evaluate mediastinal adenopathies and metastatic liver tumors. Yoon et al. reported that 80% of esophageal cancers were detectable on post-contrast CT in the venous phase although nearly 70% of T1 lesions were missed [18].

3.3.3.2 Diagnostic Criteria of the Esophageal Cancer

Esophageal Wall Thickness

In general, CT is considered incapable of distinguishing the layers of the esophageal wall. Wall thickening of the esophagus is the most important CT feature to detect the esophageal cancer and its (mainly, longitudinal) extent. Precise localization of the esophageal cancers is helpful for planning radiation therapy.

Generally, any esophageal wall thicker than 5 mm is considered abnormal (Figs. 3.7b, 3.8b, and 3.9a) [19]. Wall thickness more than 5 mm is the criterion for abnormal wall thickening of the esophagus, suggested by an M.D. Anderson study without consideration of the status of the esophagus [20, 21]. Moss et al. proposed criteria as follows: the esophageal wall thicker than 5 mm is abnormal on CT images (Moss stages II); thickness of the esophageal wall between 3 and 5 mm indicated early lesions that did not make the wall apparently thickened (Moss stages I) [22].

The esophageal wall thickness seems to largely depend on the status of the esophagus. The esophageal wall thicker than 3 mm is abnormal when the esophagus is distended [22, 23]. Xia et al. reported that normal esophagus has a wall thickness around 5 mm in contraction status, 3 mm in dilatation (Fig. 3.9b), and roughly no more than 5.5 mm in any status [20]. In their study the largest wall thickness of the esophagus was 4.70 mm in contraction and 2.11 mm in dilatation. When dilating, the esophageal wall thickness was between 1.87 and 2.70 mm and the cervical esophageal wall was the thickest. When contracting, wall of the abdominal esophagus is thicker than the cervical and thoracic esophagus. They also reported that average of esophageal wall thickness was about 1 mm larger in males than females. Age and the thickness of subcutaneous fat had no significant impact on the esophageal wall thickness [20].

Asymmetric wall thickening of the esophagus is a primary but nonspecific CT finding of esophageal cancer (Figs. 3.7a and 3.9a) [5].

Other Features

High-resolution, post-contrast CT of good quality may differentiate three layers of the esophageal wall; a well-enhancing inner layer, fat-attenuation middle layer, and poorly enhancing outer layer representing the mucosa, submucosal fat, and muscularis propria, respectively (Figs. 3.1b, 3.2, and 3.10). An external contour of the outer layer should be surrounded by the adventitia. Theoretically, understanding of such zonal anatomy helps estimating depth of tumor invasion for T staging of the esophageal cancer. When the outer layer (muscularis propria) is preserved, the disease is assigned as T1 (Fig. 3.11). When the outer layer is partly encroached by a moderately enhancing tumor, the disease is assigned as T2. The transmural tumor invasion of the outer layer (muscularis propria) suggests T3 disease

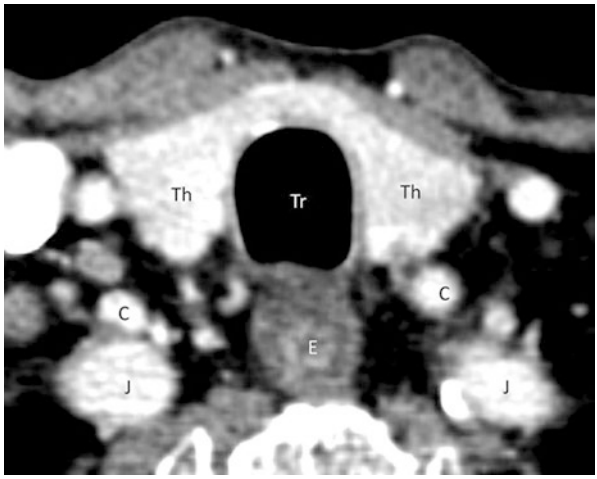

Fig. 3.10 Zonal anatomy of the esophageal wall on CT. Contrast-enhanced axial CT image of the cervical esophagus reveals three different layers of the esophageal (*E*) wall: the inner enhancing layer, middle fatty layer, and outer soft tissue density layer representing the mucosa, submucosal fat, and muscularis propria, respectively. *C* common carotid artery, *J* internal jugular vein, *Th* thyroid gland, *Tr* trachea

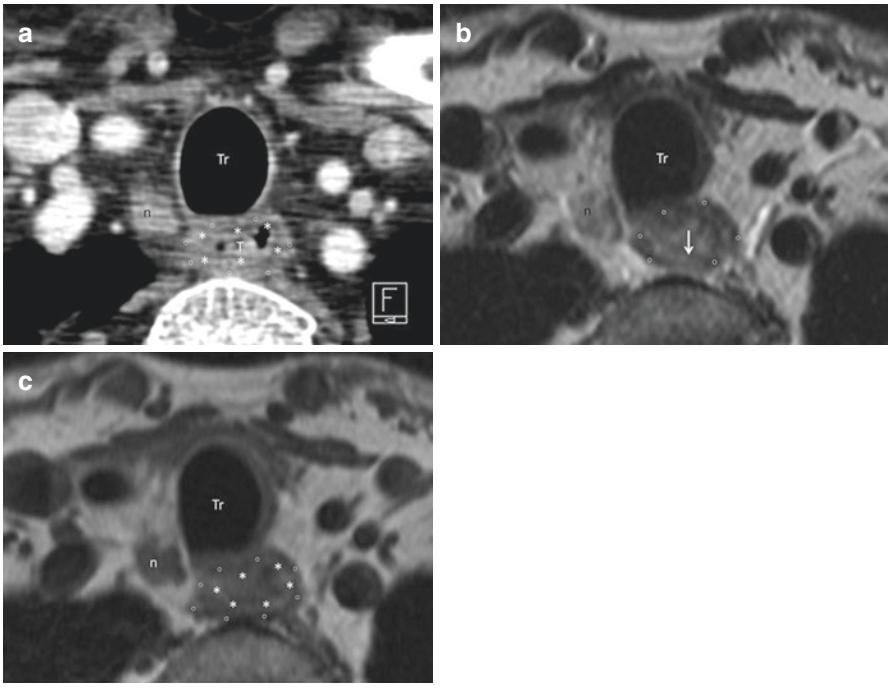

Fig. 3.11 Esophageal cancer (cervical esophagus; T1). Contrast-enhanced axial CT image of the level of the cervical esophagus (**a**) shows a nodular lesion (*T*) arising from the posterior aspect of esophageal wall. A fatty submucosal layer (*asterisk*) and soft tissue muscular layer (*open circle*) are entirely maintained. Metastatic adenopathy of the right paratracheal node (*n*) is noted. On T2-weighted axial image (**b**) the indistinct low-intensity muscular layer (*open circle*) at the posterior aspect (*arrow*) raises possibility of partial invasion of the muscularis propria (T2 disease). However, both the high-intensity submucosal fat (*asterisk*) and tissue-intensity muscular layer (*open circle*) are well preserved on T1-weighted image (**c**). Findings on T1-weighted axial image (**c**) exclude deep invasion to the muscularis propria and radiologically suggest T1 disease. *n* enlarged paratracheal node, *Tr* trachea

(Figs. 3.12 and 3.13) when the external contour of the esophagus is smooth and/or fat planes around the esophagus are preserved and T4 disease when the external contour of the esophagus is irregular and fat planes between the esophagus and adjacent structures are obliterated (Figs. 3.8 and 3.14). However, such differentiation of each layer of the esophageal wall is not always possible.

A dilated fluid- and debris-filled esophageal lumen may be noted proximal to an obstructing disease (Fig. 3.9).

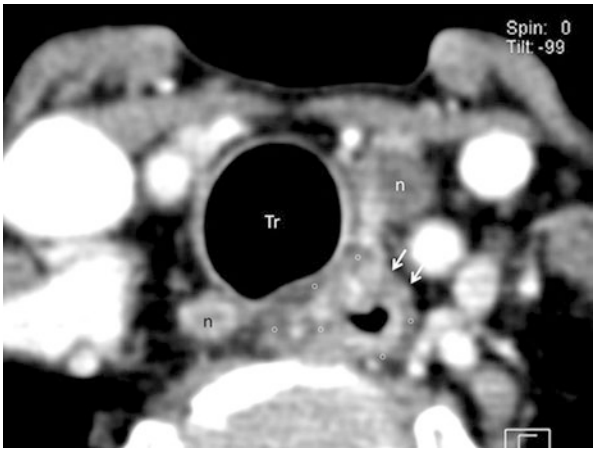

Fig. 3.12 Esophageal cancer (cervical esophagus; T3). Contrast-enhanced axial CT image at the level of the cervical esophagus differentiates the inner enhancing mucosal layer and outer poorly enhancing muscular layer (*open circle*). The relatively thickened inner layer at the anterior aspect represents the primary lesion. A combination of a focal encroachment of the muscular layer (*arrows*) and smooth external contour of the esophagus suggests T3 disease. There are metastatic paratracheal nodes (*n*) on both sides. *Tr* Trachea

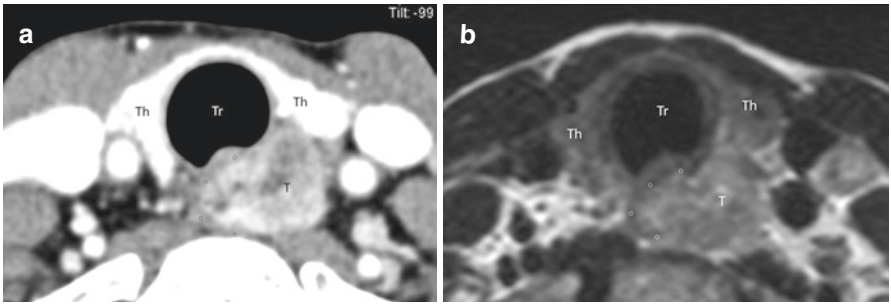

Fig. 3.13 Esophageal cancer (cervical esophagus; T3). Contrast-enhanced axial CT image (**a**) and T2-weighted axial image (**b**) at the level of the cervical esophagus show an infiltrative tumor (*T*). No detectable muscular layer (*open circle*) on the *left side* without loss of tissue planes among the esophagus and adjacent structures is suggestive of T3 disease. *Th* thyroid gland, *Tr* trachea

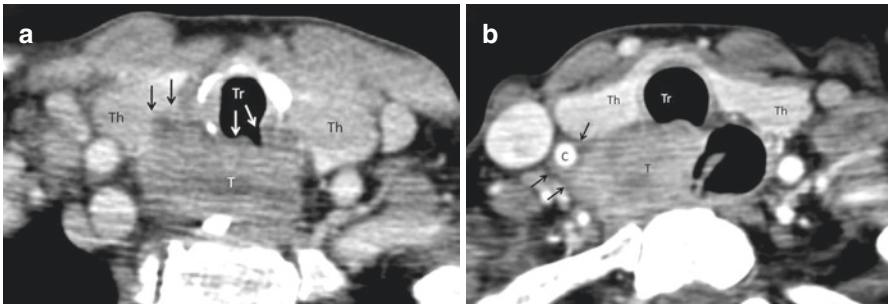

Fig. 3.14 Esophageal cancer (cervical esophagus; T4). Contrast-enhanced axial CT image at the level of the cervical esophagus (**a**) shows an irregularly shaped mass (*T*). The mass anteriorly invades to the trachea (Tr) (*white arrows*) and right lobe of the thyroid gland (*Th*) (*black arrows*). Contrast-enhanced axial CT image at the level of the cervical esophagus of different patients (**b**). There is an eccentric mass (*T*) representing the primary lesion and possible metastatic adenopathy of the paraesophageal node. The tumor laterally encompasses more than two-thirds of the right common carotid artery (*C*) (*arrows*). Findings strongly suggest carotid invasion. *Th* thyroid gland, *Tr* trachea

3.3.3.3 Diagnostic Criteria for Tumor Invasion to the Adjacent Structures

It is essential to evaluate resectability of the primary lesion when considering appropriate treatment strategy for patients with esophageal cancer. Tumor invasion to the mediastinal structures such as the aorta (Fig. 3.15) and tracheobronchial tree (Figs. 3.8, 3.14a, 3.16, and 3.17) is crucial.

CT is fairly reliable in determining resectability by excluding T4b cancers (Figs. 3.7b and 3.9a) [23]. The CT criteria for local invasion include loss of fat planes between the tumor and adjacent structures in the mediastinum and displacement or indentation of other mediastinal structures. The sensitivity and specificity of CT for predicting mediastinal invasion of the esophageal cancer are 88–100% and 85–100%, respectively [24, 25]. The sensitivity, specificity, and accuracy of CT for aortic invasion are 6, 85, and 58%, respectively, and for tracheobronchial invasion are 31–100%, 68–98%, and 74–97%, respectively [24, 26–28].

Although the presence of the fat plane rules out invasion (Figs. 3.7b and 3.9a), absence of the fat plane does not always indicate invasion. Nevertheless, tumor invasion is likely if the fat plane is obliterated at the site of probable invasion (Fig. 3.15b) and CT scans obtained immediately above and below that level show an intact fat plane [23]. We must notice that fat planes can be obliterated after radiotherapy/chemoradiotherapy or surgical intervention.

Lefor et al. reported that lesions more than 3.0 cm wide on CT scans were associated with a statistically significantly higher frequency of extraesophageal spread. The duration of survival was affected by lesion width and the presence of extraesophageal spread of disease [29]. Ruf et al. reported that esophageal cancer was unresectable when four contiguous CT sections demonstrated periesophageal infiltration [13, 30].

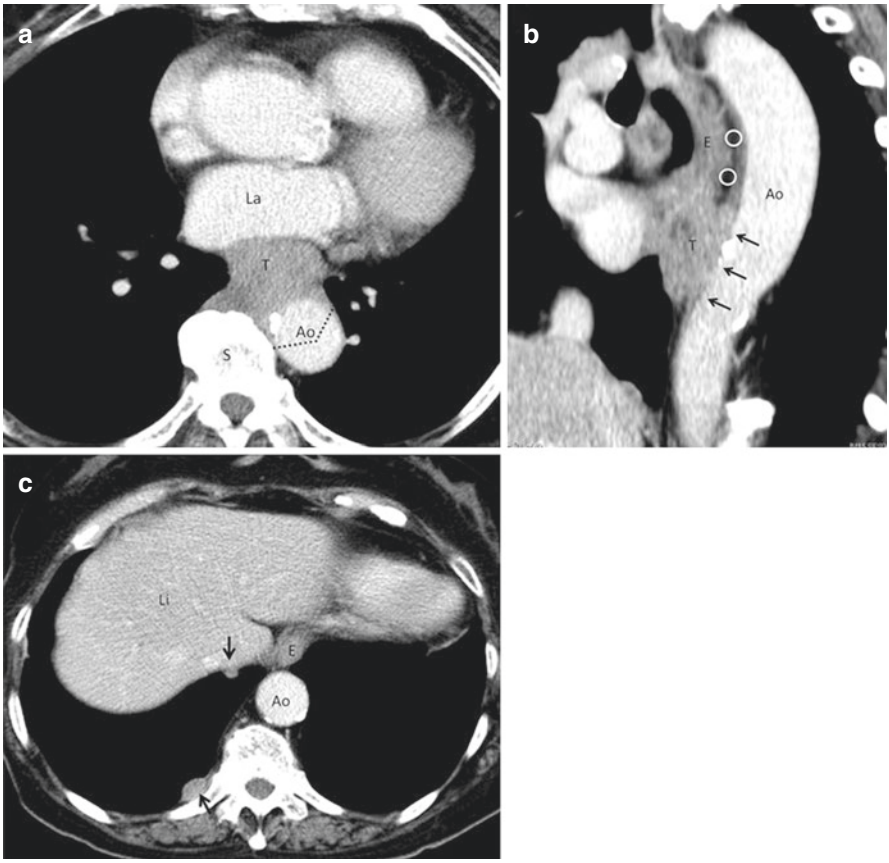

Fig. 3.15 Esophageal cancer (middle and lower thoracic esophagus; T4). (**a**) Contrast-enhanced axial CT image at the level of the left atrium (*La*). There is an infiltrative tumor (*T*) of the esophagus in the posterior mediastinum. The tumor directly abuts upon the anterior aspect of the descending aorta (*Ao*) with obliteration of the triangular fat space (please see Figs. 3.7b and 3.9a) among the esophagus, aorta (*Ao*), and spine (*S*). The area of contact between the tumor (*T*) and aorta (*Ao*) creates an arc of approximately 120° (greater than 90°); dotted lines creating "Picus angle." Findings strongly suggest aortic invasion. Oblique sagittal image (**b**) shows that the tumor (*T*) broadly abuts upon the descending aorta (*Ao*) with obliteration (*arrows*) of fat plane (*open circle*) between the esophagus (*E*) and the aorta. Axial image at the level just above the diaphragm (**c**). There are several nodular tumor deposits (*arrows*) on the pleural surface on the right side, representing pleuritis carcinomatosa (pleural seeding). *Ao* descending aorta, *E* esophagus, *Li* liver

Invasion to the Aorta (Defined as T4b)

Aortic invasion by esophageal cancer detected at autopsy or during surgery varies from 2 to 20% [13, 14, 25]. On CT, aortic invasion is suggested if 90° or more of the aorta is in contact with the tumor [25] or if there is obliteration of the triangular fat space between the esophagus, aorta, and spine adjacent to the primary lesion (Fig. 3.15) [27].

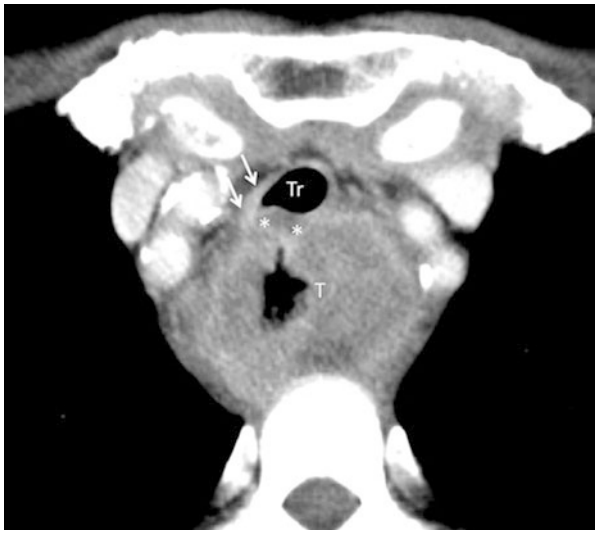

Fig. 3.16 Esophageal cancer (upper thoracic esophagus; T4). Contrast-enhanced axial CT image at the level of superior mediastinum shows irregular thickening of the esophageal wall (*T*). The tumor (*T*) indents the membranous portion (*asterisk*) and infiltrates along the right lateral wall (*arrows*) of the trachea (*Tr*). Such findings strongly suggest tracheal invasion

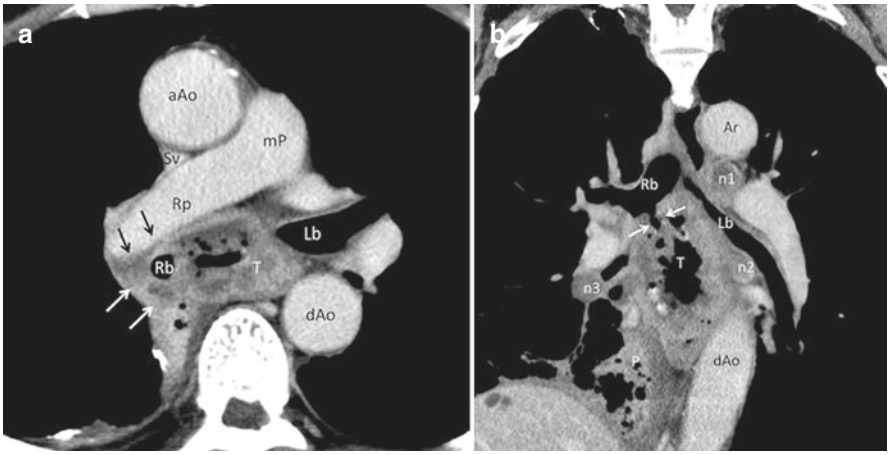

Fig. 3.17 Esophageal cancer (middle thoracic esophagus; T4). (**a**) Contrast-enhanced axial CT image at the level of middle thoracic esophagus. A necrotic tumor (*T*) arising from the middle thoracic esophagus encompasses the right main bronchus (*Rb*) (*arrows*). *aAo* ascending aorta, *dAo* descending aorta, *Lb* left main bronchus, *mP* main pulmonary artery, *Rp* right pulmonary artery, *Sv* superior vena cava. (**b**) Reformatted coronal CT image. A tracheoesophageal fistula (*arrows*) between the tumor (*T*) and right main bronchus (*Rb*) is well depicted. Significant enlargement and internal low attenuation of the left tracheobronchial (*n1*), middle thoracic paraesophageal (*n2*), and right hilar nodes (*n3*), representing multiple metastatic adenopathies in the mediastinum and right pulmonary hilum. *Ar* aortic arch, *dAo* descending aorta, *P* (aspiration-induced) pneumonia in the right lung base

Picus et al. proposed the first criteria. They determined aortic invasion with approximately 80% overall accuracy. Aortic invasion was diagnosed if the area of contact between the esophagus and the aorta created an arc of greater than 90° (Fig. 3.15a). If the arc was less than 45°, aortic invasion was considered absent; an arc of 45–90° was considered indeterminate [25].

Takashima et al. proposed the second criteria: obliteration of the triangular fat space between the esophagus, aorta, and spine suggestive of aortic invasion (Fig. 3.15a). And they reported that both sensitivity (100%) and specificity (86%) for the MRI were high with such criteria; CT and MRI have the same accuracy in predicting resectability. In their study, no patients had a false-negative result (Figs. 3.7b and 3.9a) [27]. Ogawa et al. reported that the second criteria (obliteration of the triangular fat space) was correlated with definitive invasion of the adventitia but not necessarily into the aorta itself and suggested that only when tumor is observed between the aorta and spine it strongly indicates the presence of aortic invasion [31].

Invasion to the Tracheobronchial Tree (Defined as T4b)

A tracheobronchial fistula (Figs. 3.8 and 3.17b) or tumor growth into the airway lumen (Fig. 3.14a) is a definite sign of tracheobronchial invasion. Displacement or indentation of the posterior wall of the trachea (Figs. 3.14a and 3.16) or bronchus (usually the left mainstem bronchus) (Figs. 3.8 and 3.17) by the tumor have also proved accurate in predicting tracheobronchial invasion (Fig. 3.8) [25].

Invasion to the Other Structures

Gastric invasion is manifested by a soft tissue mass extending from the primary esophageal tumor into the gastric fundus [27].

And pericardial invasion (defined as T4a) is diagnosed when pericardial thickening, pericardial effusion, or indentation of the heart with loss of pericardial fat pat plane is noted [5].

3.3.4 MRI

MRI is superior to CT in evaluation of the cervical esophageal cancer because of its higher contrast resolution (Fig. 3.11). However, it is not much helpful in the thoracic esophagus and EGJ because it is often degraded by motion artifact. Currently, MRI has not yielded significant advantages compared to CT. The sensitivity and specificity of MRI for the determination of tumor invasion are roughly equivalent to those of CT. MRI and CT have nearly the same accuracy in predicting resectability of esophageal cancer [27]. Generally, MRI is considered not superior to CT for staging esophageal cancer [12]. MRI's role in the evaluation of esophageal cancer has been somewhat limited to date [24].

However, MRI's ability to depict esophageal cancer is continuously improving. MRI potentially complements the limitation of other imaging strategies [24]. Sakurada et al. reported that 1.5 T MRI examinations with faster sequences and

cardiac/respiratory gating using both T2-weighted and diffusion-weighted images revealed T1 lesions in 33%, T2 lesions in 58%, T3 lesions in 96%, and T4 lesions in 100% [32]. 3 T MRI system is, currently, widely available worldwide. Although 3 T MRI system has higher signal-to-noise ratio than 1.5 T MRI system, it is more vulnerable to motion artifact. Hence, it does not significantly improve diagnostic performance in the evaluation of esophagus which is affected by breathing, swallowing, and heartbeat.

T2-weighted axial images at the neck can differentiate two distinct layers of the cervical esophageal wall: a high-intensity inner layer and low-intensity outer layer representing a complex of the mucosa and submucosa and muscularis propria, respectively (Fig. 3.11). T3 disease is manifested by encroachment of the low-intensity outer layer (muscularis propria) with preservation of tissue planes between the tumor and adjacent structures (Fig. 3.13b), and T4 disease is manifested by encroachment of the outer layer with obliteration of tissue planes.

The areas of infiltrating tumor will usually enhance more than muscle. The submucosal extent of tumor is best appreciated on T2-weighted or contrast-enhanced T1-weighted MR images [2]. T1-weighted images may differentiate the submucosal fat as a high-intensity layer and muscularis mucosa as a tissue-intensity layer (Fig. 3.11) and complement T2-weighted images. Fat planes around the esophagus are best evaluated on T1-weighted images (Fig. 3.11c).

3.3.5 PET

PET is useful for assessment of distant metastases but is inappropriate for detecting and staging primary tumors [5]. In general, it is impossible to detect tumor foci smaller than 5 mm on PET. The cost remains the primary limitation of PET.

3.4 N Staging by Imaging

The esophagus has an extensive lymphatic drainage system [5]. N factor is the most significant prognosticator in esophageal cancer.

Precise evaluation of the N status is difficult. Currently, regional lymph node metastases are evaluated using EUS, CT, and/or FDG-PET [24]. The most common sites of metastatic adenopathy in the mediastinum and around the celiac trunk (Fig. 3.18) often can be evaluated by CT and EUS [24]. EUS has been considered to be superior to CT in detection of metastatic lymph nodes [5]. However, using EUS, only lymph nodes close to the esophageal wall can be visualized whereas CT can demonstrate both regional and distant lymph node metastases (Fig. 3.18) [11]. And CT is superior to EUS for evaluating celiac nodes due to non-traversable stenoses [32]. Representative nodal groups on CT images are illustrated in Fig. 3.19.

Detection of metastatic lymphadenopathies on CT depends primarily on nodal size (size criteria) (Figs. 3.8b, 3.11, 3.12, and 3.17b) [5]. Lymph nodes larger than 1 cm in short-axis dimension are considered suggestive of metastatic

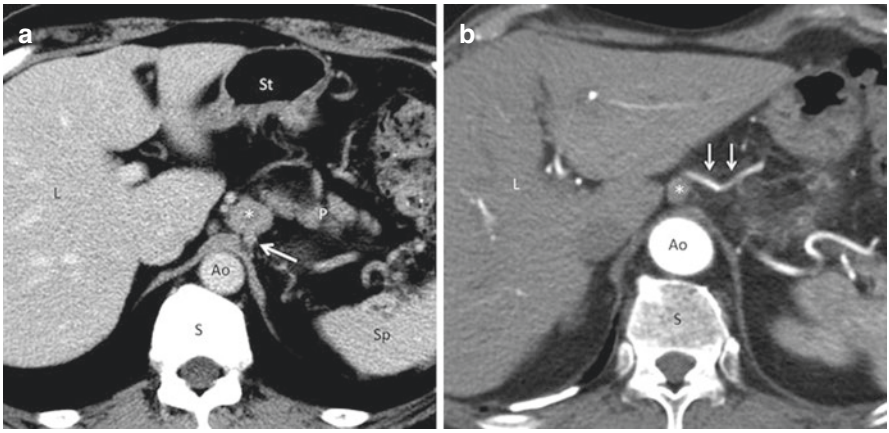

Fig. 3.18 Metastatic adenopathy of the abdominal nodes. Contrast-enhanced axial CT image (**a**) of the upper abdomen shows an enlarged lymph node (*asterisk*) adjacent to the celiac trunk (*arrow*). The node contains low attenuation within it. *Ao* aorta, *L* liver, *P* pancreas, *S* spine, *Sp* spleen, *St* stomach. Contrast-enhanced axial CT image (on arterial phase) of the different patients (**b**) shows an enlarged node (*asterisk*) along the left gastric artery (*arrows*). *Ao* aorta, *L* liver, *S* spine

disease although size is known to be an insensitive parameter for determining nodal spread because tumor can be present in subcentimeter nodes [33]. Generally, mediastinal and abdominal nodes are abnormal when a maximum axial diameter is greater than 1 cm [27]. A short-axis diameter greater than 1 cm is considered abnormal for mediastinal nodes except the subcarinal node in which 1.4 cm is the upper limit of normal. The sensitivity is 30–60% and specificity is 60–80% in most studies adopting 1 cm as size criterion to define an enlarged node on CT [34, 35]. We must recognize that enlargement of lymph nodes is nonspecific and can easily be reactive or inflammatory and lymph nodes harbor metastatic foci without significant enlargement. Enlarged paraesophageal nodes near the tumor are sometimes difficult to distinguish from contiguous tumor spread (Fig. 3.20) [15].

Focal defect (intranodal low attenuation) is a reliable feature to determine metastatic adenopathy when identified even in normal-sized nodes (Figs. 3.12, 3.17b, and 3.21).

The sensitivity of CT in detecting mediastinal lymphadenopathy is not high [23]. CT sensitivity and specificity are generally considered as 60–80% and around 90%, respectively. Regarding determination of regional lymph node metastases, meta-analysis studies reported that CT showed sensitivity of 50% and specificity of 83% and FDG-PET showed sensitivity of 51% and specificity of 84% [36, 37]. Lehr reported that the accuracy of CT for diagnosing mediastinal and abdominal lymph nodes was 56 and 45%, respectively, which are not significantly different from that found with MRI [26].

MRI's role to assess regional nodal metastasis is limited so far although MRI values have improved over the years [24].

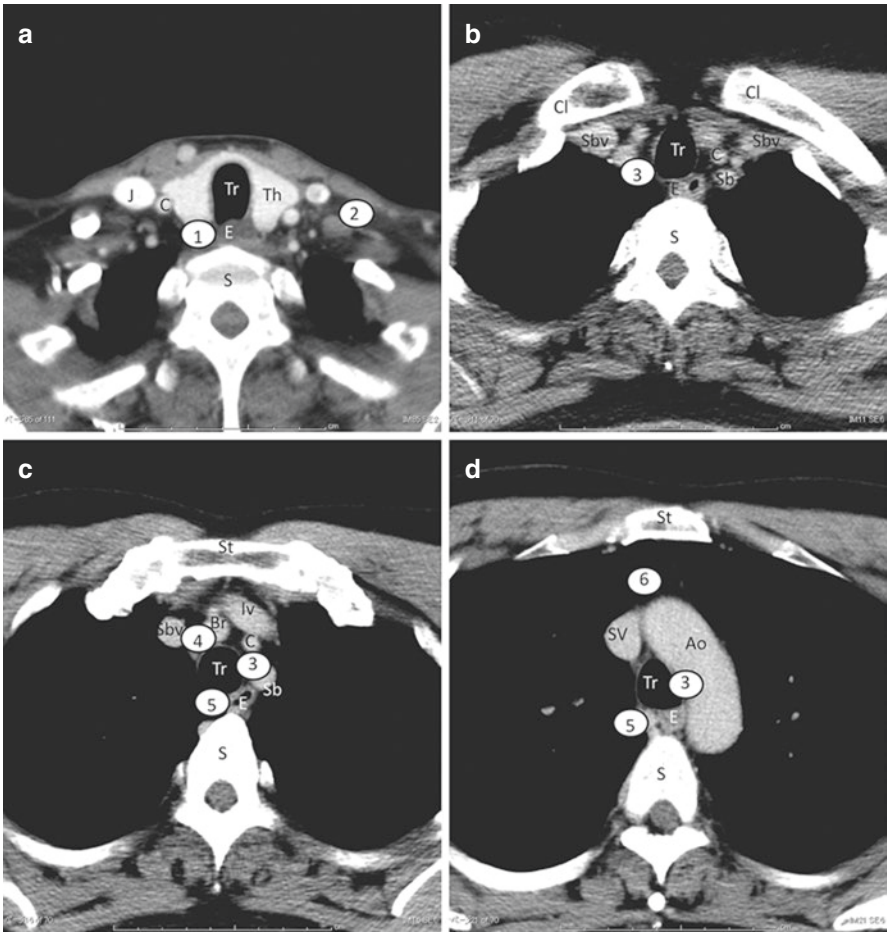

Fig. 3.19 Representative nodal groups in the lower neck and mediastinum on CT. (**a**) CT image at the level of the lower neck. (1) cervical paraesophageal node; (2) supraclavicular node. (**b**) CT image at the level of the thoracic inlet. (3) right recurrent nerve node. (**c**) CT image at the level of the superior mediastinum. (3) *left* recurrent nerve node; (4) pretracheal node; (5) upper thoracic paraesophageal node. (**d**) CT image at the level of the aortic arch. (3) *left* recurrent nerve node; (5) upper thoracic paraesophageal node; (6) anterior mediastinal node. (**e**) CT image at the level below the aortic arch. (4) pretracheal node; (5) upper thoracic paraesophageal node; (6) anterior mediastinal node; (7) tracheobronchial node. (**f**) CT image at the level below the tracheal bifurcation. (8) subcarinal node; (9) middle thoracic paraesophageal node. (**g**) CT image at the level of the inferior pulmonary vein. (10) lower thoracic paraesophageal node; (11) posterior mediastinal node. (**h**) CT image at the level just above the diaphragm. (10) lower thoracic paraesophageal node; (11) posterior mediastinal node. *AA* ascending aorta, *Ao* aortic arch, *Br* brachiocephalic vein, *C* common carotid artery, *Cl* clavicle, *DA* descending aorta, *E* (*cervical*) esophagus, *IP* inferior pulmonary vein, *Iv* innominate vein, *IV* inferior vena cava, *J* internal jugular vein, *La* left atrium, *LB* left main bronchus, *Li* liver, *LP* left pulmonary artery, *Lv* left ventricle, *Pa* pulmonary artery main trunk, *Ra* right atrium, *RB* right main bronchus, *RP* right pulmonary artery, *Rv* right ventricle; *Th* thyroid gland, *Tr* trachea; *S* spine, *Sb* subclavian artery, *Sbv* subclavian vein; *St* sternum, *SV* superior vena cava

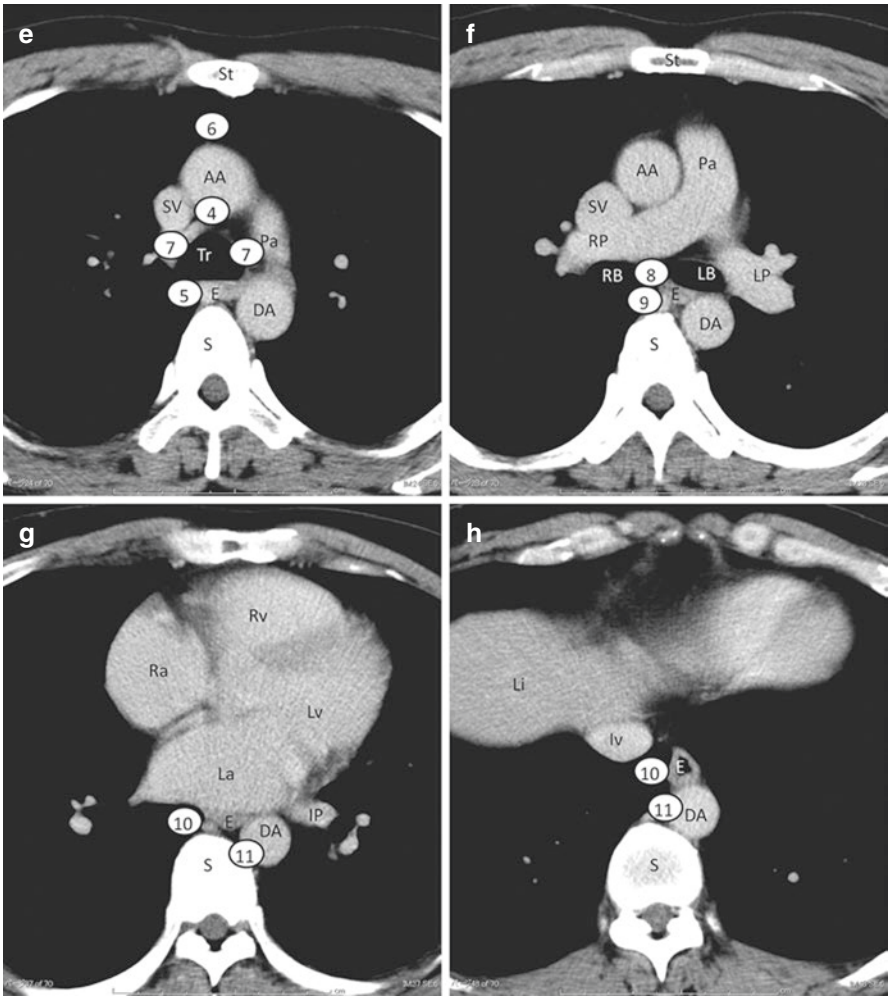

Fig. 3.19 (continued)

3.5 M Staging by Imaging

Esophageal cancer is often associated with metastatic deposits at presentation. The distant metastases are most commonly diagnosed in the abdominal lymph nodes (Fig. 3.18) [37]. Hematogenous metastases, often found in patients with esophageal cancer, commonly involve the liver (Fig. 3.22a), lung (Fig. 3.22b), bone (Fig. 3.23), adrenal gland, kidney, and brain in descending order of frequency of occurrence [5, 38, 39].

Early detection of distant metastatic foci is important for the accurate staging and appropriate treatment plan. CT is the most commonly used on this purpose. Neither MR nor CT is sensitive in detecting metastases to distant nodes, but the

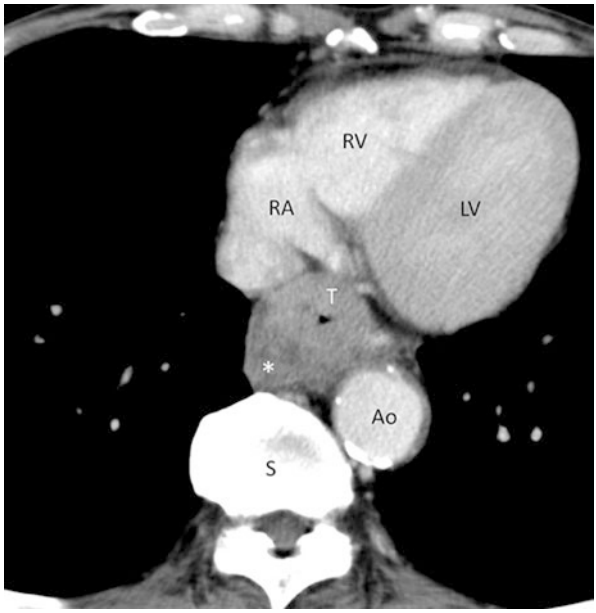

Fig. 3.20 Esophageal cancer (lower thoracic esophagus). Contrast-enhanced axial CT image at the level of the lower thoracic esophagus shows an irregularly shaped tumor (*T*). The tumor (*T*) is indistinguishable from enlarged paraesophageal node (*asterisk*) with extranodal spread. *Ao* aorta, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *S* spine

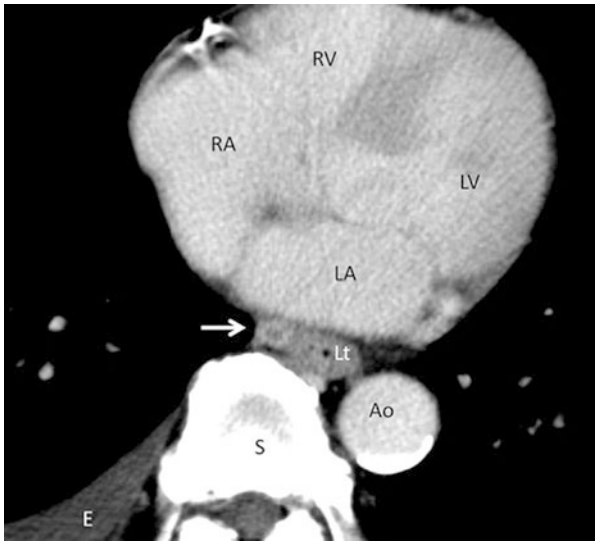

Fig. 3.21 Esophageal cancer (same patient as Fig. 3.8). Contrast-enhanced axial CT image at the level of the lower thoracic esophagus (*Lt*) shows metastatic adenopathy of the paraesophageal node (*arrow*). Metastatic deposit in the node is manifested by focal defect (intranodal low attenuation). The node is marginal by size criteria. *Ao* aorta, *E* pleural effusion, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *S* spine

specificity is high [27]. CT is currently the best diagnostic method to detect metastases and may also reveal enlarged lymph nodes around the celiac axis [12].

CT depicts metastatic deposits in the liver as low-attenuation areas on non-contrast and post-contrast images, best visualized on the portal/delayed phases (Fig. 3.22a). CT also depicts metastatic lung tumors as, usually rounded, smoothly

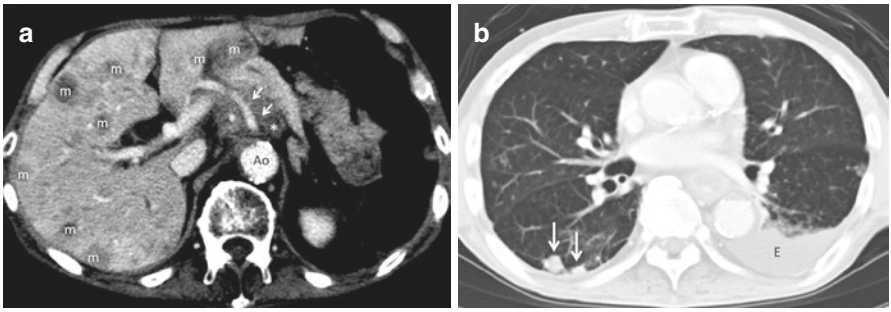

Fig. 3.22 Distant metastases to the liver and lungs. (**a**) Contrast-enhanced axial CT image of the liver on delayed/portal phase. There are numerous metastatic deposits (*m*) in the liver. Enlarged abdominal nodes (*asterisk*) encase the celiac artery (*arrows*). (**b**) Axial CT image in lung window of the same patient. Metastatic lung tumors are manifested by several round-shaped nodules (*arrows*) in the right lower lobe. Pleural effusion (*E*) is noted on the *left side*

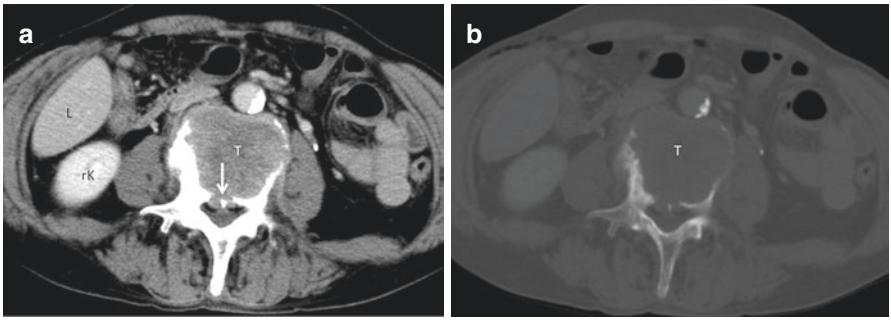

Fig. 3.23 Distant metastasis to the fourth lumbar spine. Axial CT image in soft tissue window (**a**) and bone window (**b**) shows a destructive lesion (*T*) of the fourth lumbar spine. Posteriorly, the lesion protrudes into the anterior aspect of the spinal canal (*arrows*) with impingement upon the anterior aspect of dural sac. *L* liver, *rK* right kidney

bordered and non-calcific, nodules and/or masses (Fig. 3.22b). CT of the lung field window setting is suitable for the evaluation.

PET is a powerful tool and more sensitive than CT for the detection of distant metastases [40]. PET can reveal metastatic diseases in 15% of patients who were considered to be without distant disease only on the basis of findings on conventional diagnostic modalities [41, 42]. The major problems with FDG-PET staging of esophageal cancer are failure to detect metastatic deposits less than 1 cm in diameter and lack of anatomic definition [43].

3.6 Follow-Up

Imaging is commonly used to follow-up esophageal cancers during therapy and document response. Whereas EUS and barium esophagography may show response of the primary lesion, CT is useful to reveal response of not only the primary lesion

but also the regional and distant metastases [33]. CT is considered complementary to EUS and barium esophagography on this purpose.

The ability to detect local recurrence is variable because inflammation or fibrosis may cause anatomical distortion and esophageal wall thickening, mimicking local recurrence on imaging [33]. Comparison with baseline study is mandatory to early detection of recurrent disease. The overall accuracy of CT in detecting recurrence is reported to be 87% [44].

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Diagnostic Imaging: PET/CT(PET)

4

Koji Murakami

Abstract

PET (Positron-Emission Tomography) has a unique feature that is visualized "metabolic activities" of cell, or tissue. Malignant tumors including esophageal cancers usually show hypermetabolism of glucose to be depicted clearly by using FDG-PET.

The role of FDG-PET for esophageal cancer includes staging (detecting lymph node, distant metastases), response assessment for chemo (radiation) therapy, and early detection of recurrence (surveillance). FDG-PET/CT is a very useful imaging modalities not for all, but for selected esophageal cancer patients.

Keywords

FDG · PET · Esophageal cancer · Staging · Response assessment

4.1 PET/CT(PET)

PET (Positron-Emission Tomography) is a unique imaging modality that has different features from CT and MRI. Generally speaking, CT and MRI are called "morphological imaging" as these modalities composed images based on anatomical information. On the other hand, PET makes images based on metabolic information such as glucose and amino acid in cells or tissues.

^{18}F-FDG (2-[^{18F}]-fluoro-2-deoxy-D-glucose) is the most widely used radiopharmaceuticals in oncological PET in the world, and most common probe for diagnosing esophageal cancer same as other kinds of malignancy. ^{18}F-FDG is a glucose analog

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labeled with ^{18}F, and has the disposition of strongly accumulating in cells or tissues that shows hypermetabolism of glucose. The principle of PET is to capture the weak gamma rays emitted from accumulated ^{18}F using a special camera (PET camera), and image the lesion and tissue distribution with increased glucose metabolism.

Though it is sure that many kinds of malignancy including esophageal cancer shows hyper glycolysis to have strong accumulations in FDG-PET, FDG deposit is not specific. For example, inflammatory tissue also reveals strong FDG uptake as active inflammatory cells such as macrophage, neutrophil shows hypermetabolism of glucose. On the other hand, FDG accumulation is sometimes weak in low glade malignancy or slow-growing tumors for it reflects low glucose metabolism. Size of the tumor is another important factor that affects tumor detectability. Though recent advancement of PET camera improves the performance of tumor detection, the smaller the tumor, and the lower the detection rate. PET/CT has great advantage as we can evaluate not only FDG uptake but also tumor size by CT part simultaneously.

The degree of accumulation in FDG is expressed by a numerical value "SUV" (Standardized Uptake Value), which is calculated by the following equation:

$$\begin{aligned}\mathrm{SUV} = {} & \text{tissue radioactivity}\left(\mathrm{cpm}*/\mathrm{g}\right) / \text{administrative radiation dose}\left(\mathrm{cpm}*\right) \\ & \cdot \text{body weight}\left(\mathrm{g}\right) * \mathrm{cpm};\mathrm{count}/\mathrm{minute}\end{aligned}$$

SUV is often used as an index of semiquantitative analysis in FDG deposit, but it is a relative value and it varies due to many kinds of factors such as imaging time, equipment, algorism for reconstruction, blood sugar level, etc. Therefore, in case of using SUV for evaluating the therapeutic effect, it is necessary to establish the acquisition parameters identical with previous study as much as possible. In clinical practice, measurement of SUV is not indispensable because the visual assessment is identical diagnostic performance to that of based on SUV.

FDG accumulation is affected by the level of blood sugar. Though the efficacy of FDG-PET worsens in DM patients due to insufficient tumor contrast, FDG-PET is not contraindicated with high-BS patients. FDG-PET may be performed according to clinical requirements.

The detection rate of esophageal cancer is 0% in pT1a where the tumor confined in the mucosal layer, and 20% in pT1b up to the submucosal layer, and 100% when depth reached pT2 or more [1].

According to NCCN (National Comprehensive Cancer Network) guidelines Ver.1. 2019. [2]· FDG-PET/CT is recommended as one of the workup if no evidence of M1 disease. The guideline described that clinical staging should be performed to assess resectability by CT scan of the chest and abdomen, wholebody FDG-PET and endoscopic ultrasound.

4.2 N Staging by Imaging

Though the frequency of lymph node metastasis in esophageal cancer is high, accurate diagnosis remains still challenging. Evaluation based on size criteria using CT, MRI, or US is proved to be insufficient diagnostic performance in many literatures.

FDG-PET shows additional value, especially it improves specificity over morphological image to assess locoregional lymph node metastases [3, 4].

Lymph nodes with higher accumulation than background are basically diagnosed as metastasis regardless of its size. Although high specificity for the diagnosis of lymph node metastases, microscopic metastasis sometimes causes false negative. On the other hand, mediastinum lymphadenopathy due to inflammatory diseases such as COPD, interstitial pneumonia, and sarcoidosis may cause false positives. In such cases, a comprehensive diagnosis combining with contrast-enhanced CT or MRI findings are important. The distribution, shape, size of lymph nodes are sometimes crucial to discriminate metastatic lymph nodes with inflammatory lymphadenopathy.

4.3 M Staging by Imaging

As PET can cover a wide area of the body for screening, it is possible to detect metastasis that appears in unexpected sites. Moreover, high contrast of PET enables to clearly delineate a lesion that is missed or overlooked only by CT and MRI (Fig. 4.1). Therefore, it is particularly useful in advanced cancer which has a possibility of distant metastasis. Though dedicated PET shows low special

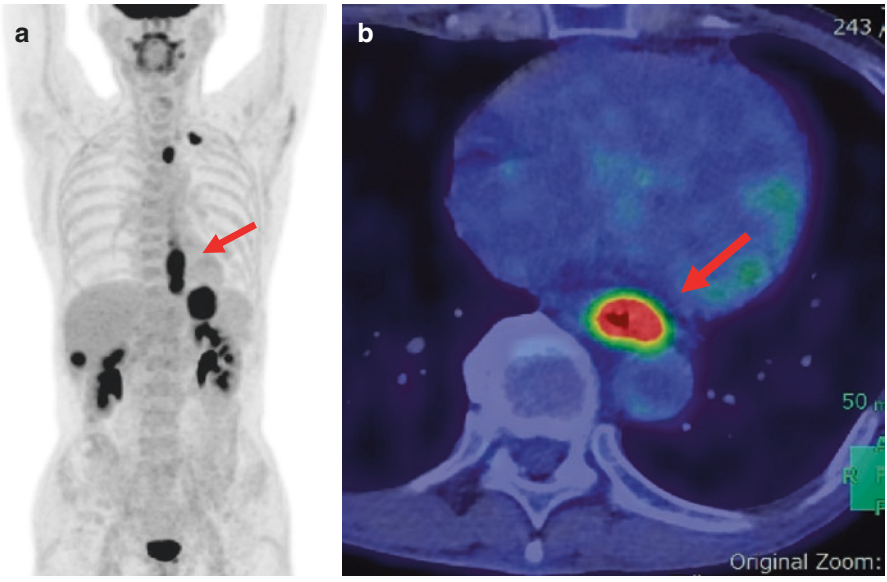

Fig. 4.1 Detection of multiple metastases (**a**) MIP (maximum intensity projection) image of FDG-PET. Primary esophageal cancer was clearly revealed (arrow). (**b**) Image of esophageal cancer on axial section of PET/CT. (**c**) Detection of supraclavicular lymph node (arrow) is difficult by contrast-enhanced CT(CECT). (**d**) PET/CT apparently demonstrated the metastatic lymph node (arrow). (**e**) Liver metastases (arrow) is sometimes misdiagnosed for cyst only by CECT. (**f**) PET/CT showed a strong accumulation in liver metastases (arrow)

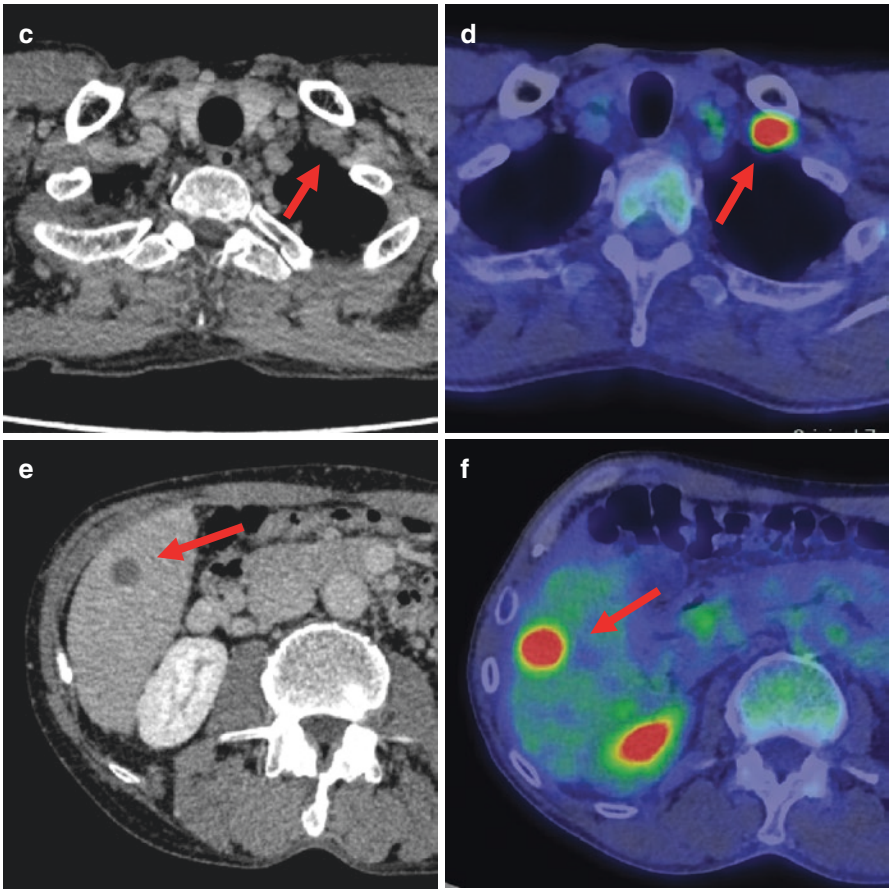

Fig. 4.1 (continued)

resolution, PET/CT can compensate the demerit and it can detect small lung metastases by using CT part.

PET/CT sometimes can play a role of "one-stop shopping" for screening distant metastases, however, MRI is indispensable for screening brain metastasis.

Esophageal cancer is known to have a high incidence of double cancer. PET sometimes can detect unexpected lesions that are difficult to find conventional preoperative imaging [5]. The possibility of multiple (synchronous) cancers should be considered rather than metastases if FDG accumulation is found at unreasonable sites.

4.4 Follow-up

4.4.1 Response Assessment

According to NCCN guidelines [2], FDG-PET(PET/CT) are recommended as response assessment for preoperative chemoradiation and definitive chemoradiation, that is, the same role of CT and endoscopy. The guideline also defined that the assessment by FDG-PET should be performed from 5 to 8 weeks after completion of preoperative therapy. The implementation time of PET is very important because if it is performed too early, the treatment effect will not be reflected properly. Especially when radiation therapy is added, longer intervals are required because radiation-induced inflammation affects the degree of accumulation of FDG.

In case responders and non-responders were separated by a threshold of 35% or more decreased in SUVmax, PET after induction chemotherapy highly predicts outcomes in esophageal cancer patients who receive chemoradiation (Fig. 4.2). On the

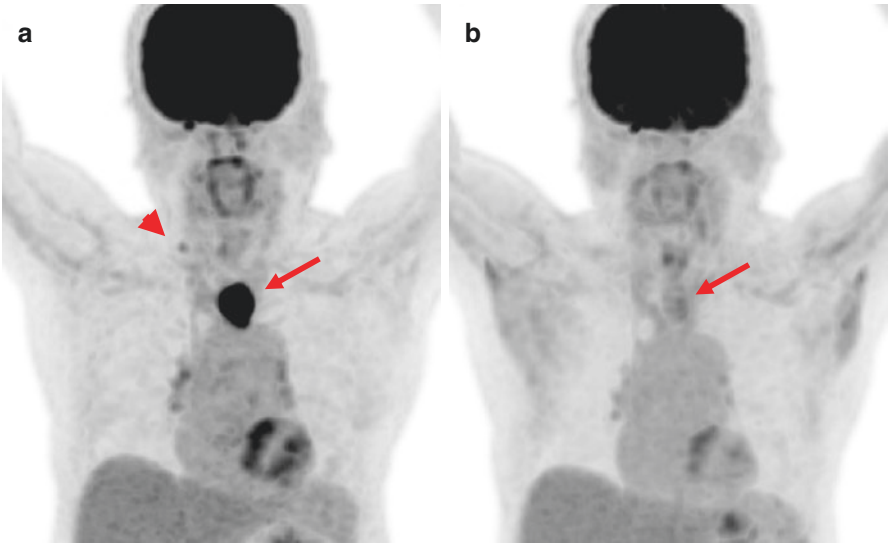

Fig. 4.2 Evaluation of therapeutic effect after neoadjuvant chemotherapy (NAC), a case of the responder. (**a**) PET image before NAC. Primary tumor showed strong FDG uptake (SUVmax;20.7, arrow) with right supraclavicular lymph node metastases (arrowhead). (**b**) PET after NAC revealed a remarkable decrease of FDG accumulation (SUVmax;3.1, arrow) in the primary tumor with almost disappearance of lymph node

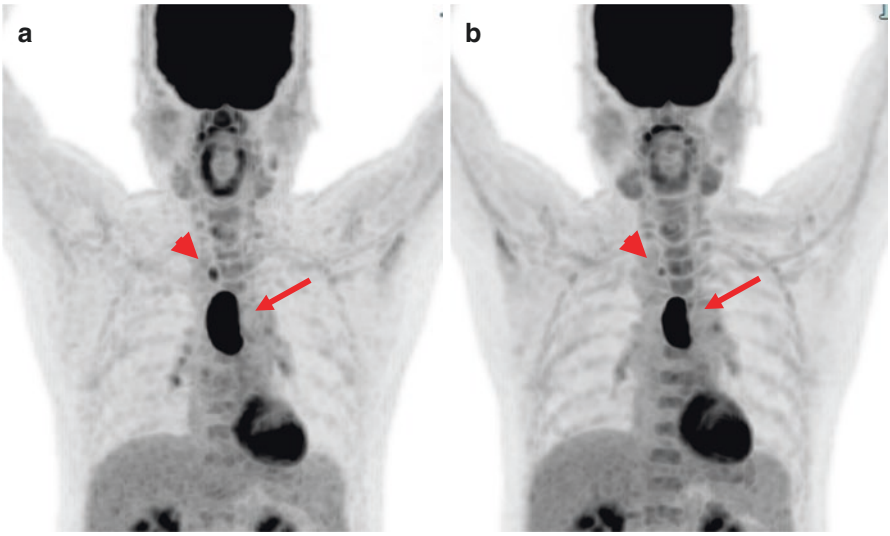

Fig. 4.3 Evaluation of therapeutic effect after neoadjuvant chemotherapy (NAC), a case of non-responder. (**a**) PET image before NAC. Primary tumor showed strong FDG uptake (SUVmax;31.3, arrow) with right mediastinal lymph node metastases (arrowhead). (**b**) PET after NAC still showed strong FDG accumulation in the primary tumor (SUVmax;27.0, arrow), which represented insufficient therapeutic effect. A mediastinal lymph node also remained FDG uptake though slightly decreasing metabolic activity (arrowhead)

other hand, non-responders do not benefit from changing chemotherapy during radiation (Fig. 4.3) [6]. Another report described that TLG (total lesion glycolysis) based on 40% SUV threshold are the best criteria to discriminate histopathologic responders on AUC (area under the receiver operating characteristic curve) analysis [7].

4.4.2 Surveillance

Although there is no evidence of PET examination as postoperative follow-up of esophageal cancer, implementation may be considered (image diagnostic guideline by JRS [8] recommends as grade C1).

Regarding NCCN guidelines [2], recommended surveillance varies according to the depth of invasion and treatment modality. In the case of "T1b, any N after the treatment of chemoradiation," CT (chest/abdomen with contrast unless contraindicated or FDG-PET/CT) should be considered every 6–9 months for the first 2 years, then annually up to 5 years (Fig. 4.4).

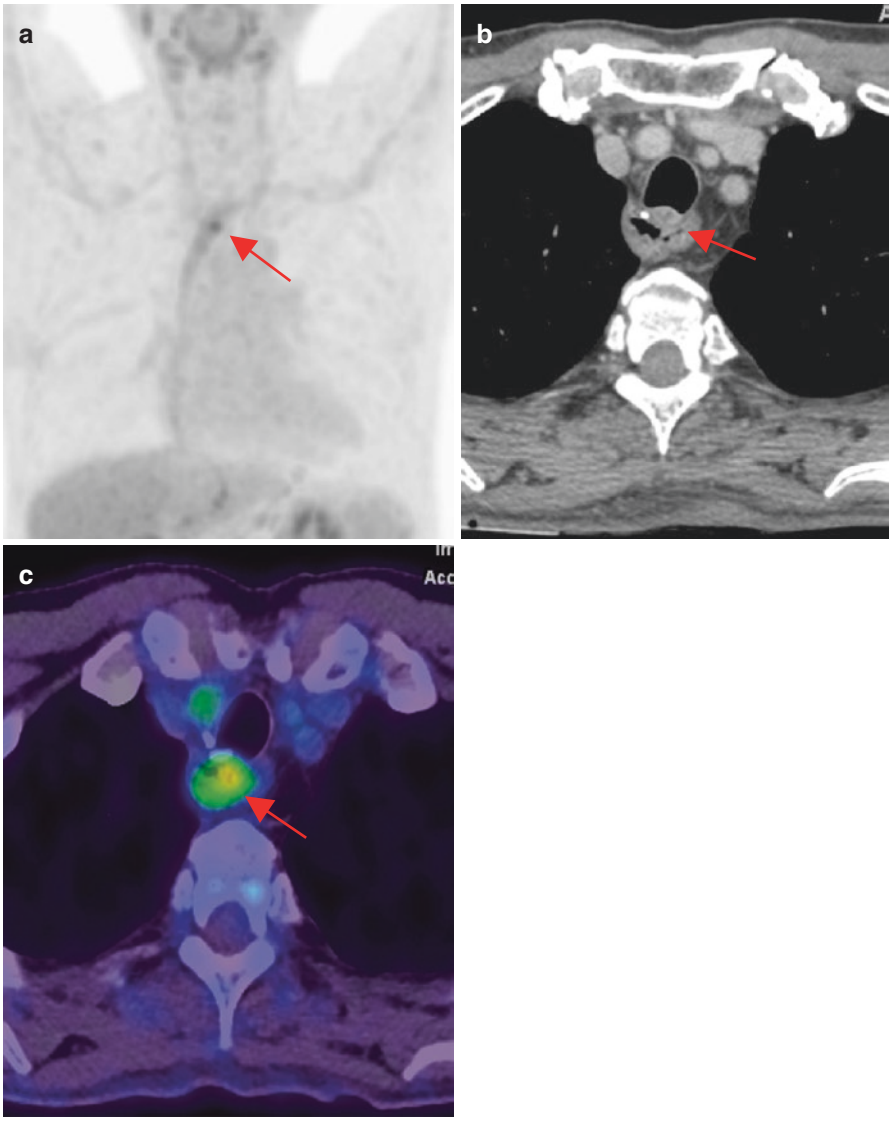

Fig. 4.4 Early detection of local recurrence. (**a**) A faint FDG accumulation was noted at reconstructed esophagus (arrow). (**b**) A small nodule was disclosed adjacent to surgical clip though detection may be difficult only by CT. (**c**) PET/CT fusion image clarified the FDG spot was consistent with the nodule, which was proved to recurrent focus later by biopsy

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Endoscopic Diagnosis of Squamous Cell Carcinoma of the Esophagus

5

Manabu Muto

Abstract

Recent advance in endoscopic imaging technology enables the endoscopists to detect esophageal squamous cell carcinoma (ESCC) more accurately than conventional white light imaging (WLI) and Lugol chromoendoscopy. Especially, a combination of narrow-band imaging (NBI) (Kaltenbach T, Gastroenterology 134:327–40, 2008) and magnifying endoscopy opened a brand new door of the endoscopic diagnostic field. NBI is classified in the category of equipment-based image-enhanced endoscope (IEE). Equipment-based IEE includes blue laser imaging (BLI) and i-scan optical enhancement (OE), which were developed after NBI.

Equipment-based IEE combined with magnifying endoscopy can visualize the microstructure of the squamous epithelial surface and microvasculature. Based on the morphological changes in these structures, we can make diagnosis ESCC more correctly and objectively. Therefore, in addition to the previous conventional strategy of endoscopic diagnosis, new diagnostic strategies based on morphological changes in the microvasculature and epithelial surface are now required and needed for the endoscopists.

In this chapter, we explained diagnostic strategies by practical endoscopy including detection, differential diagnosis, evaluation of depth of invasion, and histological confirmation of ESCC.

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Keywords

Endoscopic diagnosis · Lugol chromoendoscopy · Image enhanced endoscopy · Narrow-band imaging · Endoscopic ultrasound

5.1 Endoscopic Imaging of the Esophagus and ESCC

Endoscopy plays an important role in the detection and evaluation of the lateral and vertical extent of ESCC as well as other gastrointestinal cancers. Endoscopic imaging technology is now dramatically improved, and in particular, magnifying endoscopy and equipment-based IEE [1] provided dramatic breakthroughs in the endoscopic diagnosis of ESCC. High vision technology also contributed to the improvement of image quality.

In an endoscopic image, nonneoplastic and noninflammatory squamous epithelium appears as a flat surface, with a pink colored mucosa and an irregular vascular network (Figure 5.1a). In contrast, superficial cancerous lesions show an irregular

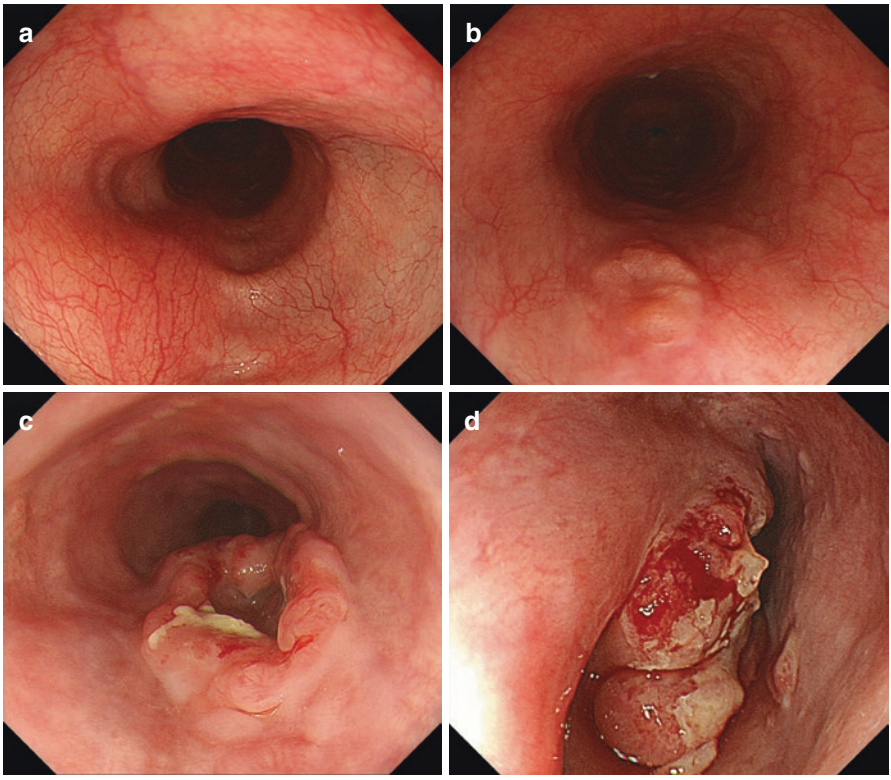

Fig. 5.1 (**a**) White light endoscopic image of normal esophageal epithelium. (**b**) Superficial squamous cell carcinoma of the esophagus (type 0-IIa). (**c**) Advanced esophageal squamous cell carcinoma (type 2). (**d**) Obstruction due to advanced esophageal cancer (type 3)

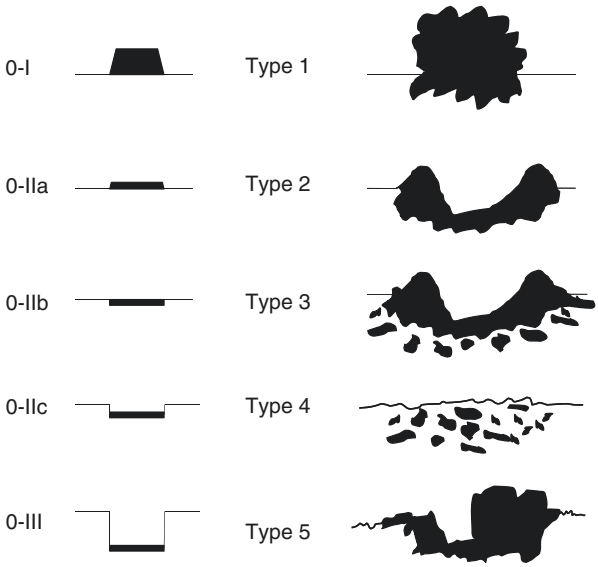

Fig. 5.2 Classification of macroscopic tumor type by the Japan Esophageal Society

surface (Figure 5.1b) and a reddish or whitish color change, while advanced cancerous lesions show clearly apparent irregular elevations or irregular ulceration (Figure 5.1c). In the most advanced ESCC, the esophageal lumen is obstructed by tumor and the endoscope cannot pass the stricture (Figure 5.1d).

The macroscopic findings of ESCC by endoscopy are very important for understanding the location, shape, and extent of the cancerous lesion, because these parameters are usually used for making decisions on their treatment. The distance of the tumor from the incisor teeth is usually measured by endoscopy. The Japanese Classification of Esophageal Cancer classifies the macroscopic tumor type into 6 categories (Types 0–5, Fig. 5.2) [2]. Tumor is defined as type 0 and recognized as superficial when the invasion is limited to the submucosa. Superficial (Type 0) ESCC is divided into 3 subtypes (0-I, 0-II, and 0-III). When the tumor invasion extends to the muscularis propria or beyond, the tumor is classified as advanced. Advanced ESCC is divided into 4 categories (Types 1, 2, 3, and 4). When a tumor cannot be classified into any of the first 5 categories (Types 0–4), it is classified as Type 5.

5.2 Endoscopic Detection and Differential Diagnosis of Superficial ESCC

Detection of advanced ESCC by endoscopy is easy. However, early detection of superficial ESCC is not always easy even for experienced endoscopists, because the endoscopic changes are usually minimal. Therefore, an ideal strategy for the early detection of ESCC is required.

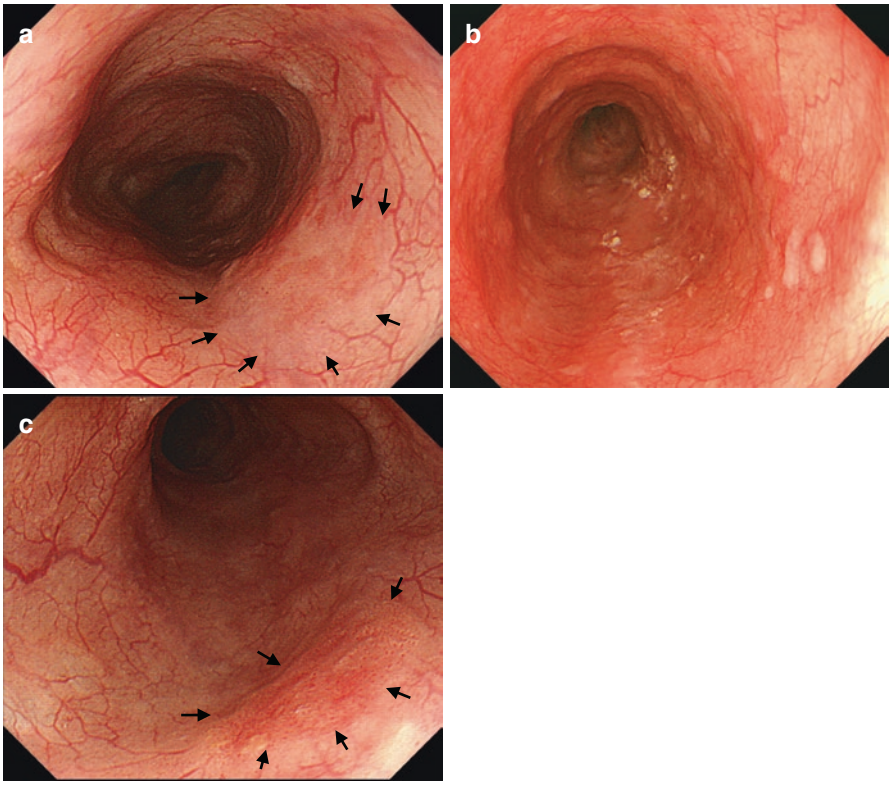

Fig. 5.3 (**a**) Superficial esophageal cancer (type 0-IIc) is clearly identified by disappearance of vascular network. (**b**) Superficial esophageal cancer (type 0-IIb) shows an uneven surface with a thin white coating. (**c**) Superficial esophageal cancer (type 0-IIa) is identified as a slight reddish lesion

5.2.1 Conventional White Light Imaging (WLI)

Conventional WLI of superficial ESCC shows disappearance of the vascular network in the mucosa (Figure 5.3a) and/or an uneven surface with a thin white coating (Figure 5.3b) or a reddish color change (Figure 5.3c). The presence of these features in a suspected lesion indicates the possible presence of superficial ESCC.

5.2.2 Lugol Chromoendoscopy

Iodine solution (Lugol solution) stains nonneoplastic esophageal squamous epithelium dark brown (Figure 5.4a). In contrast, neoplastic lesions do not stain (Figure 5.4b) [3]. Thus, Lugol chromoendoscopy is a useful method for detecting and identifying the lateral extension of ESCC. However, it causes unpleasant side effects including chest pain and discomfort in those who undergo endoscopic

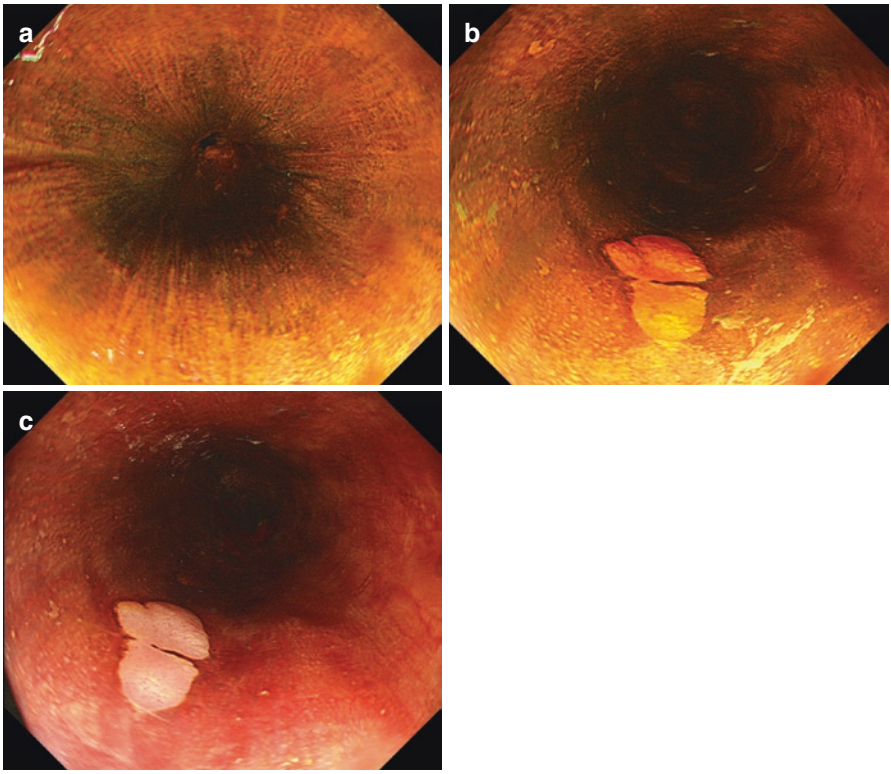

Fig. 5.4 (**a**) Normal esophageal epithelium is stained as dark brown by Lugol chromoendoscopy. (**b**) Cancerous lesion is clearly revealed as Lugol-voiding lesion after Lugol staining. (**c**) Definite cancerous lesion shows pink color change after Lugol staining

examination, and occasionally causes allergic reactions including flushing, asthma, and iodine shock. Sodium thiosulfate solution is useful in reducing these adverse symptoms. Intravenous administration of steroids before the examination is sometimes effective in preventing allergic reactions.

After staining with Lugol solution, superficial ESCC shows a pink color change (Figure 5.4c). [4]) reported that when used as a diagnostic index for high-grade intraepithelial squamous neoplasia and SCC, the pink color sign has sensitivity and specificity of 91.9% and 94.0%, respectively. [5]) also reported that its sensitivity and specificity for the diagnosis of high-grade intraepithelial neoplasia or invasive cancer were 88% and 95%, respectively.

In some cases, multiple Lugol-voiding lesions (multiple LVLs) could be detected in the entire esophagus (Fig. 5.5) [6, 7]. This phenomenon was explained by the "field carcinogenesis" theory [8], in which multiple neoplastic lesions develop not only in the esophagus but also in the head and neck region and lung, and so on. The patients with multiple LVLs in the background esophageal mucosa are at risk of multiple cancers in the upper aerodigestive tract. Abstention from drinking decreases

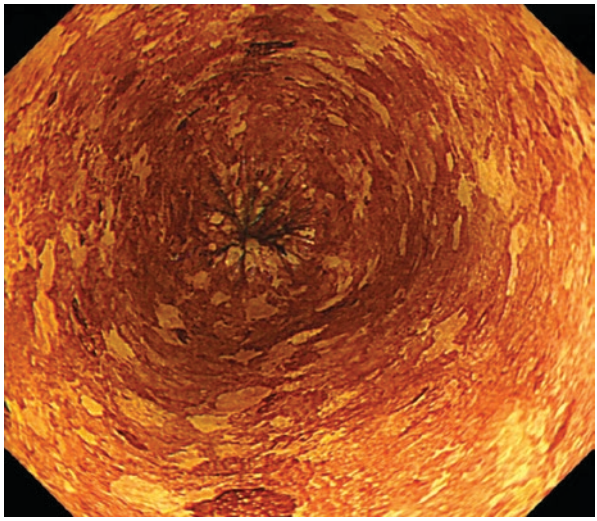

Fig. 5.5 Multiple Lugol-voiding lesions (multiple LVLs)

the risk of multiple developments of ESCC after endoscopic resection for superficial ESCC [9].

5.2.3 Equipment-Based Image-Enhanced Endoscopy (IEE)

Equipment-based IEE can accurately diagnose superficial ESCC.

Among the equipment-based IEE technologies, narrow-band imaging (NBI) [10, 11] can provide a highly accurate diagnosis of superficial ESCC. The NBI system uses two narrow-band wavelengths of 415 nm and 540 nm, corresponding to the peaks of absorption of hemoglobin. Therefore, thin blood vessels such as capillaries in the epithelium or mucosal layer can be seen more distinctly by NBI than by conventional WLI. Under NBI observation, most of the area of a superficial ESCC is seen as brownish (Figure 5.6a, b) [12, 13]. In addition, the morphological changes of the intrapapillary capillary loop (IPCL) have been recognized as a useful parameter for ESCC diagnosis [14]. With magnification, irregularities in the IPCL are also more clearly identified by NBI than by conventional WLI (Figure 5.6c, d) [12, 13].

Using the simple criteria of "brownish area" and "irregular microvascular pattern" as diagnostic findings of superficial ESCC, we [15] reported in the prospective multicenter randomized controlled trial that NBI detected more frequently superficial ESCC than did WLI (97% vs. 55%, $P < 0.001$). In addition, the sensitivity and accuracy of NBI for the diagnosis of superficial ESCC was 97.2% and 88.9%, respectively. Even small lesions (< 10 mm) were more effectively detected by NBI with magnification than by WLI (94% vs. 39%, $P = 0.03$).

[16]) also reported in their retrospective study that the specificity of NBI for diagnosis of superficial ESCC was significantly superior to that of conventional WLI (95.4% vs. 84.7%, $P < 0.001$), while the sensitivity of NBI and Lugol

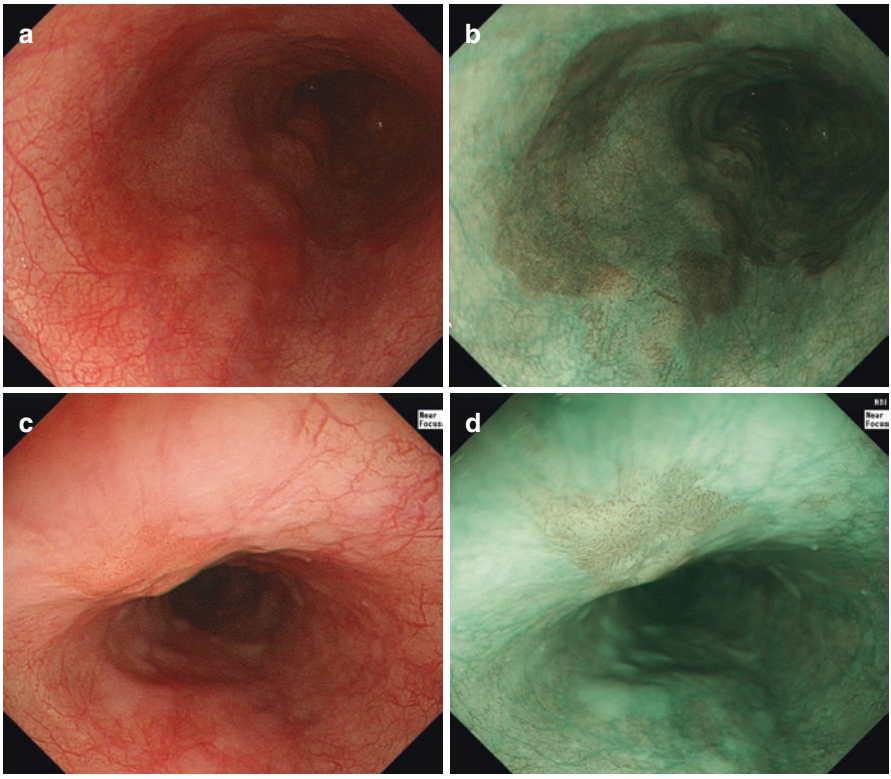

Fig. 5.6 (**a**) Slight reddish color changed is identified but its margin is unclear. (**b**) well-demarcated brownish area is clearly identified. (**c**) Magnifying white light images show irregular microvascular pattern. (**d**) Narrow-band image enhanced the irregular microvascular pattern compared to the conventional white light image

chromoendoscopy was equivalent (90.9% vs. 100%, not significant). Furthermore, most of the Lugol-unstained lesions overlooked by NBI were low-grade intraepithelial neoplasia or lesions with atypical findings. This means that Lugol chromoendoscopy detects the lesions unnecessary to treat while NBI detects those indicated for endoscopic treatment. These results indicate that NBI is a useful and less invasive screening method than Lugol chromoendoscopy for identifying superficial ESCC.

In contrast, the false-positive rate of NBI without magnification is high. Therefore, NBI is recommended for use with magnification to provide both higher sensitivity and higher specificity.

BLI (Fujifilm, Tokyo, Japan) is also one of the methods of equipment-based IEE. BLI uses two different lasers as light sources. Of note, one short wavelength laser is used to apply a blue light to the tissue, highlighting the mucosal vascular pattern morphology. The second laser produces high-contrast white light images. Diao et al. reported magnifying BLI has a diagnostic profile similar to that of magnifying NBI [17].

5.3 Estimation of the Depth of Invasion of Superficial ESCC

Estimation of the depth of tumor invasion is important to decide the appropriate treatment because the depth of invasion is closely associated with metastasis to lymph nodes [18]. The frequency of metastasis to the lymph nodes in mucosal ESCC is 3% [18]. The risk increases to 12% for cancer invading the muscularis mucosae, and increases markedly to 26%–46% in those that invade the submucosa [18].

For mucosal ESCC, minimally invasive treatment such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is indicated, because of the low risk of metastasis. Superficial ESCC invading the muscularis mucosae is usually indicated for surgical resection because of the risk of lymph node metastasis, but may still be treated by ESD, especially in comorbid patients. Superficial ESCC with submucosal invasion necessitates surgical resection and/or chemoradiotherapy (CRT).

However, accurate diagnosis of the depth of tumor invasion has been difficult. Minashi et al. reported a new treatment strategy of diagnostic endoscopic resection and selective chemoradiotherapy [19]. In this strategy, based on the pathological findings of endoscopic resection, patients received the following: (1) no additional treatment for patients with mucosal ESCC with a negative resection margin and no lymphovascular invasion, (2) prophylactic CRT with 41.4 Gy delivered to locoregional lymph nodes for patients with submucosal ESCC with a negative resection margin or mucosal ESCC with lymphovascular invasion, or (3) definitive CRT (50.4 Gy) with a boost to the primary site for patients with a positive vertical resection margin. The survival rate of this strategy is compatible with esophagectomy and could be minimally invasive treatment strategy.

5.3.1 Conventional WLI

In conventional WLI, irregularity of the surface is one of the most important features for evaluation of the depth of invasion. Apparent nodules or apparent depressions indicate tumor invasion beneath the mucosal layer. The so-called "tatami-no-me sign" is also a useful indicator of the depth of invasion (Fig. 5.7). Tatami is a traditional Japanese style flooring. If the tatami-no-me sign is not seen in the cancerous lesion, the neoplasia may invade the deep layers of the lamina propria mucosae. If the tatami-no-me sign is seen, the lesion has not invaded the deep layers of the lamina propria mucosae.

5.3.2 Lugol Chromoendoscopy

Lugol chromoendoscopy sometimes makes the evaluation of invasion of superficial ESCC difficult, because the deep staining reduces the difference in height between the cancerous lesion and the surrounding normal epithelium. Therefore, the

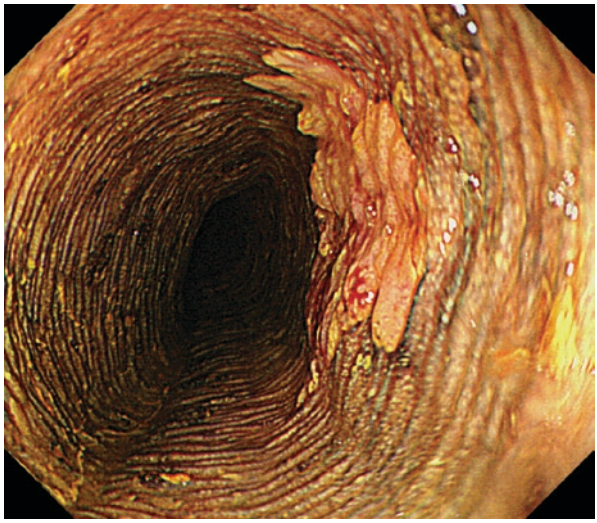

Fig. 5.7 So-called tatami-no-me sign

evaluation of invasion by Lugol chromoendoscopy should be done with care. In contrast, the tatami-no-me sign is sometimes more easily seen with Lugol chromoendoscopy because the Lugol solution irritates the mucosa.

5.3.3 Equipment-Based IEE

There has been no evidence that equipment-based IEE is useful for evaluation of the depth of invasion. However, as magnifying NBI can evaluate objectively the irregularity of IPCL, it is expected to improve the accuracy of diagnosis of tumor depth [20].

5.3.4 Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is considered to be the best method for estimation of the depth of invasion of superficial ESCC. To evaluate the depth of invasion, the distinct tissue layers of the esophageal wall should be identified, and 20 MHz or 30 MHz miniature probes should be used. To obtain a clear EUS image, a balloon should be attached to the tip of the endoscope to keep de-aerated water in the esophageal lumen and to prevent regurgitation toward the pharynx. An endoscope with a water-jet function is desirable to keep the esophageal lumen wide open and to obtain clear images. Under good conditions, these high-resolution probes provide nine-layered echo structures of the esophageal wall (Figure 5.8a).

Generally, a tumor can be seen by EUS as a low echoic mass (Figure 5.8b). If the cancerous lesion invades the submucosal layer, EUS shows a low-echo mass in the high-echo layer corresponding to the submucosal layer. In protruding superficial

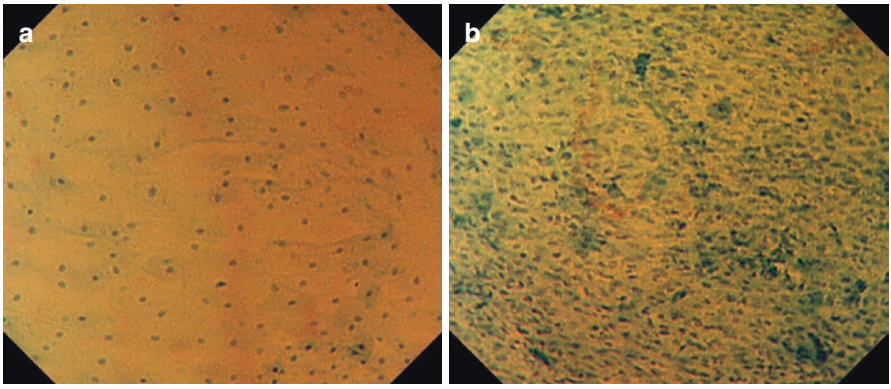

Fig. 5.8 (**a**) EUS image of the normal esophageal wall by 20 MHz mini probe demonstrates 9-layered structures (arrow). The first 5 layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), and submucosa (high echo). Next are inner circular (low echo) and outer longitudinal layers (low echo) of muscularis propria. They are separated by a thin hyperchoic layer of the connective tissue (high echo). (**b**) EUS image demonstrates a low echoic mass located in the submucosal layer

ESCC (Type 0-I) and advanced ESCC, the ultrasound waves are attenuated by the deeper layers and the EUS image becomes poor. In such cases, evaluation of tumor depth can be difficult.

EUS is also a useful method for evaluating paraesophageal lymph node metastasis of ESCC. [21]) compared lymph node staging obtained by EUS and contrast-enhanced computed tomography (CT) in patients with ESCC. In their prospective case series, the overall accuracy of EUS was 64% (sensitivity 68%, specificity 58%, positive predictive value [PPV] 68%), while that of CT was 51% (sensitivity 33%, specificity 75%, PPV 64%). Although EUS diagnosis is more accurate than contrast-enhanced CT, this is not a satisfactory outcome. Lymph node metastasis in the neck or the abdominal field is anatomically difficult to detect by EUS. Thus, a combination of EUS and CT should be performed for evaluation of lymph node staging in patients with ESCC.

5.3.5 Optical Coherence Tomography

Optical coherence tomography (OCT) is a high-resolution across-sectional optical imaging technique in real time and provides micrometer-scale spatial resolutions with millimeter-scale tissue imaging depths by measuring the echo time delays of light back-reflected from the tissue. OCT is similar in principle to ultrasonography but uses light waves rather than acoustical waves. As the axial resolution of OCT is 10 μm, much higher than that of EUS, the resolution of which is greater than 100 μm, OCT images can identify structures on a microscopic scale. [22]) reported in their prospective study that the accuracy for EP/LPM by using OCT was significantly higher than that by using EUS (OCT, 94.6%; HF-EUS, 80.6%; $P < 0.05$). Interobserver

agreement of OCT and EUS was good and moderate, respectively. Then, they concluded that the preoperative staging of superficial ESCC by using OCT was more useful than that by using EUS. However, OCT is still not the standard method for assessment of the depth of invasion of ESCC. The clinical usefulness of OCT should be assessed by multicenter prospective randomized controlled study.

5.4 Endoscopic Diagnosis of Advanced ESCC

Type 1 ESCC is easy to identify by endoscopy. However, the discrimination of type 0-I and type 1 is sometimes difficult because of borderline lesions. In such cases, the tumor volume and esophageal wall hardness should be considered, because the former suggests deeper invasion and the latter indicates invasion of the muscular layer. To discriminate type 2 and type 3 tumors, it is important to identify whether the tumor ridge is well-demarcated or poorly demarcated. Esophageal metastasis from breast cancer sometimes shows scirrhous infiltration resulting in a type 4 appearance. In cases of severe stricture, macroscopic evaluation is difficult because the endoscope cannot pass through the stricture. In such cases, tumor types are classified based only on images of the oral side of the tumor.

5.5 Differential Diagnosis of Squamous Cell Carcinoma and Adenocarcinoma

Adenocarcinoma is the other major histological esophageal cancer. This histological type is closely associated with Barrett's esophagus in the background esophageal mucosa. As Barrett's esophagus is not covered by squamous epithelium but columnar epithelium, the surface pattern is relatively easy to identify by endoscopy. However, it should be histologically confirmed to contain gastric fundic glands, gastric cardia, or intestinal-type epithelium containing goblet cells. Clinically, the cancerous lesion combined with Barrett's esophagus in the background mucosa is relatively easy to diagnose as adenocarcinoma. In contrast, cardiac cancer extends to the esophagus is sometimes difficult to diagnose by endoscopy as squamous cell carcinoma or adenocarcinoma. In such a case, the superficial spread of IIc-like extension, which is frequently observed in the squamous cell carcinoma, could be one of the key endoscopic findings for differential diagnosis.

5.6 Histological Confirmation by Biopsy

Confirmation of histology by biopsy specimen is required to decide the treatment. Biopsy specimens should be carefully taken by biopsy forceps from viable tumor tissue, not necrotic tissue. If other histological types of tumors such as adenocarcinoma or small cell carcinoma are identified by histological examination, the treatment strategy will be changed in some cases.

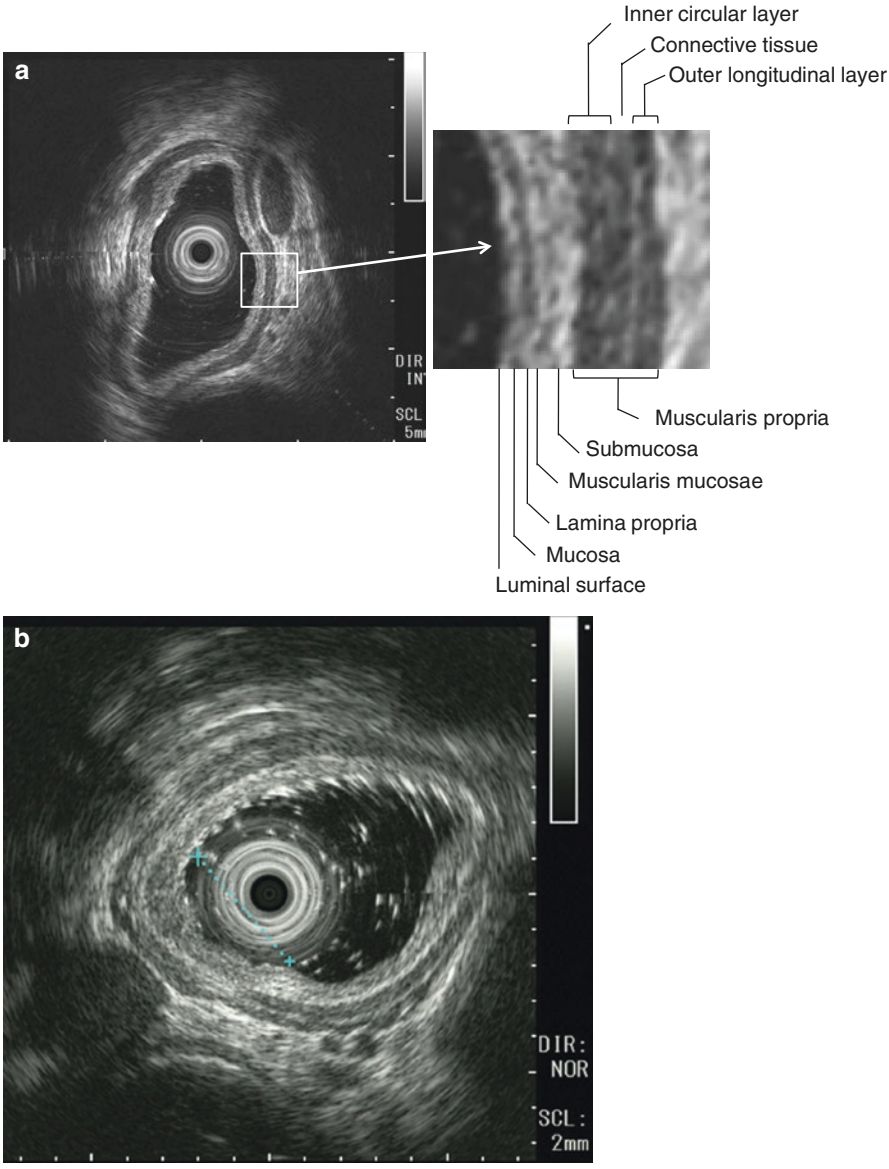

Fig. 5.9 ECS images. (**a**): Nonneoplastic epithelium. (**b**) Neoplastic lesion

5.7 Virtual Biopsy

The endocytoscopy system (ECS) enables in vivo observation of cellular nuclei in the gastrointestinal tract at up to 1400-fold magnification (Fig. 5.9) [23–25]. This technology has been predicted to provide the possibility of "virtual biopsy,"

especially in the esophagus and colon. Inoue et al. reported that ECS could characterize various tissues including nonneoplastic lesions, inflammatory lesions, and neoplastic lesions. [26]) reported in their prospective ex vivo study that ECS images of the esophagus closely corresponded with those of conventional histology. If ECS could be applied in clinical practice, the number of biopsies required and the risks of biopsy including bleeding would be reduced.

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6 Stage Classifications: UICC/AJCC Classifications and the Japanese Classification

Hiromasa Fujita

Abstract

The history, TNM categories, stage grouping, and related categorizations are compared between the UICC/AJCC stage classifications and the Japan Esophageal Society (JES) stage classification which is the official classification of esophageal cancer in Japan. The most commonly used staging system throughout the world is the TNM Classification of Malignant Tumours which is published collaboratively by the UICC and the AJCC. On the other hand, the Japanese Classification of Esophageal Cancer is used throughout Japan and rarely in other countries. There are significant differences between the UICC/AJCC Classifications and the JES Classification in the N categories and in the stage classifications. The N categories are classified by the *number* of metastasis-positive lymph nodes in the UICC/AJCC Classification, whereas the N categories are classified by the *spread* of the metastasis-positive lymph nodes in the JES Classification. The UICC/AJCC strongly considers that stage classification should be based on prognostic outcomes, thus they have six-stage classifications—three for squamous cell carcinoma, and three for adenocarcinoma. On the other hand, the JES has only the one stage classification, and this is adopted for prognostic prediction and also plays a role in the guidelines for lymphadenectomy.

Keywords

American Joint Committee on Cancer (AJCC) · AJCC Cancer Staging Manual · Japan Esophageal Society (JES) · Japanese Classification of Esophageal Cancer · Union for International Cancer Control (UICC) · TNM Classification of Malignant Tumours

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6.1 Introduction

Several cancer staging systems are used worldwide for esophageal cancer and for cancer of the esophagogastric junction. Three staging systems are presented here and compared—(1) the TNM Classification of Malignant Tumours authorized by the Union for International Cancer Control (UICC), (2) the AJCC Cancer Staging Manual authorized by the American Joint Committee on Cancer (AJCC), and (3) the Japanese Classification of Esophageal Cancer authorized by the Japan Esophageal Society (JES). The most commonly used staging system is the TNM Classification which is published collaboratively by the UICC and AJCC. The TNM Classification seems to be a simplified form of the AJCC Cancer Staging Manual. On the other hand, the Japanese Classification of Esophageal Cancer includes not only stage classification but also many definitions and clinical classifications concerning esophageal cancer.

6.2 Historical Overview

6.2.1 History of the UICC and the TNM Classification (Fig. 6.1) [1–8]

In 1933, the International Union Against Cancer—Union Internationale Contre le Cancer (UICC) was established as a nonprofit and nongovernment organization. Then in the 1940s, the TNM system was developed for the classification of malignant tumors. In 1950, the UICC appointed a Committee on Tumor Nomenclature and Statistics and agreed general definitions for the local extension of malignant tumors. In 1954, the Research Committee of the UICC set up a special Committee on Clinical Stage Classification and Applied Statistics to extend the general technique of classification to cancer at any site.

Between 1960 and 1967, the Committee published nine pamphlets describing proposals for the classification of 23 sites. In 1968, these pamphlets were combined into a booklet, which was substantially the first edition of the TNM Classification of Malignant Tumours (Fig. 6.2) [1].

In 1995, the project started to publish Prognostic Factors in Cancer, a compilation and discussion of the prognostic factors in cancer, both anatomic and nonanatomic, at each of the body sites. The seventh edition of the TNM Classification [7] contained rules of classifications, stage grouping, and prognostic groupings that corresponded with anatomic stage/prognostic groups appearing in the seventh edition of the AJCC Cancer Staging Manual (2009) [11].

In 2010, the name of the UICC was changed to the Union for International Cancer Control.

In 2017, the eighth edition of the TNM Classification [8] was published at the same time as the eighth edition of the AJCC Cancer Staging Manual [12] with the TNM stage and prognostic groups corresponding with AJCC prognostic stage groups.

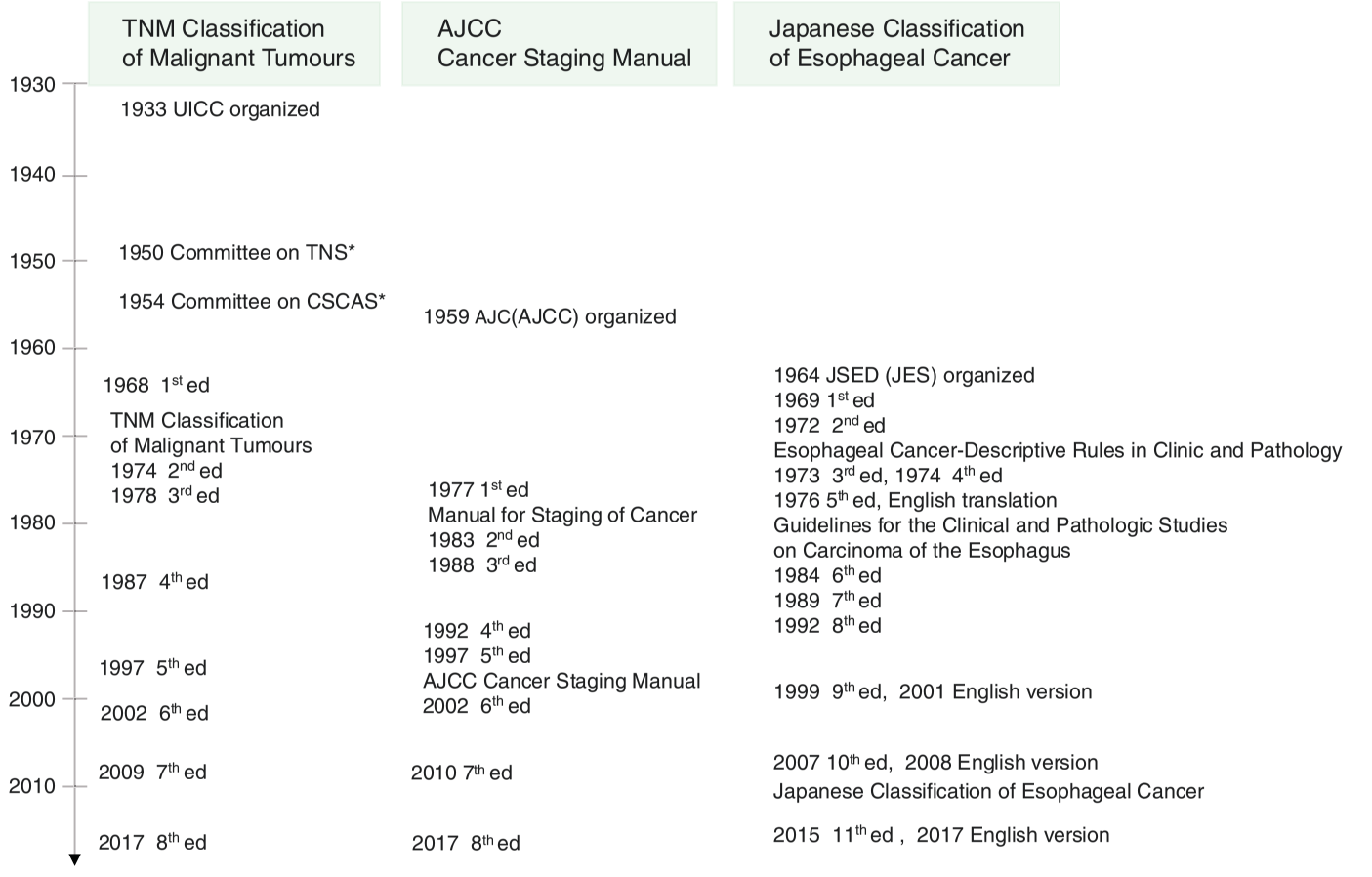
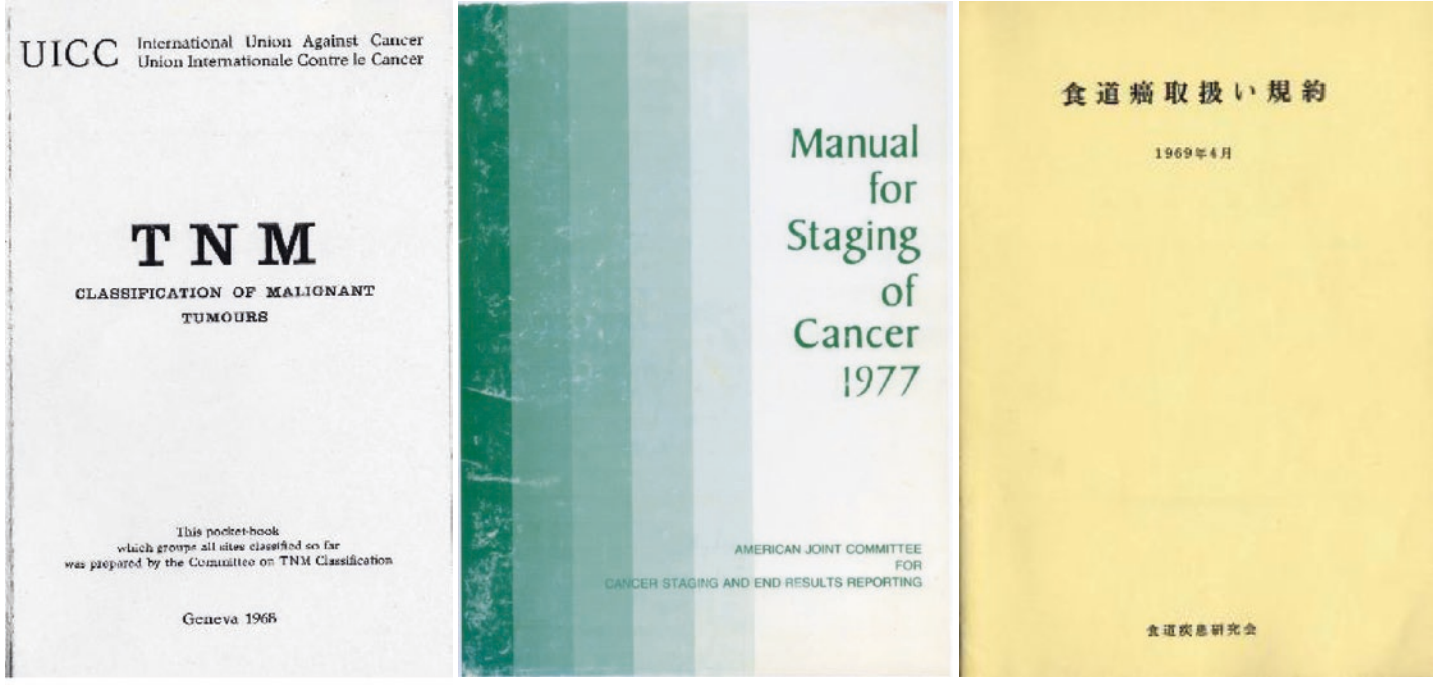


Fig. 6.1 History of the TNM Classification of Malignant Tumours, the AJCC Cancer Staging Manual, and the Japanese Classification of Esophageal Cancer. *TNS** Tumor Nomenclature and Statistics, *CSCAS** Clinical Stage Classification and Applied Statistics



1st edition of the TNM Classification of Malignant Tumours prepared by International Union Against Cancer (UICC, 1968)

1st edition of the Manual for Staging of Cancer prepared by American Joint Committee for Cancer Staging and End-results Reporting (AJCC, 1977)

1st edition of the Esophageal Cancer – Descriptive Rules in Clinic and Pathology prepared by Japanese Society for Esophageal Diseases (JSED, 1969)

Fig. 6.2 First edition of the TNM Classification of Malignant Tumours [1], of the Manual for Staging of Cancer [9] (former name of AJCC Cancer Staging Manual), and of the Esophageal Cancer—Descriptive Rules in Clinic and Pathology [10] (former name of Japanese Classification of Esophageal Cancer)

6.2.2 History of the AJC/AJCC and the AJCC Cancer Staging Manual (Fig. 6.1) [9, 11–17]

The American Joint Committee (AJC) for Cancer Staging and End-Results Reporting was first organized in 1959. The founding organizations of the AJC were several scientific societies including the American College of Surgeons and the National Cancer Institute. In 1976, the AJC sponsored a National Cancer Conference on Classification and Staging. The deliberation at this conference led to the development of the first edition of the Manual for Staging of Cancer that was published in 1977 (Fig. 6.2) [9].

In 1980, the new name—the American Joint Committee on Cancer (AJCC)—was selected. Since the early 1980s, the close collaboration of the AJCC and the UICC has resulted in uniform and identical definitions and stage groupings of cancers for all anatomic sites, initially in the third edition of the Manual for Staging of Cancer (AJCC, 1988) [14] and the fourth edition of the TNM Classification of Malignant Tumours (UICC, 1987) [4], and subsequently the same TNM categories and stage grouping for esophageal cancers have been presented by both organizations.

Since the 1990s, the TNM staging of cancer has become widely adopted throughout the United States, and the terminology in the AJCC-TNM system is used for cancer reporting. Since the fifth edition published in 1997 [15], the new name—the AJCC Cancer Staging Manual—has been used.

The AJCC esophageal cancer stage systems in the seventh and eighth editions of the AJCC Cancer Staging Manual adopted a scientific staging system based on a large worldwide database and on novel statistical techniques [18–20]. In particular, the eighth staging system analyzed the data of 22,123 clinically staged patients, 13,300 pathologically staged patients with no preoperative therapy, and 7,773 pathologically staged neoadjuvant patients, from 33 Worldwide Esophageal Cancer Collaboration (WECC) institutions in 13 countries on six continents [21–23]. However, Japanese institutions did not participate in that WECC, and Japanese data were not included in the WECC database.

6.2.3 History of the JSED/JES and the Japanese Classification (Fig. 6.1) [10, 24–38]

The Japanese Society for Esophageal Diseases (JSED) was founded in 1965, and the first scientific meeting of the JSED was held later the same year, leading to the publication in 1969 of the first edition of Esophageal Cancer—Descriptive Rules in Clinic and Pathology (Fig. 6.2) [10].

To date, there have been seven chairmen of the editorial board of the Japanese Classification [39]. The first was Hiroshi Sato, who chaired the editorial board for 25 years from 1966 to 1991. During this period, the first to the seventh editions [10, 29–34, 38] were published. In 1976, the first English translation of the Japanese Classification was published under the title Guidelines for Clinical and Pathologic

Studies on Carcinoma of the Esophagus, in the *Japanese Journal of Surgery* [38]—the official journal of the Japan Surgical Society (JSS), which is the forerunner of the journal *Surgery Today*.

During the period from 1991 to 1999, when the second to fourth chairmen led the editorial board, the eighth and ninth editions of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus were published [35, 36]. These chairmen and the Lymph Node Committee of the JSED contributed significantly to settle the new lymph node classification for cancer in the thoracic esophagus based on the results from three-field lymphadenectomy, which was published in the ninth edition in 1999 [36]. The ninth edition was republished in English in 2001 [37].

During the period from 1999 to date, the fifth to seventh chairmen led the editorial board. In 2003, the Japanese Society for Esophageal Diseases (JSED) changed its name to the Japan Esophageal Society (JES). The Japanese version of its tenth edition was published in 2007 [24], and the following year its English version was published under the name of The Japanese Classification of Esophageal Cancer [25], in which the lymph nodes classification for cancers in the cervical esophagus and in the esophagogastric junction was revised [39]. The latest 11th edition was published in 2015 [26], and in 2017, its English version was published in the *Esophagus*—the official journal of the Japan Esophageal Society [27, 28].

6.3 Anatomical Subsites: Esophagus and Esophagogastric Junction

6.3.1 The TNM Classification

The TNM classifications of the esophagus and the stomach were included in the first edition (UICC, 1968) [1]. At that time the esophagus was divided into three subsites/regions—(1) the cervical esophagus, (2) the intrathoracic esophagus excluding the distal part of the esophagus, and (3) the distal part of the esophagus including the abdominal portion. There was, however, no particular description of the esophagogastric junction or the cardia (where the cardia was included in the upper third of the stomach). In the second edition (UICC, 1974) [2], the intrathoracic esophagus was divided into two portions—(1) the upper thoracic portion and (2) the middle thoracic portion. Those regions of the esophagus were anatomically defined by the level of the vertebrae and the distance from the upper incisor teeth.

In the third edition (UICC, 1978) [3], those anatomical regions and subsites were labeled, according to the International Classification of Diseases for Oncology (ICD-O, World Health Organization, 1976), as being the cervical esophagus (150.0), the upper thoracic portion of the intrathoracic esophagus (150.3), the mid-thoracic portion of the intrathoracic esophagus (150.4), and the lower esophagus (150.5). However, the esophagogastric junction and the cardia were still not labeled by the ICD-O.

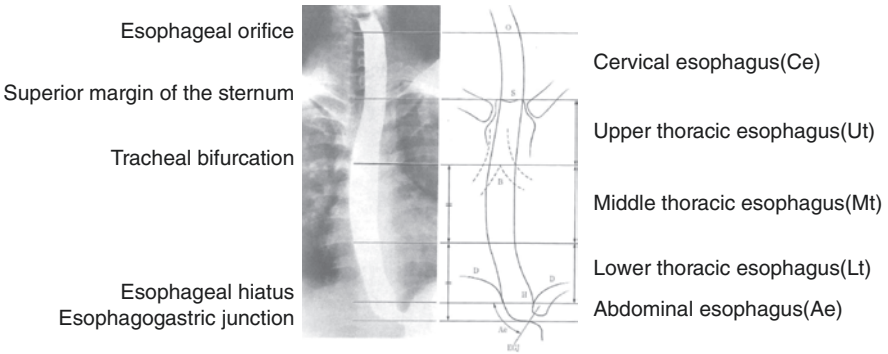


Fig. 6.3 Anatomical subsites (tumor location and anatomical esophageal nomenclature) in the latest 11th edition of the Japanese Classification of Esophageal Cancer (JES, 2015) [26–28], which is slightly modified from that in the second edition of the Esophageal Cancer—Descriptive rules in Clinic and Pathology—(JSED, 1972) [29]

In the fourth edition (UICC, 1987) [4], together with the third edition (AJCC, 1988) [14], the anatomical subsites of the esophagus were defined as in the first edition (JSED/JES, 1969) (Fig. 6.3) [10]. As a result, all three-stage classifications have the same definition for the esophageal subsites.

In the seventh edition (UICC, 2009) [7], the definition of the esophagogastric junction for adenocarcinoma was remarkably changed together with the seventh edition (AJCC, 2010) [11] according to Siewert's Classification [40], although the definition of anatomical subsites of the cervical and intrathoracic esophagus remained unchanged.

In the latest eighth edition (UICC, 2017) [8], the definition of cancer involving the esophagogastric junction is further modified together with the latest eighth edition (AJCC, 2017) [12].

6.3.1.1 Anatomical Subsites [4, 14]

1. Cervical esophagus (150.0): This commences at the lower border of the cricoid cartilage and ends at the thoracic inlet (suprasternal notch), approximately 18 cm from the upper incisor teeth.
2. Intrathoracic esophgagus.
   a. The upper thoracic portion (150.3) extending from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm from the upper incisor teeth.
   b. The mid-thoracic portion (150.4) is the proximal half of the esophagus between the tracheal bifurcation and the esophagogastric junction. The lower level is approximately 32 cm from the upper incisor teeth.
   c. The lower thoracic portion (150.5), approximately 8 cm in length (includes the abdominal esophagus), is the distal half of the esophagus between the tracheal bifurcation and the esophagogastric junction. The lower level is approximately 40 cm from the upper incisor teeth.

6.3.1.2 Definition of the Esophagogastric Junction (C16.0) in the Seventh Edition (UICC, 2009) [7]

A tumor (adenocarcinoma) the epicenter of which is within 5 cm of the esophagogastric junction and also extends into the esophagus is classified and staged using the esophageal scheme. Tumors with an epicenter in the stomach greater than 5 cm from the esophagogastric junction or those within 5 cm of the esophagogastric junction without extending in the esophagus are classified and staged using the gastric carcinoma scheme.

6.3.1.3 Definition of Esophagogastric Junction (C16.0) in the Eighth Edition (UICC, 2017) [8]

Cancers involving the esophagogastric junction (OGJ) whose epicenter is within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as esophageal cancers. Cancers whose epicenter is more than 2 cm distal from the OGJ will be staged using the Stomach Cancer TNM and Stage even if the OGJ is involved.

6.3.2 The AJCC Cancer Staging Manual

The anatomical subsites of the esophagus and the stomach in the first edition (AJC/AJCC, 1977) [9] were classified as in the third edition (UICC, 1978) [3]. The anatomical regions of the esophagus were defined by the distance from the upper incisor teeth.

In the third edition (AJCC, 1988) [14], the anatomical subsites of the esophagus were labeled according to the ICD-O and defined in the same fashion as in the first edition (JSED/JES, 1969) (Fig. 6.3) [10].

In the fifth edition (AJCC, 1997) [16], the lower thoracic portion of the intrathoracic esophagus (C15.5) includes the intra-abdominal portion of the esophagus and the esophagogastric junction.

In the seventh edition (AJCC, 2010) [11], the definitions of cancers involving the esophagogastric junction were revised to align with those in the seventh edition (UICC, 2009) [7]. However, the definitions of the anatomical subsites of the esophagus were also modified, so they were now different from those in the seventh edition (UICC, 2009) and different from those in the Japanese Classification.

Further, in the eighth edition (AJCC, 2017) [12], the definitions of cancers involving the esophagogastric junction were changed to align with the eighth edition (UICC, 2017) [8], as mentioned above, while the definitions of the anatomical subsites of the esophagus remain different from those of the eighth edition (UICC, 2017).

6.3.3 The Japanese Classification

The anatomical subsites of the esophagus—tumor location and anatomical esophageal nomenclature—were defined in the first edition (JSED/JES, 1969) (Fig. 6.3) [10]. They have remained unchanged up to the latest 11th edition (JES, 2015) [26–28]. In the second edition (JSED/JES, 1972) [29], cancer of the esophagogastric junction was defined as a tumor limited between superiorly the lower and abdominal esophagus and inferiorly the upper-third of the stomach, and lymph node groups for cancer of the esophagogastric junction (EC, E = C, CE)—N category—were classified.

In the tenth edition (JES, 2008) [24, 25], several criteria for the clinical diagnosis of cancers in the esophagogastric junction were presented, and the zone of the esophagogastric junction was newly defined according to Nishi's Classification [41].

In the latest 11th edition (JES, 2015) [26–28], a precise definition is presented for the esophagogastric junction, in cooperation with the Japan Gastric Cancer Association.

6.3.3.1 Definition of the Esophagogastric Junction (EGJ) [26–28]

The esophagogastric junction (EGJ) should be defined systemically in accordance with the criteria listed below. Endoscopic findings should take priority over findings obtained using other diagnostic modalities.

1. Endoscopic findings.
   - The lower margin of palisading small vessels in the lower esophagus.
   - The oral margin of the longitudinal folds of the great curvature of the stomach, if the palisading small vessels cannot be clearly identified.
2. X-ray: Upper gastrointestinal series.
   - The narrowest focus of the lower esophagus.
   - The oral margin of the longitudinal folds, in cases with a sliding hiatal hernia or in the presence of Barrett's esophagus.
3. Pathological study.
   - Macroscopically, the point at which the luminal caliber changes in the area where the tubular esophagus is connected to the vestibule lumen of the stomach.
   - Microscopically, the squamocolumnar junction (SCJ) in the non-Barrett esophagus.
   - Histological structures such as proper esophageal glands and their ducts, a double-layer muscularis mucosa, or palisading small vessels in the Barrett's esophagus.

6.3.3.2 Definition of the Zone of the EGJ [26–28]

The zone of the esophagogastric junction is defined as the region between 2 cm in the esophagus and 2 cm in the stomach from the esophagogastric junction. The abdominal esophagus is included within this zone.

In the first to 11th editions of the General Rules for the Gastric Cancer Study (Japanese Research Society for Gastric Cancer: JRSGC), there was no description on the esophagogastric junction or of cancer in the esophagogastric junction. In the 12th edition (JRSGC, 1993) [42], and in the first English edition of the Japanese Classification of Gastric Carcinoma (JRSGC, 1995) [43], it was stated that if a tumor was located within the upper-third (C) of the stomach and extending into the esophagus (E), then it should be described as CE, and that tumors in the esophagogastric junction should be subdivided as CE or EC. Lymph node groups for dissection of regional lymph nodes—N categories—were added, when the tumor invaded the esophagus.

In the 14th and latest 15th editions of the Japanese Classification of Gastric Carcinoma (Japanese Gastric Cancer Association: JGCA, 2010 and 2017) [44, 45], the zone of the esophagogastric junction and cancer in the esophagogastric cancer were defined as in the tenth edition (JES, 2008) [24, 25].

6.4 T Category: Primary Tumor

6.4.1 The TNM Classification

In the first edition (UICC, 1968) [1], the T category was classified by regional extension and morbidity. In the second edition (UICC, 1974) [2], the T category was classified by the length of the tumor, circumferential extension, and extra-esophageal spread.

In the third edition (UICC, 1978) [3], the TNM pre-treatment clinical classification and the pTNM postsurgical histopathological classification were introduced. The latter was classified by the depth of tumor invasion as in the second edition (JSED/JES, 1972) [29].

In the fourth edition (UICC, 1987) [4], the clinical T and pathological T categories were unified to the same classification as the pT category, as shown in Fig. 6.4.

In the seventh and latest eighth editions (UICC, 2009 and 2017) [7, 8], the T category is modified. T1 was divided into T1a and T1b, and became the same as in the ninth edition (JSED/JES, 1999) [36, 37]. High-grade dysplasia was added into the same group as Tis. T4 was divided into two categories—T4a, where the tumor invaded resectable organs, and T4b, where the tumor invaded unresectable organs (Fig. 6.5).

T– Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis carcinoma in situ

T1 Tumour invades lamina propria or submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades adventitia
T4 Tumour invades adjacent structures

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M – Distant Metastasis

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

The categories M1 and pM1 may be further specified according to the following notations:

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	HEP	Peritoneum	PER
Brain	BRA	Skin	SKI
Lymph nodes	LYM	Others	OTH

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	Mo
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Fig. 6.4 TNM categories and stage grouping in the fourth edition of the TNM Classification of Malignant Tumours (UICC, 1987) [4], which were aligned to those in the third edition of the Manual for Staging of Cancer (AJCC, 1988) [14]

6.4.2 The AJCC Cancer Staging Manual

In the first edition (AJC/AJCC, 1977) [9], the same T category was adopted as in the second edition (UICC, 1974) [2]. In the third edition (AJCC, 1988) [14], the T category was classified by the depth of tumor invasion as in the fourth edition (UICC, 1987) [4]. After this unification, the T category of the AJCC Cancer Staging Manual became the same as that of the TNM Classification to date.

6.4.3 The Japanese Classification

In the first edition (JSED/JES, 1969) [10], the T category was classified by the extent of invasion to the adventitia: A0, where there was no invasion to the adventitia; A1, where there was a possible invasion to the adventitia; A2, where there was

definite invasion to the adventitia; and A3, where there was invasion to neighboring structures. In the second edition (JSED/JES, 1972) [29], clinical and histological T categories were introduced. The histological T category was classified by the depth of tumor invasion.

6.4.3.1 Histological T Categories [29]

ep: Carcinoma in situ
mm: Invasion to muscularis mucosa
sm: Invasion to submucosa
mp: Invasion to muscularis propria
a1: Possible invasion to adventitia
a2: Definite invasion to adventitia
a3: Invasion to neighboring structures

In the ninth edition (JSED/JES, 1999) [36, 37], both clinical and histological T categories were unified and were classified only by the depth of tumor invasion.

In the tenth edition (JES, 2007) [24, 25], the subclassification for superficial cancer was newly described, where T1a and T1b are each divided into three layers (Figs. 6.6 and 6.7).

In the latest 11th edition (JES, 2015) [26–28], T4 was divided into two categories—T4a, where the tumor invaded resectable organs, and T4b, where the tumor invaded unresectable organs (Fig. 6.6), as in the seventh edition of the TNM Classification (UICC, 2009) [7] and that of the AJCC Cancer Staging Manual (AJCC, 2010) [11].

T–Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ/high-grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosae
- T1a Tumour invades lamina propria or muscularis mucosa
- T1b Tumour invades submucosa

T2 Tumour invades muscularis propria
T3 Tumour invades adventitia
T4 Tumour invades adjacent structures
- T4a Tumour invades pleura, pericardium, or diaphragm
- T4b Tumour invades other adjacent structures such as aorta, vertebrabody, or trachea

N–Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1-2 regional lymph nodes
N2 Metastasis in 3-6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes

M–Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis

Fig. 6.5 TNM categories and stage grouping modified from those in the eighth edition of the TNM Classification of Malignant Tumours (UICC, 2017) [8]. Clinical TNM classifications (cTNM) for squamous cell carcinoma and for adenocarcinoma of the UICC are the same as those of the AJCC. Pathologic prognostic groups for squamous cell carcinoma and for adenocarcinoma of the UICC are the same as pathologic TNM classifications (pTNM) for squamous cell carcinoma and for adenocarcinoma of the AJCC

cTNM Squamous Cell Carcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1	I	I	III	IVA	IVB
T2	II	II	III	IVA	IVB
T3	II	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

cTNM Adenocarcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1	I	IIA	IVA	IVA	IVB
T2	IIB	III	IVA	IVA	IVB
T3	III	III	IVA	IVA	IVB
T4a	III	III	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

pTNM Squamous Cell Carcinoma & Adenocarcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1a	IA	IIB	IIIA	IVA	IVB
T1b	IB	IIB	IIIA	IVA	IVB
T2	IIA	IIIA	IIIB	IVA	IVB
T3	IIB	IIIB	IIIB	IVA	IVB
T4a	IIIB	IIIB	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

Pathologic Prognostic Group Squamous Cell Carcinoma

		N0		N1	N2	N3	M1
		L	U/M				
Tis		0					
T1a	G1	IA	IA	IIB	IIIA	IVA	IVB
	G2-3	IB	IB				
T1b		IB		IIB	IIIA	IVA	IVB
T2	G1	IB	IB	IIIA	IIIB	IVA	IVB
	G2-3	IIA	IIA				
T3	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIB				
T4a		IIIB	IIIB	IIIB	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVA	IVB

Pathologic Prognostic Group Adenocarcinoma

		N0	N1	N2	N3	M1
Tis		0				
T1a	G1	IA	IIB	IIIA	IVA	IVB
	G2	IB				
	G3	IC				
T1b	G1	IB	IIB	IIIA	IVA	IVB
	G2	IC				
	G3					
T2	G1	IC	IIIA	IIIB	IVA	IVB
	G2	IIA				
	G3	IIB	IIIB	IIIB	IVA	IVB
T3		IIIB	IIIB	IIIB	IVA	IVB
T4a		IVA	IVA	IVA	IVA	IVB
T4b						

Fig. 6.5 (continued)

Depth of Tumor Invasion (T)

TX Depth of tumor invasion cannot be assessed
T0 No evidence of primary tumor
T1a Tumor Invades mucosa
  T1a-EP Carcinoma in situ (Tis)
  T1a-LPM Tumor Invades lamina propriamucosae (LPM)
  T1a-MM Tumor Invades muscularis mucosae (MM)
T1b Tumor Invades submucosa (SM)
  SM1 Tumor Invades the upper third of the submucosal layer
  SM2 Tumor Invades the middle third of the submucosal layer
  SM3 Tumor Invades the lower third of the submucosal layer
T2 Tumor Invades muscularis propria(MP)
T3 Tumor Invades adventitia (AD)
T4 Tumor Invades adjacent structures (AI)
  T4a Pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein. nerve.
  T4b Aorta (great artery), trachea, bronchus, pulmonary vein, pulmonary artery, vertebral body.

Grading of Lymph Node Metastasis (N)

NX Lymph node metastasis cannot be assessed
N0 No lymph node metastasis
N1 Metastasis involving only Group 1 lymph nodes
N2 Metastasis to Group 2 lymph nodes, regardless of involvement of Group 1 lymph nodes
N3 Metastasis to Group 3 lymph nodes, regardless of involvement of Group 1 or 2 lymph nodes
N4 Metastasis to distant (Group 4) lymph nodes, regardless of whether any other group(s) of regional lymph nodes are involved or not

Distant Organ Metastasis (M)

MX Distant organ metastasis cannot be assessed
M0 No distant organ metastasis
M1 Distant organ metastasis

Stage grouping

Depth of tumor invasion \ Metastasis	N0	N1	N2	N3	N4	M1
T0, T1a	0	II	II	III	IVa	IVb
T1b	I	II	II	III	IVa	IVb
T2	II	II	III	III	IVa	IVb
T3	II	III	III	III	IVa	IVb
T4a	III	III	III	III	IVa	IVb
T4b	IVa	IVa	IVa	IVa	IVa	IVb

T4a pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, nerve
T4b aorta (large vessel), trachea, bronchus, pulmonary vein, pulmonary artery, vertebra

Fig. 6.6 TNM categories and stage grouping of the 11th edition of the Japanese Classification of Esophageal Cancer (JES, 2017) [26–28]

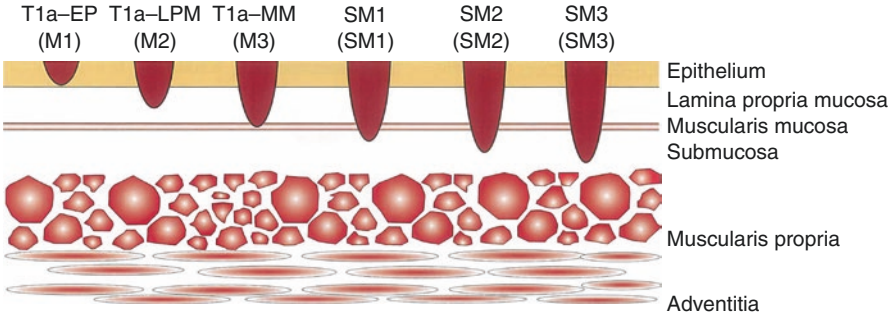


Fig. 6.7 Subclassification of superficial esophageal cancer in the 11th edition of the Japanese Classification of Esophageal Cancer (JES, 2015) [26–28] (modified from that in the Guidelines for Esophageal Cancer Treatment 2002)

6.5 N Category—Lymph Node Metastasis

6.5.1 TNM Classification

In the first edition (UICC, 1968) [1], the regional lymph nodes for cancer in the cervical esophagus are defined to be the cervical nodes. Those for cancer in the intrathoracic esophagus and for any cancer in the distal esophagus are defined to be the intrathoracic and intra-abdominal lymph nodes (although added here was a note that those lymph nodes cannot be assessed). In the third edition (UICC, 1978) [3], the regional lymph nodes of the intrathoracic esophagus were classified into two grades—N0, where there was no evidence of involvement of regional lymph nodes, and N1, where there was evidence of involvement of those on surgical exploration or mediastinoscopy.

In the fourth edition (UICC, 1987) [4], the regional lymph nodes for the cervical esophagus were defined to be the cervical nodes including supraclavicular nodes, and those for the intrathoracic esophagus were defined to be the mediastinal and perigastric nodes excluding the coeliac nodes. The N category was classified only by no evidence (N0), or by evidence (N1) of involvement with regional lymph node metastasis (Fig. 6.4).

In the sixth edition (UICC, 2002) [6], the regional lymph node stations were defined for the cervical esophagus and for the intrathoracic esophagus.

In the seventh and latest eighth editions (UICC, 2009 and 2017) [7, 8], coeliac axis nodes and paraesophageal nodes in the neck were defined as the regional lymph nodes, irrespective of the site of the primary tumor. The supraclavicular nodes were excluded from being regional lymph nodes. The N category was classified into four groups as N0 to N3 according to the number of metastasis-positive nodes among the regional lymph nodes, as in the seventh and eighth editions (AJCC, 2010 and 2017) [11, 12] (Fig. 6.5).

6.5.2 The AJCC Cancer Staging Manual

In the first edition (AJC/AJCC, 1977) [9], the regional lymph nodes were defined to be the cervical and supraclavicular nodes for the cervical esophagus and the adjacent mediastinal lymph nodes for the thoracic esophagus. The N category—nodal involvement—was classified as in the third edition (UICC, 1978) [3]. The regional lymph nodes for the thoracic esophagus were considered to be not assessable (NX). After surgical evaluation, the N category can be assessed as N0, no positive nodes, or as N1, positive nodes.

In the third edition (AJCC, 1988) [14], the lymph node stations belonging to specific regional lymph nodes were defined for each esophageal subsite as (1) cervical; (2) intrathoracic, upper and middle; and (3) intrathoracic, lower. Here, the abdominal nodes were considered to be regional for the lower esophagus. The N category was defined by metastasis positivity among the regional lymph node as N0 or N1 (Fig. 6.4). In the fourth edition (AJCC, 1992) [15], the left gastric nodes and

cardiac nodes were added to the specific regional lymph nodes for the upper and middle intrathoracic esophagus, as in the lower intrathoracic esophagus.

In the sixth edition (AJCC, 2002) [17], esophageal lymph node maps indicating the regional lymph node stations were presented. Specific regional lymph nodes for the esophagogastric junction were added.

In the seventh edition (AJCC, 2010) [11], more detailed lymph node maps for esophageal cancer were presented. The N category was classified into four groups as N0 to N3 according to the number of metastasis-positive lymph nodes, in line with the evidence-based staging developed through statistical analysis of a worldwide database [18, 19]. In the latest eighth edition (AJCC, 2017) [12], lymph node maps for esophageal cancer were modified from those in the seventh edition (AJCC, 2010) [11]. Non-regional nodes were omitted from the lymph node maps.

6.5.3 The Japanese Classification

In the first edition (JSED/JES, 1969) [10], an esophageal lymph node map indicating the regional lymph node stations was presented, and its modified map was included also in the latest 11th edition (JES, 2015) [26–28] (Fig. 6.8), and the regional lymph nodes were classified into three categories, N1, N2, and N3, in each tumor location:

Cervical lymph nodes
100 Superficial lymph nodes of the neck
101 Cervical paraesophageal lymph nodes
102 Deep cervical lymph nodes
103 Peripharyngeal lymph nodes
104 Supraclavicular lymph nodes

Thoracic lymph nodes
105 Upper thoracic paraesophageal lymph nodes
106 Thoracic paratracheal lymph nodes
106rec Recurrent nerve lymph nodes
106recL Left recurrent nerve lymph nodes
106recR Right recurrent nerve lymph nodes
106pre Pretracheal lymph nodes
106tb Tracheobronchial lymph nodes
106tbL Left tracheobronchial lymph nodes
106tbR Right tracheobronchial lymph nodes
107 Subcarinal lymph nodes
108 Middle thoracic paraesophageal lymph nodes
109 Main bronchus lymph nodes
109L Left meinbronchus lymph nodes
109R Right main bronchus lymph nodes
110 Lower thoracic paraesophageal lymph nodes
111 Supradiaphragmatic lymph nodes
112 Posterior mediastinal lymph nodes
112aoA Anterior thoracic paraaortic lymph nodes
112aoP Posterior thoracic paraaortic lymph nodes
112pul Pulmonary ligament lymph nodes
113 Ligament arteriosum lymph nodes (Botallo lymph nodes)
114 Anterior mediastinal lymph nodes

Abdominal lymph nodes
1 Right paracardial lymph nodes
2 Left paracardial lymph nodes
3a Lesser curvature lymph nodes along the branches of the left gastric artery
3b Lesser curvature lymph nodes along the 2nd branches and distal part of the right gastric artery
4 Lymph nodes along the greater curvature
4sa Lymph nodes along the short gastric artery
4sb Lymph nodes along the left gastroepiploic artery
4d Lymph nodes along the right gastroepiploic artery
5 Suprapyloric lymph nodes
6 Infrapyloric lymph nodes
7 Lymph nodes along the left gastric artery
8a Lymph nodes along the common hepatic artery (anterosuperiorgroup)
8p Lymph nodes along the common hepatic artery (Posterior group)
9 Lymph nodes along the coeliac artery
10 Lymph nodes at the splenic hilum
11 Lymph nodes along the splenic artery
11p Lymph nodes along the proximal splenic artery
11d Lymph nodes along the distal splenic artery
12 Lymph nodes in the hepatoduodenal ligament
13 Lymph nodes on the posterior surface of the pancreatic head
14 Lymph nodes along the superior mesenteric vessels
14A Lymph nodes along the superior mesenteric artery
14V Lymph nodes along the superior mesenteric vein
15 Lymph nodes along the middle colic artery
16 Lymph nodes along the abdominal aorta
17 Lymph nodes on the anterior surfaceof the pancreatic head
18 Lymph nodes along the inferior margin of the pancreas
19 Infradiaphragmatic lymph nodes
20 Lymph nodes in the esophageal hiastusof the diaphragm

Fig. 6.8 Station numbers and names of regional lymph nodes in the 11th edition of the Japanese Classification of Esophageal Cancer (JES, 2015) [26–28]

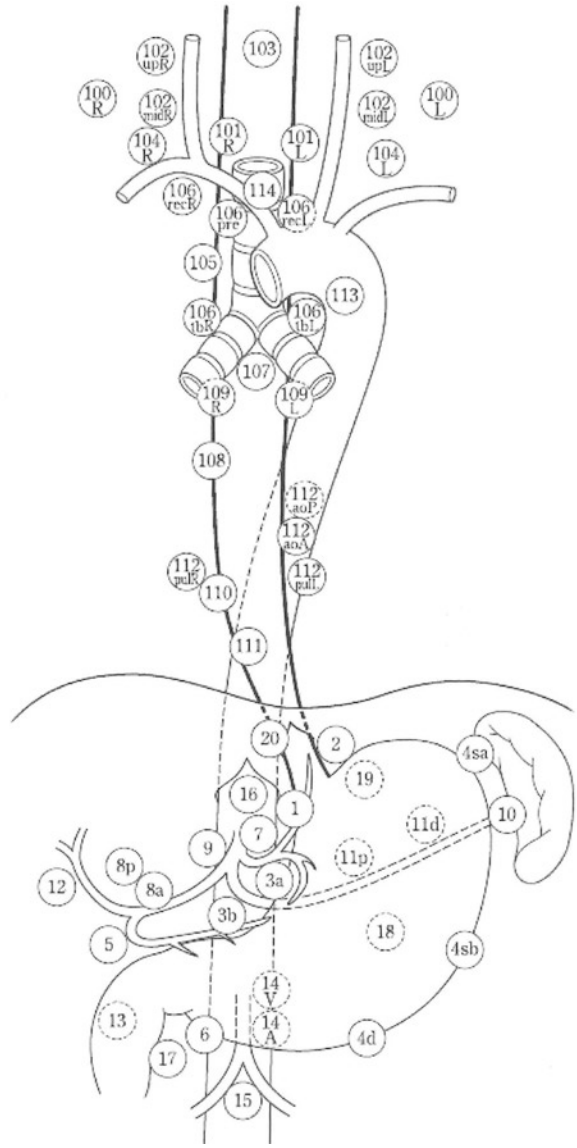


Fig. 6.8 (continued)

the cervical, thoracic and abdominal esophagus. In the second edition (JSED/JES, 1972) [29], the lymph nodes were classified into four categories; three categories for the regional nodes (N1, N2, and N3), and one category for the distant nodes (N4). In this edition, the N category was defined also for a tumor in the esophagogastric junction. In the sixth edition (JSED/JES, 1984) [33], the regional lymph node maps were illustrated using different colors for each N category.

In the ninth edition (JSED/JES, 1999) [36, 37], the N categories—lymph node groups—for a cancer in the thoracic esophagus were modified based on evidence from three-field lymphadenectomy. The regional lymph node stations were newly defined, and new lymph node colored maps were presented. Among members of the editorial board, there was a little controversy over whether the N category should be classified by the spread or by the number of the lymph nodes with metastasis. Consequently in the ninth edition, a modified N category was added into the appendix according to both the spread and the number of the lymph nodes with metastasis.

In the tenth edition (JES, 2007) [24, 25], the N category was defined by the anatomical spread of lymph node metastasis, in the same way as in all former Japanese Classifications (JSED/JES). In this edition, the N categories—lymph node groups—were modified for a cancer in the cervical esophagus and for a cancer in the esophagogastric junction (Fig. 6.8).

In the latest 11th edition (JES, 2015) [26–28], the definitions of some lymph node stations and the N categories—lymph node groups—for the thoracic and abdominal esophagus were modified based on data from the Comprehensive Registry for Esophageal Cancer in Japan [46] (Figs. 6.8 and 6.9). The modified N category according to both the spread and the number of lymph nodes with metastasis, adopted in the ninth and tenth editions (JES, 1999 and 2007) [24, 25, 36, 37], was deleted.

6.6 M Category: Distant Metastasis

6.6.1 The TNM Classification

In the first edition (UICC, 1968) [1], distant metastasis was indicated by M. In the second edition (UICC, 1974) [2], M1 was divided into two categories; M1a for metastases to the distant lymph nodes, and M1b for other distant metastases. In the third edition [3], the category M1 was subdivided according to sites, and was, for example, described as M1-LYM (Fig. 6.4).

In the fifth edition (UICC, 1997) [5], distant metastasis was divided into two groups M1a and M1b. Metastasis in the coeliac nodes for a tumor in the lower thoracic esophagus and metastasis in the cervical nodes for a tumor in the upper thoracic esophagus were both classified into M1a, while other distant metastasis and non-regional lymph nodes were classified into M1b.

In the seventh and the latest eighth editions (UICC, 2009 and 2017) [7, 8], the coeliac axis nodes and the paraesophageal nodes in the neck were included into the regional lymph nodes, so that the classification of M1a/M1b was superfluous and deleted (Fig. 6.5).

6.6.2 The AJCC Cancer Staging Manual

In the first and second editions (AJC/AJCC, 1977 and AJCC, 1983) [9, 13], the M category was classified according to the third edition (UICC, 1978) [3]. In the third edition (AJCC, 1988) [14], specific regional lymph nodes were listed in each subsite

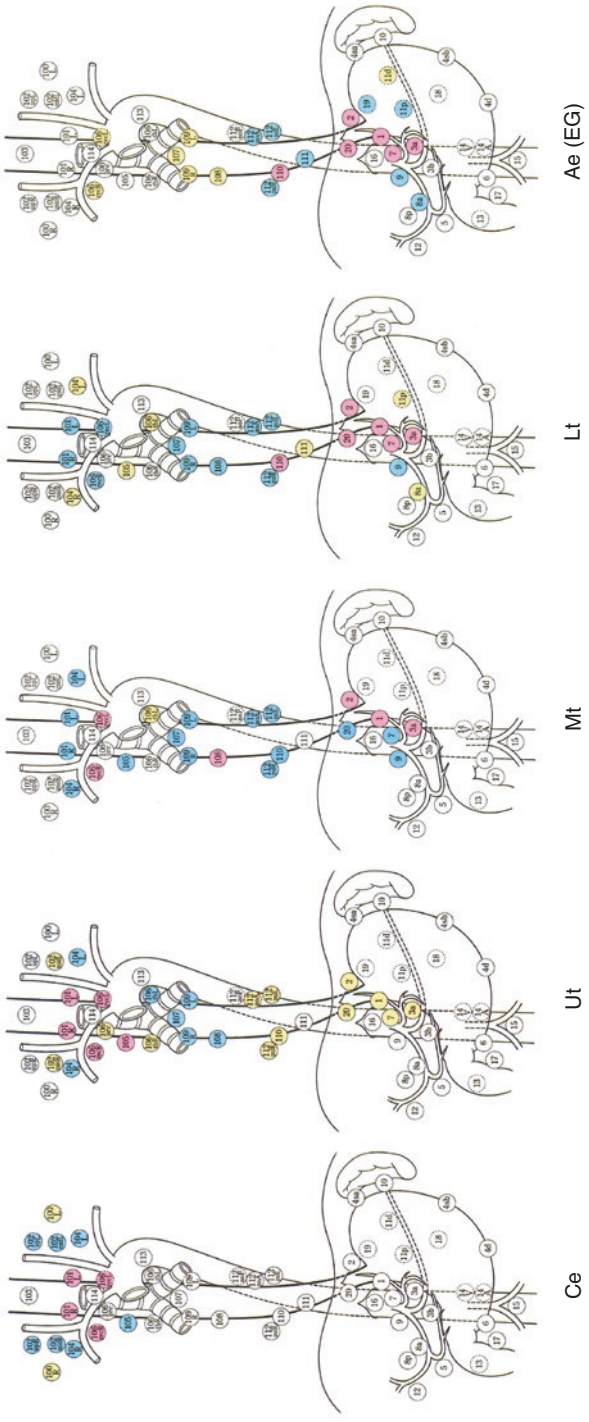


Fig. 6.9 Lymph node maps illustrating the lymph node groups—N category—for cancers in the cervical, thoracic, and abdominal esophagus presented in the 11th edition of Japanese Classification of Esophageal Cancer (JES, 2015) [26–28]

of the esophagus similarly to the Japanese Classification. Involvement of more distant nodes was defined as distant metastasis (M1-LYM) (Fig. 6.4).

In the fifth edition (AJCC, 1997) [16], distant lymph node metastasis was classified into two groups M1a and M1b, in a similar way as in the fifth edition (UICC, 1997) [5].

In the seventh and latest eighth editions (AJCC, 2010 and 2017) [11, 12], distant metastatic sites were defined as those which were not in direct continuity with the esophagus, and included the non-regional lymph nodes (M1) (Fig. 6.4). The M1a and M1b subclassification was deleted as in the TNM Classification.

6.6.3 The Japanese Classification

In the first edition (JSED/JES, 1969) [10], the M category was defined as distant organ metastasis, and metastasis to lymph nodes was not included in M1. In the second edition (JSED/JES, 1972) [29], pleural dissemination was classified as Pl category, and was excluded from the M category—organ metastasis. In the ninth edition (JSED/JES, 1999) [36, 37], pleural and peritoneal dissemination were included into M1—distant organ metastasis.

In the tenth edition (JES, 2007) [24, 25], metastasis to a distant organ not in direct continuity with the esophagus was categorized into M1, while metastasis to the non-regional lymph nodes was categorized into N4 (Fig. 6.6). In particular, metastasis to the supraclavicular lymph node was categorized as being in the regional lymph nodes for cancers in the upper and middle thoracic esophagus, and as the non-regional lymph nodes for those in the lower thoracic esophagus. On the other hand, in the latest 11th edition (JES, 2015) [26–28], metastasis to the supraclavicular lymph nodes was categorized as being in the regional modes for all cancers anywhere in the thoracic esophagus (Fig. 6.9).

6.7 Stage Groups

6.7.1 The TNM Classification

In the first edition (UICC, 1968) [1], only the breast and cervix were staged, and the stage grouping for the esophagus was not described. In the second edition (UICC, 1974) [2], the stage grouping for esophagus was classified into three groups; stage I, II, and III. The T3 (extra-esophageal spread), the N3 (fixed nodes), and the M1 (distant metastasis) were all classified as stage III. In the third edition (UICC, 1978) [3], the stage grouping was divided into four groups; stage I, II, III, and IV (anyTanyNM1), and the different stage grouping was adopted for the cervical and intrathoracic esophagus.

In the fourth edition (UICC, 1987) [4], the stage grouping for cervical and intrathoracic esophagus was unified. Stage 0 (TisN0M0) was added, and stage II was divided into Stage IIA (T2/T3N0M0) and Stage IIB (T1/T2N1M0) (Fig. 6.4). In the

fifth edition (UICC, 1997) [5], Stage IV was divided into Stage IVA (anyTanyNM1a) and Stage IVB (anyTanyNM1b).

In the seventh edition (UICC, 2009) [7], the stage grouping was divided in Stage 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, and IV, because the T category was divided into T4a-resectable and T4b-unresectable, and the N category was divided into N0, N1, N2, and N3 according to the number of metastasis-positive nodes. Besides the novel stage grouping, the prognostic grouping for squamous cell carcinoma and that for adenocarcinoma were presented. In the prognostic grouping for squamous cell carcinomas, the G histological grading and the tumor location were added to prognostic factors as well as TNM categories, while in that for adenocarcinomas, the G histological grading was added to prognostic factors.

The latest eighth edition (UICC, 2017) [8] has different staging and prognostic grouping between squamous cell carcinomas and adenocarcinomas. They have in each two staging systems; clinical stage and pathological stage, and a prognostic grouping; pathological prognostic group. In the stage classification, TNM categories are used. In the pathological prognostic group classification for squamous cell carcinomas, the G histological grading and the tumor location are added to prognostic factors as well as TNM categories, while in that for adenocarcinomas, the G histological grading is added similar to the seventh edition (UICC, 2009) [7] (Fig. 6.5).

6.7.2 The AJCC Cancer Staging Manual

In the first edition (AJC/AJCC, 1977) [9], the stage grouping was classified into Stage I, II, and III, and Stage II was different between the cervical esophagus and the thoracic esophagus. It was explained that patients at Stage I had a fairly good prognosis, whereas those at Stage III had a fulminating and rapidly fatal prognosis, and those at Stage II had an intermediate prognosis. In the second edition (AJCC, 1983) [13], two stage classifications—clinical-diagnostic classification for cervical esophagus (Stage 0 to IV) and postsurgical resection-pathological classification of all segments (Stage I to IV)—were described.

In the third edition (AJCC, 1988) [14], the stage grouping was classified into Stage 0, I, IIA, IIB, III, and IV in the same way as in the fourth edition (UICC, 1987) (Fig. 6.4) [4]. In the fifth edition (AJCC, 1997) [16], Stage IV was divided into Stage IVA and Stage IVB in the same way as in the fifth edition (UICC, 1997) [5].

In the seventh edition (AJCC, 2010) [11], two prognostic groups were described for squamous cell carcinoma and for adenocarcinoma, as presented in the seventh edition (UICC, 2009) [7].

In the latest eighth edition (AJCC, 2017) [12], three prognostic stage groups, cTNM, pTNM, and ypTNM, were described, for squamous cell carcinoma and also for adenocarcinoma. The clinical staging cTNM, and the postneoadjuvant therapy staging ypTNM, were consistent with the TNM categories. The clinical staging for squamous cell carcinoma and that for adenocarcinoma of the AJCC [12] are the

same as in the UICC [8]. The pathological staging pTNM for squamous cell carcinoma and that for adenocarcinoma of the AJCC [12] are the same as the pathological prognostic groups of the UICC [8] (Fig. 6.5).

6.7.3 The Japanese Classification

In the first edition (JSED/JES, 1969) [10], the macroscopic staging based on surgical findings and the histologic staging based on histological findings were described. Stages were classified into Stage I, II, III, and IV, according to the T category (A0 to A3), N category (N0 to N3) and to the M category (M0 and M1). In the second edition (JSED/JES, 1972) [29], the macroscopic staging was classified based on the A, N, M, and Pl categories, while the histologic staging was classified into Stage 0 to IV, using the depth of tumor invasion, the n category (n0 to n4), m category (m0 and m1), and the pl category (pl0 and pl1).

In the ninth edition (JSED/JES, 1999) [36, 37], the macroscopic staging and the histologic staging were unified, and the new staging was classified in six groups; Stage 0, I, II, III, IVa, and IVb, according to the T category (Tis, T1a, T1b, T2, T3, and T4), N category (N0, N1, N2, N3, and N4), and the M category (M0 and M1).

In the stage classification of the tenth edition (JES, 2007) [24, 25], the Tis, carcinoma in situ, and T0, no evidence of primary tumor, were included into T1a, in order to adapt for nonsurgical patients. The stage groups were classified in a block style because there were many T categories (T1a, T1b, T2, T3 and T4) and N categories (N0, N1, N2, N3 and N4).

Also in the latest 11th edition (JES, 2015) [26–28], the stage groups were classified in a block style of T categories (T1a, T1b, T2, T3, T4a, and T4b), N categories (N0, N1, N2, N3 and N4), and of M categories (M0 and M1) (Fig. 6.6). The T0/T1aN1M0 was upgraded to Stage II compared with the tenth edition (JES, 2007) [24, 25]. The T4aN0-3 M0 was classified as Stage III, and the T4banyNM0 was classified as Stage IVa.

6.8 Other Classifications

The UICC/AJCC Classifications and the Japanese Classification have many detailed classifications and definitions beyond stage classifications.

6.8.1 The TNM Classification/AJCC Cancer Staging Manual

6.8.1.1 G: Histopathological Grading [8, 12]

The G grading was adopted as a prognostic factor for both squamous cell carcinoma and adenocarcinoma of the esophagus in the eighth edition [8, 12]. In the AJCC

Cancer Staging Manual [12], the definition of histologic grade (G) was described for squamous cell carcinoma and for adenocarcinoma.

GX Grade of differentiation cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Notes.

- Grade 3 and grade 4 can be combined in some circumstances as "G3–4 poorly differentiated or undifferentiated."

6.8.1.2 Residual Tumor (R) Classification [8, 12]

The absence or presence of residual tumor after treatment is described by the symbol R. It reflects the effect of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. Also in the 11th edition (JES, 2015) [26–28], the same R classification was presented. In cases with endoscopic treatment, the residual tumor was described as eR after the clinical assessment and as pR after the pathological assessment.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

6.8.1.3 y Symbol: Post-Therapy Classification [8, 12]

In the eighth editions (UICC, 2017 and AJCC, 2017) [8, 12], the cTNM or pTNM categories were identified by a y prefix, in those cases in which classification was performed during or following multimodality therapy.

yc After multimodality therapy without subsequent surgical resection, the y-clinical (yc) classification is assessed based on clinical history, physical examination, and any imaging findings.
yp After surgery following multimodality therapy, the y-pathological (yp) classification is assessed based on the y-clinical stage information, operative findings, and pathological evaluation of the resected specimen.

6.8.2 The Japanese Classification

6.8.2.1 Macroscopic Tumor Type [24, 25]

The tumor type classification is defined based on the macroscopic findings. Radiological and endoscopic classifications are based on the macroscopic classification (Fig. 6.10). The tumor type classification is useful to assess T categories.

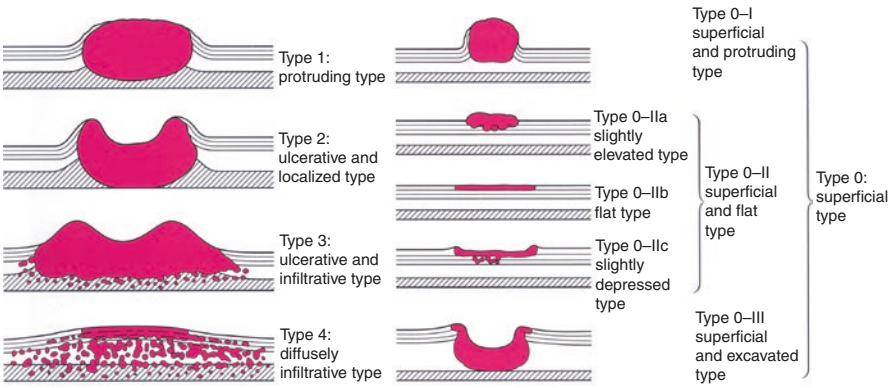


Fig. 6.10 Macroscopic classification (Type 0–4) presented in the 11th edition of the Japanese Classification of Esophageal Cancer (JES, 2015) [26–28]

6.8.2.2 Extent of Lymph Node Dissection (D) [26–28]

The extent of lymphadenectomy is described by the symbol "D." It is defined according to the location of the tumor. The UICC/AJCC recommends to resect all the regional lymph nodes according to the location of the tumor and to resect more than 5 lymph nodes [8, 12]. The JES recommends that the extent of lymphadenectomy should be wider than the grading of the lymph node metastasis (D > N) [26–28].

Extent of Lymph Node Dissection (D)

DX Extent of lymph node dissection cannot be assessed.

D0 No or incomplete dissection of Group-1 lymph nodes.

D1 Complete dissection of Group-1 lymph nodes but no or incomplete dissection of Group-2 lymph nodes.

D2 Complete dissection of Group-1 and Group-2 lymph nodes, but no or incomplete dissection of Group-3 lymph nodes.

D3 Complete dissection of Group-1, Group-2, and Group-3 lymph nodes.

6.8.2.3 Curativity (Cur) [26–28]

Curativity is decided by the relationship between the tumor extension (TNM stage) and the extent of surgery, and by the relationship between the grading of lymph node metastasis (N) and the extent of lymph node dissection (D).

Cur A Complete removal of the tumor is strongly believed.

- sStage 0–III, and sR0, and sD > sN.

Cur B Neither Cur A nor Cur C

- sStage IVa, sStage IVb or sD ≦ sN, but R0 was achieved with resection of a T4b tumor or complete removal of metastatic tumor (M1) or lymph nodes.

Cur C Residual tumor

- R2, i.e., M1 evident residual tumor in distant organ(s) (M1), lymph nodes, or surgical margin(s) (PM1, DM1, RM1).

6.9 Discussions

6.9.1 Definition of Cancer at the Esophagogastric Junction

In the seventh editions (UICC/AJCC) [7, 10], adenocarcinoma at the esophagogastric junction was defined as a tumor the epicenter of which was within 5 cm of the esophagogastric junction and also extending into the esophagus according to the Siewert's classification, and was classified and staged using the esophageal scheme. In the latest eighth editions (UICC/AJCC) [8, 12], both squamous cell carcinomas and adenocarcinomas were defined as tumors whose epicenter was within 2 cm of the esophagogastric junction and extending into the esophagus (Siewert types I/II), and were classified and staged using the esophageal scheme. On the other hand, in the tenth and latest 11th editions (JES, 2007 and 2015) [24–28], cancers at the esophagogastric junction were defined as tumors whose epicenter was within 2 cm of the esophagogastric junction irrespective of histology, according to Nishi's classification. The definitions of the eighth editions (UICC/AJCC) appeared to be unified with the Japanese definition, namely Nishi's classification. Both in UICC/AJCC classifications [8, 12] and in JES/JGCA classifications [26–28, 45], cancers whose epicenter was more than 2 cm distal from the esophagogastric junction were staged using the gastric scheme.

6.9.2 N Category

The most significant difference between the UICC/AJCC Classifications and the JES Classification is in the N category. In the UICC/AJCC Classifications, the N category is classified by the number of metastasis-positive lymph nodes, while in the JES Classification this N category is classified by the spread of metastasis-positive lymph nodes. The N category of the UICC/AJCC Classifications is easy to use in practice. In particular, pathologists can easily assess the number of metastasis-positive lymph nodes in the resected specimen which is strongly prognostic. The N category in the UICC/AJCC Classification was based on statistical analysis of worldwide databases [18–23] with which only surgical cases were registered. On the other hand, the N category of the JES Classification is clinically complex to use. It is difficult for pathologists to assess lymph node stations of metastasis-positive lymph nodes in the resected specimen. This work is commonly done by surgeons in Japan. Moreover, the spread of metastasis-positive lymph nodes is not so much strongly prognostic as the number of metastasis-positive lymph nodes. This is the main reason why the JES Classification has not been adopted outside of Japan.

However, it remains difficult to determine the absence or presence of metastasis in the lymph nodes preoperatively even using computed tomography (CT) or positron emission tomography (PET). Thus, the number of metastasis-positive lymph nodes (clinical N staging) cannot be preoperatively assessed with any accuracy. The N category in the UICC/AJCC Classification is, therefore, not practical for nonsurgical cases. This is the main reason for deleting the N category modification according to both the spread and the number of lymph nodes with metastasis from the JES Classification in the latest 11th edition (JES, 2015) [26–28]. On the other hand, clinical N staging using the spread of metastasis-positive lymph nodes is more easily done than using the number of metastasis-positive lymph nodes. Moreover, the spread of metastasis-positive lymph nodes is useful for deciding the treatment strategy such as the surgical procedure or the radiation field. Accordingly, the JES Classification plays not only a role for predicting prognosis, but also a role as informative guidelines for lymphadenectomy, similar to other Japanese staging classifications and rules for cancers.

Almost all Japanese oncological surgeons believe that metastasis to the regional lymph nodes still constitutes a local disease, and that surgery should be done with intent to cure the disease. On the other hand, as presented by the N-category in the first to sixth editions (UICC/AJCC) [1–6, 9, 13–17], Western oncological surgeons seem to believe that lymph node metastasis is a sign of systemic disease which is difficult to cure by surgery. Such a difference in these conceptions of lymph node metastasis seems to make the N categories different in each classification.

6.9.3 M1-Lym Category

In the UICC/AJCC Classifications, metastasis to distant lymph nodes is categorized as being M1-Lym, while in the JES Classification, it is categorized as N4. Supraclavicular lymph nodes (No.104) are defined as distant nodes in the eighth editions (UICC, 2017/AJCC, 2017) [8, 12], while they are defined as regional nodes in the 11th edition (JES, 2015) [26–28]. These nodes are categorized as N2 for cancer in the cervical esophagus, in the upper thoracic esophagus, or in the middle thoracic esophagus, as N3 for cancer in the lower thoracic esophagus, and as N4 (distant lymph nodes) for cancer in the abdominal esophagus. On the other hand, celiac lymph nodes (No. 9) are defined as regional nodes in the eighth editions (UICC, 2017/AJCC, 2017) [8, 12], while they are categorized as N2 for cancer in the middle thoracic esophagus, in the lower thoracic esophagus or in the abdominal esophagus, as N3 for cancer in the upper thoracic esophagus, and as N4 (distant lymph nodes) for cancer in the cervical esophagus, in the 11th edition (JES) [26–28]. Concerning lymph nodes around the abdominal aorta (No.16), there is still some controversy in Japan over whether they are regional lymph nodes or distant lymph nodes for cancer at the esophagogastric junction. As mentioned above, Japanese oncological surgeons consider that the border between regional lymph nodes and distant lymph nodes is not clear and such a distinction is relative. This is the main reason why distant lymph nodes are categorized as N4 in the JES Classification.

6.9.4 Anatomical Staging and Prognostic Staging

In the seventh and eighth editions (UICC, 2009 and 2017) (AJCC, 2010 and 2017) [7, 8, 11, 12], prognostic staging is adopted as well as anatomic staging. The UICC/AJCC strongly consider that stage classification should predict prognosis and that for this purpose, prognostic factors, even if they are nonanatomical factors, should be added to the category for staging. In particular, the eighth edition (UICC, 2017) has six stage classifications—clinical stage, pathological stage and pathological prognostic stage for squamous cell carcinoma and also for adenocarcinoma [8]. The eighth edition (AJCC, 2017) also has six stage classifications—clinical stage (cTNM), pathological stage (pTNM), and postneoadjuvant therapy stage (ypTNM) for squamous cell carcinoma and for adenocarcinoma [12]. They are further subdivided using statistical techniques and become relatively complex to describe. The JES has no such consideration at present.

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Comprehensive Registry in Japan

7

Soji Ozawa

Abstract

We reviewed the history of the esophageal cancer registry in Japan. The Registration Committee for Esophageal Cancer, a part of the Japan Esophageal Society, has registered cases of esophageal cancer since 1976 and published the first issue of the Comprehensive Registry of Esophageal Cancer in Japan in 1979. The Act on the Protection of Personal Information was promulgated in 2003 and began to be enforced in 2005. The esophageal cancer registry required some improvements to comply with the Acts. A new registration system was considered for several years and was finally completed in 2008. Specifically, "anonymity in an unlinkable fashion" using encryption with a "hash function" was introduced. Finally, the registry resumed registering esophageal cancer cases that had been treated in 2001. Here, we briefly summarize the Comprehensive Registry of Esophageal Cancer in Japan for the years 2001–2012. A total of 65,762 cases were registered from a total of 3,038 institutions in Japan. Histological diagnoses of biopsy specimens showed that squamous cell carcinoma and adenocarcinoma accounted for 88.3–92.9% and 2.3–6.0% (ranges between 2001 and 2012) of all the cases, respectively. The 5-year survival rates of patients treated using endoscopic resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, or esophagectomy were 80.0–88.1%, 19.3–32.4%, 15.1–32.3%, 1.7–9.4%, and 42.6–55.9% (ranges between 2001 and 2012), respectively. Concerning the approach used to perform an esophagectomy, 14.3–42.1% (ranges between 2001 and 2012) of the cases were performed thoracoscopically, laparoscopically, or mediastinoscopically. Since 2019, the registration method for esophageal cancer cases of the Japan Esophageal Society has been changed to the registration method using the National Clinical Database

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(NCD), with some modifications, to improve the efficacy of registering esophageal cancer cases. We hope that this Comprehensive Registry of Esophageal Cancer in Japan helps to improve all aspects of the diagnosis and treatment of esophageal cancer.

Keywords

Comprehensive registry · Act on the protection of personal information · Anonymity in an unlinkable fashion · Hash function · National clinical database

7.1 Introduction

Since the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) began collecting data on cancer cases in 1973 in the United States [1], many registry programs have been introduced worldwide. In Japan, cancer registry programs for esophageal cancer, gastric cancer, and colorectal cancer have been established in 1976 [2], in 1963 [3], and in 1980 [4], respectively. Because the Act on the Protection of Personal Information was promulgated in 2003 and began to be enforced in 2005 [5] and because the computerized case registry system was complicated, the registry activities were interrupted for several years. After the resolution of these problems, the registry activities were resumed. In this chapter, the history of the esophageal cancer registry in Japan, the method and process used to resolve the registry problems, the present situation and problems, and the future prospects are described.

7.2 History of the Registry of Esophageal Cancer Cases in Japan

The Japan Society of Esophageal Diseases, that is, the former name for the Japan Esophageal Society, was established in October 1965. Guidelines for esophageal cancer were published in October 1969, and the Registration Committee for Esophageal Cancer was organized in October 1976 [2]. In December 1976, the Registration Committee started registering not only esophageal cancer cases that had been treated in 1976, but also cases that had been treated between 1969 and 1975. The first issue of the Comprehensive Registry of Esophageal Cancer in Japan, 1976, was published in March 1979. Registration software was developed, and a computer-based registration system was introduced for the purpose of improving efficiency in 1997. After the issue of the Comprehensive Registry of Esophageal Cancer in Japan, 2000, which was published in 2003, the registration project was interrupted, because of the promulgation of the Act on the Protection of Personal Information in 2003 and because the patients' personal information was difficult to handle appropriately [5].

7.3 Attempts to Resume the Registration Project

7.3.1 Handling of Personal Information

The Act on the Protection of Personal Information was promulgated in 2003 and began to be enforced in 2005 [5]. The purpose of this Act was to protect the rights and interests of individuals while taking into consideration the usefulness of personal information, keeping in mind the remarkable increase in the use of personal information arising from the development of today's advanced information and communications society. Some improvements to the esophageal cancer registry were thus required to comply with the Acts.

The registration project also had to comply with the Ethical Guidelines for Epidemiologic Studies, which began to be enforced in November 2007 [6]. These Ethical Guidelines do not apply to studies where personal information characterized as "anonymity in an unlinkable fashion" is being analyzed.

7.3.2 Hash Function

The Secure Hash Standard (SHS) is a set of cryptographically secure hash algorithms specified by the US National Institute of Standards and Technology (NIST) [7]. The algorithm is an iterative, one-way hash function that can process a message to produce a condensed representation called a message digest. The algorithm enables the determination of a message's integrity: any change to the message will, with a very high probability, result in a different message digest. This property is useful for the generation and verification of digital signatures and message authentication codes and for the generation of random numbers or bits.

The patient data were divided into personal data (name, date of birth, medical record number, etc.) and disease data (tumor location, T-factor, N-factor, M-factor, pathological data, treatment method, etc.). The personal data was encrypted as the Hash value, and data packages consisting of the personal data encrypted as the Hash value and the disease data were exported from each institution to the data center. An examination of the Hash data enables double registrations to be identified and patient outcomes to be followed.

The ethics committee of the Japan Esophageal Society reviewed and approved the registration project and the use of "hash function" encryption. The registration project was also reviewed and approved by the institutional review board of each institution.

7.3.3 Certification of the Registration Project

In the era of the Japan Society of Esophageal Diseases, that is, the former name for the Japan Esophageal Society, the membership consisted of institutions. In the era of the Japan Esophageal Society, however, the membership is composed of


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2007年12月1日

第62回日本食道学会会長
田久保 海誉

日本食道学会
全国登録委員会委員長
小澤 壯治

Fig. 7.1 Certificate of approval for institutional registration issued by the Registration Committee for Esophageal Cancer of the Japan Esophageal Society

doctors. Basically, the institutions where the members work should be requested to register esophageal cancer cases, and cooperative institutions for the registration project were approved and certificates were issued to 456 institutions in February 2008 (Fig. 7.1).

7.3.4 Preparation of Registration Sheets

Each item in the registration sheets was revised according to the Japanese Classification of Esophageal Cancer ninth edition [8, 9], and new treatments, such as endoscopic submucosal dissection, were added. Items with low importance were deleted, and the total number of items was reduced.

7.3.5 Trial of the New Registration Project

Next, each member of the Registration Committee for Esophageal Cancer tested the new registration system using the "hash function" encryption (Fig. 7.2). A CD-R containing the recording software and the "hash function" encryption software and a return CD-R, on which the data would be recorded, were sent to each member. Each member recorded the data package of the encrypted personal data as a Hash value and the disease data of patients who were treated in 2001 and then returned the CD-R back to the data center which was managed by the Japan Esophageal

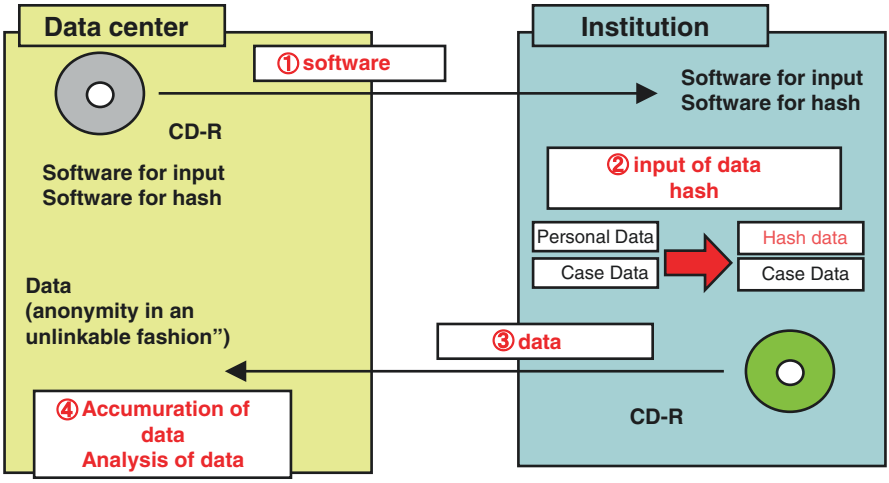

Fig. 7.2 Outline of data collection

Society and the laboratory of Dr. T. Teshima and Dr. H. Numasaki in Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Osaka, Japan. No difficulties were encountered in the mailing of the CD-R, and that the registration and encryption software worked correctly. Moreover, the data center succeeded in a similar analysis of data collected as the Comprehensive Registry of Esophageal Cancer in Japan, 2000 [10], and the functionality of the new analyzing software was confirmed.

7.4 Resumption of the Registration Project

To resume the registration project, many problems were resolved, one by one. In March 2008, the new registration project was started for patients who had been treated in 2001. The CD-R containing the recording software and the "hash function" encryption software and the return CD-R, on which the data would be recorded were sent to the approved institutions. A website for the registration project was created on the homepage of the Japan Esophageal Society. As of August 2008, a total of 3,940 cases from 241 institutions (52.9% of 456 approved institutions) were registered.

7.5 Publication of the Resumed Reports

The committee members reviewed the analyzed results of the registered data, and the Comprehensive Registry of Esophageal Cancer in Japan, 2001, which was published in March, 2009, was sent to the approved institutions (Fig. 7.3). The Comprehensive Registry included 76 tables and 16 figures and showed the

Fig. 7.3 Front cover of the Comprehensive Registry of Esophageal Cancer in Japan, 2001

current status of esophageal cancer treatment in Japan. Twenty-three selected tables and 16 figures were published in *Esophagus* (Vol. 6, pages 95–110) [2], the official journal of the Japan Esophageal Society, to ensure wide and easy access to the latest information regarding esophageal cancer treatments (Fig. 7.4).

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DOI 10.1007/s10388-009-0189-9

SPECIAL ARTICLE

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Comprehensive Registry of Esophageal Cancer in Japan, 2001

Preface

The Registration Committee for Esophageal Cancer of the Japan Esophageal Society, has registered cases of esophageal cancer since 1976 and published the first issue of the Comprehensive Registry of Esophageal Cancer in Japan in 1979. The Act for the Protection of Personal Information was promulgated in 2003, and began to be enforced in 2005. The purpose of this Act is to protect the rights and interests of individuals while taking into consideration the usefulness of personal information, keeping in mind the remarkable increase in the use of personal information arising from the development of today's advanced information and communications society. The Registry of Esophageal Cancer Cases has required some adjustments to comply with these Acts. The new registration system has been considered for several years and was finally completed in 2008. The most important point was achieving unlinkable anonymity through hash function encryption. Finally, the registry resumed registering cases of esophageal cancer that had been treated in 2001.

A brief summary follows: a total of 3940 cases were registered from 241 institutions in Japan. As for the histologic type of cancer according to biopsy specimens, squamous cell carcinoma and adenocarcinoma accounted for 91.7% and 2.3%, respectively. The 5-year survival rates of patients treated using endoscopic mucosal resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, or esophagectomy were 88.5%, 19.3%, 19.6%, 4.0%, and 42.6%, respectively. Regarding the approach used to perform esophagectomy, 14.3% of the cases were performed endoscopically, that is, thoracoscopically, laparoscopically, or mediastinoscopically. The percentage of operative deaths occurring within 30 days or less after operation and the percentage of postoperative hospital deaths occurring 31 days or more after operation were 2.8% and 3.2%, respectively.

We hope that this Comprehensive Registry of Esophageal Cancer in Japan for 2001 helps to improve all aspects of the diagnosis and treatment of esophageal cancer.

These data were first issued on 12 March, 2009, as the *Comprehensive Registry of Esophageal Cancer in 2001*. Not all pages are reprinted here; however, the original tables and figure numbers have been kept. The authors were at the time members of the Registration Committee for Esophageal Cancer, the Japan Esophageal Society, and made great efforts and contributions in preparing this material.

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Fig. 7.4 Excerpted version of the Comprehensive Registry of Esophageal Cancer in Japan, 2001, published in *Esophagus* (Vol. 6, pages 95–110)

7.6 Next Year Registration

After problems with the registration system used for the cases treated in 2001 were improved, a registration project for cases treated in 2002 was started in March, 2009. As of August, 2009, a total of 4,281 cases from 222 institutions (48.7% of 456 approved

institutions) had been registered. The committee members reviewed the analyzed results of the registered data, and the Comprehensive Registry of Esophageal Cancer in Japan, 2002, was published in March, 2010 [11], and sent to the approved institutions.

7.7 Problems Arising During the First Two Years

Although the new registration system required "anonymity in an unlinkable fashion," some institutions very nearly returned data packages containing nonencrypted personal data and disease data to the data center. The number of institutions that submitted CD-Rs to the data center was about 50% of the total number of approved registration institutions. To grasp the real status of esophageal cancer treatment in Japan, more institutions need to return CD-Rs on which their activities have been recorded. The number of items on the registration forms was reduced, compared with the former registration form used for cases in 2000, to lighten the workload of the doctors in charge of registration.

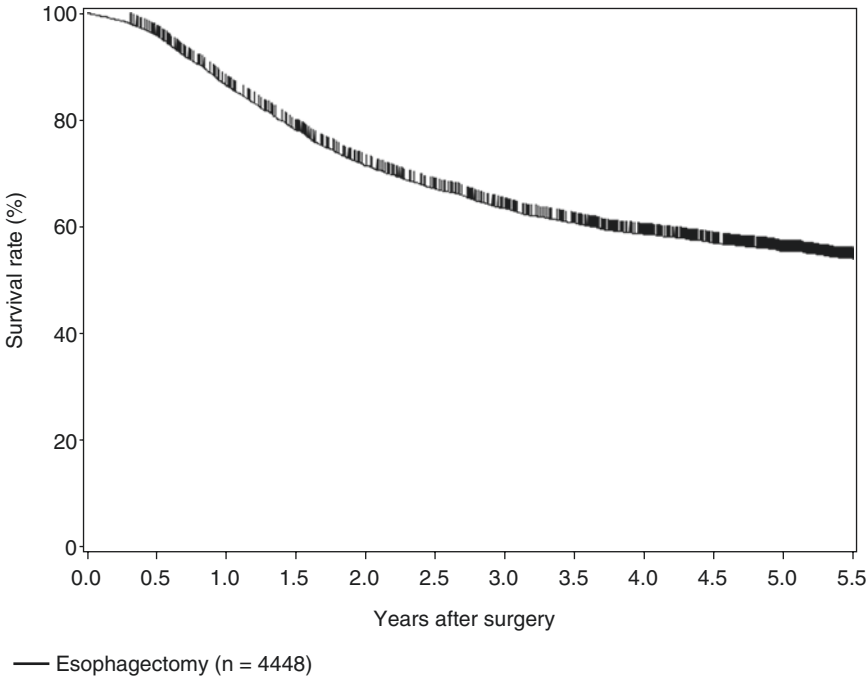
7.8 Summary of the Comprehensive Registry of Esophageal Cancer in Japan, 2001–2012

We summarized the Comprehensive Registry of Esophageal Cancer in Japan, 2001–2012 (Table 7.1) [2, 11–21]. A total of 65,762 cases were registered from a total of 3,038 institutions in Japan. As for the histologic type of cancer according to

Table 7.1 Summary of the Comprehensive Registry of Esophageal Cancer in Japan, 2001–2012

			Pathology		5 year survival rate					
Year	No. of institution	No. of patient	Rate of SCC (%)	Rate of adenoca.(%)	ER	CRT	RT	CT	Ope	Rate of MIE
2001	241	3,940	91.7	2.3	86.9	19.3	19.6	4.0	42.6	14.3
2002	222	4,281	92.9	2.4	87.7	22.9	15.1	1.7	44.1	16.5
2003	199	4,659	92.2	3.0	80.0	21.9	30.0	3.0	46.6	15.3
2004	214	5,066	88.7	2.9	83.7	26.4	15.5	8.6	50.2	17.8
2005	237	5,547	91.4	3.6	85.3	24.9	18.0	6.9	50.9	20.9
2006	239	4,994	90.8	3.9	84.5	25.8	22.0	3.0	48.0	20.2
2007	257	5,216	90.1	3.9	88.1	25.1	16.0	9.4	52.8	25.5
2008	257	4,925	89.3	4.3	85.7	24.1	23.4	4.8	53.1	23.3
2009	276	6,260	90.5	3.8	86.2	27.9	20.2	5.8	55.9	28.9
2010	280	5,878	90.5	4.0	85.5	27.3	32.3	-	55.3	33.8
2011	300	6,993	88.3	5.3	86.0	28.1	26.5	4.4	54.5	39.3
2012	316	8,003	89.5	6.0	84.4	32.4	24.9	6.3	55.6	42.1

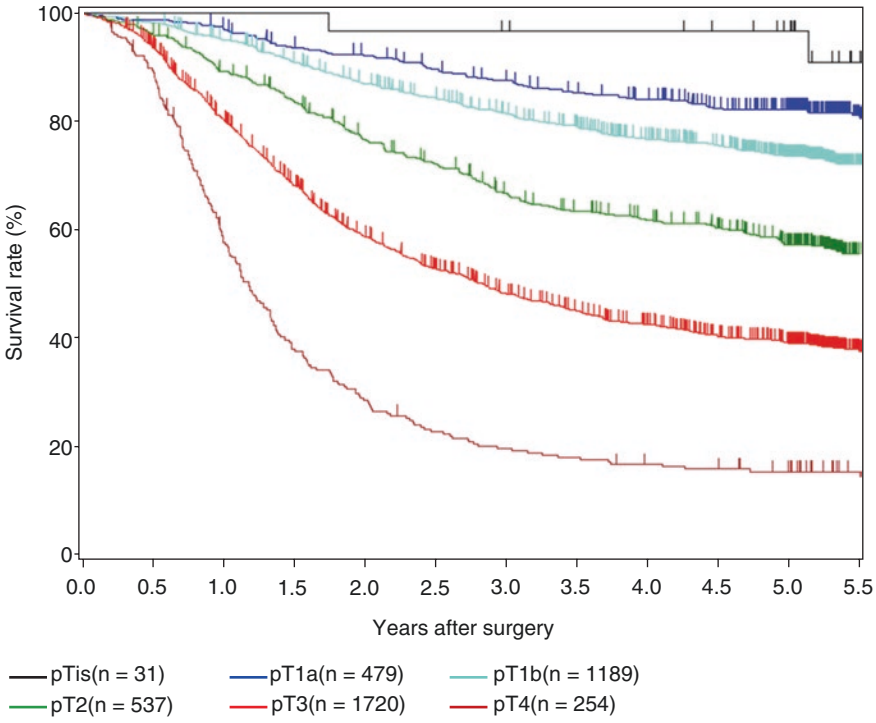
SCC squamous cell carcinoma, *adenoca*. adenocarcinoma, *ER* endoscopic resection, *CRT* chemo-radiotherapy, *RT* radiotherapy, *CT* chemotherapy, *Ope* operation, *MIE* minimally invasive esophagectomy



	Years after surgery				
	1	2	3	4	5
Esophagectomy	86.4%	71.6%	63.5%	58.8%	55.6%

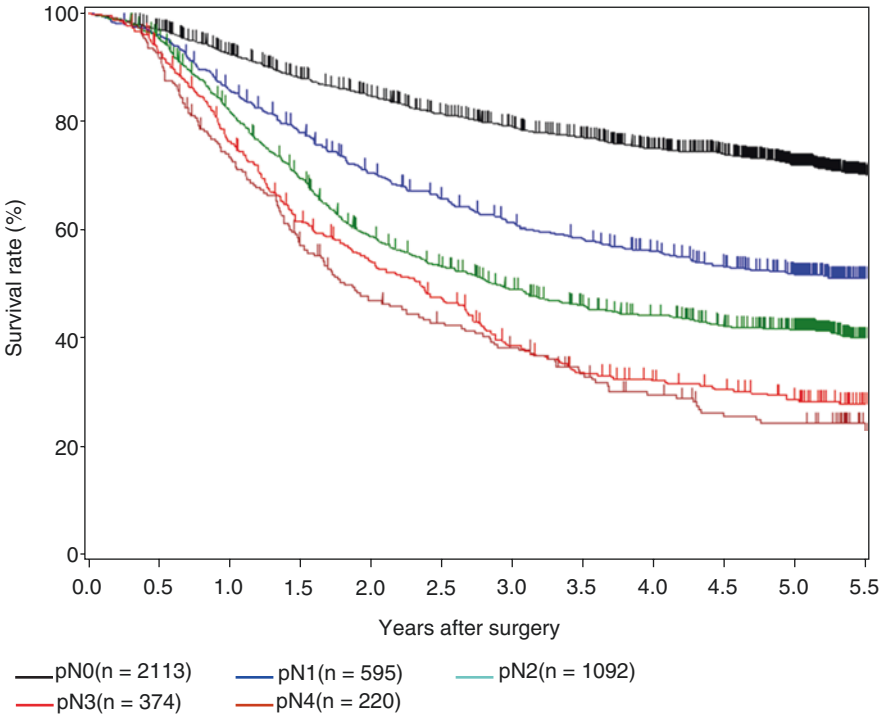
Fig. 7.5 Survival of patients who underwent esophagectomy in 2012

biopsy specimens, squamous cell carcinoma and adenocarcinoma accounted for 88.3–92.9% and 2.3–6.0% (ranges between 2001 and 2012), respectively. Regarding the clinical results, the 5-year survival rates of patients treated using endoscopic resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, and esophagectomy were 80.0–88.1%, 19.3–32.4%, 15.1–32.3%, 1.7–9.4%, and 42.6–55.9% (ranges between 2001 and 2012), respectively. Survival curves of patients treated by esophagectomy in 2012 according to the Japanese Classification of Esophageal Cancer tenth edition [22, 23] and UICC TNM Classification of Malignant Tumours seventh edition [24] are shown in Figs. 7.5, 7.6, 7.7, 7.8, and 7.9. Concerning the approach used to perform an esophagectomy, 14.3–42.1% (ranges between 2001 and 2012) of the cases were performed thoracoscopically, laparoscopically, or mediastinoscopically.



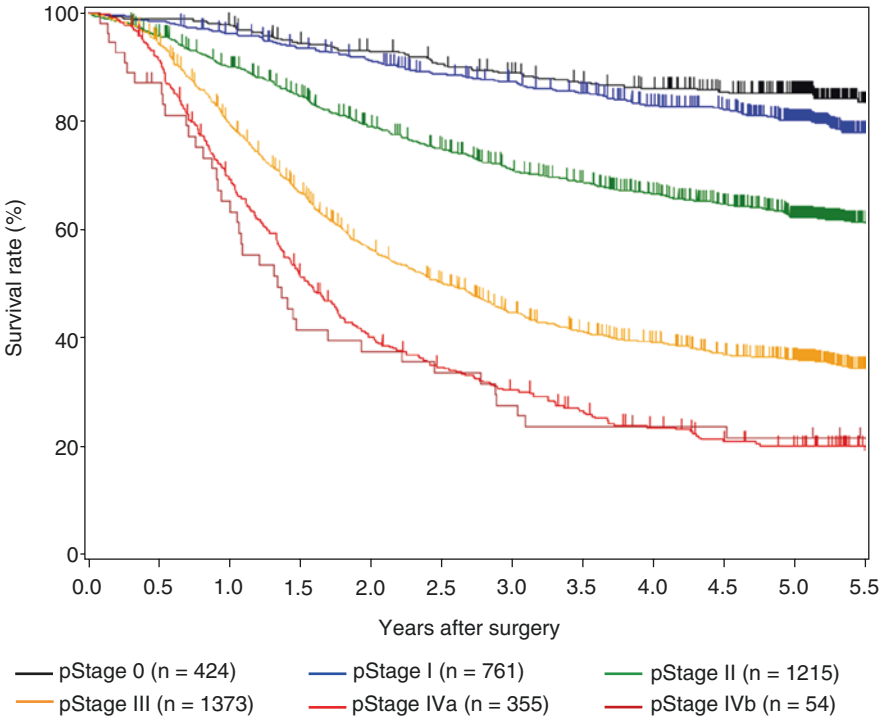
	Years after surgrey				
	1	2	3	4	5
pTis	100.0%	96.6%	96.6%	96.6%	96.6%
pT1a	97.0%	92.0%	87.4%	84.0%	82.1%
pT1b	95.0%	86.9%	81.5%	76.8%	73.7%
pT2	89.1%	76.7%	66.8%	61.8%	57.3%
pT3	80.3%	58.8%	48.2%	42.6%	39.1%
pT4	57.7%	28.7%	19.7%	16.8%	15.5%

Fig. 7.6 Survival of patients who underwent esophagectomy according to the depth of tumor invasion, pT in 2012 (JES 10th)



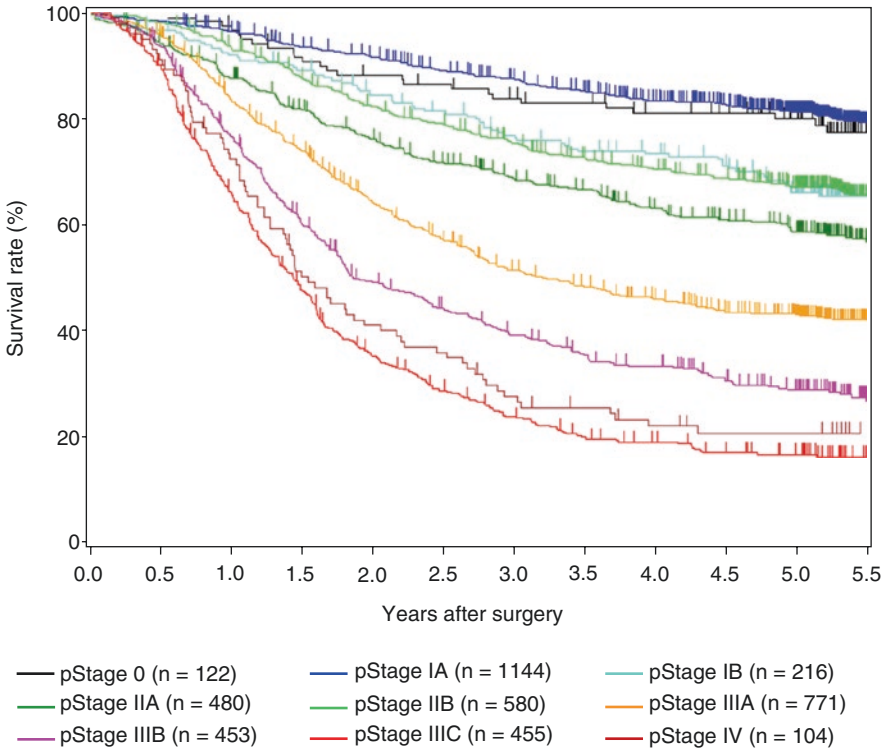
	Years after surgrey				
	1	2	3	4	5
pN0	92.4%	84.7%	79.1%	75.0%	72.0%
pN1	85.8%	70.5%	61.3%	56.1%	52.0%
pN2	82.1%	58.8%	49.2%	44.3%	41.7%
pN3	76.4%	54.3%	38.8%	32.4%	28.9%
pN4	73.5%	47.0%	38.5%	29.7%	24.4%

Fig. 7.7 Survival of patients who underwent esophagectomy according to lymph node metastasis, pN in 2012 (JES 10th)



	Years after surgrey				
	1	2	3	4	5
pStage 0	97.8%	92.9%	88.9%	86.1%	85.2%
pStage I	96.1%	91.3%	87.4%	83.0%	80.2%
pStage II	90.0%	79.1%	71.1%	66.6%	62.3%
pStage III	79.5%	56.3%	44.8%	39.3%	36.1%
pStage IVa	69.3%	40.2%	30.5%	23.6%	20.1%
pStage IVb	65.3%	37.6%	27.7%	23.7%	21.6%

Fig. 7.8 Survival of patients who underwent esophagectomy according to pathological stage in 2012 (JES 10th)



	Years after surgrey				
	1	2	3	4	5
pStage 0	96.7%	88.2%	83.9%	81.1%	80.0%
pStage IA	96.5%	91.7%	87.6%	83.4%	81.4%
pStage IB	92.1%	84.4%	76.9%	73.3%	66.1%
pStage IIA	87.7%	76.2%	68.5%	63.0%	58.6%
pStage IIB	93.2%	82.3%	75.4%	70.4%	67.2%
pStage IIIA	83.3%	64.1%	51.3%	46.0%	42.9%
pStage IIIB	76.5%	49.0%	39.2%	33.2%	28.7%
pStage IIIC	65.6%	35.0%	23.6%	18.8%	16.5%
pStage IV	72.3%	40.9%	27.5%	21.8%	20.5%

Fig. 7.9 Survival of patients who underwent esophagectomy according to pathological stage in 2012 (UICC TNM 7th)

7.9 New Registry System

We have a policy of not changing our software frequently so that doctors who become accustomed to the registration software can input the data easily. However, the Japanese Classification of Esophageal Cancer was revised as the tenth edition in 2007 [22, 23] and as the eleventh edition in 2017 [25, 26], and some changes to the registration forms were necessary to comply with the revised guidelines.

Treatment outcome is the most important information regarding esophageal cancer. Taking a more than 5-year follow-up period into consideration, cases should be registered 6 years after the initial treatment. This schedule is very effective for reporting the latest information to the world. Fortunately, the Comprehensive Registry of Esophageal Cancer in Japan, 2012, was published in 2019 [21]. This ideal time schedule should be continued in the future. The registration project of the Japan Esophageal Society should cooperate with the registration project of the National Clinical Database (NCD) for more efficient registration.

The NCD was founded in 2010 and managed by ten surgical societies in Japan as the parent body of the database system linked to the board certification system. The NCD database project, which started recordkeeping in January 2011, contains records for more than 95% of the surgeries performed by regular surgeons in Japan. In the gastrointestinal surgery section, all surgical cases are registered, and the details of eight procedures that represent the surgical performance (including esophagectomy) must be inputted [27].

Since 2019, the registration method for esophageal cancer cases of the Japan Esophageal Society has been changed to the registration method using the NCD, with some modifications, to improve the efficacy of registering esophageal cancer cases. Specifically, only surgical cases operated on during 2013 and 2018 should be registered in the NCD, and the outcomes at 5 years after operation must be retrospectively added to the NCD for each case. On the other hand, all the cases treated in 2019, including nonsurgical cases, must be registered in the NCD, and the outcomes must be added to the NCD 5 years after the treatment for each case. This new registry system will cover a larger number of esophageal cancer cases because almost all the surgical cases should be registered, unlike the conventional registration system in which only about 300 institutions participated. However, the question of "how many nonsurgical cases will be registered" is a concern. We hope that not only the quantity of registered cases, but also the quality of the registered details will increase.

7.10 Significance of the Registration Project

Three books are essential for the treatment of esophageal cancer patients in Japan: the Japanese Classification of Esophageal Cancer [25, 26], the Esophageal Cancer Practice Guidelines [28, 29], and the Comprehensive Registry of Esophageal Cancer in Japan. To improve the quality of the Comprehensive Registry, not only are more cases needed, but also a more accurate means of data input is necessary.

It is hoped that all doctors who are in charge of the management of esophageal cancer patients will understand the importance of the registry project and will contribute to the project.

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Conflicts of Interest The author declares that there are no conflicts of interest related to the contents of this manuscript.

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Esophageal Cancer Practice Guidelines in Japan

8

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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.

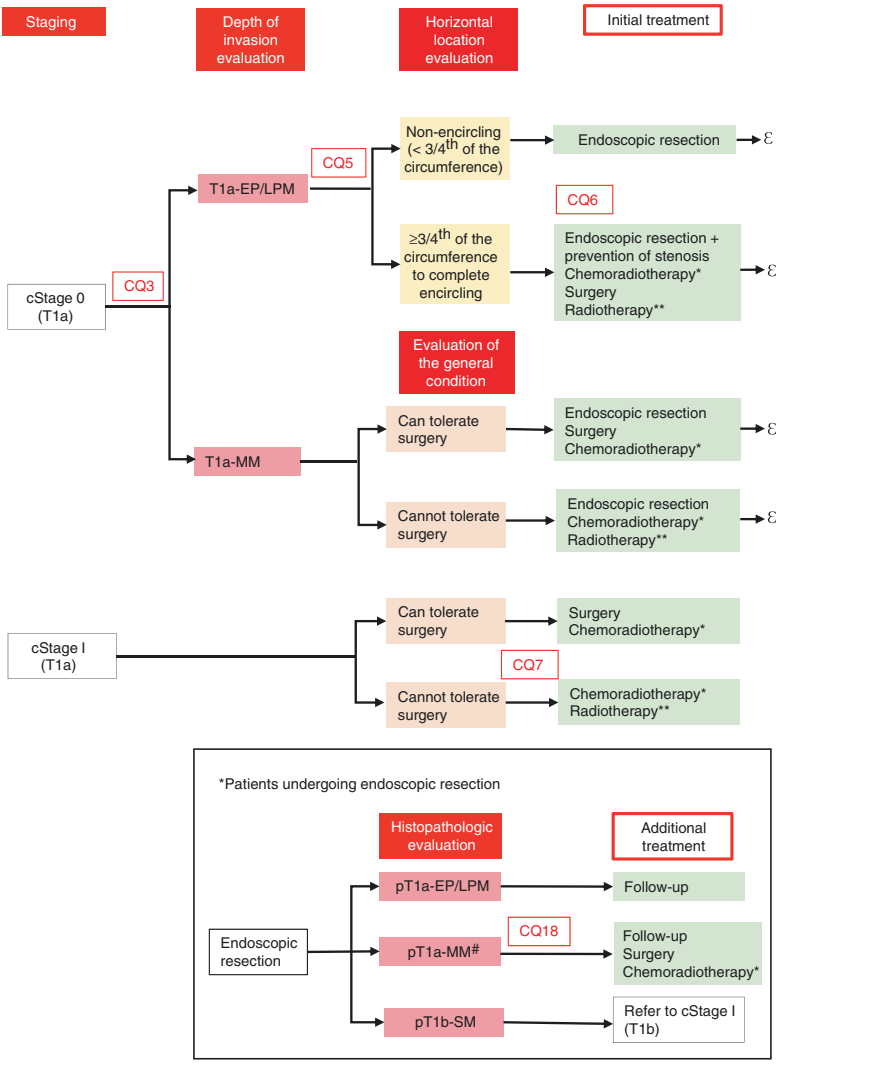
CQ3 What is the recommended method for the clinical diagnostic differentiation between T1a-EP/LPM and T1a-MM disease in patients with superficial cancer of the esophagus?

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.

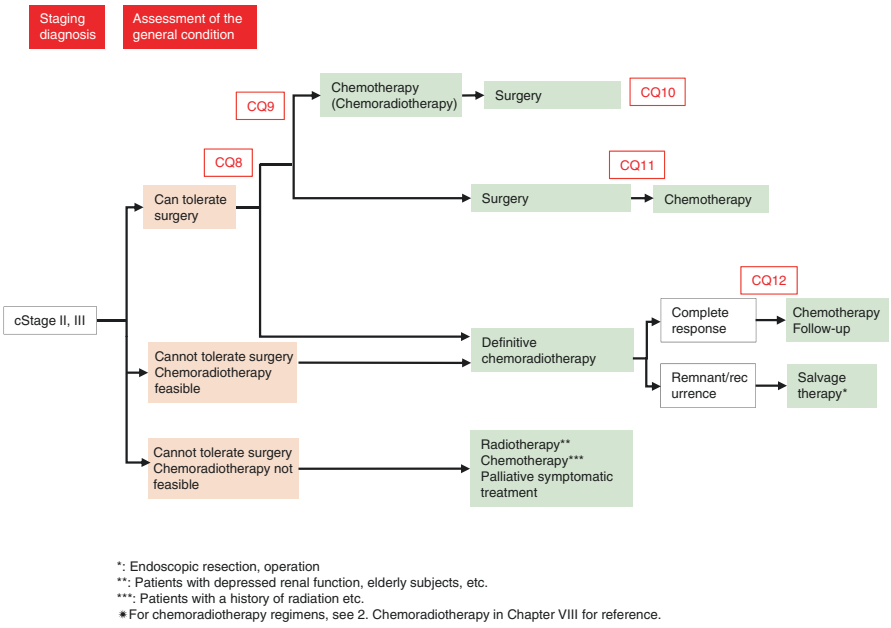


Fig. 8.2 Treatment algorithms for cStage II, III esophageal cancer

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.

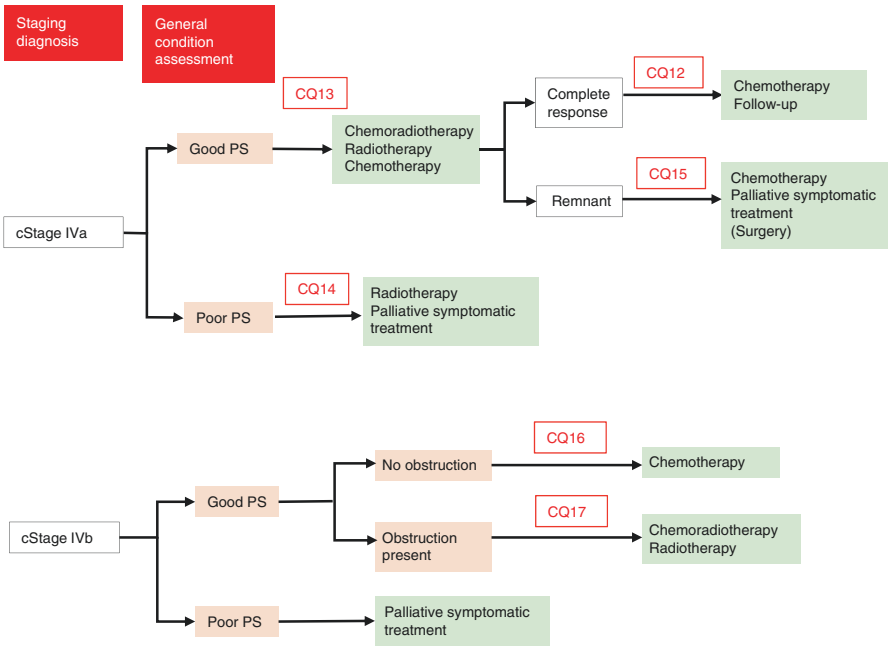
There is weak evidence showing that additional chemotherapy can be recommended for patients with cStage II, III, or IVa esophageal carcinoma who show complete response after radical chemoradiotherapy [rate of consensus: 90% (18/20); evidence level: C].

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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Endoscopic Treatment: EMR and ESD

9

Naohisa Yahagi and Motohiko Kato

Abstract

Esophageal superficial cancers with negligible risk for lymph node metastasis can be cured by endoscopic local resection. Endoscopic mucosal resection (EMR) is a conventional technique, which can resect relatively small lesions by using a snare. On the contrary, endoscopic submucosal dissection (ESD) can resect superficial lesion in an en bloc fashion irrespective of size or presence of submucosal fibrosis, which has made the indication of endoscopic resection expanded. Although skillful hands of endoscopy and sufficient knowledge for management of complications such as perforation and stricture formation are required, ESD is a promising technique as a minimally-invasive treatment.

Keywords

Endoscopic mucosal resection · Endoscopic submucosal dissection · Indication · Complication

9.1 Introduction

Due to improvement of therapeutic endoscopy in recent years such as endoscopic submucosal dissection (ESD), size limitation of a resectable extent by endoscopy has disappeared. In a so-called "pre-ESD" era, endoscopic mucosal resection (EMR) using an electrocautery snare was one and only available technique. This technique, however, could be applied only to small mucosal lesions because of the

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limitation in size. In case of large lesions, piecemeal resection is unavoidable, which may make histological evaluation difficult and even inaccurate [1, 2]. Development of ESD has changed the indication of endoscopic resection, owing to the unique characteristics of this technique. That is, ESD has technically enabled early gastrointestinal cancers to be resected endoscopically in an en bloc fashion irrespective of size or presence of submucosal fibrosis [3, 4]. Indication and methods of each technique, as well as the management of complications, are summarized in this chapter.

9.2 Indication of Endoscopic Resection

According to the Japanese classification of esophageal cancer, superficial carcinoma of the esophagus is defined as one invading up to the submucosa [5]. Among them, superficial carcinoma confined to the mucosa is called early cancer of the esophagus. Indication of endoscopic resection is determined mainly by the risk of lymph node metastasis [5–9]. If early cancer invading up to lamina propria mucosae (T1a-EP or LPM), where the risk of lymph node metastasis is thought to be less than 5% [5] is resected completely, curative resection will be expected. Therefore, T1a-EP and LPM are accepted as an absolute indication of endoscopic resection. Meanwhile, superficial cancer invading to muscularis mucosae (MM) or superficial submucosa up to 200 μm (SM1) has 10 to 15% of the risk of lymph node metastasis [8]. However, other treatment options for esophageal cancer, e.g., chemoradiotherapy or surgery are generally more invasive and also inheres considerable risks for major complications, therefore, endoscopic local resection for such cancers is acceptable as a relative indication. Obviously, negative lymphovascular infiltration should be confirmed histologically after complete resection of the tumor, to be judged as curative in both conditions.

On the other hand, extensive resection of the mucosa could be accompanied with severe stricture after treatment, which causes dysphagia and consequently loses the quality of life of the patients seriously [10, 11]. Although endoscopic balloon dilatation can avoid surgical intervention, frequent dilatation, and a risk of perforation during the procedure must be a burden for the patients [12, 13]. For this reason, a general indication of endoscopic resection for lateral tumor extension is up to three-fourths of the circumference. However, complete circumferential resection can be available as a relative indication if the patient accepts the risk for severe stricture and this additional troublesome endoscopic treatment.

9.3 Endoscopic Mucosal Resection

EMR is composed of fluid injection into the submucosa and mucosal resection with part of the submucosa using an electrocautery snare. There are some technical variations in EMR (Fig. 9.1).

EMR with a ligation device (EMR-L) requires an O-ring used for esophageal varices ligation (Fig. 9.1a) [14]. In this technique, after suctioning a lesion and

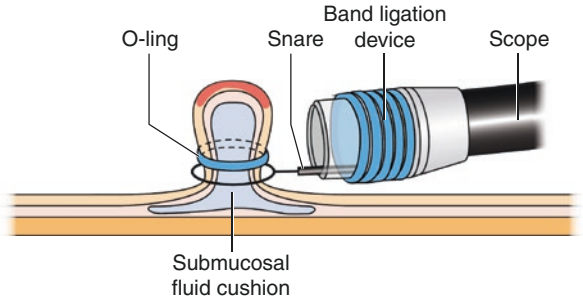

Fig. 9.1 Variety of EMRs. (**a**) EMR with a ligation device (EMR-L). A lesion is suctioned into a ligation device and ligated with O-ring before resection. (**b**). EMR using a cap-fitted endoscope (EMR-C). A lesion is suctioned into a transparent hood and resected by the snare. (**c**). Endoscopic esophageal mucosal resection (EEMR)-tube method. A long transparent silicon overtube is used for suctioning the lesion. (**d**). Two-channel EMR method. A forceps is used for grasping and pulling the lesion

ligating it with the O-ring to create a pseudopolyp, endoscopic resection is performed just below the O-ring using a snare. Although submucosal injection before the resection is desirable in order to avoid unexpected perforation, endoscopic resection using a ligation device without submucosal injection seems to be also acceptable due to its good clinical outcomes especially for early Barrett's neoplasia [15].

In EMR using a cap-fitted endoscope (EMR-C), a transparent hood attached to the tip of the endoscope is used (Fig. 9.1b) [16]. After opening a semilunar snare along the rim of the hood, an elevated lesion by submucosal injection is suctioned into the hood and resected by the snare.

In the endoscopic esophageal mucosal resection (EEMR)-tube method, a long transparent silicon overtube is used (Fig. 9.1c) [17]. After submucosal injection, the lesion is suctioned by the overtube introduced over the endoscope, and tightened by a snare preliminarily introduced through the side channel of the overtube. Resection should be done after confirming that the muscular layer is not involved because a diameter of the overtube is much larger than any other EMR caps.

A grasping and pulling technique using a two-channel endoscope is called two-channel EMR method (Fig. 9.1d) [18]. A grasping forceps from one working channel is passed through a snare introduced from the other channel. The elevated lesion by submucosal injection is grasped with the forceps and tightened with the snare at the bottom of the grasped mucosa. Again, resection should be done after confirming that the muscular layer is not involved within the captured tissue.

Because the size of snares is limited in these EMRs, the available size of en bloc resection is also limited [3, 4, 19, 20]. Expected maximal size of one specimen is thought to be approximately 2 cm. Besides, the resectable size is also limited by the diameter of the O-ring in EMR-L, the hood in EMR-C, and the overtube in EEMR-tube. Furthermore, in case of having severe fibrosis under the lesion, it usually becomes quite difficult to resect the lesion by these EMRs because a snare is easily

slipped from the target. Accordingly, early esophageal cancer in 1 cm or less without fibrosis would be suitable for a candidate of EMR in usual clinical settings.

9.4 Endoscopic Submucosal Dissection

This epoch-making technique is composed of four steps; marking around the lesion after chromoendoscopy with Lugol's iodine solution, submucosal injection, circumferential mucosal incision, and dissection of the submucosal connective tissue (Fig. 9.2). Because the operator can determine the extent of resection and dissect the submucosal tissue under the direct vision, ESD can offer reliable en bloc, margin-free resection irrespective of size or presence of submucosal fibrosis.

9.4.1 Details of Practical Skill

Since ESD takes longer procedure time than EMR, sufficient sedation is necessary for a safe and successful procedure. And in case of difficult ESD cases such as lesions located at cervical esophagus or large lesions with severe fibrosis, general anesthesia should be used to have much stable condition throughout the procedure.

Among various electrocautery knives specialized for ESD, pointed tip-type knives would be suitable, especially for esophageal ESD due to the narrow lumen and the thin wall of the esophagus[21–23]. Moreover, it is reported that the revised type of insulated knife and scissors type electrocautery knives are useful for esophageal ESD as well [24–26] (Fig. 9.3).

Successful resection requires an accurate endoscopic diagnosis of a tumor extent. Although promising image-enhancement endoscopy techniques have been introduced, conventional chromoendoscopy using Lugol's iodine solution would be still most useful for demarcating the tumor extent. Using a tip of the knife, markings are made 2–3 mm outside the lesion at intervals of approximately 3 mm.

In creating a submucosal fluid cushion, an injection needle is gently advanced into the submucosa at the outside of markings, and fluid colored with a small amount of indigo carmine, which is helpful to visualize the submucosa, is injected into the submucosa to make sufficient submucosal space for incision and dissection. Hypertonic or viscous injection fluid such as Glyceol™ (Chugai Pharmaceutical Co., Japan; consisted of 10% glycerine, 5% fructose, and 0.9% sodium chloride) or hyaluronic acid solution is desirable for long-lasting submucosal fluid cushion. Injection directly through the cancerous area should be avoided in order to prevent cancer cell implantation in the deeper layer.

The mucosa 1–2 mm outside of markings is usually cut with cutting current using a specific knife. Right after partial mucosal incision, initial submucosal dissection should be made along the incision line with coagulation current. To make sure the end point of submucosal dissection, it is better to cut the anal side of the lesion first, subsequently, mucosal incision and submucosal dissection are conducted from the oral side.

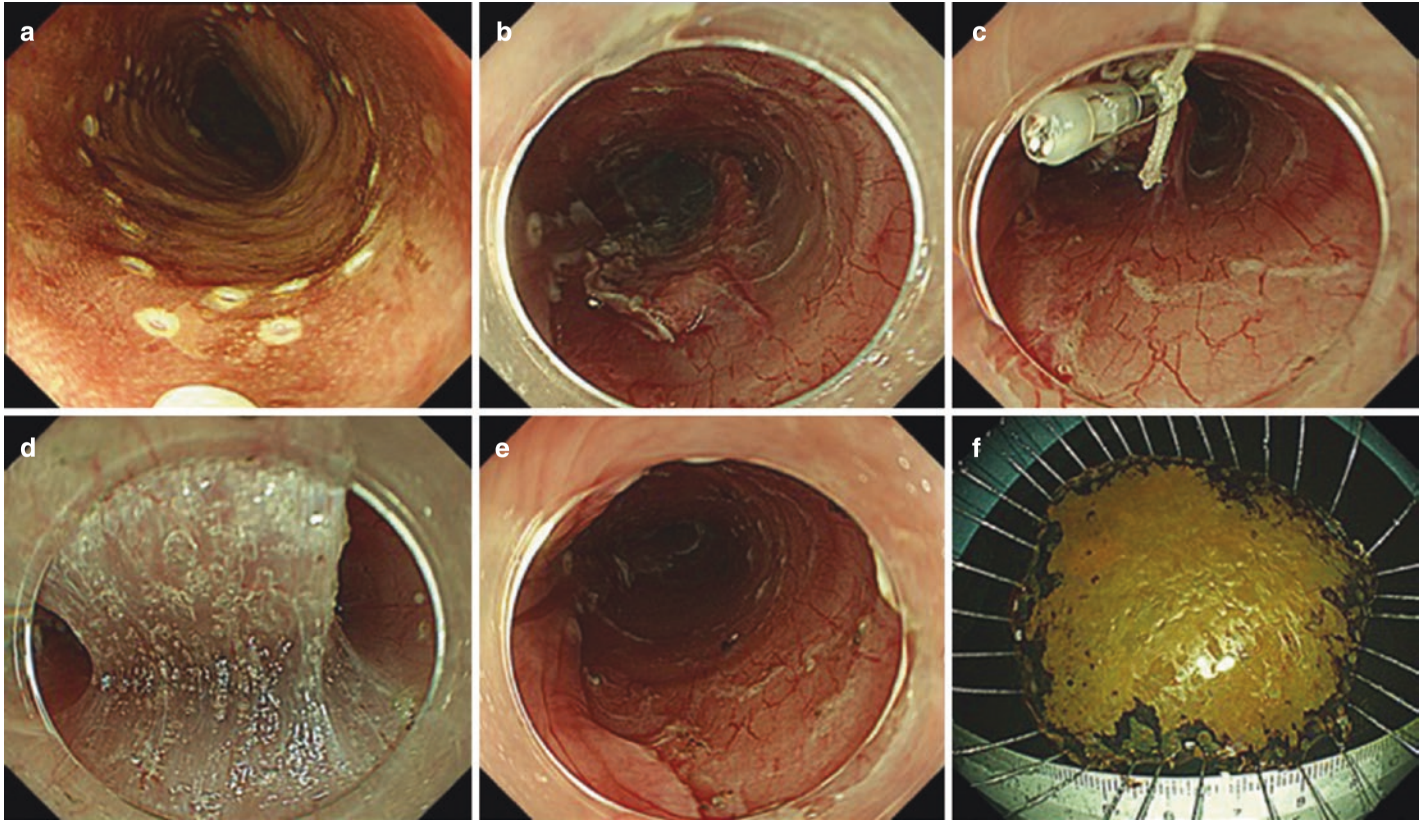

Fig. 9.2 Esophageal endoscopic submucosal dissection (ESD) using Dualknife J and clip with string traction method for large esophageal SCC. (**a**) Markings are placed around the lesion with an appropriate margin. (**b**) Submucosal dissection was started from the oral side. (**c**) A clip with string was deployed on the proximal side of the lesion. (**d**) Good visualization of the submucosal layer was obtained by pulling the string. (**e**) Resection wound after ESD. (**f**) An en bloc resection enables precise histological assessment (esophageal squamous cell carcinoma, pT1-a, 55x40mm, ly0, v0, pHM0, and pVM0)

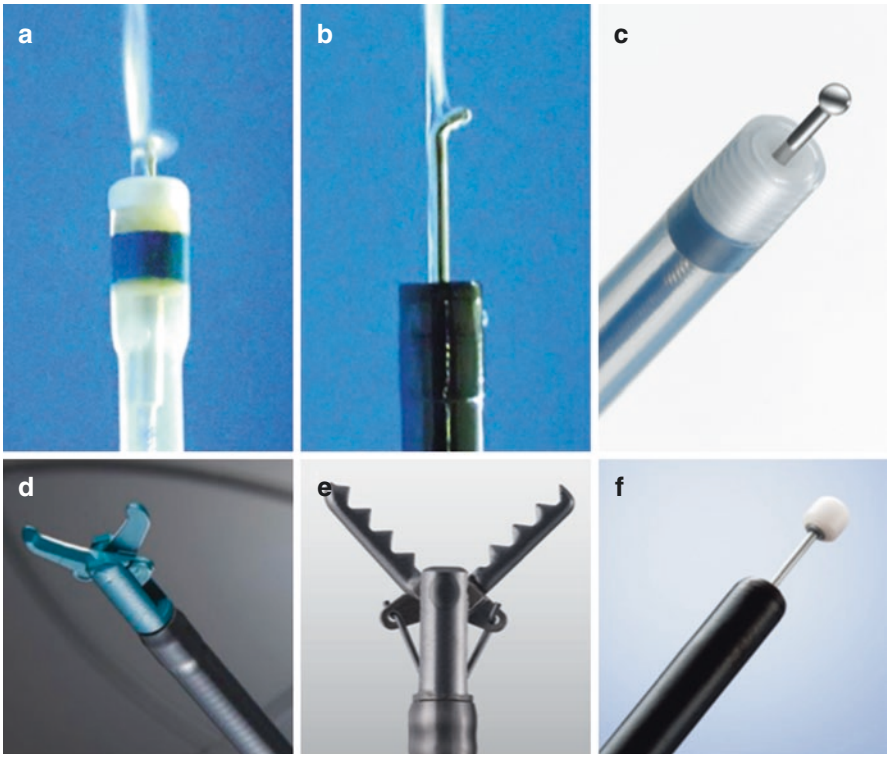

Fig. 9.3 Electrocautery knives for esophageal ESD (**a**) DualKnifeJ™. (**b**) HookKnifeJ™. (**c**): FlushKnife BT-S™. (**d**) SB knife Jr.™. (**e**) ClutchCutter™. (**f**) IT knife nano™

It is very important to conduct submucosal dissection under the direct vision, using a transparent hood. For large lesions, tunneling technique or traction device such as a clip with line is helpful to obtain good submucosal deployment (Fig. 9.2). The knife should be moved parallel to the plane of the muscular layer during submucosal dissection, to avoid muscular injury or perforation. Repeat submucosal injection, mucosal incision and submucosal dissection step by step until end of the procedure.

9.5 Management of Complications

9.5.1 Bleeding

Unlike gastric ESD, the rate of postoperative bleeding is relatively low (0–2%) [27–30]. In case of minor bleeding, hemostasis using the tip of the knife is initially attempted. When it is difficult to stop bleeding or it bleeds massively,

hemostatic forceps should be used. After the retrieval of the resected specimen, the resection wound should be thoroughly checked for visible vessels. And every thick exposed blood vessels should be carefully coagulated, avoiding excessive thermal damage.

9.5.2 Perforation

Perforation should be paid more attention, especially in esophageal ESD. Because the esophagus has no serosa, exposure of the muscular layer may cause pneumomediastinum [31, 32]. Indeed, pneumomediastinum was found by CT-scan in half of treated cases after esophageal ESD, although fortunately, these were almost subclinical [31]. Damage of the muscular layer might lead to delayed perforation, which could become fatal mediastinitis. Therefore, it is necessary to follow-up the patient carefully, especially after perforation, muscular injury and severe thermal damage. In case of perforation, we should keep patients at rest with fasting and intravenous administration of antibiotics until a fever and inflammation are relieved. Generally, emergency endoscopy for the purpose of detection and closure of a perforation site is not indicated because it may be not only ineffective but also a cause of expansion of mediastinitis.

9.5.3 Postoperative Stricture

The risk of postoperative stricture is particularly higher in esophageal ESD [10, 11]. Because the probability of stricture mostly depends on the resected size, a lesion over three-fourths of the circumference is relative indication of ESD as previously mentioned. Several attempts to prevent postoperative stricture have been tried [33–39]. Of them, locoregional injection or systemic treatment of steroids are known to be effective to prevent stricture formation after wide field ESD. Triamcinolone acetonide (TAC) is a type of corticosteroid that is used for locoregional injection as a slurry (Fig. 9.4). Some studies have revealed the significant superiority of locoregional TAC injection to historical control in preventing post-ESD esophageal stricture [33, 34]. Though it is effective to prevent post ESD stricture, the effectiveness is not enough for wider lesion such as full circumferential lesion and incidental TAC injection into proper muscle layer would cause mural necrosis [40]. Systemic administration of steroid is another option, which would prevent stricture formation even after circumferential ESD [31], but there is also a concern over adverse events of systemic administration of steroids. Moreover, preclinical trials are also considered such as adipose tissue stem cell transplantation [41] or cultured cell sheet transplantation [42, 43] and small interfering RNA with anti-fibrotic properties [44] but there has been no definitive method so far. Further investigation would be necessary to overcome this problem.

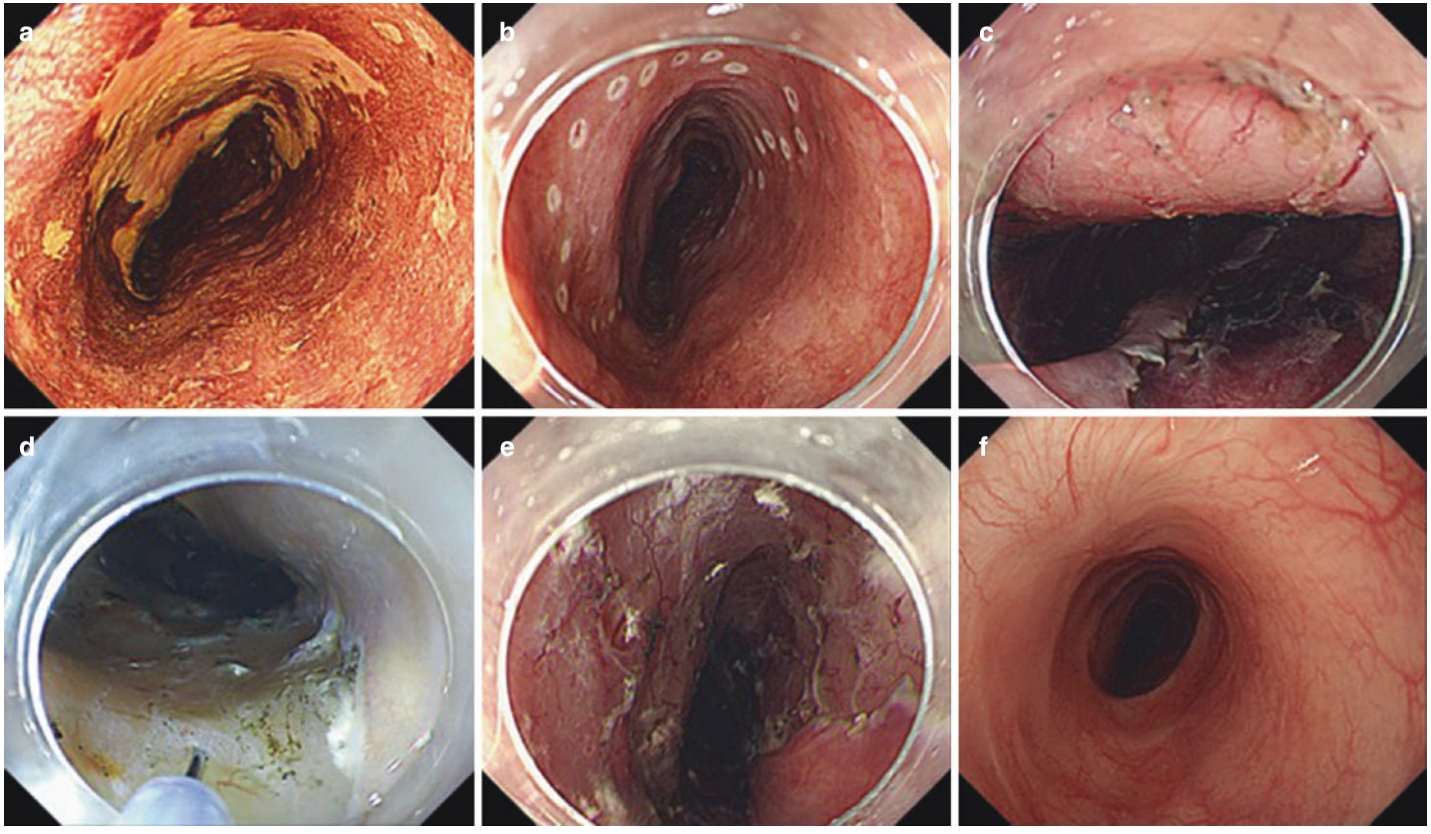

Fig. 9.4 Prevention of stricture formation after extensive resection. (**a**) Superficial cancer extending three quarters of circumference. (**b**) Placement of marking dots. (**c**) Resection wound become semi-circumferential. (**d**) Triamcinolone acetonide (TAC) is injected into the remaining submucosa in order to prevent severe stricture formation. (**e**) Artificial ulcer after resection. (**f**) Endoscopic imaging 6 months after initial ESD. The mucosal defect completely healed without severe stricture

9.6 Outcomes of ESD for Esophageal Squamous Cell Carcinoma

9.6.1 Short-Term Outcomes

Favorable treatment results have been reported from high volume centers particularly in Japan [27–30]. In short-term outcomes as a technical feasibility of esophageal ESD, over 90% of complete resection rate is obtained, whereas the rates of major complications such as delayed bleeding or perforation keep below 2% in leading centers for ESD. Even if complications occurred, it can be managed conservatively and thus hardly becomes a life-threatening condition. Considering the severity of potential post-surgical complications, ESD is an apparently less-invasive treatment option than surgery. However, in case of having severe stricture after extensive resection, multiple balloon dilatation is usually required. Stricture rate after ESD for the lesion involving over three-fourths of the circumference is reported to be 92% [12].

Technically, ESD for the lesion near the esophagogastric junction is sometimes difficult and time consuming because of intraoperative bleeding from abundant collecting vessels. The lesion located in the cervical esophagus, one of the natural constrictions, is also difficult to resect because of poor maneuverability of the endoscope and poor visibility of the lesion. Furthermore, the risk of aspiration pneumonia becomes extremely high by reflux of fluids (e.g., blood, rinsing water, and submucosal fluid). In this case, ESD with general anesthesia should be considered to avoid complications during the procedure.

9.6.2 Long-Term Outcomes

The long-term outcomes of ESD are also favorable. Five-year disease-specific survival rate is almost 100%. It means that endoscopic local resection is enough for curative resection in esophageal SCC with negligible risk for lymph node metastasis. On the other hand, close surveillance should be conducted for every patient after ESD to detect a metachronous cancer since all of them are regarded as high-risk group. Although there is no reliable evidence regarding an optimal surveillance strategy, endoscopy every 6–12 months are recommended after curative resection in cases of the absolute indication. When a treatment turned to be lateral margin positive or unknown for the absolute indication cases, endoscopy should be performed more closely (e.g., every 3–4 months) to detect local recurrence. In cases of the relative indication cases such as MM or SM1, a CT scan, as well as endoscopy every 6–12 months, is strongly recommended, if additional treatments (surgery or chemoradiatherapy) are refused after complete local resection.

9.7 Summary

Compared to other treatment options, endoscopic treatment is the most minimally invasive treatment for patients suffering from esophageal cancer with negligible risk for lymph node metastasis. To achieve successful endoscopic treatment, accurate preoperative diagnosis of the lesion, precise control of the endoscope, and adequate knowledge for possible complications are essential. ESD is far better than EMR since reliable margin free resection is available irrespective of the size or presence of submucosal fibrosis. Therefore, ESD can provide good quality of life to the patient, preserving gastrointestinal function, although it is technically demanding.

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Surgery Transthoracic Esophagectomy

10

Hirofumi Kawakubo

Abstract

Surgery has been frequently used to obtain locoregional control and has played a major role in esophageal cancer treatment. Curative resection of the primary lesion needs the removal of the gross lesion itself as well as any possible concomitant spread of the carcinoma. Thoracic esophageal carcinoma is often accompanied by extensive metastasis to the lymph nodes in the cervical, thoracic, and abdominal regions. Because sufficient dissection of the mediastinal lymph nodes is necessary, right thoracotomy and lymph node dissection plus total extirpation of the thoracoabdominal esophagus are generally performed. Transthoracic esophagectomy is one of the most invasive surgeries. The rate of morbidity and mortality for esophagectomy has been decreasing, but still remains high. Substantial advances in preoperative risk evaluation, improved operative techniques, and perioperative management are demanding. In future perspectives, to improve the rate of cure and the quality of life after surgery, more attention should be paid to minimal invasive esophagectomy and the individualization of treatment. Thoracoscopy-assisted esophagectomy including robot-assisted esophagectomy has been reported as promising surgical procedures, in views of its minimal invasiveness, better cosmetics, lesser pain, reduced postoperative respiratory complication, radical curability, and favorable long-term outcomes. If the oncological benefit is proved by the prospective studies, these procedures could become the standard procedures for transthoracic esophagectomy. Sentinel lymph node mapping acquires individual information to allow for adjustments and modifications to surgical procedures for patients. This process might be a procedure that could play a significant role in eliminating the necessity for the uniform application of highly invasive surgery.

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Keywords

Transthoracic esophagectomy · Esophageal carcinoma · Extended lymphadenectomy · Mortality · Morbidity · Three-field lymphadenectomy

10.1 Introduction

Many therapeutic options are used to treat esophageal cancer, and a multimodality treatment including surgery, radiotherapy, and chemotherapy is necessary for advanced esophageal carcinoma [1, 2]. However, traditionally, surgery has been most frequently used to obtain locoregional control and has played a major role in esophageal cancer treatment [3].

The distribution of tumor pathology is considerably different between Western countries and Japan. Adenocarcinoma (ADC) arising from Barrett's epithelium is common in Western countries, whereas squamous cell carcinoma (SCC) is common in Japan [4, 5]. There are many differences between ADC and SCC of the esophagus. The tumor site is an important factor from the standpoint of the surgical approach because the distribution and incidence of lymph node metastasis vary according to the locations of the primary tumors. The incidence of esophageal SCC is highest in the middle thoracic esophagus, whereas almost all ADC is located in the lower esophagus and at the esophagogastric junction [6]. Thoracic esophageal SCC is commonly accompanied by extensive lymph node metastasis from the cervical to abdominal regions. The status of lymph node metastases according to the location of the primary tumor reported by Ando et al. is shown in Fig. 10.1 [7]. The cervical and the upper mediastinal nodes are more commonly involved in patients with carcinoma of the upper thoracic esophagus, and the lower mediastinal and perigastric nodes are the most common sites in patients with carcinoma of the lower thoracic esophagus. In patients with carcinoma of the middle thoracic esophagus, cancer is often accompanied by extensive lymph node metastasis in the lymph nodes located from the neck to the abdomen. The concept of extensive three-field lymph node dissection including the dissection of cervical, mediastinal, and abdominal lymph nodes for surgically curable esophageal cancer located in the middle or upper thoracic esophagus was developed in Japan in the 1980s [6]. Although the effectiveness of extended lymphadenectomy for esophageal cancer has not yet been proven by randomized prospective studies [8, 9], many Japanese surgeons and some Western surgeons have reported the importance of radical lymph node dissection for locoregional control of esophageal cancer [3, 6–13]. This procedure has amassed little interest in Western countries. For the most part, the majority of Western esophageal surgeons have removed the readily accessible regional lymph nodes at the time of esophagectomy for the purpose of staging rather than with any expectation of improving survival [14]. A possible biological difference in these tumors in these respective countries has been suggested as a reason for the differences in the procedure of esophagectomy between Japan and Western countries. Our standard surgery

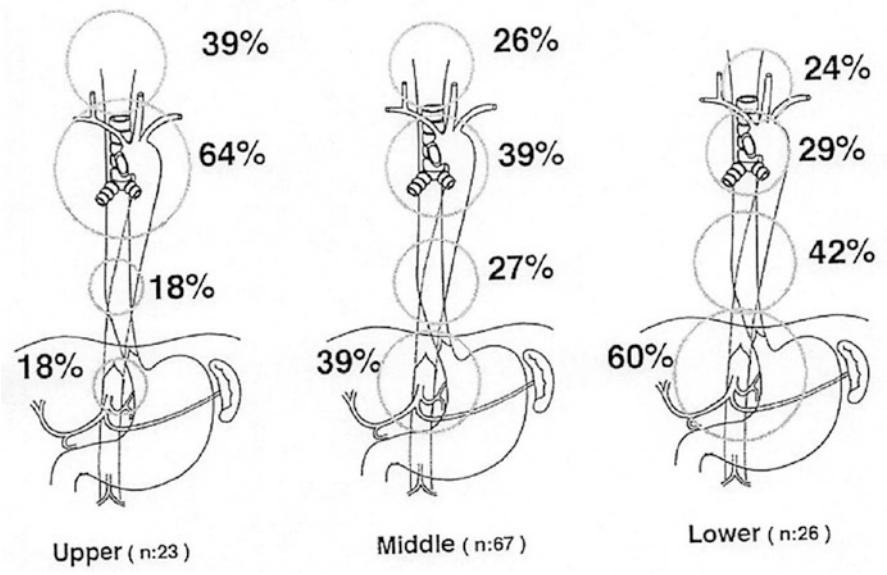


Fig. 10.1 The status of lymph node metastases according to the location of the primary tumor as reported by Ando et al.

for thoracic esophagus SCC is introduced in this chapter and the necessity of three-field lymphadenectomy is discussed in Sect. 10.5.

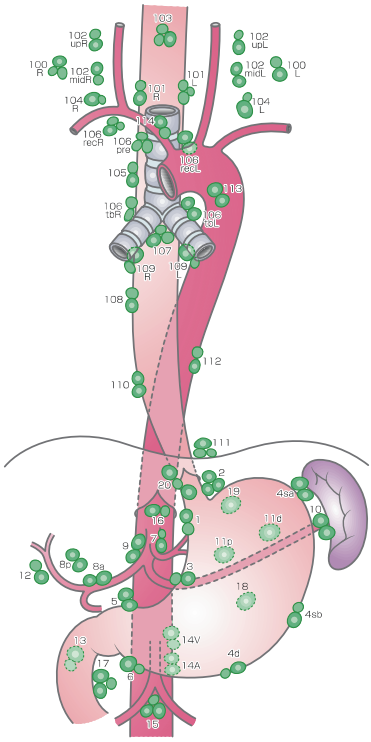
10.2 Surgery for SCC of Thoracic Esophagus

10.2.1 Esophagectomy

Curative resection of the primary lesion includes the removal of the gross lesion itself as well as possible concomitant spread of esophageal carcinoma. Because sufficient dissection of mediastinal lymph node is necessary, right thoracotomy, and lymph node dissection plus total extirpation of the thoracoabdominal esophagus are generally performed.

10.2.2 Regional Extent of Lymphadenectomy

The distribution and incidence of lymph node metastasis might vary according to the location, size, and depth of tumor invasion. Therefore, preoperative evaluation using computed tomography, ultrasonography, magnetic resonance imaging, or positron emission tomography for each patient is important for determining the extent of the lymph node dissection. The naming and number of lymph nodes defined according to the location of lymph nodes [15] are shown in Fig. 10.2.



1) Cervical lymph nodes
No. 101 Cervical paraesophageal lymp nodes
No. 104 Superclavicular lymph nodes

2) Thoracic lymph nodes
No. 105 Upper thoracic paraesophageal lymph nodes
No. 106 Thoracic paratracheal lymph nodes
No. 106rec Recurrent nerve lymph nodes
No. 106pre Pretracheal lymph nodes
No. 106tb Trancheobronchial lymph nodes
No. 107 Subcarinal lymph nodes
No. 108 Middle thoracic paraesophageal lymph nodes
No. 109 Main bronchus lymph nodes
No. 110 Lower thoracic paraesophageal lymph nodes
No. 111 Superadiaphragmatic lymph nodes
No. 112 Posterior mediastinal lymph nodes

3) Abdominal lymph nodes
No. 1 Right cardiac lymph nodes
No. 2 Left cardiac lymph nodes
No. 3 Lymph nodes along the lesser curvature
No. 7 Lymph nodes along the left gastric artery
No. 8 Lymph nodes along the common hepatic artery
No. 9 Lymph nodes along the celiac artery

Fig. 10.2 The naming and numbers of lymph nodes defined according to the location of the nodes

10.2.2.1 Upper Thoracic Esophageal Carcinoma

In cases of upper thoracic esophageal carcinoma, lymph node metastasis occurs mainly in the cervical and upper mediastinal region. Although metastasis to lower mediastinal or abdominal lymph nodes is less frequent, dissection usually covers all three regions.

10.2.2.2 Middle Thoracic Esophageal Carcinoma

In cases of middle thoracic esophageal carcinoma, lymph node metastasis occurs in cervical, the upper, middle, and lower mediastinal, and abdominal regions. In addition to the thoracic approach and abdominal approach, the cervical approach is necessary to achieve a secure dissection of the cervical lymph nodes, including those of the supraclavicular region.

10.2.2.3 Lower Thoracic Esophageal Carcinoma

In cases of lower thoracic esophageal carcinoma, lymph node metastasis occurs mainly in the mediastinal and abdominal regions, but metastasis to the cervical lymph nodes might also occur at a lower frequency. This dissection approach is controversial, and some advocate the cervical approach; however, others regard the thoracic approach as the most adequate procedure.

10.3 Surgical Procedure

10.3.1 Surgical Approach

The open approaches used for esophageal resection include transhiatal approach, right transthoracic approach, left transthoracic approach including left thoracoabdominal approach. The choice of approaches depends on various factors such as the location of the tumor, the general condition of the patient, and the choice of conduit for esophageal reconstruction. Because of the necessity for sufficient dissection of the mediastinal lymph nodes, the standard approach for thoracic esophageal SCC is right thoracotomy and mediastinal lymph node dissection plus the total extirpation of the thoracoabdominal esophagus. The McKeown esophagectomy is begun with the patients in the left lateral decubitus position, starts with the thoracic procedure, mobilization of the esophagus and mediastinal lymphadenectomy, followed by the abdominal procedure, gastric mobilization and abdominal lymphadenectomy, and esophagogastrostomy is performed through a left cervical incision. The Ivor Lewis esophagectomy is begun with the patients in the supine position, and starts with the abdominal procedure, gastric mobilization and abdominal lymphadenectomy, followed by the thoracic procedure, mobilization of the esophagus, mid to lower mediastinal lymphadenectomy and intrathoracic esophagogastric anastomosis. The Ivor Lewis esophagectomy is appropriate for tumors of the lower thoracic esophagus and gastroesophageal junction and the McKeown esophagectomy is appropriate for tumors of the mid to upper thoracic esophagus.

10.3.2 Upper Mediastinal Procedure

After the azygous arch was divided, the posterior side of the right upper mediastinal pleura was incised along the posterior edge of the esophagus up to the right subclavian artery. The right bronchial artery was carefully isolated and preserved for the open esophagectomy. The dorsal and left sides of the upper esophagus were dissected from the left pleura. The anterior side of the right upper mediastinal pleura was incised along the right vagal nerve up to the right subclavian artery. The right recurrent laryngeal nerve was identified at the caudal end of the right subclavian artery, and the lymph nodes around the right recurrent laryngeal nerve were carefully dissected to prevent nerve injury (Fig. 10.3). The anterior part of the upper esophagus was circumferentially dissected along with the surrounding nodes. By shifting the taped esophagus posteriorly and retracting the trachea anteriorly, it was possible to approach the left anterior side of the trachea. The lymph nodes around the left recurrent laryngeal nerve were dissected from the aortic arch to the cervical area. The left subclavian artery was exposed to dissect the left recurrent laryngeal lymph nodes. During dissection of the left tracheobronchial lymph nodes, the left recurrent laryngeal nerve and left bronchial artery were preserved on the face of the trunk of the left pulmonary artery between the aortic arch and the left main bronchus (Fig. 10.4).

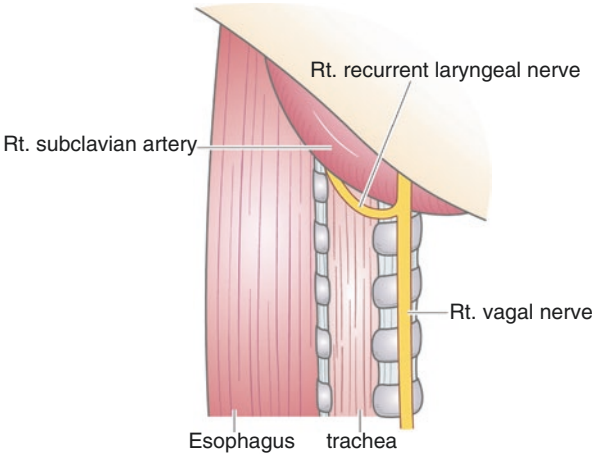


Fig. 10.3 The right recurrent laryngeal nerve was identified at the caudal end of the right subclavian artery, and lymph nodes around the right recurrent laryngeal nerve were dissected

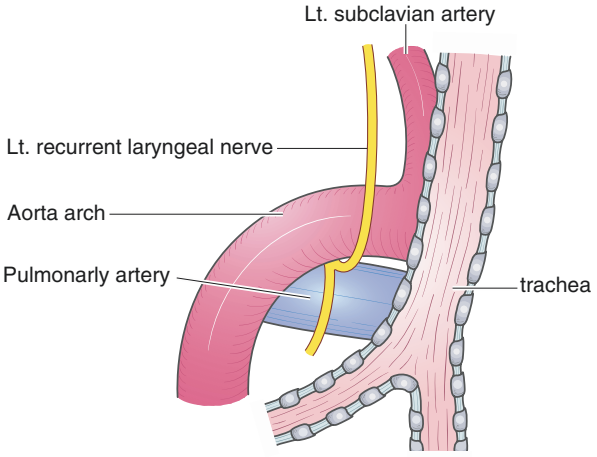


Fig. 10.4 The left subclavian artery was exposed to dissect the left recurrent laryngeal lymph nodes. The trunk of the left pulmonary artery between the aortic arch and the left main bronchus was exposed to dissect the left tracheobronchial lymph nodes

10.3.3 Middle and Lower Mediastinal Procedure

The middle and lower mediastinal pleura tissue was incised along the anterior edge of the vertebrae to the hiatus. The posterior side of the middle to lower esophagus was dissected to expose the aortic arch and the descending aorta (Fig. 10.5). The thoracic duct was ligated and divided behind the lower esophagus and resected combined with the esophagus. The esophagus was divided using a linear stapler above the primary tumor, and the proximal stump of the resected esophagus and surrounding tissue were dissected up to the hiatus. The subcarinal nodes were separately resected (Fig. 10.6). Esophageal mobilization and mediastinal lymphadenectomy were thus completed. View after esophagectomy and mediastinal lymph node dissection is shown in Fig. 10.7a–e. Bilateral recurrent laryngeal nerve, bilateral subclavian artery, trachea, bilateral bronchus, aorta, left pulmonary artery and vein, left pleura, pericardium ,and hiatus are all skeletonized.

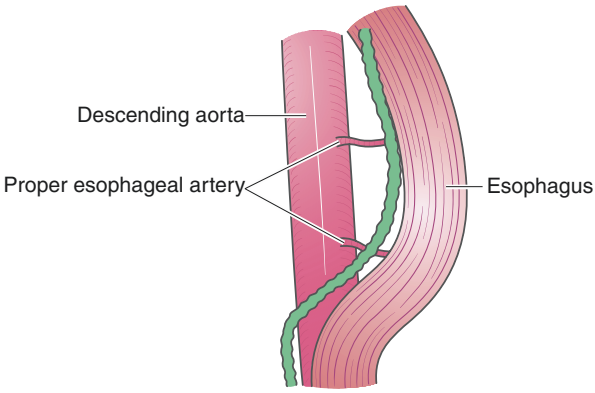


Fig. 10.5 The posterior side of the middle to lower esophagus was dissected to expose the descending aorta. The thoracic duct was ligated and divided behind the lower esophagus and resected together with the esophagus

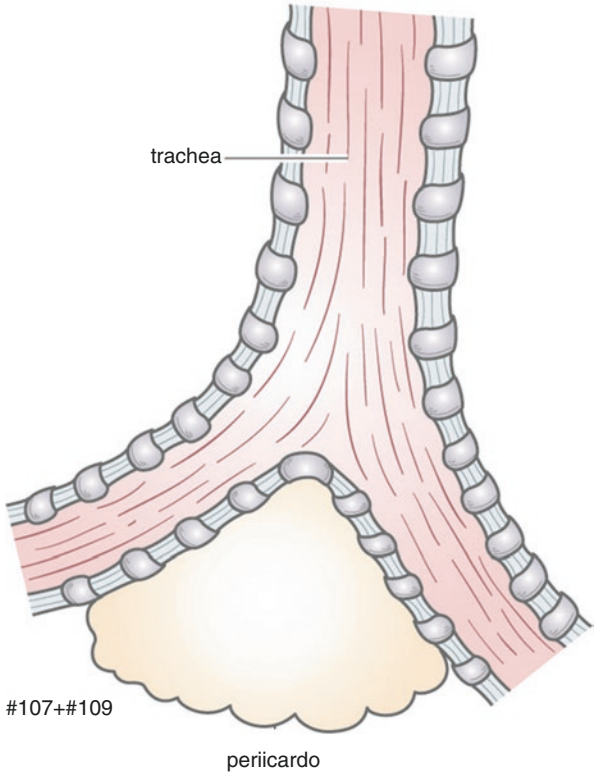


Fig. 10.6 The subcarinal nodes were separately dissected

10.3.4 Abdominal Procedures

The greater omentum was divided 4–5 cm from the arcade of the gastroepiploic vessels. The left gastroepiploic and short gastric vessels were divided along the splenic hilum. The lesser omentum was opened, and the right gastric vessels were preserved. The distal esophagus was dissected and mobilized. The distal stump of the esophagus and the dissected mediastinal tissue were then extracted from the

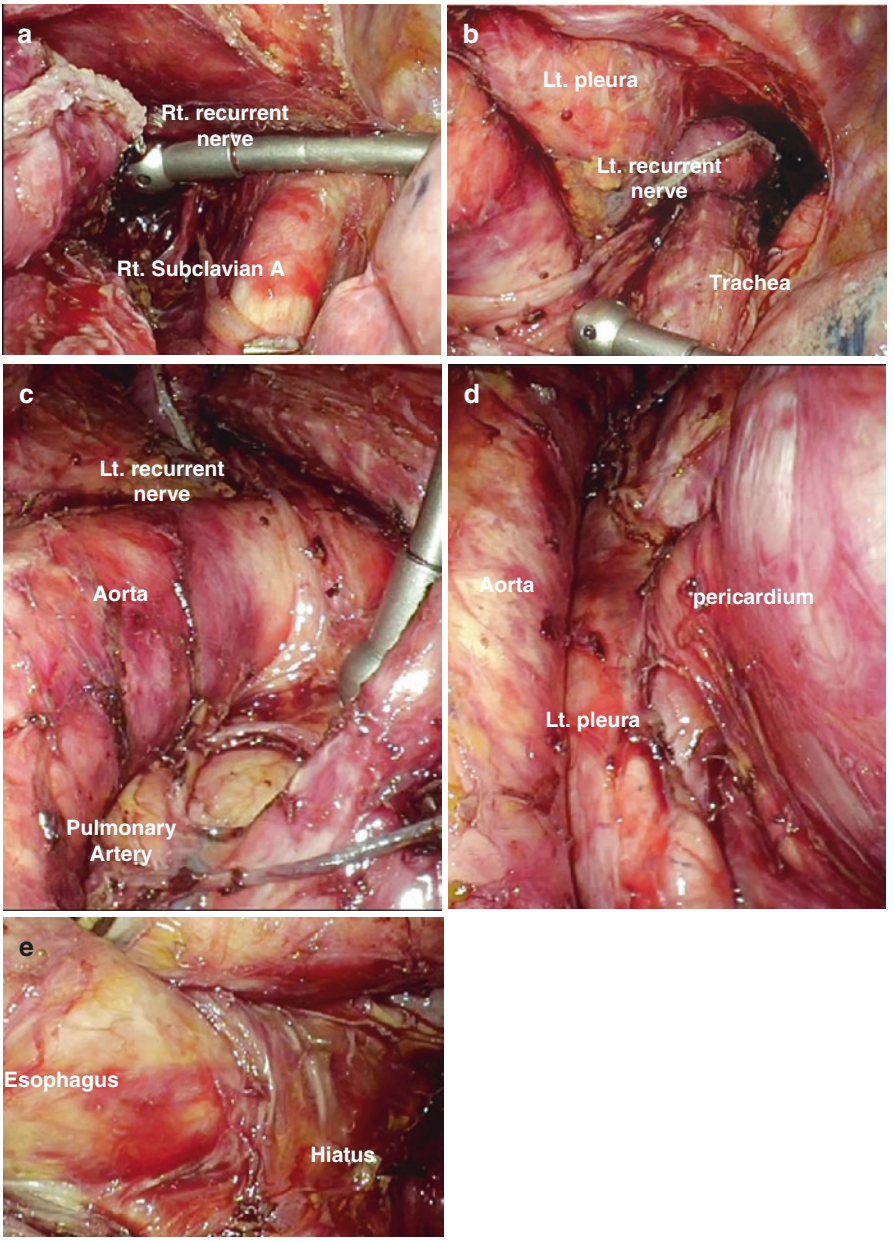


Fig. 10.7 View after esophagectomy and mediastinal lymph node dissection. (**a**) View after dissection of the right recurrent laryngeal nerve lymph node. The right recurrent laryngeal nerve and the right subclavian artery were exposed. (**b**) View after dissection of the left recurrent laryngeal nerve lymph node. The left recurrent laryngeal nerve, the left pleura, and the aortic arch were exposed. (**c**) View after dissection of the left tracheobronchial lymph nodes. Recurrent site of the left recurrent laryngeal nerve under the aortic arch and pulmonary artery were exposed and left bronchial artery was preserved. (**d**) View after procedure of mid to lower mediastinum. The descending aorta, the left pleura and pericardium were exposed. (**e**) View after dissection of the supradiaphragmatic lymph nodes

thorax to the abdomen. The lymph nodes around the celiac artery were dissected up to the hiatus. The stomach was divided from the lesser curvature to the fornix using linear staplers. Thus, gastric conduit formation and abdominal lymphadenectomy were completed.

10.4 Mortality and Morbidity after Esophagectomy

Transthoracic esophagectomy is one of the most invasive surgeries. Patients have the potential for respiratory, cardiovascular, and liver complications. Despite substantial advances in preoperative risk evaluation, improved operative techniques, and perioperative management, the risk of morbidity and mortality for esophagectomy remains high. Takeuchi et al. analyzed a total of 5354 patients who underwent esophagectomy in 713 institutes throughout Japan using the NCD study population data in 2011 [16]. The 30-day mortality rate in the NCD esophagectomy population was 1.25 and the operative morality rate was 3.4%. The overall morbidity rate was 41.9%. Various postoperative complications included pneumonia (15.4%), anastomotic leakage (13.3%), and septic shock (1.8%).

10.4.1 Mortality

Mortality has clearly linked to surgical volume. Metzer et al. performed a meta-analysis of 13 studies evaluating the impact of surgical volume on mortality after esophagectomy [17]. They showed a clear reduction in the postoperative mortality with an increasing volume of cases each year. The main reason for this phenomenon might be that the postoperative complication rates were lower in high-volume hospitals and that the management of complications was more successful. They concluded that only with the experience of >20 esophagectomies per year could a significant reduction of the mortality, which has decreased to 4.9%, be achieved and that surgery for esophageal carcinoma was a task for high-volume hospitals. Rodgers et al. identified surgical volume as a significant predictor of mortality in a retrospective review of the Nationwide Inpatient Sample database, which included 3243 esophagectomies [18]. Independent risks for mortality included comorbidity, age (65 years), female sex, race, and surgical volume. The mortality rates after esophagectomy have been decreasing in Japan. The 30-day mortality rate was 6.8% during the period from 1979 to 1982, 3.0% during the period from 1988 to 1994, and 1.0% in 2006 [19–21] from the data of the comprehensive registry of esophageal cancer in Japan. These mortality rates after esophagectomy were lower than those reported in other countries in the recent literature. Fujita et al. showed that the 30-day and the in-hospital mortality rates in low-volume hospitals (less than five esophagectomies per year) in Japan were triple those in the high-volume hospitals (>40 esophagectomies per year) from the data from 31,380 esophagectomies that were registered from 709 institutes during the period from 2001 to 2006 in Japan [22].

10.4.2 Morbidity

10.4.2.1 Pulmonary Complications

Pulmonary complications are the most frequent complication after esophagectomy and have been implicated in nearly two-third of postoperative mortalities [23]. The incidence of pneumonia has been directly linked to technical complications associated with the surgical procedure [24]. The incidence of pneumonia is reported to be higher in transthoracic esophagectomy compared with THE [25] and minimally invasive esophagectomy [26].

10.4.2.2 Cardiovascular Complications

Atrial fibrillation is a common cardiovascular complication after esophagectomy. Atkins et al. reported a 13.7% rate of arrhythmia after an esophagectomy in a retrospective review of 379 patients [23]. Some reports have demonstrated a link between atrial fibrillation and other perioperative complications, anastomotic leaks, and pulmonary complications as well as increased perioperative mortality. Murthy et al. reviewed 921 patients who underwent esophagectomy and identified a 22% rate of atrial fibrillation [27]. The authors demonstrated that there were significantly higher rates of pulmonary complications and renal failure, a 6.0-fold increase in anastomotic leak rates, and a 3.7-fold increase in mortality among patients who developed atrial fibrillation. Myocardial infarction has been reported in 1.1%–3.8% of patients undergoing esophagectomy [23, 28, 29].

10.4.2.3 Recurrent Laryngeal Nerve Injury

Recurrent laryngeal nerve injuries are more often associated with cervical anastomoses and three-field lymph node dissections. The incidence of these injuries has been variously reported between 2% and 20% [30]. The occurrence of a recurrent laryngeal nerve palsy or injury increased the incidence of perioperative pulmonary complications [31, 32]. Injury to the recurrent laryngeal nerve can occur in relation to retraction injuries and burn injuries during the extensive dissections of both recurrent nerve lymph nodes (No. 106-recL and 106-recR). Approximately half of vocal cord dysfunction after esophagectomy resolves spontaneously [33].

10.4.2.4 Chylothorax

Injury to the thoracic duct during esophagectomy can result in clinically significant chyle leak at approximately 2–4 L per day into the thoracic space. The diagnosis of a chyle leak requires an increase in the output from the chest tube with enteral alimentation and a change in the color of the fluid from serous to a milky appearance. High-volume chyle leaks clinically increase the risk of pulmonary and other complications because of the potential loss of fluids, lymphocytes, and protein that can lead to immunosuppression and malnutrition. The initial response to chylothorax should include the discontinuation of enteral alimentation and the start of total parenteral nutrition (TPN). A lymphangiogram and embolization of the thoracic duct can yield excellent success rates; however, this is highly dependent on the experience of the radiologists. Early surgical intervention is now recommended by many

surgeons. The location of the leak can be identified by administrating a liquid with a high-fat content, such as milk or cream, from the nasogastric or jejunostomy tube at least 1 hour before the procedure. If the location of the leak is identified, the duct should be ligated proximally and distally, and if the location of the leak is not identified, mass ligation of all tissue between the spine and the aorta would be performed around the hiatus.

10.5 Discussion on the Three-Field Lymphadenectomy

The concept of three-field dissection was developed in Japan in the 1980s. In Japan, three-field lymph node dissection, including dissection of the cervical, mediastinal, and abdominal lymph nodes, is the standard procedure for surgically curable esophageal cancer located in the middle or upper thoracic esophagus. The effectiveness of extended lymphadenectomy for esophageal cancer has not yet been proven by randomized prospective studies, better survival can be obtained with three-field lymph node dissection than with two-field lymph node dissection in Japan.

The largest study demonstrating the benefits of the three-field lymph node dissection from a single institution was reported by [6]. The authors performed 393 cases of esophagectomy with a two-field lymph node dissection between 1973 and 1984 and 324 cases of esophagectomy with a three-field lymph node dissection between 1984 and 1993. In both groups, the node-negative and node-positive groups, the survival of patients after extensive three-field dissection was significantly better than that after the less extensive two-field dissection. The authors speculated that the differences may be because of occult cancer-positive nodes in the cervical region and other areas, which may have been present and omitted from dissection and analysis in the group with less extensive dissections, were removed by extensive dissection. The 5-year survival rate of patients with all depth of cancer invasion after extensive three-field and the less extensive two-field dissection was 53.3% and 37.5%, respectively. Although this study was a non-randomized, historical control study, the 5-year survival rate of 53.3% in the patient after three-field dissection in those days remained very high. Tsurumaru et al. studied the state of lymph node metastasis in cases with only a single node metastasis [13]. A single node metastasis in patients with thoracic esophageal cancer may be located in the cervical (14.1%), mediastinal (upper, 31.0%; middle, 11.3%; and lower, 8.5%), and abdominal areas (35.2%). They also studied the state of lymph node metastasis in 5-year survivors of these cases and showed that 14.2% had a single node metastasis in the cervical area, 49.3% had a single node in the mediastinum (upper, 19.4%; middle, 22.4%; and lower 7.5%), and 37.3% had a single node in the abdomen. Even if there were lymph node metastases in either the cervical or the abdominal areas, many patients could be cured by extended lymphadenectomy. These results showed that lymph nodes in the cervical and abdominal areas were regional lymph nodes of the thoracic esophagus. These studies are retrospective studies with many biases. However, only two prospective studies have been published from Japan. One was a prospective randomized trial comparing three-field with two-field lymph node

dissection published by [9]. They showed a survival benefit for three-field over two-field lymph node dissection (65% versus 48%). However, the study was a low-volume study at a single institution and the difference was not statistically significant. Another prospective study was published from the National Cancer Center in Tokyo [8]. It was a non-randomized, case-matched trial, and showed that the 5-year survival rate was significantly better after three-field dissection (48% versus 33%; $p = 0.03$). The 5-year survival rate in the group of patients with a cervical lymph node was as high as 30%. These results suggested that there was a survival advantage in the three-field lymph node dissection and that lymph nodes in the cervical and abdominal areas were regional lymph nodes for thoracic esophageal squamous cell carcinoma.

Role of the three-field dissection for adenocarcinoma of the distal third of the esophagus remains unclear. In cases of lower thoracic esophageal carcinoma, lymph node metastasis occurs primarily in the mediastinal and abdominal regions, but metastasis to cervical lymph nodes can also occur at a lower frequency. The prognosis of a patient with cervical lymph node metastases from a lower thoracic esophageal carcinoma is very unfavorable [34]. Thus, mediastinal and abdominal lymphadenectomy may be adequate for lower thoracic esophageal carcinoma.

Although the incidence of esophageal cancer is increasing, the number of candidates for potentially curative resection is limited. For this reason, a prospective randomized study will be difficult to complete within a reasonable timeframe. It can also be very difficult to set up high-volume multi-institutional prospective randomized studies.

In summary, the cervical lymph nodes are at a risk of being involved by cancer metastasis from either upper or middle thoracic esophageal cancers. Therefore, three-field lymphadenectomy, bilateral cervical lymphadenectomy, mediastinal lymphadenectomy, and abdominal lymphadenectomy are recommended. In contrast, in patients with lower thoracic esophageal cancer, the appropriate extent of regional lymphadenectomy is defined by mediastinal and abdominal lymphadenectomy.

10.6 Future Perspectives

There have been many criticisms of the extension of transthoracic esophagectomy. The most common negative reason against extended lymph node dissection was the increase in mortality and morbidity [35]. The effect on postoperative quality of life has been apparent because of the invasiveness of this procedure. To improve the rate of cure and the quality of life after surgery, more attention should be paid to minimal invasive esophagectomy (MIE) and the individualization of treatment [36].

Thoracoscopy-assisted esophagectomy has been reported as promising surgical procedures, in views of its minimal invasiveness, better cosmetics, lesser pain, reduced postoperative respiratory complication, radical curability, and favorable long-term outcomes. Other various new procedures such as mediastinoscopy-assisted esophagectomy and robotic-assisted esophagectomy have been reported for

MIE. Reports have suggested these endoscopy-assisted surgeries enable conservation of the vasculature and nerves while confirming the microanatomy and also increase the accuracy of lymph node dissection, as it allows higher-power visualization. If the oncological benefit of MIE is proved by the prospective studies, MIE could become the standard procedures for transthoracic esophagectomy.

The concepts of the SLN intraoperative lymphatic mapping and sentinel lymphadenectomy appear attractive [37–40]. The identification of the sentinel node, which permits the detection of the first draining node from a primary lesion, can be used to individualize lymph-node dissection for esophageal SCC [41–43]. The pathological status of SLN might be used to predict the status of all the regional lymph nodes and might thus avoid unnecessary radical lymph node dissection. These techniques can benefit patients by avoiding various complications that might result from unnecessary radical lymph node dissection. It could allow for accurate intraoperative diagnosis and minimally invasive surgery tailored to the individual patient in the future. The extent of lymph node dissection could be determined by the distribution of SLNs. In the future, SLN mapping might play a significant role to eliminate the necessity of uniform application of a highly-invasive surgery by obtaining individual information to permit adjustments and modifications to the surgical procedure for patients.

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Surgery: Minimally Invasive Esophagectomy

11

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Abstract

Technical advances in endoscopic equipment and thoracoscopic surgery have increased the popularity of minimally invasive esophagectomy (MIE). Recently, robot-assisted thoracoscopic and/or laparoscopic esophagectomy using the da Vinci surgical system (DVSS) (Intuitive Surgical, Sunnyvale, USA) became an attractive option. More recently, nonthoracic radical esophagectomy with both transcervical and transhiatal approaches using mediastinoscopic devices were developed. However, there is currently no established scientific evidence supporting the use of MIE as an alternative to open esophagectomy (OE). In general, MIE is associated with longer operative times but lower blood loss and lower rates of pulmonary complications such as pneumonia compared with OE. To date, two patient positions were used for thoracoscopic esophagectomy, one is left lateral decubitus position, and the other is prone position. However, the optimal MIE type, approach, and position remain unclear. Over the next few years, an ongoing randomized phase III study, JCOG1409, is expected to determine the benefits of each procedure in terms of short- and long-term outcomes.

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Minimally invasive · Prone

11.1 Introduction

Although chemoradiotherapy may effectively treat esophageal cancer, esophagectomy remains the mainstay of potentially curative treatment for patients with localized esophageal cancer including squamous cell carcinoma [1]. Esophagectomy with radical lymphadenectomy was reported to improve disease control and survival [2].

Despite advances in perioperative management, esophagectomy remains one of the most invasive procedures among all gastrointestinal surgeries and is associated with serious postoperative complications [3]. A markedly high overall morbidity rate of 41.9% and 30- and 90-day mortality rates of 1.2% and 3.4%, respectively, were reported in a study analyzing data from a Japanese national database in 2011 [4]. Therefore, esophagectomy via the thoracoscopic and/or laparoscopic approach is a very attractive and less invasive alternative to the current approaches [5]. Since its first report for thoracoscopic approach by Cuschieri et al. in 1992, minimally invasive esophagectomy (MIE) has been increasingly utilized worldwide [6]. This increase in MIE's popularity can be attributable to technical advances in endoscopic equipment for thoracoscopic surgery, including dissectors, laparoscopic coagulating shears, and vessel-sealing systems, which are now available for thoracoscopic esophagus resection and extended mediastinal lymphadenectomy [5]. Moreover, laparoscopic gastric mobilization for reconstruction using a gastric conduit is widely accepted even when utilized in combination with open esophagectomy (OE) [7].

Based on a Japanese national database including 6041 esophagectomy patients, 2961 (49.0%) patients underwent MIE in 2013 [8]. According to previous studies, MIE is associated with longer operative time and lower blood loss compared with OE [9]. Moreover, MIE is associated with lower rates of pulmonary complications such as pneumonia, and both approaches have similar mortality rates. However, to date, scientific evidence supporting the use of MIE as an alternative to OE has not been sufficient. Therefore, thoracoscopic esophagectomy still does not receive a strong recommendation in the Esophageal Cancer Practice Guidelines 2017 edited by the Japan Esophageal Society [10, 11].

In this chapter, we review published studies on MIE, particularly those focusing on thoracoscopic esophagectomy and describe recent advances in MIE for esophageal cancer.

11.2 Overview of MIE

11.2.1 Terminology of MIE

To date, several thoracoscopic and laparoscopic approaches for resection of thoracic esophageal cancer have been defined as MIE, based on tumor location, clinical stage, and patient demographics [12]. Although total thoracoscopic and laparoscopic esophagectomy represent (total) MIE in a narrow sense, video-assisted thoracoscopic surgery (VATS) [13], esophagectomy with mini-thoracotomy up to an approximately 5-cm incision [14], and laparoscopic approaches are also considered within the scope of MIE. Hybrid MIE is defined as esophagectomy using either a thoracoscopic or laparoscopic approach. Recently, robot-assisted thoracoscopic and/or laparoscopic esophagectomy using the da Vinci surgical system (DVSS) (Intuitive Surgical, Sunnyvale, USA) became an attractive option [15]. More recently, nonthoracic radical esophagectomy both with transcervical and transhiatal approaches using mediastinoscopic devices was developed with feasible surgical outcomes [16, 17]. The DVSS was also applied to mediastinoscopic esophagectomy [18].

11.2.2 VATS Esophagectomy

11.2.2.1 History

Since the first report of VATS esophagectomy by Cuschieri et al. [6] where the left lateral decubitus position (LLDP) was adopted, MIE has become increasingly popular and was performed widely [6]. In 1993, the first mediastinoscope-assisted blunt dissection of the esophagus was reported [19], and in 1994, Sadanaga et al. reported the first laparoscopic transhiatal esophagectomy [20]. In 2004, the robot-assisted thoracoscopic esophagectomy was introduced by [21]), whereas in Japan, Akaishi et al. reported the first use of thoracoscopic total esophagectomy with en bloc mediastinal lymphadenectomy in 1996 [22]. In 1999, Kawahara et al. provided the details of VATS esophagectomy with extended lymphadenectomy [23], and Osugi et al. described the long-term survival of 77 patients with esophageal squamous cell carcinoma who underwent VATS esophagectomy [14].

11.2.2.2 Indication

The indications for VATS esophagectomy are relatively wider than those for laparoscopic surgery for gastric and colorectal cancer, and VATS esophagectomy is currently used for locally advanced esophageal cancer, even after neoadjuvant or definitive chemoradiotherapy as reported in several studies [5]. Only certain conditions such as obvious T4 tumors and those with severe pleural adhesion are excluded from the indications of VATS esophagectomy [7, 12].

11.2.2.3 Positioning

To date, two patient positions were used for thoracoscopic esophagectomy. VATS esophagectomy was originally performed in the LLDP, similar to that adopted for right transthoracic OE. Conversely, Cuschieri et al. reported the first case of thoracoscopic esophageal mobilization in the prone position in 1994 [24]. Based on their experience with 130 patients treated with thoracoscopic esophagectomy in the prone position, Palanivelu et al. reported excellent surgical outcomes [25], raising interest in this approach among esophageal surgeons. A number of single-institution reports of VATS esophagectomy in the prone position were published since then [25–27].

The differences between the two positions in VATS esophagectomy were discussed in the literature [5, 28]. The most significant advantage of the prone position is that it provides a good surgical field. The view of the posterior mediastinum, including the esophagus, can be obtained without any retraction of the right lung using a retractor or sutures, and blood pooling do not obscure the surgical field. The middle mediastinal organs and right lung naturally falls away because of the gravity and the additional carbon dioxide insufflation of the thoracic cavity in the prone position. The LLDP, on the other hand, requires skillful retraction of the right lung by assistants to obtain the appropriate surgical field [5].

Prone position was considered to have several theoretical physiological and ergonomic advantages for both the patient and the surgeon [29]. The prone position is well known to be beneficial for arterial oxygenation [30]. Furthermore, since the surgeon can operate in a plane parallel to the camera and the ports used by the operator are located at the elbow level of the surgeon, the ergonomics and fatigue experienced by the surgeon may be improved in the prone position. However, the prone position is still considered problematic in terms of safety, since it is technically difficult to perform urgent conversion to right thoracotomy in emergency situations such as sudden massive bleeding [5]. To resolve this issue, we previously described the utility of the left semi-prone position [31]. It was possible to perform thoracoscopic esophagectomy with safe and precise extended lymphadenectomy in the optimal position (e.g., LLDP or prone position) by rotating the operating table [31]. Robotic esophagectomy can also take either position; however, prone or semi-prone position is considered to be more suitable for the operability of the robot arms.

11.2.2.4 Lymph Node Dissection

Since lymph node (LN) metastases occur primarily from the cervical to the abdominal field, especially in esophageal squamous cell carcinoma, which is predominant in Japan and East Asia, the established strategy for extended LN dissection includes the dissection of upper mediastinal nodes along bilateral recurrent laryngeal nerves (RLNs) [32]. In the 1980s, the three-field LN dissection during transthoracic esophagectomy, a procedure for cervico–thoraco–abdominal LN dissection, was established in Japan. Currently, this procedure is widely accepted worldwide [32]. Precise upper mediastinal lymphadenectomy along bilateral RLNs is also feasible, even with thoracoscopic approaches.

Regarding the number of retrieved mediastinal and/or total LNs, most studies demonstrated that VATS esophagectomy was almost equivalent to OE, whereas a meta-analysis emphasized that the number of retrieved LNs was significantly higher with VATS esophagectomy compared with OE [33].

11.2.2.5 Reconstruction Procedures

In general, a gastric conduit is used for reconstruction after MIE as well as OE. Reconstruction after esophagectomy must be technically safe and easy to perform, and in general, intrathoracic esophagogastric anastomosis is considered superior to cervical esophagogastric anastomosis, associated with a lower incidence of anastomotic leak and a better cosmetic effect in patients undergoing OE with two-field lymphadenectomy. However, during reconstruction after VATS esophagectomy, esophagogastric anastomosis is preferred in the cervical portion, since intrathoracic esophagogastric anastomoses are technically difficult during thoracoscopic procedures with circular or linear staplers [5]. Placement of the anvil into the esophageal stump seems to be a major technical concern if the circular stapler is used, and thoracoscopic hand sewn maneuver seems to be a major technical concern if the linear stapler is used in thoracoscopic surgery. Several research groups, including us, have developed an easy and secure thoracoscopic intrathoracic esophagogastric anastomosis procedure, which uses a circular stapler with transoral placement of the anvil or linear stapler [31].

11.2.2.6 Our Procedures

Patients are placed in the left semi-prone position using beanbags, and thoracic procedures were performed in the optimal position (left lateral decubitus or prone positions) by rotating the operating table in our institution [34].

Six trocars in total are placed on the thoracic wall, and a 7-mmHg CO_2 pneumothorax is induced (Fig. 11.1). The upper mediastinal procedure is performed by initially placing the patient in the left lateral decubitus position. The azygos arch is divided using a linear stapler, and the posterior portion of the right upper mediastinal pleura is incised along the posterior edge of the esophagus up to the right subclavian vein. The dorsal and left sides of the upper esophagus are dissected along with the thoracic duct. The right upper mediastinal pleura is incised along the right vagal nerve from the level of the azygos arch to the edge of the right subclavian vein, and the right RLN is identified at the caudal end of the right subclavian artery. Lymph nodes around the nerve are dissected and resected up to the cervical level with meticulous care to prevent nerve injury (Fig. 11.2). Next, the anterior part of the upper esophagus is dissected from the trachea, and the upper esophagus is circumferentially dissected along with the surrounding nodes. By shifting the taped esophagus posteriorly and retracting the trachea anteriorly, it is possible to approach the left side of the trachea. The nodes around the left RLN are carefully dissected from the aortic arch to the cervical level (Figs. 11.3 and 11.4). The left pulmonary artery is exposed to dissect the left tracheobronchial lymph nodes between the aortic arch and the left main bronchus. The thoracic duct is clipped and divided at the level of the thoracic inlet.

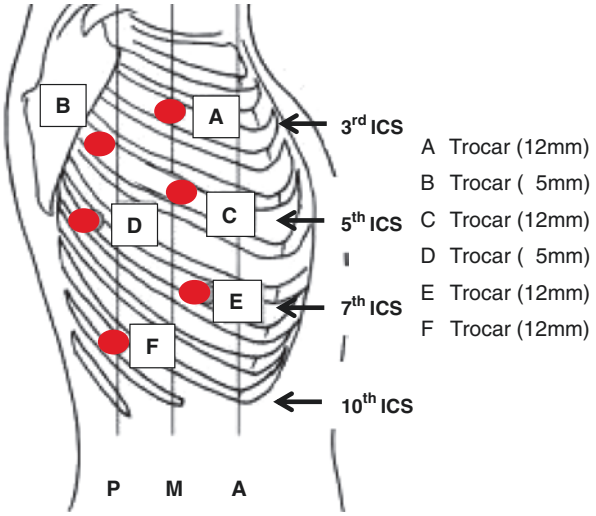

Fig. 11.1 Placement of thoracic ports. Six ports were introduced onto the thoracic wall. *ICS* intercostal space, *A* anterior axillar line, *M* middle axillar line, *P* posterior axillar line

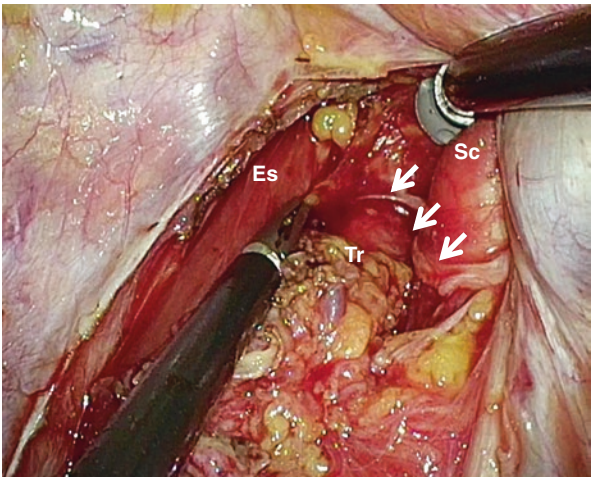

Fig. 11.2 Thoracoscopic lymphadenectomy along the right recurrent laryngeal nerve. *Arrows* the right recurrent laryngeal nerve, *Es* esophagus, *Tr* trachea, *Sc* right subclavian artery

Subsequently, the operating table is rotated so that the patient is in the prone position. The mediastinal pleura is incised along the anterior edge of the vertebrae to the hiatus, and the posterior side of the middle to lower esophagus is dissected to expose the aortic arch and descending aorta. The thoracic duct is clipped behind the lower esophagus and resected together with the esophagus. The mediastinal pleura anterior to the esophagus is then incised. The esophagus is divided using a linear stapler above the primary tumor, and the caudal stump of the esophagus and surrounding tissue are dissected up to the hiatus. The subcarinal nodes are separately resected. Esophageal mobilization and mediastinal lymphadenectomy are thus completed.

The abdominal procedures are performed through an upper midline abdominal incision or by hand-assisted laparoscopic surgery (HALS). HALS procedures are

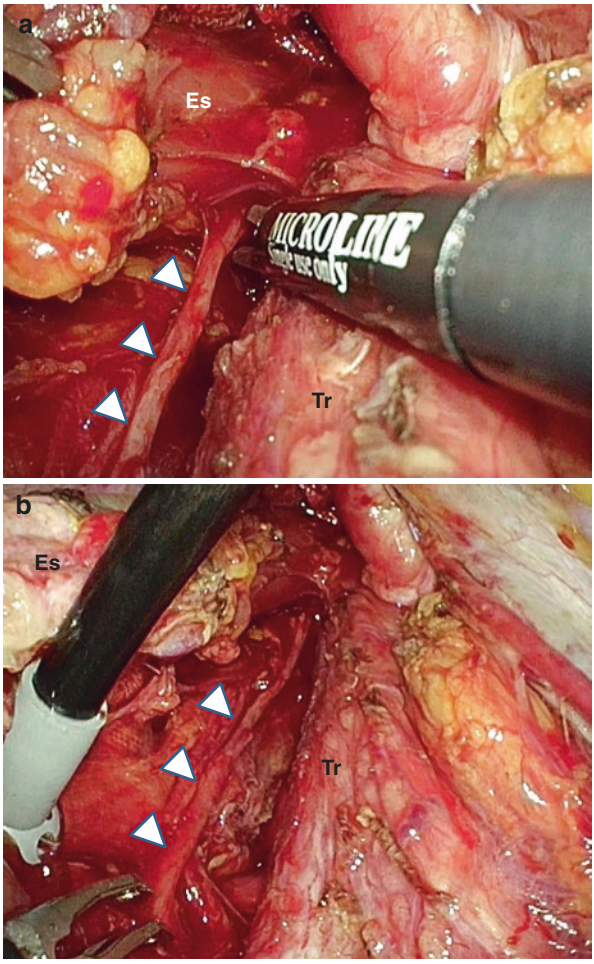

Fig. 11.3 Thoracoscopic lymphadenectomy along the left recurrent laryngeal nerve. (**a**) Magnified view, (**b**) Overview. *Arrowheads* the left recurrent laryngeal nerve, *Es* esophagus, *Tr* trachea

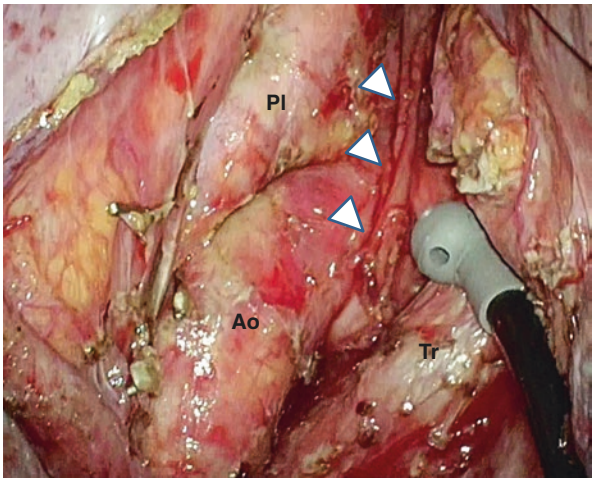

Fig. 11.4 Left upper mediastinal area after precise lymphadenectomy. *Arrowheads* the left recurrent laryngeal nerve, *Ao* aortic arch, *Tr* trachea; *Pl* left mediastinal pleura

performed through a transverse mini-laparotomy (7 cm) in the right upper quadrant, with one port below the navel and two ports in the left abdomen.

The greater omentum, short gastric vessels, and lesser omentum are divided while avoiding injury to the right gastroepiploic and right gastric vessels under an 10-mmHg pneumoperitoneum. The distal esophagus is dissected and mobilized. The fat tissue over the left gastric artery is dissected, and the artery is divided. The distal stump of the esophagus and the dissected mediastinal tissue are then extracted from the thorax to the abdomen. The stomach is then divided from the lesser curvature to the fornix using linear staplers. Thus, gastric conduit formation and abdominal lymphadenectomy are completed.

Esophagogastrostomy is performed in the neck. The gastric conduit is pulled up to the neck through the posterior mediastinal route. The cervical esophagus and gastric conduit are then anastomosed by hand-sewn maneuver.

11.2.3 Short-Term Outcomes of VATS Esophagectomy

To date, several single-institution studies demonstrated acceptable short-term outcomes of VATS esophagectomy for thoracic esophageal cancer in terms of operating time, blood loss, and postoperative complications, which were comparable with those of conventional OE (Tables 11.1, and 11.2) [12, 27, 35, 42, 43].

Table 11.1 Retrospective comparison of operative outcomes between conventional esophagectomy and MIE

Author (year)	No. of cases	Operative time (min)	*p* value	Blood loss (ml)	*p* value
Osugi et al.	VATS (77)	227	0.031	284	NS
(2003) [14]	OE (72)	186		310	
Shiraishi et al.	tMIE (78)	426	0.01	670	NS
(2006) [35]	VATS (38)	461		640	
	OE (37)	487		883	
Gao et al.	MIE (96)	330	<0.01	346	<0.01
(2011) [36]	OE (78)	284		512	
Kinjo et al.	tMIE (72)	308	<0.0001	320	<0.001
(2012) [37]	hMIE (34)	264		536	
	OE (79)	268		680	
Daiko et al.	VATS (29)	388	0.004	527	NS
(2012) [38]	OE (30)	335		495	
Miyasaka et al.	MIE (68)	483	NS	664	0.001
(2013) [39]	OE (30)	508		975	
Hsu et al.	VATS (66)	511	0.021	462	NS
(2014) [40]	OE (63)	461		615	
Takeuchi et al.	MIE (1751)	523	<0.001	466	<0.001
(2014) [4]	OE (3603)	450		618	
Tapias et al.	MIE (56)	337.4	NS	200	0.0003
(2016) [41]	OE (74)	361.6		250	

VATS video-assisted thoracoscopic surgery, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *tMIE* total MIE, *hMIE* hybrid MIE, *NS* not significant

Table 11.2 Retrospective comparison of short-term outcomes between conventional esophagectomy and MIE

Author (year)	No. of cases	In-hospital mortality (%)	*p* value	Hospital stay (days)	*p* value	Morbidity (%)					
						Pulmonary	*p* value	AL	*p* value	RLNP	*p* value
Osugi et al.	VATS (77)	0	NS	NA		15.6	NS	1.3	NS	14.3	NS
(2003) [14]	OE (72)	0				19.4		2.8		19.4	
Shiraishi et al.	tMIE (78)	2.6	0.003	NA		20.5	NS	11.5	0.005	33.3	NS
(2006) [35]	VATS (38)	10.5				23.7		10.5		42.1	
	OE (37)	13.5				32.4		24.3		27	
Gao et al.	MIE (96)	2.1	NS	12.6	<0.01	13.5	NS	7.3	NS	2.1	NS
(2011) [36]	OE (78)	3.8		17.5		14.1		7.7		5.1	
Sundaram et al.	MIE (47)	4.2	NS	16	NA	10.6	0.01	8.5	NS	2.1	NS
(2012) [42]	TTE (26)	0		14		34.6		0		0	
	THE (31)	3.2		16		32.3		12.9		3.2	
Kinjo et al.	tMIE (72)	0	NS	23	<0.001	13	0.001	4	NA	23	NA
(2012) [37]	hMIE (34)	0		32		38		24		12	
	OE (79)	0		53		39		17		13	
Daiko et al.	VATS (29)	0	NS	20	NS	3	NS	14	NS	17	NS
(2012) [38]	OE (30)	0		20		3		10		20	
Miyasaka et al.	MIE (68)	2.9	NS	35.0	<0.0001	32.4	NS	7.4	NS	25.0	NS
(2013) [39]	OE (30)	13.3		85.5		43.3		16.7		30.0	
Hsu et al.	VATS (66)	7.6	NS	NA		10.6	0.028	27.3	NS	NA	
(2014) [40]	OE (63)	7.9				25.4		30.2			
Takeuchi et al.	MIE (1751)	3.0	NS	NA		15.0	NS	14.9	0.016	NA	
(2014) [4]	OE (3603)	3.6				15.5		12.5			
Tapias et al.	MIE (56)	0	NS	7	<0.0001	8.9	0.004	0	NS	0	NS
(2016) [41]	OE (74)	2.7		9		29.7		1.4		4.1	

AL anastomotic leakage, *VATS* video-assisted thoracoscopic surgery, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *TTE* transthoracic esophagectomy, *THE* transhiatal esophagectomy, *tMIE* total MIE, *hMIE* hybrid MIE, *NS* not significant, *NA* not assessed, *RLNP* recurrent laryngeal nerve palsy

A study group in Europe reported the results of the first multicenter RCT, the TIME trial, that compared MIE with OE [7]. The primary outcome of the TIME trial was the incidence of pulmonary infections within the first 2 weeks after surgery and during the entire hospital stay. The incidence of pulmonary infection was considerably lower in the MIE group than the OE group, both within the first 2 weeks after surgery and during the entire hospital stay. MIE was also beneficial with lower operative blood loss, better postoperative quality of life, and shorter hospital stay; however, the 30-day and the in-hospital mortality rates did not differ significantly between the groups. Pathological parameters such as the number of retrieved LNs did not differ markedly between the two treatment groups.

We recently reported one of the largest propensity score-matched comparison studies between MIE (n = 3515) and OE (n = 3515) for esophageal cancer, based on a Japanese nationwide database [8]. The incidence of postoperative atelectasis and the number of patients requiring more than 48 hours of postoperative respiratory ventilation were significantly lower in the MIE group compared with the OE group (3.6% versus 5.1%, $p = 0.002$; 8.9% versus 10.9%, $p = 0.006$; respectively). Conversely, the incidence of postoperative RLNP was significantly higher in the MIE group than the OE group (10.3% versus 8.1%, $p = 0.002$). Moreover, the rate of reoperation within 30 days was significantly higher in the MIE group than the OE group (7.0% versus 5.3%, $p = 0.004$) [8]. However, no significant differences in the 30-day mortality rate (0.9% versus 1.1%) or the operative mortality rate (2.5% versus 2.8%) were observed between the MIE and the OE groups.

Recently, several studies compared the short-term outcomes in MIE with those of OE using nationwide or prospective data (Table 11.3) [7, 8, 44–46]. These studies also reported that MIE was associated with lower rates of respiratory complications than OE. Taken together, those results indicated that MIE and conventional OE were associated with comparable short-term outcomes after esophagectomy and that MIE reduced the occurrence of postoperative respiratory complications [8].

11.2.4 Long-Term Outcomes of VATS Esophagectomy

To date, several case-control studies investigated the long-term survival of patients undergoing MIE (Table 11.4). Although no significant differences in overall survival were observed between MIE and OE, recent studies by Miyasaka et al., Takeno et al., and Hsu et al. reported that VATS esophagectomy was associated with a significantly higher overall survival than OE [39, 40, 47]. A recent meta-analysis found that long-term survival rates were comparable between MIE and conventional OE. However, the benefits of MIE for oncological patients have not been scientifically shown, as no RCTs were performed to compare the long-term survival of patients undergoing MIE and OE, especially those with esophageal squamous cell carcinoma [5].

Recently, the TIME trial investigating long-term survival, reported no significant differences in disease-free and overall 3-year survival rates between MIE and OE [48]. In addition, a study comparing long-term survival after MIE and OE using a

Table 11.3 Comparison of the short-term outcomes of MIE with those of OE using nationwide or prospective data

Author (year)	Country	Study design	Periods	No. of cases (OE versusMIE)	Respiratory complications	Surgical complications	30-day mortality
Biere et al. [7]	Europe	RCT	2005–2008	56 versus 59	OE > MIE	Equivalent	Equivalent
Seesing et al. [44]	Netherlands	National data	2011–2015	433 versus 433	Equivalent	OE < MIE	Equivalent
Mamidanna et al. [45]	England	National data	2005–2010	6347 versus 1155	Equivalent	OE < MIE	Equivalent
Nozaki et al. [46]	Japan	Prospective	2006–2013	109 versus 101	OE > MIE	OE < MIE	Equivalent
Takeuchi et al. [8]	Japan	National data	2011–2012	3515 versus 3515	OE > MIE	OE < MIE	Equivalent

MIE minimally invasive esophagectomy, *OE* open esophagectomy, *RCT* randomized controlled trial

Table 11.4 Retrospective comparison of oncologic outcomes between conventional esophagectomy and MIE

Author (year)	No. of cases	No. of retrieved lymph node	*p* value	Overall survival	*p* value
Osugi et al.	VATS (77)	33.9	NS	55% (5yOS)	NS
(2003) [14]	OE (72)	32.8		57% (5yOS)	
Sundaram et al.	MIE (47)	20	NS	51 M (median OS)	NS
(2012) [42]	TTE (26)	19		51 M (median OS)	
	THE (31)	12		41 M (median OS)	
Kinjo et al.	tMIE (72)	28	0.002	72% (2yDFS)	NS
(2012) [37]	hMIE (34)	24		58% (2yDFS)	
	OE (79)	18		58% (2yDFS)	
Miyasaka et al.	MIE (68)	37.0	NS	61.5% (5yOS)	0.0051
(2013) [39]	OE (30)	41.5		26.7% (5yOS)	
Takeno et al.	VATS (91)	43.5	0.013	62% (5yOS)	0.011
(2013) [47]	OE (166)	37.4		44% (5yOS)	
Hsu et al.	VATS (66)	28.3	NS	70.9% (3yOS)	0.031
(2014) [40]	OE (63)	25.9		47.6% (3yOS)	
Tapias et al.	MIE (56)	20	NS	49.6% (5yOS)	NS
(2016) [41]	OE (74)	20		60.9% (5yOS)	

VATS video-assisted thoracoscopic surgery, *OE* open esophagectomy, *MIE* minimally invasive esophagectomy, *TTE* transthoracic esophagectomy, *THE* transhiatal esophagectomy, *tMIE* total MIE, *hMIE* hybrid MIE, *NS* not significant, *OS* overall survival, *DFS* disease-free survival, *y* year, *M* months

national cancer database [49] revealed an acceptable long-term survival rate after MIE; however, only 16% of the patients in the database were diagnosed with esophageal squamous cell carcinoma. To date, the non-inferiority or the superiority of MIE to OE for esophageal squamous cell carcinoma has not been empirically established. In 2015, the Japan Clinical Oncology Group initiated a randomized phase III study (JCOG1409) to compare MIE with OE for short-term and overall survival in patients with stage I–III esophageal squamous cell carcinoma [50]. This ongoing RCT is expected to determine the impact of each method on the short- and long-term outcomes, especially the non-inferiority of MIE to OE in terms of overall survival.

11.2.5 Robotically-Assisted Esophagectomy

Robotic surgery is a recently developed technique to overcome some of the limitations of conventional open and scope-based surgeries [29]. The meticulous and precise movements of the robotic instrument provide numerous advantages during gastrointestinal surgery [29]. Robotically assisted esophagectomy is performed less commonly than robotically assisted gastrectomy, and the impact of the use of DVSS on esophagectomy was assessed primarily in case series with small sample sizes [15]. The LLDP was used commonly in the case series from Western countries, and

some studies tried thoracic anastomosis. In contrast, in the case series from Asian countries, the preferred positions were the prone or semi-prone positions followed by cervical anastomosis [15].

Robotic esophagectomy may reduce the incidence of postoperative pain in the intercostal space due to the instruments' articulation inside the thorax and through the chest wall [29]. The DVSS is preferable during the thoracoscopic phase of esophageal resection and LN dissection, as it allows a very precise dissection along the vital mediastinal structures [51].

Although several groups reported the feasibility and safety of a wide range of esophagectomy approaches with good short-term outcomes, all were retrospective studies with a small number of patients [15]. In 2015, Ruurda et al. conducted a systematic review of 16 case series with case numbers ranging from 11 to 118 [52]. The systematic review included a total of 300 cases. The most common morbidities were pneumonia (6–45%), anastomotic strictures (10–68%), anastomotic leakage (4–35%), cardiac complications (most often atrial fibrillation, 5–36%), and, in cases of three-stage esophagectomy, recurrent nerve injury (4–35%) with low mortality (0–6%). These results suggested that, in terms of morbidity, robotic esophagectomy remained challenging. Robotic esophagectomy was expected to enable meticulous dissection of the mediastinum, translating into good short-term outcomes [52].

Previously, Suda et al. reported a comparative study of robotic esophagectomy and conventional thoracoscopic esophagectomy and showed that robotic esophagectomy significantly reduced the incidence of vocal cord palsy and hoarseness (Table 11.5) [51]. The robotic surgery was proposed to reduce the incidence of RLN injury, resulting in preserved laryngopharyngeal function [51]. Since 2012, a single-institutional RCT comparing robotic esophagectomy and open transthoracic esophagectomy for resectable esophageal cancer (the ROBOT trial) was conducted to determine whether robotic esophagectomy reduced the occurrence of postoperative complications, blood loss, and hospital stay [58]. The trial results revealed that robotic esophagectomy was associated with a lower percentage of overall surgery-related and cardiopulmonary complications with less postoperative pain as well as better short-term quality of life compared to OE [57]. Conversely, a recent meta-analysis that compared surgical outcomes between MIE and robotic esophagectomy demonstrated that there were no obvious differences in postoperative complications except RLNP between the two groups. The benefits of robotic esophagectomy compared with MIE remain unclear and should be evaluated in future studies [59].

11.2.6 Laparoscopy/Mediastinoscopy-Assisted Esophagectomy

Several institutions reported the use of laparoscopic and/or mediastinoscopic-assisted transhiatal esophagectomy with esophagogastric anastomosis in the cervical portion [20], which avoids blunt dissection of the thoracic esophagus by a blind maneuver [5]. Endoscopy is used in laparoscopy/mediastinoscopy-assisted transhiatal esophagectomy via the neck and the hiatus. However, laparoscopy/mediastinoscopy-assisted transhiatal esophagectomy has been limited to esophageal mobilization and

Table 11.5 Comparison of the short-term outcomes of Robotic esophagectomy with those of Open esophagectomy or MIE

Author (year)	Country	Study design	No. of cases	Operative time (min)	Blood loss (ml)	Morbidity (%)	Mortality (%)	No. of retrieved lymph node	Advantage of RE
Suda et al. [51] [51]	Japan	Nonrandomized prospective	RE (16)	336	145	50.0	0.0	37.5	Reduction of right RLN palsy
			TE (20)	336	139	55.0	0.0	39.0	
Jeong et al. [53] [53]	Korea	Propensity-score matching	RE (88)	288	200	16.0	1.1	NA	Reduction of postoperative delirium
			OE (159)	264	200	35.0	0.6		
Park et al. [54] [54]	Korea	Retrospective review	RE (62)	185*	462	16.1	1.6	37.3*	Increase of retrieved lymph node
			TE (43)	120*	466	20.9	0.0	28.7*	
Chao et al. [55] [55]	Taiwan	Propensity-score matching	RE (34)	231*	92	NA	0.0	35.8	Increase of retrieved lymph node along left RLN
			TE (34)	200*	103		2.9	32.0	
He et al. [56] [56]	China	Propensity-score matching	RE (27)	349*	119*	37.0	0.0	20.0	
			TE (27)	285*	158*	33.3	3.7	19.0	
Sluis et al. (2018) [57]	Netherlands	RCT (ROBOT trial)	RE (56)	170*	400*	59.0	4.0	27.0	Reduction of cardiopulmonary complications
			OE (56)	135*	568*	80.0	2.0	25.0	

RE robotic esophagectomy, *TE* transthoracic esophagectomy, *OE* open esophagectomy, *NA* not assessed, *RLN* recurrent laryngeal nerve
aindicated significant differences

mediastinal LN dissection due to the narrow surgical space and poor visualization. Mediastinoscopy-assisted cervical approach using pneumomediastinum, which provides enhanced visualization and wide space in the mediastinum, has overcome these disadvantages [60]. Fujiwara et al. developed an en bloc lymphadenectomy method in the upper mediastinum by using a single-port mediastinoscopic cervical approach with pneumomediastinum [16]. Mediastinoscopic-assisted transhiatal esophagectomy is a minimally invasive option for thoracic esophageal cancer, which carries the potential benefit of reduced pulmonary complications by avoiding one-lung ventilation and transthoracic procedures [16]. Recently, Mori et al. and Nakauchi et al. reported the results of robotic-assisted nonthoracic radical esophagectomy for esophageal cancer, including mediastinal lymphadenectomy with a transcervical approach [17, 18]. This procedure was confirmed to be technically feasible and safe, potentially comprising a useful surgical option for esophageal cancer [17].

11.3 Discussion

The several advantages of MIE over OE include better cosmesis, less tissue trauma and pain, reduced postoperative inflammatory response, and lower morbidity [13, 61]. In particular, postoperative respiratory complications were significantly lower after MIE than OE, as shown by a meta-analysis as well as an RCT (the TIME trial) [7, 13]. We also reported that the incidence of postoperative atelectasis and prolonged respiratory ventilation beyond 48 hours after surgery were significantly lower in the MIE group than in the OE group, based on a Japanese national database analysis [8]. The incidence of postoperative pneumonia also tended to be lower with MIE than OE [8]. The randomized phase III MIRO trial compared hybrid MIE (laparoscopic gastric mobilization and OE) with OE (open gastric mobilization and OE) and demonstrated that the rate of major pulmonary complications was significantly lower with hybrid MIE than OE [62]. It remains controversial whether total MIE or hybrid MIE is necessary to reduce postoperative pulmonary complications after esophagectomy. A large-scale RCT is necessary to determine the superiority of specific MIE approaches.

The comparison of the LLDP with the prone position as the optimal positioning for MIE should also be evaluated in RCTs [28]. The clinical benefit of MIE in lowering the occurrence of respiratory complications might be due to the different positions used. In fact, in the TIME trial, MIE was performed in the prone position, whereas OE was performed in the LLDP [7]. Therefore, additional comparative studies are needed to confirm the superiority of prone position over LLDP in MIE [5].

Surgical robots with impressive dexterity and precise dissection skills have been developed to aid surgeons in performing operations [51]. Both short- and long-term outcomes suggest that robotic esophagectomy is safe and feasible, although the superiority of robotic esophagectomy in comparison with conventional thoracoscopic esophagectomy without robot assistance remains to be empirically

demonstrated [57, 59]. Further studies are warranted to determine the advantages and disadvantages of robotic esophagectomy in terms of operative feasibility and oncological outcomes.

Although VATS esophagectomy is an established MIE approach, mediastinoscope-assisted transhiatal esophagectomy represents another MIE option, introducing the potential benefit of decreasing pulmonary complications by avoiding one-lung ventilation or transthoracic procedures [16]. Fujiwara et al. aimed to achieve extensive mediastinal lymphadenectomy, including the upper mediastinum along the bilateral RLNs, by mediastinoscope-assisted transhiatal esophagectomy with pneumomediastinum [16]. Future multicenter prospective studies are needed to evaluate the short- and long-term outcomes of mediastinoscope-assisted transhiatal esophagectomy. This procedure constitutes a reasonable and advantageous approach for non-thoracic radical esophagectomy in patients with esophageal cancer.

In conclusion, MIE appears to be comparable with conventional OE in terms of short-term outcomes after esophagectomy. MIE is particularly beneficial in reducing postoperative respiratory complications. However, the optimal MIE type, approach, and position remain unclear. Over the next few years, an ongoing randomized phase III study, JCOG1409, is expected to determine the benefits of each procedure in terms of short- and long-term outcomes.

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Surgery: Esophageal Reconstruction

12

Michio Sato

Abstract

Esophageal substitutes and reconstruction routes should be considered depending on the location and the extent of the tumor.

Subtotal esophagectomy and esophageal reconstruction with cervical or high intrathoracic anastomosis are generally performed for thoracic esophageal cancer. In Japan, the stomach, colon, and jejunum are used at rates of 86%, 3%, and 6%, respectively, as esophageal substitutes. Esophagogastric anastomotic techniques can largely be classified into hand sewn, circular stapler, and linear stapler techniques.

If the stomach cannot be used, the colon or jejunum with a vascular pedicle is selected as an esophageal substitute. The middle colic artery or ascending branch of the left colic artery is utilized as a vascular pedicle in use of the right or left colon, respectively. In case of a long segment of jejunal flap that cannot reach the neck, vascular anastomosis for supercharge and superdrainage is required to ensure blood supply to the tip of the flap.

Subcutaneous, anterior mediastinal, posterior mediastinal, and intrathoracic reconstruction routes are used, with posterior mediastinal (including intrathoracic) and anterior mediastinal routes preferably selected in Japan at rates of 49% and 38%, respectively.

Free jejunal transfer is selected for reconstruction in cases of cervical esophageal cancer limited to the cervical esophagus. If the cancer extends to the thoracic portion or another tumor is present in the thoracic esophagus, esophageal reconstruction using the stomach or colon is generally performed after transhiatal esophagectomy.

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Keywords

Esophageal reconstruction · Gastric tube · Colon interposition · Free jejunal transfer · Esophagogastric anastomosis

12.1 Introduction

Minimally invasive esophagectomy is rapidly getting worldwide popularity [1–3], but this endoscopic surgery still accounted for only 33 and 36% of all esophageal surgeries in Japan in 2011 and 2012, respectively [4, 5]. In this chapter, we describe the open procedure of esophageal reconstruction for esophageal squamous cell carcinoma (ESCC). There is little evidence related to esophageal reconstruction based on randomized clinical trials, and thus we are limited to description of our own experience in this approach. Reconstruction for thoracic esophageal carcinoma is described in Sect. 12.2 and that for cervical esophageal carcinoma is discussed in Sect. 12.3.

The middle thoracic esophagus is the most common tumor site (45.6%) in Japan (Table 12.1) [4], with ESCC being common. The incidence of lymph node metastasis in the superior mediastinum is quite high [6]. Thus, the most preferable approach is subtotal esophagectomy with superior mediastinal lymphadenectomy and esophageal reconstruction with cervical or high intrathoracic anastomosis between the remnant esophagus and the esophageal substitute.

12.2 Thoracic Esophageal Cancer

The stomach, colon, and jejunum are the most popular organs used for esophageal reconstruction in thoracic esophageal cancer. The stomach is used most frequently because fewer anastomoses are required and the operative procedure is relatively simple and consequently less invasive. In Japan, the stomach is used for reconstruction in 86.0% of cases (Table 12.2) [4]. If the stomach cannot be used because of

Table 12.1 Tumor location in Japan (2012)

	All cases		Surgical cases	
Location of tumor	Total	(%)	Total	(%)
Cervical	370	(4.6)	152	(3.2)
Upper thoracic	1023	(12.8)	581	(12.3)
Middle thoracic	3832	(47.9)	2151	(45.6)
Lower thoracic	2085	(26.1)	1344	(28.5)
EG	455	(5.7)	356	(7.5)
E = G	81	(1.0)	56	(1.2)
GE	71	(0.9)	59	(1.2)
Unknown	82	(1.0)	23	(0.5)
Total	7999		4722	

Table 12.2 Organs used for reconstruction in Japan (2012)

Organs	Cases	(%)
None	62	(1.3)
Whole stomach	49	(1.0)
Gastric tube	4057	(85.0)
Jejunum	286	(6.0)
Free jejunum	94	(2.0)
Colon	157	(3.3)
Free colon	12	(0.3)
Others	24	(0.5)
Unknown	33	(0.7)
Total organs	4774	
Total cases	4722	

previous history of gastrectomy or synchronous gastric cancer, the colon or jejunum with the vascular pedicle is indicated as an esophageal substitute.

12.2.1 Stomach

Use of the stomach as an esophageal substitute can involve three types of conduit with different widths: a whole stomach, a subtotal gastric tube, and a narrow gastric tube. Types of conduits are selected by surgeons considering the length and blood flow in the conduit. Blood supply in the relocated stomach is mainly from the right gastroepiploic artery and only from intramural blood flow in its upper tip. A wide gastric tube has a rich blood supply, but a short length. A narrow stomach is longer, but has poor blood supply at the tip and tends to be ischemic.

12.2.1.1 Operative Technique

The gastrocolic omentum is divided 3–4 cm from the right gastroepiploic vessels, the left gastroepiploic vessels are divided near their roots, and the short gastric vessels are also divided. During this series of procedures, a vessel sealing device (LigaSure™ or Enseal™) is useful for reduction of the operation time and blood loss. The portion of the right crus of the diaphragm passing to the left of the esophagus is exposed and the recurrent branch of the left inferior phrenic artery is divided. The lesser omentum is then divided and the portion of the right crus of the diaphragm passing to the right of the esophagus is exposed. The nodes along the celiac artery (No. 9; Japanese classification of lymph node [7]) and the nodes along the left gastric artery (No. 7) are dissected and the root of the left gastric artery is ligated and divided. The thoracic esophagus dissected during thoracic procedure is pulled out of the esophageal hiatus and the stomach with the thoracic esophagus is mobilized. The esophageal hiatus is sutured and closed in a case in which the anterior mediastinal or the subcutaneous route is used.

The surgeon picks up the fundus of the mobilized stomach to find the highest point of it [8] and decides the position of the cut line in the lesser curvature (Fig. 12.1). For a whole stomach conduit, the cut line is on the esophagogastric junction; for a subtotal stomach tube, the cut line is a line connecting the points

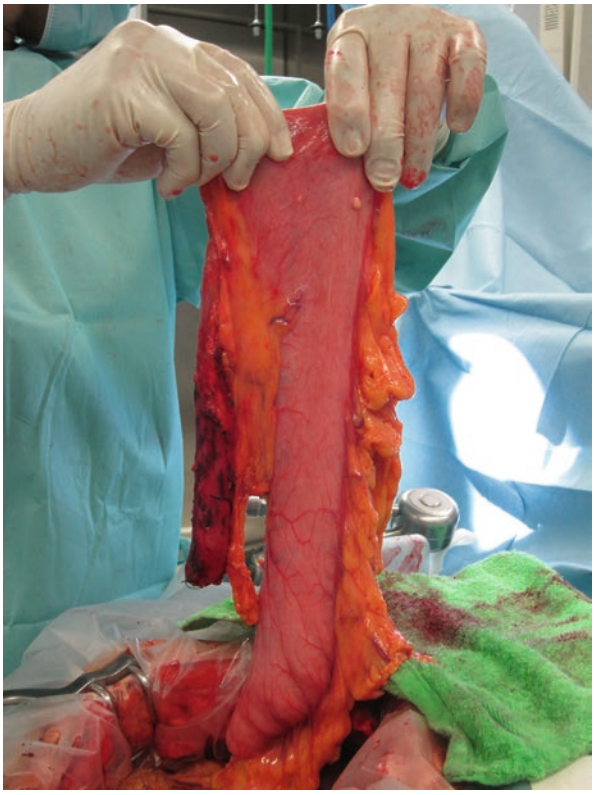


Fig. 12.1 The surgeon picks up the fundus and finds the highest point of the stomach

where the anterior gastric branches of the left gastric artery enter the gastric wall; and for a narrow stomach tube, the cut line is 3–4 cm from the greater curvature (Fig. 12.2). Generally, the lesser curvature is divided by a linear stapler several times and seromuscular sutures are added. When the lesser curvature is divided, the right and left cardiac nodes (No. 1 and No. 2) and the nodes along the lesser curvature (No. 3) are removed together. A gastric tube is put into a narrow vinyl bag and brought up to the cervical portion through the selected route. If the length of the gastric tube is insufficient, procedures such as mobilization of the duodenum, circular cutting in the seromuscular layer of the gastric tube, changing the reconstruction route to a shorter one, and hand sewing on the lesser curvature instead of stapling are effective for elongation of the length of a gastric tube.

12.2.1.2 Esophagogastric Anastomosis

There are many kinds of anastomotic procedures, and these can largely be classified into hand sewn (HS), circular stapler (CS), and linear stapler (LS) techniques. In the HS technique, an interrupted or running suture is generally performed using 4–0 or

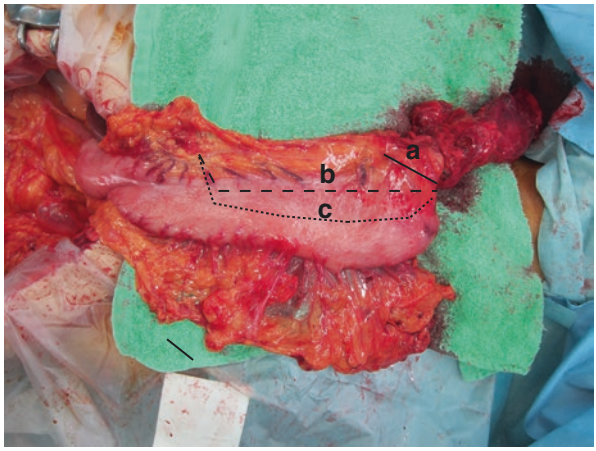


Fig. 12.2 Cut lines of the lesser curvature. For a whole stomach conduit, the cut line is made on an esophageal gastric junction (A, continuous line). For a subtotal stomach tube, the cut line is a line connecting the points where the anterior gastric branches of the left gastric artery enter the gastric wall (B, dashed line). For a narrow stomach tube, the cut line is 3–4 cm from the greater curvature (C, dotted line)

5–0 absorbable sutures through all single layers (Olsen, Gambee) or through double layers (layer to layer, Albert-Lembert) in an end-to-end or end-to-side fashion [9–11].

In the CS technique, a circular stapler with a diameter of 25 mm is most often used. First, an anvil head is inserted and secured in the remnant esophagus. The staple line in the tip of the gastric tube is opened and the body of the circular stapler is inserted. The remnant esophagus and greater curvature are then stapled in an end-to-side fashion (Fig. 12.3a). The hole where the stapler was inserted is closed using a linear stapler and the staple line is inverted by seromuscular sutures.

The LS technique can be used for side-to-side or end-to-end anastomosis. In the side-to-side technique, there are two kinds of methods in terms of alignment of the remnant esophagus and the stomach tube. Collard et al. reported that the posterior wall of the esophageal stump and that of the gastric fundus are placed side by side and the two forks of a linear stapler are placed catching the two opposing walls and anastomose between the two posterior walls of the esophagus and the stomach (Fig. 12.3b) [12–14]. On the other hand, Orringer et al. reported that the tip of the stomach tube is positioned behind the esophageal stump, a linear staple cartridge is inserted into the remnant esophagus and stomach from gastrostomy performed on the anterior wall of the gastric tube in parallel alignment and the posterior wall of the esophagus and the anterior wall of the gastric tube are then stapled (Fig. 12.3c) [15, 16]. In both techniques, the gastric staple suture line should be well away from the anastomosis to avoid ischemia between the gastric staple suture line and the anastomosis. The edges of the opened esophagus and stomach are closed with a linear stapler or are hand sewn.

In the end-to-end LS technique, a linear stapler is applied three times for anastomosis; thus, this technique is referred to as the triangulating stapling technique. A narrow gastric tube with a width of 3.5 cm is suitable. First, anastomosis is applied to the posterior wall of the remnant esophagus and the edge of the gastric tube in an

inverted fashion (Fig. 12.3d). A linear stapler is then applied to the anterior wall twice in an everted fashion to complete the end-to-end esophagogastric anastomosis. It is important that the staple lines are securely intersected among all layers and that the linear staple line of the gastric tube is positioned at the center of the right side of the triangle [17–20].

There are some randomized controlled studies and meta-analysis reported to compare these anastomotic techniques for cervical esophagogastric anastomosis (Table 12.3) [21–29]. HS may require longer operating time than stapler methods but not result in higher incidence of leakage or stricture than stapler methods. LS technique may reduce the rate of stricture compared with CS and HS. Because causes of anastomotic morbidities include not only these anastomotic techniques but also many kinds of factor such as patient's physical conditions, tumor location, perioperative management, blood supply in the tip of gastric tube, and tension between the esophagus and the stomach, it is hardly decided which is the best

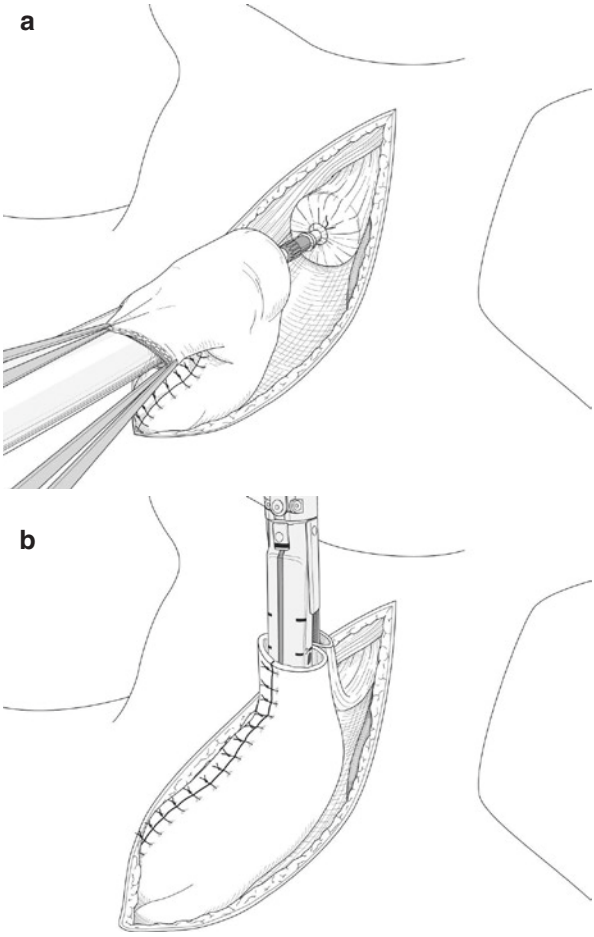
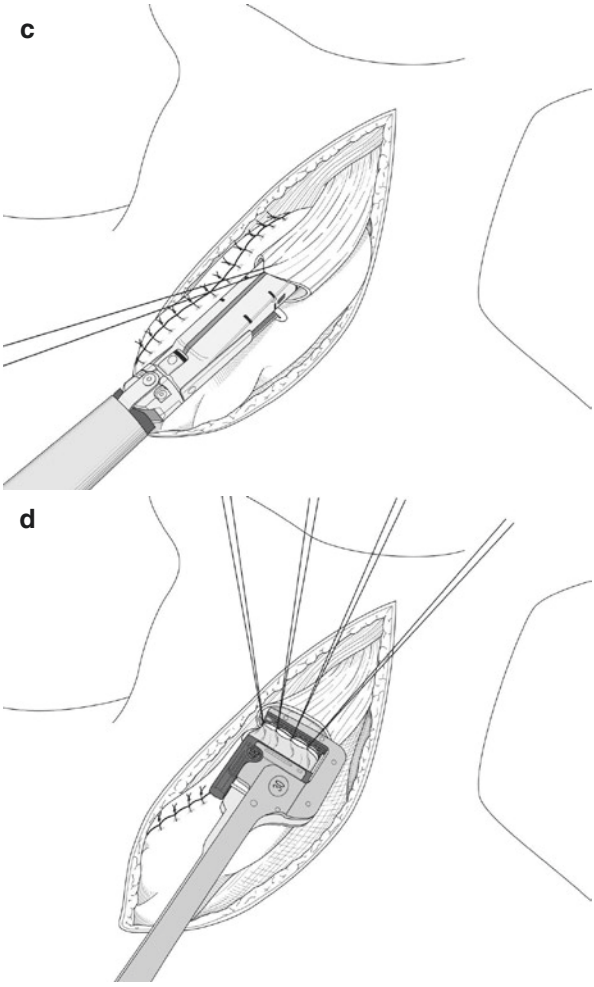


Fig. 12.3 Schema of esophagogastric anastomosis using various staplers. (**a**) Esophagogastric anastomosis by a circular stapler in an end-to-side fashion. (**b**) First stapling by a linear stapler in a side-to-side fashion with Collard's method. (**c**) First stapling by a linear stapler in a side-to-side fashion with Orringer's method. (**d**) First stapling by a linear stapler in an end-to-end fashion (triangulating stapling technique)

Fig. 12.3 (continued)



anastomotic technique. It is important that operators should acquire enough knowledge of advantage and disadvantage of each technique and become to master the skill of the technique which is chosen.

12.2.2 Colon

Reconstruction using the colon with a vascular pedicle as an esophageal substitute can be achieved by the right colon with the middle colic artery or the left colon with the left colic artery in an isoperistaltic fashion. The advantages of using the right colon with the terminal ileum are that the diameter of the terminal ileum is similar to the cervical esophagus and the Bauhin valve prevents regurgitation of food. However, the disadvantages are that the cecum is bulkier and vessel anomalies are

Table 12.3 Randomized controlled trial and meta-analysis for esophagogastric anastomosis

				LS			Results	
		HS	CS	m-Co.	Orri.	trian.	Favors	Statistical analysis
1996	Valverde [21]	74	78				NS	Leakage (%); 16 vs. 15 NS Stricture (%); 13 vs. 13 NS
1997	Law [22]	61	61				HS	Operating time (min); 214 vs. 217 NS Leakage (%); 1.6 vs. 4.9 NS Stricture (%); 9.1 vs. 40 $p = 0.0003$
2004	Hsu [23]	32	31				CS	Operating time (min); 524 vs. 447 $p < 0.001$ Leakage (%); 22 vs. 26 NS Stricture (%); 14 vs. 18 NS
2011	Saluja [24]	87			87		Orringer's	Leakage (%); 16.1 vs. 18.3 $p = 0.33$ Time of anastomosis (min); 27 vs. 25 $p < 0.02$ Stricture (%); 20.7 vs. 8.6 $p = 0.045$
2013	Wang [25]	57	50		48		Orringer's	Stricture (%); 9.6 vs. 19.1 vs. 0 $p < 0.001$ Diameter (mm); 11.5 vs. 9.5 vs. 11.5 $p < 0.001$
2017	Hayata [26]		49			51	Triangle	Time of anastomosis (min); 18 vs. 22 $p = 0.028$ Stricture (%); 17 vs. 19 $p = 0.935$ Leakage (%); 11% vs. 2 $p = 0.073$
2017	Huang [27]		42			39	Triangle	Leakage (%); 19.0 vs. 7.7 $p = 0.197$ Stenosis (%); 23.8 vs. 2.6 $p = 0.007$ Diameter (mm); 11.7 vs. 16.1 $p < 0.001$
2019	Sugiura [28][a]	127		127			m-Collard's	Leakage (%); 7 vs. 3 $p = 0.127$ Stricture (%); 59% vs. 13 $p < 0.001$ Postoperative stay (days); 32 vs. 23 $p < 0.001$
2013	Honda [29][b]	640 629 579	668 626 606				Viable alternatives	Leakage; RR(CS/HS) 1.02 NS Stricture; RR(CS/HS) 1.67 $p = 0.006$ Operating time; CS 15.3 min shorter $p = 0.020$

m-Co modified Collard's method, *Orri* Orringer's method, *trian* triangulating method
[a]Propensity score-matched analysis
[b]Meta-analysis

more common than in the left colon. The final decision on which side of the colon is used is made during the operation. Contraindications for using the colon as an esophageal substitute include severe mesenteric atherosclerosis, anatomical discontinuity of the marginal artery, abdominal aortic aneurism, chronic constipation, and multiple diverticulosis found in a preoperative barium enema.

12.2.2.1 Operative Technique

The ascending colon with the terminal ileum and the descending colon are dissected from retroperitoneal tissues. The mesocolon is transilluminated and the colonic vascular anatomy is thoroughly examined. The length of the colon to be repositioned depends on the length of the marginal vessels. Therefore, the length of the marginal vessels is measured by attaching a cotton tape and the artery to be used as a pedicle is selected. Before dividing the vessels and the intestine, a blood flow blocking test is performed. The colic vessels, marginal vessels, and intestine that are planned to be cut are clamped for about 10 min and the color of the colon graft is checked to ensure not to be ischemic changes. When the middle colic artery is used as a pedicle, the right colic vessels (if any) and ileocolic vessels are divided at their roots and the ascending colon is mobilized with or without the terminal ileum (Fig. 12.4a). When the left colic artery is selected, the middle colic vessels are divided at the root and the transverse and descending colon is mobilized. Griffith's point and the Riolan arc must be carefully examined. If the marginal artery is disconnected at Griffith's point it is better not to use the left colon. If the Riolan arc is present it should be preserved if possible (Fig. 12.4b).

The colon graft is put into a narrow vinyl bag and brought up above the clavicula through the selected route. Anastomosis between the cervical esophagus and the colon is performed using a circular stapler of diameter 25 mm or hand sewing.

12.2.3 Jejunum

When the stomach cannot be used as esophageal conduit jejunal Roux-en-Y reconstruction is technically easier and less invasive than colon interposition. Passage of food is relatively preferable due to jejunal peristalsis. However, jejunal reconstruction has a limitation of its pull up length, which depends on the length of pedicled marginal artery. If the intrathoracic route is selected secure and safe anastomosis between pull up jejunum with a vascular pedicle and remnant esophagus is only below the tracheal bifurcation and if subcutaneous route it is only below the clavicula. If cervical anastomosis is needed microvascular blood flow augmentation is required.

12.2.3.1 Operative Technique of Jejunal Roux-en-Y Reconstruction with Vascular Anastomoses for Supercharge and Superdrainage

The superior mesenteric artery and roots of the first to third branch of the jejunal artery are exposed. The first branch of the jejunal vessels is preserved, and the second and third branches are ligated and divided near their roots. The proximal

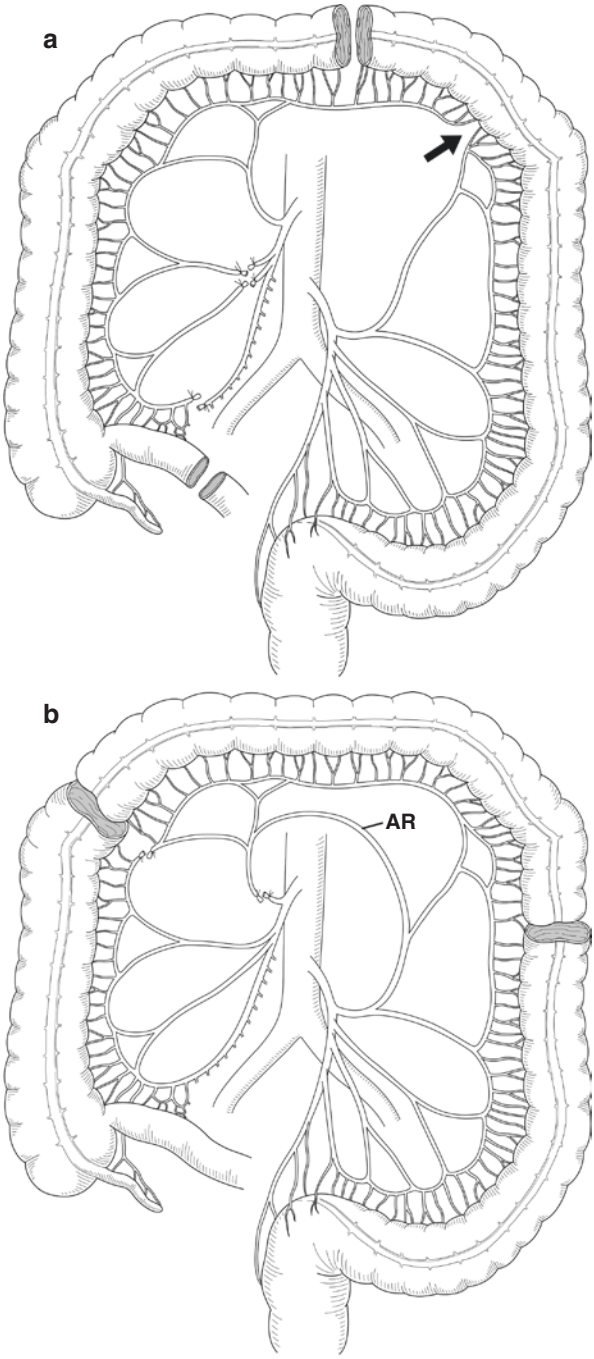


Fig. 12.4 Schema of colon replacement. (**a**) Isoperistaltic right colon replacement with arterial supply on the middle colic artery. Discontinuity of marginal artery has appeared at Griffith's point (arrow). (**b**) Isoperistaltic left colon replacement with arterial supply on the left colic artery. *AR* Arc of Riolan

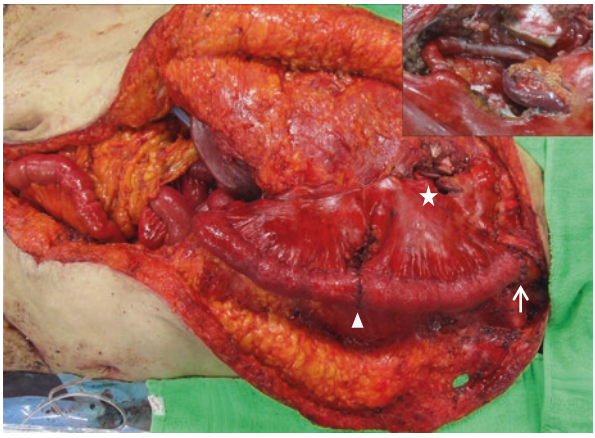


Fig. 12.5 Large picture: A vascular pedicled jejunal flap brought up through an opened subcutaneous route, with anastomosis between the cervical esophagus and the pulled up jejunum (arrow); anastomosis of the jejunum after resection of the redundant jejunum (arrowhead); and microvascular anastomosis (star). Small picture: Anastomosis of the internal thoracic vessels below the right third costal cartilage to the second jejunal artery and vein

jejunum is divided approximately 15 cm distal to the ligament of Treitz. The jejunal mesentery is divided between every jejunal branch preserving the marginal vessel's continuity to lengthen the jejunal flap. If the jejunum does not reach the cervical esophagus preserving the marginal vessel's continuity, these vessels have to be cut and divided. A jejunal flap without isotropic marginal arterial blood flow requires additional microvascular blood flow augmentation.

A 4-cm long segment connecting to the left third costal cartilage is removed and the internal thoracic artery and vein are exposed. The vascular pedicled jejunal flap is brought up through the subcutaneous route. The cut edges of the second jejunal artery and vein are anastomosed to the internal thoracic vessels under a microscope with interrupted 8–0 or 9–0 nylon sutures. Pulsation of the marginal artery of the proximal jejunum resumes with vascular anastomosis [30, 31].

The anastomosis between the cervical esophagus and the pull-up jejunum is performed in an end-to-end fashion with hand sewing. Because the repositioned jejunum is longer than the mesentery and winds on the anterior chest wall, the redundant portion of the jejunum is resected and anastomosed to straighten the conduit (Fig. 12.5). Roux-en-Y jejunal anastomosis is performed in the abdomen.

12.2.4 Reconstruction Route

The esophageal substitute can be repositioned through a subcutaneous, anterior mediastinal, posterior mediastinal, or intrathoracic route. The most desirable route

is selected by the surgeon based on the patient's physical condition and other factors. In Japan, posterior mediastinal (including intrathoracic) and anterior mediastinal routes are preferably selected at rates of 49.0% and 38.1%, respectively (Table 12.4) [4]. The advantages and disadvantages of the four routes are shown in Table 12.5.

Table 12.4 Reconstruction route in Japan (2012)

Route	Cases	(%)
None	66	(1.4)
Subcutaneous	414	(8.8)
Anterior mediastinal	1799	(38.1)
Posterior mediastinal	519	(11.0)
Intrathoracic	1794	(38.0)
Cervical	46	(1.0)
Others	49	(1.0)
Unknown	35	(0.7)
Total	4722	

Table 12.5 Advantages and disadvantages of reconstruction routes

Reconstruction route	Advantages	Disadvantages
Subcutaneous	1. Easy to anastomose 2. Easy and safe to manage anastomotic leakage 3. Easiest to treat secondary cancer of the reconstructive organ	1. Longest distance among all reconstructive routes 2. Higher risk of anastomotic leakage 3. Stasis of foods in the bending conduit 4. Esthetic problems regarding the patient's appearance
Anterior mediastinal	1. Shorter distance than the subcutaneous route 2. Easy and safe to manage anastomotic leakage compared with a posterior or intrathoracic route	1. The reconstructive organ presses against the heart 2. Risk of compression necrosis of the conduit in a case with a narrow outlet below the sternoclavicular joint
Posterior mediastinal (Intrathoracic)	1. Physiological route and a short distance 2. Lower frequency of anastomotic leakage 3. Less surgical stress	1. Serious postoperative morbidity in a case with anastomotic leakage (intrathoracic) 2. Inability to divide high position of the cervical esophagus (intrathoracic) 3. Regurgitation 4. Risk of serious morbidity in a case with ulcerative perforation in the reconstructive conduit 5. Difficulty with radiotherapy in a case with intrathoracic recurrence 6. Difficulty of treatment for secondary cancer in the reconstructive organ

12.3 Cervical Esophageal Cancer

Free jejunal transfer is selected for esophageal reconstruction in a case in which the tumor is limited to the cervical esophagus. If the tumor extends to the thoracic portion or multiple lesions are present in the thoracic esophagus, esophageal reconstruction using the stomach or colon is usually performed after transhiatal esophagectomy. If the stomach or colon cannot reach the cervical esophagus or the inferior pharynx, a free jejunal graft is additionally transferred between the proximal organ and the distal conduit.

12.3.1 Free Jejunal Transfer

The transverse coli artery and the superior thyroidal artery are the respective first and second choices as the recipient artery. The facial artery and the lingual artery are also candidates, but these arteries are hard to handle because of protrusion of the mandible. The external jugular vein (end-to-end fashion) or an internal jugular vein (end-to-side fashion) is used as the recipient's vein.

12.3.1.1 Operative Technique

After dissection of the neck nodes, the recipient artery and vein are dissected and prepared. These dissected vessels are covered with wet gauze to avoid drying before vascular anastomosis.

A segment of jejunum of 30–40 cm length is harvested at approximately 50 cm distal from the ligament of Treitz. The mesentery of the jejunum to be grafted is transilluminated and the vessels of J2 or J3 to be used as donor vessels are carefully inspected and dissected. A marking suture on the donor jejunum is required to detect the direction of intestinal peristalsis before resection and the jejunal vessels are divided at their roots just before transfer. Irrigation of the vessels in the jejunal graft is not needed.

The resected jejunum is placed in the cervical space in the direction of isoperistalsis. Vascular anastomoses are performed microscopically. The best order of performance of vascular anastomosis and intestinal anastomosis is unclear. We think initial anastomosis of vessels has advantages that microscopic vessel anastomosis can be performed without limitation of mobilization of the jejunal graft and that blood flow patency can be checked for a longer time during operation. Regions with arterial plaque are removed and donor and recipient arteries are anastomosed atraumatically in the whole layer with 9–0 nylon sutures. Before vein anastomosis, the surgeon should check that the veins are not twisted and sagged via direct vision. Vein anastomosis is performed with 9–0 nylon sutures. Clamps on the vein and artery are taken off in order and blood flow and jejunal peristalsis should resume. The mesentery near the vessel anastomoses is secured to the deep cervical fascia to avoid tension on the anastomoses.

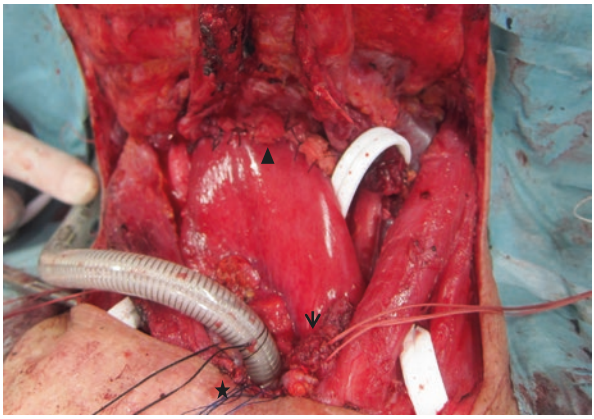


Fig. 12.6 Operative photograph of free jejunal transfer showing anastomosis between the inferior pharynx and jejunum (arrowhead) and between the jejunum and esophagus (arrow). The tracheostoma is indicated by a star

The jejunal graft is placed as straightly as possible without tension against the vessel anastomoses. The length of jejunum for use as the graft is 12–15 cm and unneeded portions of the jejunum on the proximal and distal side are removed. The redundant mesentery is filled into dead space around the trachea and wrapped around the vessel anastomoses. The jejunum is anastomosed to the orifice of the inferior pharynx layer-to-layer in an end-to-side fashion and anastomosed to the proximal esophagus using an Albert Lembert or layer-to-layer suture in an end-to-end manner (Fig. 12.6).

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Perioperative Nutritional Management of Esophageal Cancer Surgery

13

Satoshi Aiko

Abstract

Perioperative nutritional status is known to be associated with the incidence of postoperative complications as well as the oncologic prognosis after esophagectomy. Several nutritional indicators such as the Controlling Nutritional Status Score, the Geriatric Nutritional Risk Index, the Prognostic Nutritional Index, the Nutrition Risk Screening, and the Skeletal Muscle Index were investigated to affect the morbidity and/or prognosis after esophagectomy or other treatment modalities for esophageal cancer. Meanwhile, early enteral nutrition (EN) has been introduced to improve the nutritional status in the early postoperative period. The postoperative early EN could decrease the morbidity of severe complications and maintain patients at a better nutritional status compared to parenteral nutrition support in patients undergoing esophageal surgery. The early EN started within several hours after gastrointestinal surgery, termed "immediate EN," was proven safe and feasible. A combination of preoperative feeding and postoperative immediate enteral feeding should be recommended to achieve continuous nutrition support with a minimum interruption of enteral feedings. Immunonutrition refers to the oral or enteral administration of a formula containing one or more added nutrients such as omega-3 fatty acids (FAs), nucleic acid, arginine, glutamine, or antioxidants. Although the anti-inflammatory effects of omega-3 FAs were demonstrated, there remains insufficient evidence to recommend the routine use of immunonutrition in patients undergoing esophageal cancer surgery. The perioperative management of esophageal cancer surgery evolved from only nutritional and transfusional support into a multidisciplinary team medicine approach and the application of an enhanced recovery after surgery (ERAS) program. According to the ERAS Society, the documented high levels

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of perioperative morbidity and mortality after esophagectomy accentuated the need for providing an ERAS program. Immediate start of oral nutrition following esophagectomy seems to be feasible and does not increase complications. However, the most appropriate timing for starting oral intake after esophagectomy remains controversial.

Keywords

Nutritional assessment · Esophageal cancer · Morbidity · Postoperative complication · Prognosis · Early enteral nutrition · Immunonutrition · ERAS

13.1 Introduction

Among gastrointestinal (GI) operations, esophagectomy for esophageal carcinoma is one of the most invasive procedures and is associated with high morbidity due to postoperative complications. Minimally invasive esophagectomy significantly improved the systemic inflammatory and catabolic response to surgical trauma [1, 2]. Recently, video-assisted thoracoscopic esophagectomy was shown to significantly reduce the incidence of pulmonary complications compared to that of the conventional open procedure [1, 3]. However, an analysis involving 5354 Japanese patients from a nationwide database who underwent esophagectomy in 2011 showed a significantly higher overall morbidity in the minimally invasive esophagectomy group than in the open esophagectomy group (44.3% vs. 40.8% respectively) [4].

Preoperative nutritional status is highly associated with the incidence of postoperative complications [5–8]. Furthermore, the nutritional status directly influenced the prognosis after esophagectomy [9–15]. Approximately 50–80% of patients with esophageal cancer are malnourished at the time of diagnosis [6, 7, 16, 17]. Therefore, nutritional management is a key strategy to improve both short-term and long-term results in patients with esophageal cancer.

13.2 Nutritional Assessments

Several nutritional indicators have been proposed for the initial prediction of the incidence of complications after esophagectomy. Some of these indicators also affect the oncologic prognosis.

13.2.1 CONUT

The Controlling Nutritional Status score (CONUT), first validated and reported by Ulíbarri JI. et al. [16], is a screening tool for the early detection and continuous control of hospital undernutrition. The formula for the calculation of CONUT,

Serum albumin g/dl	Score
≧3.5	0
3.0-3.4	2
2.5-2.9	4
< 2.5	6

Total lymphocyte count /μl	Score
≧1600	0
1200-1599	1
800-1199	2
< 800	3

Total cholesterol mg/dl	Score
≧180	0
140-179	1
100-139	2
< 100	3

Total score	Undernutrition degree
0-1	A Normal
2-4	B Mild
5-8	C Moderate
≧9	D Severe

Fig. 13.1 Assessments of undernutrition degrees by the CONUT (Controlling Nutritional Status)

including serum albumin and cholesterol levels as well as total lymphocyte count, is shown in Fig. 13.1. A retrospective study of 352 patients who underwent elective esophagectomy for esophageal cancer reported that 58% of patients were classified as having normal nutrition, 36% of patients with light malnutrition, and 6% of patients with moderate or severe malnutrition according to CONUT assessed before surgery [18]. The length of hospital stay (LOS) in patients with moderate or severe malnutrition was significantly longer than those in the other patients. Logistic regression analysis revealed that moderate or severe malnutrition was an independent risk factor for any and severe morbidities [18]. The authors subsequently reported that patients with moderate or severe malnutrition, as determined by the preoperative CONUT, had a significantly poorer prognosis, in both overall survival and cancer-specific survival [15].

13.2.2 Geriatric Nutritional Risk Index

The geriatric nutritional risk index (GNRI), originally developed to examine the nutritional status of elderly hospitalized patients, consists of three objective nutritional variables: height, body weight, and serum albumin concentration [5] (Fig. 13.2). Recently, three studies investigated the impact of the GNRI on the long-term outcomes in patients with esophageal squamous cell carcinoma who underwent esophagectomy at different institutes in Japan [10, 12, 14]. The preoperative GNRI score was identified as an independent predictor of overall survival in

GNRI = [1.489 x albumin (g/L)] + [41.7 x (real weight / ideal weight)]

Ideal weight was calculated from the Lorentz equations (WLo) as follows:
For men: WLo = *Hight (cm)* - 100 - [(*Hight* - 150)/4]
For women: WLo = *Hight (cm)* - 100 - [(*Hight* -150)/2.5]

GNRI	Nutrition-related risk
82>	major risk
82-91	moderate risk
92-98	low risk
98<	no risk

Fig. 13.2 GNRI (geriatric nutritional risk index) formula and assessments of nutrition-related risk

PNI = 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3)

PNI < 45 is defined as moderate to severe malnutrition [19, 20]

Fig. 13.3 PNI (prognostic nutritional index) formula and a definition of malnutrition

multivariate analysis in all three studies. In one of these studies, multivariate analysis also revealed that severe and moderate nutritional risk (GNRI: <92) (hazard ratio 0.50; $p = 0.002$), T factor (≥T2) (hazard ratio 0.52; $p = 0.026$), and N positive factor (hazard ratio 0.47; $p = 0.004$) were independent prognostic factors [14]. Another study showed that the GNRI was significantly associated with tumor depth ($p = 0.001$), level of carcinoembryonic antigen (CEA; $p = 0.009$), and C-reactive protein (CRP) level ($p = 0.028$) [12].

13.2.3 Prognostic Nutritional Index

Onodera's prognostic nutritional index (PNI) is calculated using the serum albumin concentration and total lymphocyte count in the peripheral blood (Fig. 13.3). The PNI was originally defined as a predictor of postoperative complications in patients with GI cancer. A recent study demonstrated the usefulness of the preoperative PNI in predicting the occurrence of complications and LOS following esophagectomy in esophageal cancer patients [11]. The study further demonstrated a positive correlation between PNI at 6 months post-surgery and overall survival. The preoperative PNI is also an independent predictor of long-term postoperative survival for patients with various cancers [19–23], including esophageal squamous cell carcinoma [9, 13]. Preoperative PNI was also shown to be an independent prognostic factor for overall survival in patients undergoing salvage esophagectomy [24].

13.2.4 Skeletal Muscle Index

Clinical imaging is another method used for nutritional assessment. To investigate the impact of preoperative sarcopenia on postoperative complications or survival in patients undergoing esophagectomy, skeletal muscle mass was assessed using preoperative computed tomographic scans by measuring the cross-sectional muscle area at the third lumbar vertebral level, which was defined as the skeletal muscle index (SMI). Multivariate analyses revealed that sarcopenia was significantly associated with pulmonary complications [25] as well as the comprehensive complications index (CCI) and Clavien–Dindo complication (CDC) [26]. However, sarcopenia did not impact disease-specific or overall survival after esophagectomy [26].

13.2.5 Nutritional Risk Screening

The associations between nutritional status and prognosis were assessed in patients with locally advanced esophageal cancer treated by concurrent chemoradiotherapy (CRT) [27], and also in patients with metastatic or recurrent esophageal cancer treated by chemotherapy [28]. In both studies, the nutritional risk screening (NRS)-2002 scores, established in 2003 as part of the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline for nutrition screening [29] (Table 13.1), were determined prior to commencement of treatments and were significant prognostic indicators.

Table 13.1 Nutrition risk screening (NRS)-2002

Impaired nutritional status		Severity of disease	
Absent (score 0)	Normal nutritional status	Absent (score 0)	Normal nutritional requirements
Mild (score 1)	Weight loss >5% in 3 months or food intake below 50–75% of normal requirements	Mild (score 1)	Hip fracture, chronic patients in particular with acute complications; cirrhosis, COPD, chronic hemodialysis, diabetes, and oncology
Moderate (score 2)	Weight loss >5% in 2 months or BMI < 18.5–20.5 + impaired general condition or food intake below 25–60% of normal requirements in preceding week	Moderate (score 2)	Major abdominal surgery, stroke, severe pneumonia, hematological malignancy
Severe (score 3)	Weight loss >5% in 1 months (>15% in 3 months) or BMI < 18.5 + impaired general condition or food intake 0–25% of normal requirements in preceding week	Severe (score 3)	Head injury, bone marrow transplantation, intensive care patients (APACHE > 10)
Total score	Add scores		
Age	If ≥ 70 years: Add 1 to total score above		

Score ≥ 3: the patient is nutritionally at-risk and a nutritional care plan is initiated
Score < 3: weekly rescreening of the patient. If the patient, e.g., is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status
Adapted from Kondrup et al. [29]

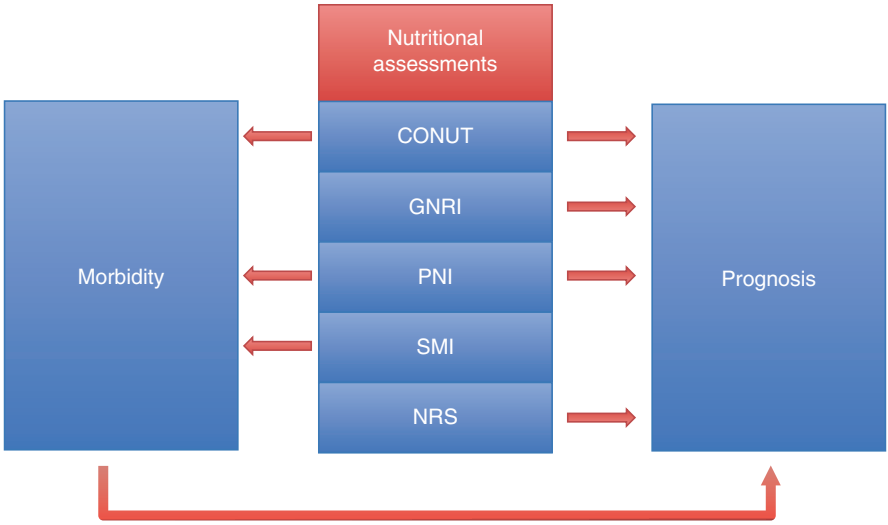

Fig. 13.4 The reported associations between each nutritional assessment method and morbidity and/or prognosis following esophagectomy or other treatment modalities for esophageal cancer. The red arrows show significant associations. *CONUT* controlling nutritional status score, *GNRI* geriatric nutritional risk index, *PNI* prognostic nutritional index, *SMI* skeletal muscle index, *NRS* nutritional risk screening

To organize information on these nutritional assessments, the reported associations between each assessment method and morbidity and/or prognosis following esophagectomy or other treatment modalities for esophageal cancer are shown in Fig. 13.4. Whichever method is chosen, the most important goal is the improvement of nutritional status by appropriate management before and after esophageal cancer surgery.

13.3 Nutritional Management of Patients with Esophageal Cancer

13.3.1 Early Enteral Nutrition

Since the latter half of the 1990s, early enteral nutrition (EEN) has been widely used to improve the nutritional status in the early postoperative period and to potentially decrease the incidence of postoperative complications. Systematic review and meta-analysis of randomized controlled trials (RCTs) comparing any type of enteral feeding started within 24 h after surgery with nil by mouth management in elective GI surgery revealed that early feeding reduced the risk of any type of infection and the mean length of hospital stay [30]. They concluded that there seems to be no clear advantage to keeping patients nil by mouth after elective GI resection. However, some studies involving patients with upper GI malignancies found no beneficial

effects of EEN [31, 32]. In particular, the study by Braga et al. found no significant differences in nutritional, immunologic, and inflammatory variables; overall complication rate; LOS; and mortality between the EEN and total parenteral nutrition (TPN) groups. A significant difference was observed only in medical costs. EEN was fourfold less expensive than TPN [31]. However, similar studies in which the objective was limited to esophageal cancer patients who underwent esophagectomy demonstrated various beneficial effects of EEN such as a significant reduction in intensive care unit (ICU) and total hospital stays [33]; a lower incidence of postoperative infections in the blood, lungs, and intestinal tract [34]; a lower rate of life-threatening surgical complications [35]; and a suppression of excessive inflammatory responses [36]. A recent meta-analysis of 10 RCTs concluded that the postoperative EEN for esophageal cancer patients after esophagectomy could decrease the morbidity of severe complications such as pulmonary complications and anastomotic leakage and maintain patients at a better nutritional status compared to parenteral nutrition support [37]. Patients undergoing radical esophageal surgery who are subjected to severe surgical stress might benefit the most from EEN because few studies did not demonstrate the beneficial effects of EEN compared to TPN in those patients.

13.3.2 The Starting Timing of Enteral Nutrition After Esophagectomy

Studies on the effects of postoperative EEN have used various protocols for EN beginning from within 24 h to within 72 h or more after surgery. Two studies investigated the ideal period of initiating EN after surgery for esophageal cancer. In one study, 42 patients were retrospectively divided into two groups. Group D1 started EN within 24 h after surgery, while Group D2–3 started EN within 24–72 h after surgery [38]. There was no significant difference between the groups in clinical factors including days to first fecal passage, dose of postoperative albumin infusion, difference in serum albumin levels between pre- and post-operation, incidence of postoperative infection, and use of total parenteral nutrition. Therefore, the authors concluded that EN should be scheduled within 24–72 h according to the patient's condition. In the other study, a total of 208 patients were divided into three groups (Groups 1, 2 and 3) based on whether they received EN within 48 h, 48–72 h, or more than 72 h, respectively [39]. Group 1 had the lowest thoracic drainage volume, the earliest first fecal passage, and the lowest LOS and hospitalization expenses. The incidence of pneumonia was highest in Group 3. All postoperative outcomes of nutritional conditions were worse by a significant margin in Group 3. The author concluded that it is safe and valid to start EEN within 48 h in postoperative esophageal cancer patients.

Recently, EEN in the area of critical care medicine has been defined as a standard formula commenced within 24 h of injury or admission to the ICU or burn unit [40–42]. It is promising that this defined EEN significantly reduced mortality in critically ill patients. EEN started within several hours after GI surgery, termed

"immediate EN," was proven safe and feasible in previous studies [36, 43, 44]. Although the clinical significance of immediate EN compared to the EEN started within 48 h has yet to be determined, a combination of preoperative feeding and postoperative immediate EN should be recommended to achieve a continuous nutrition support with a minimum interruption of enteral feedings. Because of the potential development of a new EN component that can inhibit excessive biological reaction early after esophagectomy, immediate EN should not be considered without value. According to the ESPEN guidelines on nutrition in cancer patients [45], cancer patients undergoing surgery should be managed within an enhanced recovery after surgery (ERAS) program. The nutritional components of the ERAS program include avoiding fasting, preoperative fluid and carbohydrate loading, and recommencement of oral diet on the first postoperative day (POD). The ERAS program for patients who undergo esophageal resection is addressed in a later chapter.

13.3.3 Advancement Schedule of Immediate Enteral Feeding

Table 13.2 shows an example of an advancement schedule of immediate EN through a jejunostomy tube. This schedule has been used in over 250 esophageal cancer patients and has proven to be feasible for all patients with gastric conduits regardless of age or gender. Two types of nutrition formulas were chosen based on the preservation or ligation of the thoracic ducts (TD). Patients with preservation of the TD received a standard EN formula containing moderate amounts of omega-3 FAs (Racol®, Otsuka Pharmaceutical Factory, Japan or Enevo®, Abbott Japan, Japan), whereas patients without preservation of the TD due to tumor invasion into the TD or intraoperative lesion of the TD received an elemental diet (Elental®, EA Pharma, Japan) and, through the parenteral route, 250 ml of 10% lipid emulsion (Inrtalipos®, Otsuka Pharmaceutical Factory, Japan) daily from POD 1. All patients received a continuous infusion of a parenteral mixture (Elneopa-NF®, Otsuka Pharmaceutical Factory, Japan) to compensate for the shortfall of daily caloric requirement through a central venous catheter from POD 1. This elemental diet was selected for patients whose TDs were ligated because it contains almost no fat. Of the fatty acid present in standard EN products, on average, 80% are long-chain fatty acids (LCFAs). While mid-chain fatty acids (MCFAs) are directly absorbed and diffuse into portal

Table 13.2 Advancement schedules of enteral feeding after esophageal cancer surgery in Eiju General Hospital

Postoperative day	Patients whose thoracic ducts were preserved	Patients whose thoracic ducts were ligated or resected
	Standard EN	Elemental diet
0	20 ml (kcal)/h (from 2 h after the operation)	20 ml (kcal)/h (from 2 h after the operation)
1	750 ml (kcal)/day	500 ml (kcal)/day
2	1000	750
On and after 3	1500	1250

circulation, absorbed LCFAs from chylomicrons and are subsequently carried into the systemic circulation via the TD. Chylomicrons, cholesterol esters, and phospholipids are primary components of chyle, which is normally produced at a rate of about 2.4 liters per day [46]. Imamura and colleagues reported that soon after the TD was resected during esophagectomy for esophageal cancer, retroperitoneal edema was observed in 23/24 patients when the abdomen was opened following the thoracic procedure [47]. The authors further indicated that lymphaticovenous anastomosis was not large enough to compensate for the abrupt obstruction of the TD. In a study investigating the effects of TD blockage in patients who received early EN following esophageal cancer surgery, it was found that the postoperative diuretic phase in patients without preservation of the TD was delayed by 1 day in comparison to that in patients with preservation of the TD [48]. Early enteral feeding with the standard formula containing a large amount of LCFAs may enhance fluid retention in patients without preservation of the TD, especially in the early postsurgical period. Thus, EN formulae containing no or little fat as well as EN formulae with a lipid component mostly of MCFAs (Twinline-NF®, Otsuka Pharmaceutical Factory, Japan, as one example) might be appropriate for EEN in patients without preservation of the TD.

13.3.4 Immunonutrition

Immunonutrition (IN) refers to the oral or enteral administration of a formula containing one or more added nutrients such as omega-3 fatty acids (FAs), nucleic acid, arginine, glutamine, or antioxidants; these formulae are called immuno-enhanced or immuno-modulating diets. Omega-3 FAs which are invariably present in immuno-enhanced diets were separately studied for their potentially positive effects on the postoperative course of esophageal cancer patients. Among the effects of omega-3 FAs in the acute phase after esophageal surgery, immediate EN with a formula containing omega-3 FAs was shown to reduce platelet aggregation, coagulation activity, and cytokine production compared to those in a formula without omega-3 FAs [49]. These effects of omega-3 FAs are thought to be largely mediated by their biological effects in human, such as the competitive inhibition of the inflammatory action induced by metabolic products of arachidonic acid (Fig. 13.5). The anti-inflammatory effects of omega-3 FAs were confirmed by the clinical findings of lower body temperature early after surgery [49]. This effect to inhibit the elevation of body temperature was enhanced by the preoperative administration of a formula enriched with eicosapentaenoic acid (EPA; one of the omega-3 FAs) for 5 days [50]. The latter study also showed that EPA had a significant effect on the attenuation of stress response based on levels of tumor necrosis factor (TNF) alpha, interleukin (IL)-10, and IL-8. This study also revealed that EPA-supplemented EEN was associated with a preservation of lean body mass on POD 21 compared to that in standard EN.

As a key mediator of the anti-inflammatory effects of the omega-3 FAs, resolvin has received attention in recent years (Fig. 13.5). Resolvin E1, a lipid mediator derived from EPA, was recently identified in resolving exudates [51]. Increasing

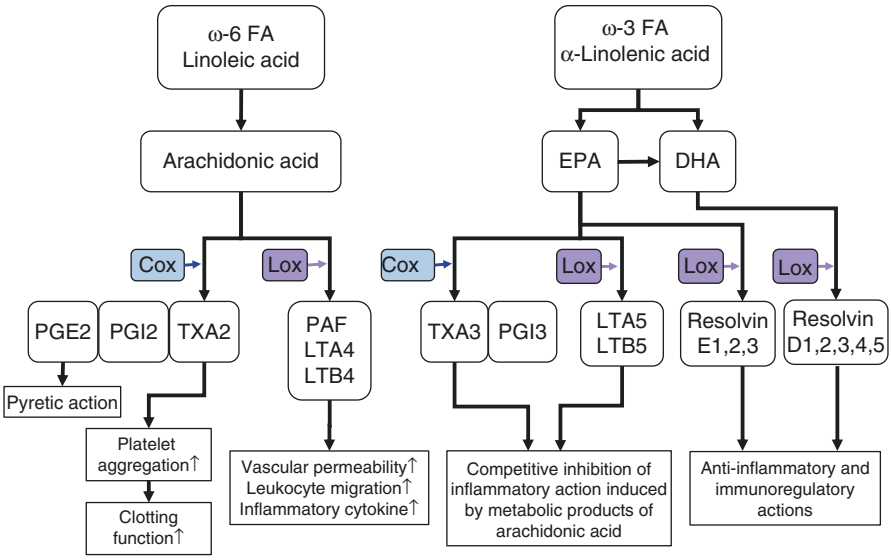

Fig. 13.5 Metabolic products of polyunsaturated fatty acids and their bioactivities. *FA* fatty acid, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *Cox* cyclooxygenase, *Lox* lipoxygenase, *PG* prostaglandin, *TX* thromboxane, *PAF* platelet-activating factor, *LT* Leucotriene

Table 13.3 Function effects of resolvins in the pathological animal model

Pathological animal model	Resolvin	Function effects
Peritonitis	E1	Inhibition of neutrophil infiltration Activation of phagocytes migration into the lymph system
Enteritis	E1	Inhibition of neutrophil infiltration Stabilization of weight loss Reduction in mortality
Asthma	E1	Inhibition of neutrophil and eosinophil accumulation
Retinopathy	D1, E1	Suppression of abnormal angiogenesis
Inflammatory pain reaction	D1, E1	Reduction of pain Control of hyperalgesia
Sepsis	D2	Inhibition of neutrophil infiltration Inhibition of inflammatory cytokine production

evidence in basic research indicates that resolvin E1 possesses potent anti-inflammatory and immunoregulatory actions that include blocking the production of proinflammatory cytokines, organized leukocyte traffic to inflammatory sites [52], and dendritic cell motility [53] as well as the clearance of neutrophils from the mucosal surface [54, 55] (Table 13.3).

A meta-analysis of the clinical impact of perioperative enteral IN in major GI elective surgery drew a positive conclusion [56]. The analysis of 12 pivotal studies resulted that IN significantly reduced the rate of overall complications when used before surgery, both before and after surgery, and after surgery. The use of IN led to

a shorter hospital stay, with a mean difference of—2.12 days. In 2018, the results of a multicenter RCT to determine the impact of preoperative and postoperative IN versus standard nutrition in patients with esophageal cancer were published [57]. This comparatively large trial including 276 patients from 11 Australian sites did not observe any positive effects of IN. The incidence of infective complications was similar for all groups (37% in the perioperative standard nutrition group, 51% in the perioperative IN group, 34% in the preoperative IN group, and 40% in the postoperative IN group). There were no significant differences in any other clinical or quality of life (QOL) outcomes.

It is definite that the use of IN is associated with clinical benefits in patients undergoing elective GI surgery, without any adverse effects on mortality. The administration of arginine as one content of IN formula that provides a substrate for nitric oxide (NO) synthesis did not lead to excessive NO production in the early phase after elective surgery for esophageal cancer [58]. However, it is still unclear whether patients who develop sepsis following elective surgery continue to benefit from an immune-enhancing formula containing arginine.

Thus, there remains insufficient evidence to recommend the routine use of IN in patients undergoing esophageal cancer surgery. It may be more important for clinicians to introduce EEN with any type of enteral feeding products than the use of an IN formula.

13.3.5 Immunonutrition in the Multidisciplinary Treatments for Esophageal Cancer

Neoadjuvant therapy, particularly neoadjuvant chemoradiotherapy (CRT) for esophageal cancer, significantly reduced perioperative immunological parameters such as total lymphocyte counts, B-cell counts, and CD4/CD8 ratio [59]. Preoperative immune-enhanced diet (IED) feeding for several days did not effectively restore the immunological deterioration caused by neoadjuvant therapy [59]. However, IN provided throughout the duration of CRT might provide a significant patient benefit. Seventy-one locally advanced esophageal squamous cell carcinoma patients treated with concurrent CRT (5-FU and cisplatin) were randomized into two groups; namely, the IN group that received an IED and the control group that received a standard formula throughout the duration of CRT. The levels of CRP ($p = 0.001$) and TNF ($p = 0.014$) increased more during treatment in the control group than those in the IN group, whereas levels of interferon (IFN), IL-6, and IL-10 were similar in both groups. While levels of CD3, CD4, CD8, white blood cells, neutrophils, and total lymphocytes decreased more in the control group than those in the IN group, the difference was not statistically significant [60].

The current evidence from clinical research on IN suggests that long-term feeding of IN, such as continuous feeding throughout 5–7 weeks of CRT, produces more definite immunological, nutritional, and anti-inflammatory benefits compared to perioperative short-term feeding of IN.

13.3.6 Enhanced Recovery After Surgery (ERAS)

The perioperative management of esophageal cancer surgery evolved from only nutritional and transfusional support into a multidisciplinary team medicine approach and the application of the ERAS program. The ERAS program, also known as fast-track surgery (FTS), is a patient-centered, surgeon-led system combining anesthesia, nursing, nutrition, and psychology that was initiated by Henrik Kehlet in the 1990s [61–63]. It aims to minimize surgical stress, reduce surgery-related complications, and accelerate postoperative recovery during the perioperative period. The ERAS program has been successfully implemented in various surgically treated diseases, especially in colorectal surgeries [64]. The ERAS Society was founded in 2010 to consolidate and promote ERAS principles.

The ERAS guidelines for esophagectomy were developed relatively late because esophagectomy is a particularly complex surgical procedure due to the documented high levels of perioperative morbidity and mortality. However, in the introduction to the guidelines for perioperative care in esophagectomy [65], the ERAS Society indicated that the high morbidity and mortality after esophagectomy accentuate the need for providing an ERAS program, a standardized format for esophagectomy which can be routinely applied and audited to improve international outcomes. The ERAS guidelines for esophagectomy are comprehensive and are comparable to an entire textbook of esophageal cancer surgery. Initially, over 60 potential sections for inclusion into the ERAS guidelines were proposed. Following two Delphi surveys, 39 sections were identified for inclusion in the esophagectomy ERAS project. The ERAS sections were divided into procedure- and non-procedure-specific components. The procedure-specific components were further divided into preoperative, operative, and post- and perioperative sections (Table 13.4). The summary and recommendation of preoperative nutritional intervention section state that nutritional intervention should be based on the level of risk and that in high-risk cases, enteral support is indicated preferably using the GI tract with selective use of feeding tubes. The summary and recommendation of preoperative oral pharmaconutrition section state that evidence in support of pharmaconutrition for patients undergoing surgery for esophageal cancer is conflicting and its routine use cannot be supported at this time.

13.3.7 A Practicable Example of the ERAS Program

A practicable example of the ERAS program for esophagectomy is shown in Table 13.5. This ERAS program was designed with reference to several recently published studies [66–68] and is therefore mostly composed of pre- and postoperative sections. Oral cavity care, nutritional management, and respiratory training required important emphasis in the preoperative period [68]. Early EN and early ambulation are key pillars of postoperative management. A multidisciplinary team including dentists, nutritionists, physical therapists, nurses, and pharmacists are required to achieve perioperative goals. Prior research has suggested that in addition to having an interdisciplinary team, intensive pain control resulted in significant

Table 13.4 Elements, levels of evidence, and recommendation grade of ERAS recommendations for esophagectomy

Elements	Level of evidence	Recommendation grade
Procedure-specific components		
Preoperative issues (5 sections)		
Preoperative nutritional assessment and treatment	C	A
Preoperative nutritional intervention	C	A
Preoperative oral pharmaconutrition	B	A
Multidisciplinary tumor board	B	A
Prehabilitation programs	C	B
Operative issues (14 sections)		
Timing of surgery following neoadjuvant therapy	B	B
Access: Minimally invasive or open	B	B
Choice of conduit (gastric conduit/tubulized stomach)	C/B[a]	A
Role of pyloroplasty (no strong evidence of effect)	C	A
Lymphadenectomy	B	A
Perianastomotic drains	B	B
NG tube/gastric decompression	B	A
Chest drain management following esophagectomy	C	B
Routine use of enteric feeding tubes	B	B
Esophagectomy: Perioperative fluid management	A/B[a]	A/B/C[a]
Anesthetic management	B	A
Anesthetic maintenance	A/B[a]	A
Two-lung ventilation	A/B[a]	A
One-lung ventilation	A/B/C[a]	A/B[a]
Post- and perioperative issues (6 sections)		
Intensive care unit utilization	B	A
Perioperative pain control for esophagectomy	B/C[a]	A/C[a]
Postoperative early nutrition: Oral vs. jejunostomy	B	A
Early mobilization	B	A
The role of multidisciplinary standardized clinical pathways	C	A
Audit (continuous institutional audit of outcomes)	B	A
Non-procedure-specific components (14 sections)		
Preoperative counseling patient/family	C	A
Smoking–alcohol cessation	B	A
Cardiopulmonary assessment	C	B
Bowel preparation (taking into account issues regarding colonic reconstruction)	B	A
Preoperative fasting (avoidance of fasting)	A	A
Preanesthetic analgesics and anxiolytics	B	C
Postoperative nausea and vomiting	C	A
Beta-blockade	B	A
Prophylaxis of atrial dysrhythmia	B	B
Antithrombotic prophylaxis	A	A
Hypothermia (avoidance of intraoperative hypothermia)	A	A
Postoperative glycemic control	B	A
Bowel stimulation	C	C
Foley catheter management (expeditious removal of urinary catheter)	A	A

Adapted from Low et al. [65]
Level of evidence; High: A, Moderate: B, Low: C
Recommendation grade; Strong: A, Moderate: B, Weak: C
[a]Depending on the subdivided recommendations

Table 13.5 A practicable example of ERAS program for esophagectomy

Periods	Components of ERAS program
Preoperative	1. Thorough oral cavity care 2. Nutritional therapy if needed 3. Smoking–alcohol cessation 4. Respiratory training
The day before and the morning of the operation	1. Reduction in laxative medication 2. Oral carbohydrate loading drink until 2 h before the operation
In the operation room	1. Placement of a thoracic epidural catheter 2. Use of short-acting anesthetics 3. Intraoperative placement of a feeding jejunostomy 4. Keeping the patient warm (using the 3 M™ Bair Hugger™normothermia system) and transfusion fluid warmed to 35–36°C 5. Extubation and removal of a nasogastric tube at the end of surgery
Postoperative	1. Early enteral feeding from POD 0 2. Early ambulation, physical and respiratory rehabilitation from POD 1 3. Antibiotics administration only as prophylaxis until POD 1 4. Intensive pain control (a) Continuous epidural analgesia with 0.2% ropivacaine 200 ml, physiological saline 80 ml, and fentanyl 20 ml (1000 μg) at a rate of 4 ml/h Additional pain control with NSAIDs and as-needed basis administration of weak opioid (fentanyl 1A, 100 μg) (b) An IV infusion of acetaminophen from POD 0–5 at 500–1000 mg/dose every 6 h in combination with continuous epidural anesthesia with a 300 ml mixture of 0.2% ropivacaine 288 ml and fentanyl 12 ml (600 μg) at a rate of 2–5 ml/h 5. ICU discharge on POD 1 6. Removal of a thoracic drain on POD 2 (if cervical anastomosis was performed) 7. Removal of a cervical drain on POD 2 (if intrathoracic anastomosis was performed) 8. Removal of a urinary catheter on POD 2 9. Removal of a thoracic epidural catheter on POD 3 10. Oral administration of clear fluid on POD3 and soft fractionated diet on POD 5 11. Removal of a central venous catheter on POD 7

reduction in the median time to first walking after esophagectomy (1.0 day in 69 patients) [67]. In that study, the authors used an IV infusion of acetaminophen from POD 0 to POD 5 at 1000 mg/dose every 6 h for patients weighing ≥50 kg or at 500 mg/dose every 6 h for patients weighing <50 kg in combination with the continuous epidural anesthesia (Table 13.5). To promote rapid physical rehabilitation, early removal of drains and catheters is equally recommended. The drain placed beside the anastomosis should generally be kept in place until oral intake begins. The period for commencing oral administration remains contentious in these components of ERAS program. According to a single-center experience of the ERAS

protocol in patients undergoing esophagectomy, the success rate of resuming oral intake on POD 1 was 32% (7/22 cases) [66]. The study also found that the median time to starting liquid diets was POD 3, thus providing a basis for the timing of fluid intake listed in Table 13.5. A detailed assessment of the causes of the low protocol adherence are not present in the study [66]. Therefore, the results of trials assessing the effects of immediate oral intake after esophagectomy will be introduced in the next chapter.

13.3.8 Immediate Oral Intake Following Esophagectomy

Before the application of ERAS to esophageal cancer surgery, a randomized multicenter trial evaluated immediate oral intake after major upper GI surgery [69]. They concluded that allowing patients to eat normal food at will from the first day after major upper GI surgery did not increase morbidity compared to that in traditional care with nil-by-mouth and enteral feeding. In upper GI surgery, immediate oral intake reduced the length of stay and complications compared to those for immediate jejunostomy tube feeding [69]. A recent multicenter clinical trial revealed that immediate initiation of oral nutrition, that is, starting clear liquids on POD 0 and liquid nutrition on POD 1 following esophagectomy seems to be feasible and does not increase complications compared to the results of a retrospective cohort and literature [70]. However, the authors of the clinical trial indicated that one drawback of immediate oral intake following esophagectomy was the frequent occurrence of complications that prohibit oral intake. In fact, 38% of patients required nonoral nutrition in this study. Based on the idea that the utility of the early oral intake could be enhanced in esophageal surgery with fewer complications, oral feeding on the first POD (EOF) was compared to late oral feeding (LOF) 7 days after surgery in patients who underwent minimally invasive esophagectomy [71]. This study showed that EOF was noninferior to LOF for cardiac, respiratory, and gastrointestinal complications (30.0% for EOF vs. 32.9% for LOF). They also demonstrated that the EOF group had a significantly shorter time to first flatus (median of 2 days vs. 3 days, $p = 0.001$) and bowel movement (median of 3 vs. 4 days, $p < 0.001$). Two weeks after the operation, patients in the EOF group had higher global QOL and function scores and lower symptom scores than those of the patients in the LOF group.

Early oral intake after esophagectomy seems to have no disadvantages compared to the conventional postoperative feeding protocol. However, the most appropriate timing for starting oral intake after esophagectomy remains controversial. It might be that the best strategy, for now, would be to select patients based on their capacity to safely accept oral intake.

In the years ahead, the effects of early oral intake should be investigated in the context of the control of psychological stress after highly invasive surgeries. The prevention of postoperative delirium is one expected benefit of early oral intake after esophagectomy.

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Neoadjuvant and Adjuvant Therapy

14

Nobutoshi Ando

Abstract

Most clinicians today are conscious of the necessity of a multimodality approach with surgery as the mainstay to improve the outcome of esophageal cancer victims. What results of clinical trials are available in Western countries are not applicable to clinical practice related to esophageal cancer in Asia, because of considerable East–West differences in this field. In Japan, the emphasis in surgical adjuvant therapy for patients with squamous cell carcinoma shifted from postoperative radiotherapy in the 1980s to postoperative chemotherapy, including cisplatin as a key drug in the 1990s. Later, the optimal timing for perioperative adjuvant therapy returned to preoperative treatment in the late 2000s, based on the results of a JCOG study (JCOG9907) comparing preoperative chemotherapy using cisplatin and 5-fluorouracil (CF) with postoperative chemotherapy. A meta-analysis consisting of 12 randomized controlled trials comparing preoperative chemoradiotherapy vs. surgery alone showed a significant survival benefit of preoperative chemoradiotherapy in both histologic types, squamous cell carcinoma, and adenocarcinoma. While a recent meta-analysis consisting of six randomized controlled trials in patients with resectable squamous cell carcinoma comparing preoperative chemotherapy vs. surgery alone or postoperative chemotherapy using CF showed a borderline survival benefit of preoperative chemotherapy and suggested its worthy of reinvestigation. Next, the clinical question of which is better, preoperative aggressive chemotherapy or preoperative chemoradiotherapy, still requires resolution. The JEOG three-arm randomized controlled trial is in progress to confirm the superiority of DCF (CF plus docetaxel) and the superiority of chemoradiotherapy in overall survival over CF as preoperative therapy for locally advanced esophageal squamous cell carcinoma. Clinical trials

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incorporating molecular-targeted therapeutics including immune-checkpoint inhibitors into multimodality treatment for esophageal cancer have started to define their efficacy.

Keywords

Esophageal squamous cell carcinoma · Multimodality treatment · Neoadjuvant chemotherapy · Neoadjuvant chemoradiotherapy · JCOG

14.1 Introduction

Surgery has improved the survival of patients with advanced squamous cell carcinoma (SCC) of the thoracic esophagus [1]. Radical surgery for esophageal cancer, consisting of transthoracic esophagectomy, is used as a leading treatment modality with extensive lymphadenectomy, namely 3-field lymphadenectomy, became established in leading institutions in Japan since the mid-1980s [2]. Further improvement of 5-year survival rates by surgery alone appears extremely unlikely even in high volume centers in Asia, partly because of the knowledge that the surgical invasiveness of this procedure cannot be tolerated by a higher percentage of patients than at present. Most clinicians now feel that a multimodal approach is necessary to further improve the outlook for esophageal cancer patients. Therefore, optimization of multimodal treatments for localized and resectable clinical stage II/III esophageal cancer is one of the most discussed topics in this field [3], with many reports on this subject appearing in during the past four decades.

The currently available results of clinical trials in Western countries should not be considered as being directly applicable to clinical practice in Asian cases of esophageal cancer, because of the not inconsiderable East–West differences in esophageal cancer treatment approaches and outcomes [4], for example, dissimilar distribution the main histologic types, i.e., SCC or adenocarcinoma (ADC), the philosophy of surgeons regarding cancer surgery, aiming at loco-regional or local tumor control, and the survival outcomes of the surgery-alone groups. Therefore, many Asian physicians treating patients with esophageal SCC (ESCC) hesitate to directly apply the presently available results of Western evidence, which is based more on results with ADC, to Asian practice.

The Japan Esophageal Oncology Group (JEOG), a subgroup of the Japan Clinical Oncology Group (JCOG) [5], has conducted consecutive randomized controlled trials (RCT) aimed at determining the potential of new surgical adjuvant therapies. The results of these studies have seen clinical fruition in the development of new state-of-the-art treatments for ESCC in Japan [6] and have been adopted as new evidence in the Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society [7]. Therefore, this chapter begins with the results of these JCOG studies specifically in ESCC and then reviews and discusses the results of studies on esophageal cancer outside of Japan.

14.2 Adjuvant and Neoadjuvant Therapy for ESCC in Japan

14.2.1 Historical Changes in Surgical Adjuvant Therapy of ESCC in Japan

14.2.1.1 Preoperative and Postoperative Radiotherapy

When the JEOG was first established in the 1970s, preoperative radiotherapy was the prevailing treatment modality for esophageal cancer. It was commonly believed that this approach would yield improvements in resectability (esophagectomy) and prevention of local tumor recurrence [8]. Therefore, the first JEOG phase III randomized controlled trial (1978–1981) compared 30 Gy preoperative radiotherapy plus a tegafur suppository with 30 Gy preoperative radiotherapy plus bleomycin injection. The survival rate in the preoperative radiotherapy plus tegafur group was not only better than that in the preoperative radiotherapy plus bleomycin group, but the postoperative morbidity and mortality in the bleomycin group were shown to be remarkably poor [9].

In the 1970s, the era of preoperative radiotherapy, one group came to emphasize the superiority of postoperative radiotherapy, citing less operative morbidity and improved survival based on retrospective comparison with controls [10]. The second JEOG RCT, therefore, was carried out to determine which mode of radiotherapy provided better survival: preoperative or postoperative. This study (JCOG8201, 1981–1983) compared preoperative (30 Gy) plus postoperative (24 Gy) radiotherapy with postoperative radiotherapy (50 Gy) alone. The survival rate in the surgery plus postoperative radiotherapy alone group was significantly better than that in the surgery and pre- plus postoperative radiotherapy group [11] (Fig. 14.1). Based on this result, there was a general move away from preoperative radiotherapy, with the timing of the multimodal approach to esophageal cancer moving from before to after surgery.

14.2.1.2 Postoperative Chemotherapy (Adjuvant Chemotherapy aCT)

Postoperative Radiotherapy Versus Postoperative Chemotherapy

Cisplatin has been available as a key drug in the treatment of esophageal cancer in Japan since the early 1980s. The third JEOG RCT was performed to determine which postoperative therapy provided better survival: radiotherapy or chemotherapy. This study (JCOG8503, 1984–1987) compared postoperative radiotherapy (50 Gy) with postoperative chemotherapy (70 mg/m^2 cisplatin plus 3 mg/m^2 vindesine × 2 courses). The chemotherapy regimen of cisplatin plus vindesine was adopted in this study because this combination was the standard regimen for non-small cell lung cancer at that time, when cisplatin plus 5-FU (CF) was not yet popular. Although this study showed no significant difference in the 5-year overall survival (OS) rate between the two groups [12] (Fig. 14.2), the results did suggest, however, that postoperative chemotherapy including cisplatin was not inferior to postoperative radiotherapy, the standard treatment modality at that time. As a result, aCT gained common acceptance as adjuvant therapy for ESCC in Japan.

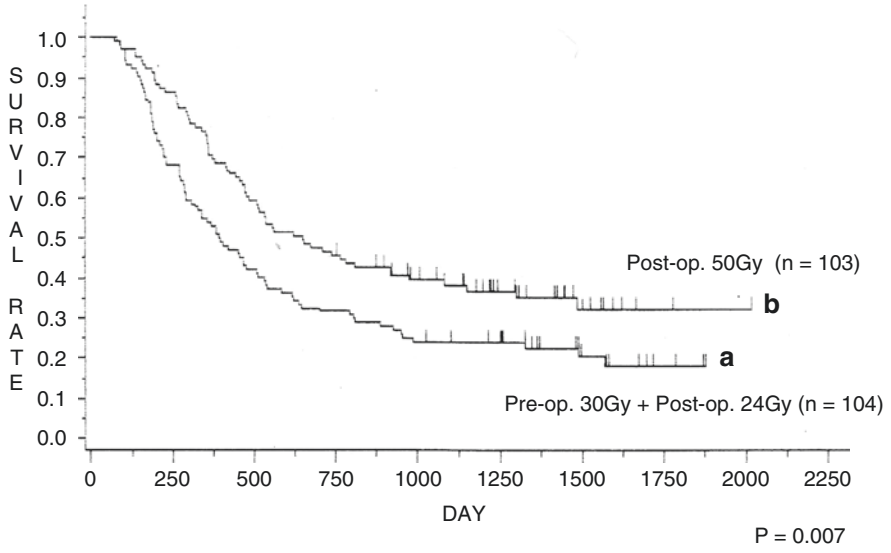

Fig. 14.1 Preoperative versus postoperative radiotherapy. Survival rate in the postoperative radiotherapy-alone group (**b**) was significantly better than that in pre- plus postoperative radiotherapy group (**a**)

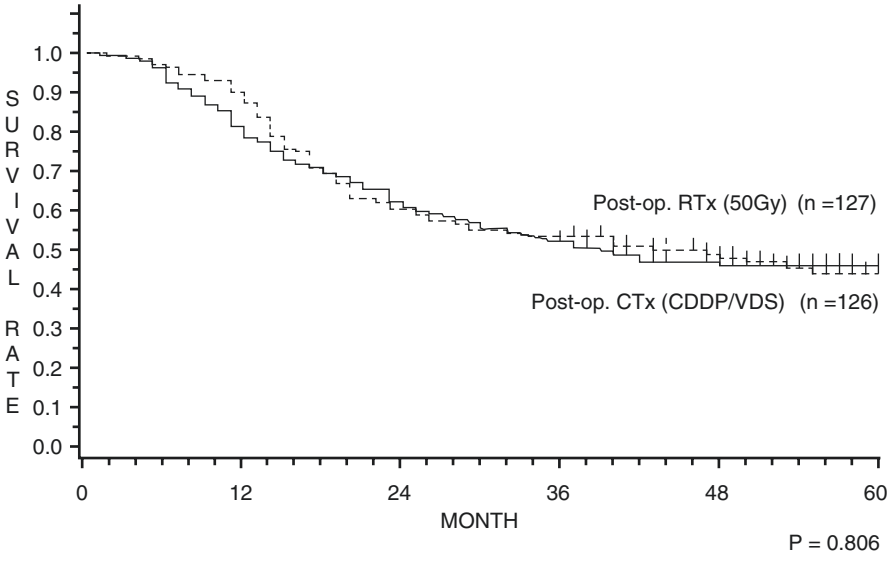

Fig. 14.2 Postoperative radiotherapy versus postoperative chemotherapy. The 5-year survival rate was 44% in the postoperative radiotherapy group and 42% in the postoperative chemotherapy group, showing no significant difference between two groups

Additive Effect on Survival of Postoperative Adjuvant Chemotherapy over Surgery Alone

Esophageal cancer surgery showed improved quality of lymphadenectomy, including specific dissection of the cervico-upper mediastinal nodes, which became the standard practice in the late 1980s in Japan. Therefore, in the fourth JEOG RCT, it was considered necessary to determine whether aCT conferred a survival benefit on patients undergoing radical esophageal cancer surgery. This study (JCOG8806, 1988–1991) compared surgery alone with surgery plus aCT (70 mg/m^2 cisplatin plus 3 mg/m^2 vindesine × 2 courses). This study showed no significant difference in the 5-year OS rate between the two groups [13] (Fig. 14.3). Based on this result, surgery alone became the standard of care for ESCC at that time.

The efficacy of a combination of CF in patients with advanced esophageal cancer was superior to that of cisplatin and vindesine, based on our experience of 2 phase II studies. The fifth JEOG RCT was, therefore, initiated to determine whether aCT using CF had an additive effect on survival in patients undergoing radical surgery alone for pathologic stage II or III, excluding T4, squamous cell carcinoma. This study (JCOG9204, 1992–1997) compared surgery alone with surgery plus aCT (80 mg/m^2 cisplatin on day 1 plus, 800 mg/m^2 5-FU on days 1–5 × 2 courses). The 5-year disease-free survival rates (primary endpoint) were 45% in the surgery-alone

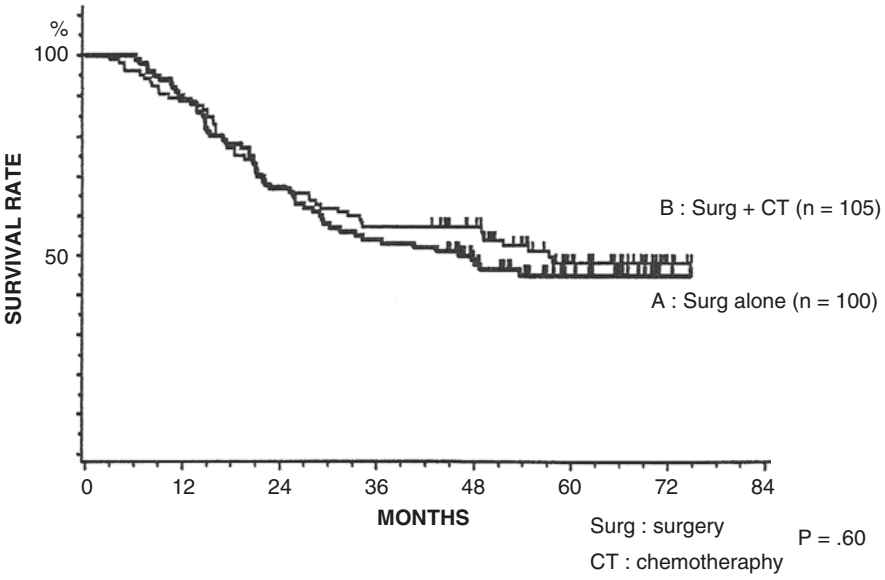

Fig. 14.3 Surgery alone versus postoperative chemotherapy (cisplatin + vindesine). The 5-year survival rate was 45% in the surgery-alone group and 48% in the postoperative chemotherapy group, showing no significant difference between two groups

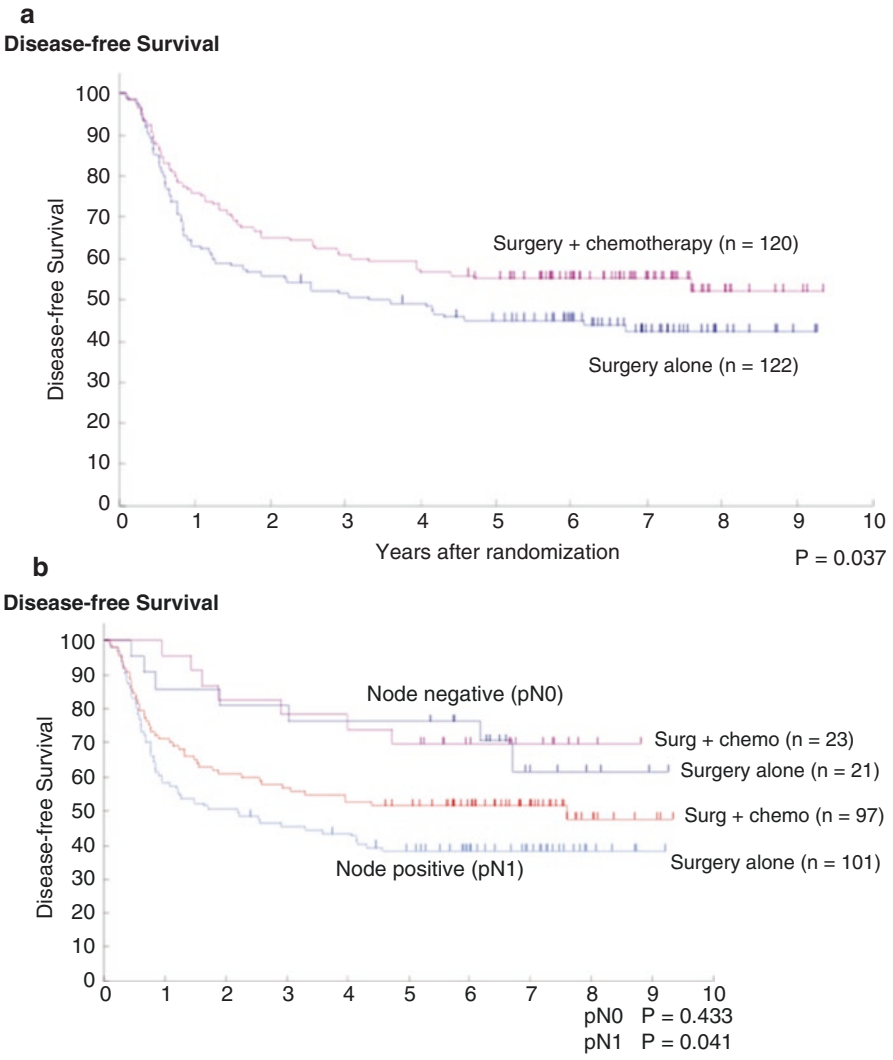

Fig. 14.4 (**a**) Surgery alone versus postoperative chemotherapy (cisplatin + 5-FU). Disease-free survival curves of all registered patients. The 5-year disease-free survival was 45% in patients with surgery alone and 55% in patients with surgery plus chemotherapy ($p = 0.037$). (**b**) Surgery alone versus postoperative chemotherapy (pN0/pN1). In the pN0 subgroup, the 5-year disease-free survival was 76% in the surgery-alone group and 70% in the surgery plus chemotherapy group ($p = 0.433$); in the pN1 subgroup, it was 38% in the surgery-alone group and 52% in the surgery plus chemotherapy group ($p = 0.041$)

group (122 patients) and 55% in the postoperative chemotherapy group (120 patients) ($p = 0.04$), while the 5-year OS were 52% and 61%, respectively ($p = 0.13$). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis [14] (Fig. 14.4a, b). On the basis of these data, aCT using CF came to be considered the standard of care for patients with ESCC in the early 2000s.

14.2.1.3 Preoperative Chemotherapy (Neoadjuvant Chemotherapy nCT)

Even though aCT was considered the standard of care for esophageal cancer patients in Japan, preoperative treatment still predominated in Western countries due to the invasiveness of esophageal cancer surgery and the attending high morbidity [15]. Therefore, the positive role of preoperative chemotherapy regarding survival in patients with esophageal cancer compared with surgery alone or postoperative chemotherapy remained controversial. Details regarding this controversy are described in the next subchapter. The sixth JEOG RCT was, therefore, initiated to determine the optimal perioperative timing of chemotherapy in patients with locally advanced ESCC, that is, before or after surgery. In this study (JCOG9907, 2000–2006), eligible patients with clinical stage II or III, excluding T4, SCC were randomly assigned to undergo surgery either followed (Post group) or preceded (Pre group) by chemotherapy (80 mg/m^2 cisplatin on day 1 plus 800 mg/m^2 5-FU, continuous infusion (c.i.) over days 1–5 × 2 courses with a 3-week interval). Progression-free survival, the primary endpoint, did not reach the discontinuation boundary, but OS in the Pre group (164 patients) was superior to that in the Post group (166 patients) ($p = 0.01$). Updated analyses showed that the 5-year OS was 43% in the Post group and 55% in the Pre group (hazard ratio, 0.73; 95% confidence interval, 0.54–0.99; $p = 0.04$) [16] (Fig. 14.5a, b). Though renal dysfunction after surgery in the Pre group was slightly higher than that in the Post group, nCT did not increase the risk of complications or hospital mortality after surgery [17]. There are three possible reasons for better preoperative chemotherapy results. First, downstaging was achieved in some patients by nCT. While the proportion of the patients with clinical stage II disease was similar in the two groups, the proportion with pathological stage II or lower was greater in the Pre group. Second, complete resection (R0) was slightly more frequent in the Pre group than the Post group. Third, the rate of completion of the protocol treatment was much better in the Pre group than the Post group. Treatment according to the protocol with two courses of chemotherapy and R0 resection was done in 85.4% of the Pre group patients, but only in 75.0% of patients in the Post group.

Based on these results, nCT with CF came to be regarded as the standard of care for patients with stage II/III SCC [18]. Thus, the optimal perioperative timing of surgical adjuvant therapy once again became before surgery.

14.2.2 Future Candidates for Surgical Adjuvant Therapy for ESCC in Japan

The results of subgroup analyses in JCOG9907 showed that nCT was more effective in clinical stage II or T1–2 cases than in stage III or T3, namely in relatively early-stage patients. Furthermore, the lower rate of single locoregional recurrence of 31% and 25% among tumor recurrence cases in every group may result from our meticulous surgical procedure. The results of our study suggest that nCT using CF is a good treatment strategy, if sufficient local tumor control is achieved by aggressive surgical procedures, while if local tumor control is insufficient, more

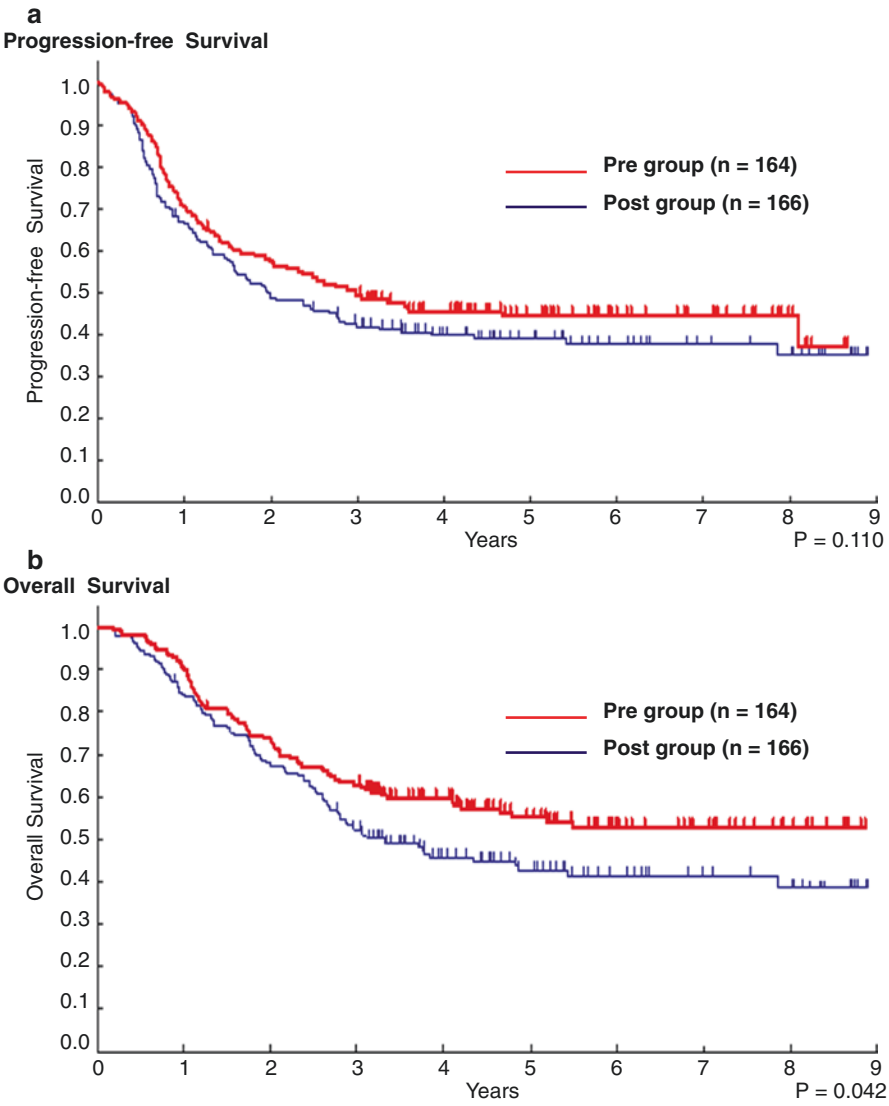

Fig. 14.5 (**a**) Preoperative versus postoperative chemotherapy. Progression-free survival. Pre group = preoperative chemotherapy (nCT), Post group = postoperative chemotherapy (aCT). No significant difference was observed in progression-free survival between two groups. (**b**) Preoperative versus postoperative chemotherapy. Overall survival. Pre group = preoperative chemotherapy (nCT), Post group = postoperative chemotherapy (aCT). The 5-year OS was 43% in the Post group and 55% in the Pre group ($p = 0.04$)

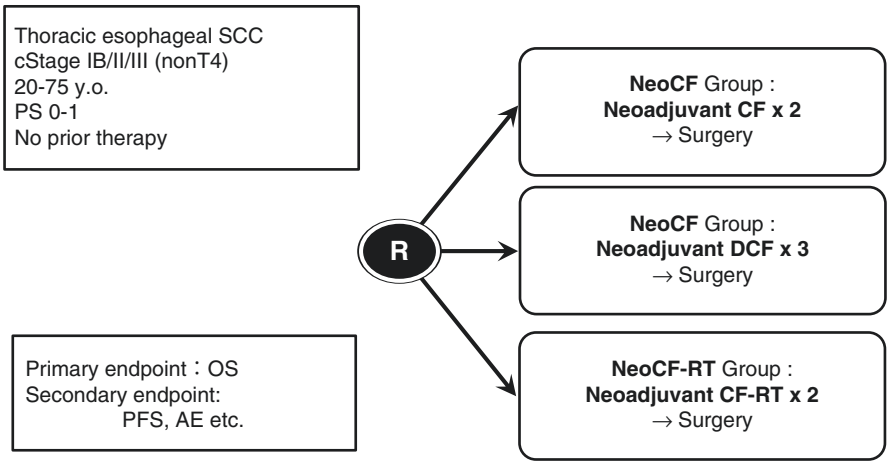

Fig. 14.6 Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiation therapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT Study)

aggressive adjuvant therapy such as preoperative chemoradiotherapy (nCRT) with the aim of local tumor control or more intensive nCT with the aim of systemic disease control may be a preferable treatment modality. Docetaxel is one of the most promising drugs for esophageal cancer and the exploratory trial of preoperative chemotherapy with docetaxel plus CF (DCF) for locally advanced ESCC showed a good response rate (61.5%) with no treatment-related deaths. DCF has been supposed to have potential as a standard nCT regimen proved by a randomized phase II study [19]. The clinical question of which is better, nCT or nCRT, still needs to be clarified.

Based on these background features, the JEOG launched a three-arm randomized controlled trial JCOG1109 in 2012 to confirm the superiority of DCF and the superiority of chemoradiotherapy with CF (CF-RT) in overall survival over CF as preoperative therapy for locally advanced ESCC [20]. Patients in arm A receive two courses of preoperative CF (80 mg/m^2 cisplatin on day 1 plus 800 mg/m^2 5-FU, c.i. on days 1–5) repeated every 3 weeks. Patients in arm B receive three courses of preoperative DCF (70 mg/m^2 docetaxel on day 1 plus 70 mg/m^2 cisplatin on day 1 plus 750 mg/m^2 5-FU, c.i. on days 1–5) repeated every 3 weeks. Patients in arm C receive preoperative chemoradiotherapy (41.4 Gy/23 fractions) with two courses of CF (75 mg/m^2 cisplatin on day 1 plus 5-FU 1000 mg/m^2 5-FU, c.i. on days 1–4) repeated every 4 weeks (Fig. 14.6). Whichever esophagectomy, transthoracic open esophagectomy or

minimally invasive esophagectomy, were acceptable in three arms. Patients accrual was over in 2018 and follow up of the enrolled patients is ongoing.

14.3 Adjuvant and Neoadjuvant Therapy for ESCC out of Japan

Table 14.1 presents a comprehensive overview of the literature-based evidence on adjuvant and neoadjuvant therapies for ESCC out of Japan and from Japan.

14.3.1 Adjuvant Therapy for ESCC

Very few studies are reported on literature-based reviews of aCT for ESCC. The French Association for Surgical Research performed a randomized controlled trial comparing surgery alone with aCT using CF for patients with ESSC [21]. Before randomization, they separated 120 patients into two strata, curative complete resection and palliative resection leaving residual macroscopic or microscopic tumor tissue. Chemotherapy consisted of a maximum of eight courses (minimum six courses) of cisplatin (80 mg/m^2 on day 1 or 30 mg/m^2 × 5 days) and 5-fluorouracil (1000 mg/m^2 × 5 days) within 1.5 months after surgery. OS was similar in the two groups, with almost identical medians of 13 months in the aCT group (52 patients) and 14 months in the surgery-alone group (68 patients). The survival curves with or without chemotherapy were similar in stratum of curative resection and also in the palliative resection stratum. On the basis of these data, it was concluded that CF preceded by surgery is not useful for patients with ESCC.

Korean oncologists carried out a prospective study of aCT (60 mg/m^2 cisplatin on day 1 plus 5-fluorouracil 1000 mg/m^2 5-FU, c.i. over days 1–4 × 3 courses) in N1 resectable ESCC patients, and also compared the results with the historical control group who underwent curative resection alone during the same period of time [22]. The 3-year disease-free survival rate was 47.6% in the adjuvant group and 35.6% in the surgery-alone group ($p = 0.049$). Their conclusion was that aCT might prolong disease-free survival in node-positive patients, and they suggested that a postoperative treatment modality for esophageal cancer patients should be determined according to the lymph node status, which was the same conclusion as the JCOG9204. A meta-analysis consisting of 11 studies, three RCTs including JCOG 8806 and 9204 and eight non-RCTs, in patients with resectable ESCC comparing surgery plus adjuvant chemotherapy vs. surgery alone showed that patients with stage III–IV disease could benefit from adjuvant chemotherapy on 3-year OS and patients with positive lymph node could benefit on 5-year DFS [23].

14.3.2 Neoadjuvant Therapy for ESCC

Numerous reports have been devoted to neoadjuvant therapies for esophageal cancer patients with both SCC and ADC histology.

Table 14.1 *CT* chemotherapy, *CRT* chemoradiotherapy, *SCC* squamous cell carcinoma, *ADC* adenocarcinoma, *TTE* transthoracic esophagectomy, *THE* transhiatal esophagectomy

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients + CT, CRT surg. alone		Survival + CT, CRT surg. alone		*p* value
Adjuvant CT vs. surgery alone										
Pouliquen X 21 (FASR)	1987–1992	excluding T4, N0	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2) × 6–8 cycles		TTE	68	52	MST: 12 mo	MST: 12 mo	NS
Ando 14 (JCOG)	1992–1997	IIA, IIB, III, IVa	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	120	122	5y-DFS: 55%	5y-DFS: 45%	0.037
Lee 22	1998–2003	IIb, III, Iva	Cisplatin (60 mg/m^2) 5-FU (1000 mg/m^2) × 3 cycles		TTE	40	52 (historical control)	3y-DFS: 47.6%	3y-DFS: 35.6%	0.049
Neoadjuvant CT vs. surgery alone										
Law 24	1989–1995	excluding T4 and stage IV	Cisplatin (100 mg/m^2) 5-FU (500 mg/m^2) × 2 cycles		TTE	74	73	MST: 16.8 mo	MST: 13 mo	0.17
Ancona 25	1992–1997	IIA, IIB, and III	Cisplatin (100 mg/m) 5-FU (1000 mg/m^2) × 2 cycles		TTE	48	48	5y-OS: 34%	5y-OS: 22%	0.55
Kelsen 26, 27 (RTOG)	1990–1995	I, II, and III	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2) × 3 cycles		TTE and THE	213 (54%; ADC)	227 (53%; ADC)	MST: 14.9 mo	MST: 16.1 mo	0.53 SCC/ADC NC/NC
MRC 28, 29	1992–1998	Resectable tumor	Cisplatin (80 mg/m^2) 5-FU (1000 mg/m^2) × 2 cycles		TTE and THE	400 (66%; ADC)	402 (67%; ADC)	MST: 16.8 mo	MST: 13.3 mo	0.004 HR: SCC/ADC 0.78/0.78

(continued)

Table 14.1 (continued)

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients + CT, CRT surg. alone		Survival + CT, CRT surg. alone		*p* value
Neoadjuvant CT vs. adjuvant CT										
Ando 16 (JCOG)	2000–2006	IIA, IIB, and III	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	Pre-op 164	Post-op 166	Pre-op 5y-OS: 55%	Post-op 5y-OS: 43%	0.04
Neoadjuvant CRT vs. surgery alone										
Nygaad 35	1983–1988	I, II, III	Cisplatin (20 mg/m^2) × 5 Bleomycin (10 mg/m^2) × 5 × 2 cycles	35 Gy	TTE	26	15	MST: Not stated	MST: Not stated	0.3
Le Prise 36	1988–1991	I, II	Cisplatin (100 mg/m^2) 5-FU (600 mg/m^2) × 2 cycles	20 Gy	Not stated	41	45	1y-OS: 46.6%	1y-OS: 46.7%	0.56
Apinop 37	1986–1992	IIB, III	Cisplatin (100 mg/m^2) 5-FU (1000 mg/m^2) × 2 cycles	40 Gy	TTE	35	34	MST: 9.7 mo	MST: 7.4 mo	0.4
Bosset 38	1986–1992	I, II	Cisplatin (80 mg/m^2) × 2 cycles	37 Gy	TTE	143	139	MST: 18.6 mo	MST: 18.6 mo	0.78
Lee 39	1999–2002	IIA, IIB, III	Cisplatin (60 mg/m^2) 5-FU (1000 mg/m^2) × 2 cycles	45.6 Gy	TTE	51	50	MST: 28.2 mo	MST: 27.3 mo	0.69 study stopped
Yang 40	2007–2014	IIB and III	Cisplatin (75 mg/m^2) Vinorelbine (25 mg/m^2 × 2) × 2 cycles	40 Gy	TTE	224	227	MST: 100.1 mo	MST: 66.5 mo	0.025
Shapiro 41 (CROSS Gr)	2004–2008	IIA, IIB, and III	Carboplatin (AUC 2) Paclitaxel (50 mg/m^2) × 23 days	41.4 Gy	TTE and THE	178 (75%; ADC)	188 (75%; ADC)	MST: 48.6 mo	MST: 24.0 mo	0.003

14.3.2.1 Neoadjuvant Chemotherapy (nCT) for ESCC

In a study in Hong Kong, Law and colleagues compared surgery alone with nCT (100 mg/m^2 cisplatin on day 1 plus 500 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses) plus surgery for resectable ESCC [24]. Most patients had a tumor in the middle third of the esophagus, and the preferred surgical procedure was transthoracic esophagectomy with mediastinal lymphadenectomy. The cancer-free survival (primary endpoint) was 13 months in the surgery-alone group (73 patients) and 16.8 months in the nCT group (74 patients) ($p = 0.17$). They concluded that survival provided by nCT was not better than that in the surgery-alone group, but they suggested a trend for survival advantage for patients who underwent nCT. They emphasized the necessity of reliable predictors, with chemo-responders being faring better than nonresponders.

In Italy, Ancona and colleagues compared surgery alone with nCT (100 mg/m^2 cisplatin on day 1 plus 1000 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses) plus surgery for stage II/III ESCC [25]. The surgical procedure adopted in this study was transthoracic esophagectomy plus two-field lymphadenectomy. The 5-year OS (primary endpoint) was 22% in the surgery-alone group (48 patients) and 34% in the nCT group (48 patients) ($p = 0.55$). They concluded that improved long-term survival was obtained in patients with clinically resectable ESCC who underwent nCT and obtained a pathologic complete response. They also emphasized the necessity of major efforts to identify patients who are likely to respond to nCT.

Two pivotal RCTs in terms of nCT are known worldwide, the RTOG trial (USA intergroup study) and the MRC trial (UK and The Netherlands), although both SCC and ADC histologic types were included. Kelsen and 4 study group investigators compared surgery alone with nCT (100 mg/m^2 cisplatin on day 1 plus 1000 mg/m^2 5-FU, c.i. over days 1–5 × 3 courses) plus surgery followed by 2 cycles of postoperative chemotherapy in operable esophageal cancer cases [26]. More than 50% of patients (53% in the surgery-alone group and 54% in the preoperative chemotherapy group) consisted of ADC, and both transthoracic and transhiatal esophagectomy were performed as the surgical procedures without limiting the extent of lymphadenectomy. The median survival was 16.1 months in the surgery-alone group (227 patients) and 14.9 months in the nCT group (213 patients) ($p = 0.53$). There were no differences in survival between patients with SCC and those with ADC. They concluded that nCT with a combination of CF did not improve OS among patients with SCC or ADC. They reported, in a long-term update, that the median survival times were 1.3 years for patients receiving nCT versus 1.3 years for those undergoing surgery alone [27]. They described similar outcomes as other researchers, with objective response to nCT being associated with better survival.

Investigators in the Medical Research Council Oesophageal Cancer Working Party compared surgery alone with nCT (80 mg/m^2 cisplatin on day 1 plus 1000 mg/m^2 5-FU, c.i. over days 1–4 × 2 courses) plus surgery for resectable esophageal cancer [28]. Two-thirds of patients (67% in the surgery-alone group and 66% in the nCT group) consisted of ADC, and the surgical procedure was chosen by the operating surgeon. The median survival was 13.3 months in the surgery-alone group (402 patients) and 16.8 months in the nCT group (400 patients) ($p = 0.004$), and the

2-year survival rates were 34% and 43%, respectively. Hazard ratios for treatment effect in patients with SCC and those with ADC were the same, showing that the effects of treatment were extremely similar for both histologic types. They concluded that nCT improved survival in patients with resectable esophageal cancer. In long-term update results of this trial, they reported that the 5-year survival was 17.1% in the surgery-alone group and 23.0% in the nCT group, with consistent treatment effect achieved in both histologic types [29]. They emphasized that nCT is an essential standard of care for patients with resectable esophageal cancer.

One of the most common failures in these two pivotal studies was local recurrence. The result of combined therapies cannot be discussed without regard to the surgical procedure and its quality employed [30]. Because two pivotal studies demonstrated completely different conclusions, the benefit of nCT, even when limited to patients with ESCC was controversial before our latest JCOG9907 study. Therefore, there seems to be no current worldwide consensus as to the optimal neoadjuvant approach. Preoperative chemoradiotherapy followed by surgery is an accepted standard of care in the United States where ADC constitutes the majority of patients with esophageal cancer [31, 32], compared with the United Kingdom where preoperative chemotherapy is the standard of care based on the result of the MRC study [33]. However, preoperative chemoradiotherapy is regarded as the standard of care in the French guidelines for treatment [34]. Even within Europe, they have no consensus as to the optimal neoadjuvant approach.

14.3.2.2 Neoadjuvant Chemoradiotherapy (nCRT) for ESCC

Numerous RCTs comparing nCRT followed by surgery with surgery alone have been reported during the past three decades. Among them, four trials specified to ESCC in the 1990s showed no survival benefit ascribable to nCRT [35–38]. In the 2000s, a Korean group compared surgery alone with nCRT (CF plus radiotherapy of 45.6 Gy in 38 fractions) followed by surgery for stage II/III ESCC. A transthoracic esophagectomy with en bloc lymphadenectomy was performed. The median survival was 27.3 months in the surgery-alone group (50 patients) and 28.2 months in the nCRT group (51 patients) ($p = 0.69$), and the 2-year survival rates were 51% and 49%, respectively. This trial was discontinued because of the unexpectedly high drop-out rate for esophagectomy and resultant excessive loco-regional failure rate in the nCRT group. Therefore, they concluded that nCRT provided no survival benefit for resectable ESCC [39]. Meanwhile, a Chinese collaborative group compared surgery alone with nCRT (cisplatin and vinorelbine plus radiotherapy of 40.0 Gy in 20 fractions) followed by surgery for potentially resectable thoracic ESCC. A transthoracic esophagectomy with two-field lymphadenectomy was performed. The median OS was 100.1 months in the nCRT group (224 patients) and 66.5 months in the surgery-alone group (227 patients) ($p < 0.001$), and the 3-year OS were 69.1% and 58.9%, respectively. They concluded that nCRT improved survival among patients with locally advanced ESCC, with acceptable and manageable adverse events [40].

A Dutch group (CROSS Group) compared surgery alone with nCRT (carboplatin and paclitaxel plus radiotherapy of 41.4 Gy in 23 fractions) followed by surgery for potentially curable SCC (23%) or ADC (75%) of the esophagus or the esophagogastric junction. A transthoracic esophagectomy with two-field lymphadenectomy was performed. A transhaital resection was preferred for the tumors involving the esophagogastric junction. The median survival was 48.6 months in the nCRT group (178 patients) and 24.0 months in the surgery-alone group (188 patients) ($p = 0.003$), while 81.6 months and 21.1 months, respectively, for patients with SCC. The 5-year OS was 47% and 33%, respectively. They concluded that nCRT improved survival among patients with potentially curable esophageal or esophagogastric junction cancer, regardless of histologic subtype [41]. The result of this study supported nCRT as a standard of care for locally advanced esophageal cancer in Western countries in which ADC is predominant histologic type, whereas criticism of a relatively small subset of SCC patients and the low R0 resection rate in the surgery-alone group appears in Asian countries.

Given this situation, with discordant results of RCTs comparing neoadjuvant therapy with surgery alone for locally advanced esophageal cancer, several meta-analyses have been conducted. Two of six meta-analyses on nCRT did not show a significant survival benefit in patients with resectable esophageal cancer [42]. This discordance can be criticized because of heterogeneity among the trials included in a meta-analysis. The most recent meta-analysis by Sjoquist et al. [43] included 12 RCTs comparing nCRT vs. surgery alone, with a total of 1854 patients. A significant survival benefit was evident for nCRT with an HR of 0.78 (0.70–0.88; $p < 0.0001$). In a subgroup analysis, the HR for SCC was 0.80 (0.68–0.93, $p = 0.004$) and for ADC it was 0.75 (0.59–0.95, $p = 0.02$). This updated meta-analysis provided stronger evidence for a survival benefit than the former meta-analysis conducted by the same group [44]. This analysis also compared nCT vs. nCRT, and demonstrated a non-statistically significant survival benefit for nCRT (HR 0.88, 0.76–1.01; $p = 0.07$). Therefore, controversy still exists as to whether nCT or nCRT is more beneficial [45]. A RCT comparing nCT (3 cycles of CF, 91 patients including 25 SCC patients) with nCRT (concurrent 40 Gy radiotherapy, 90 patients including 25 SCC patients) was conducted in Sweden and Norway. They revealed the addition of radiotherapy to nCT resulted in higher pCR rate and higher R0 resection rate, without significantly affecting survival [46].

A network meta-analysis allows the evaluation of treatments, which have not been compared directly or indirectly and the ranking multiple treatments on their efficacy. The result of a network meta-analysis including 27 eligible randomized controlled trials demonstrated that neoadjuvant CRT was the best treatment, followed by neoadjuvant CT, and surgery alone. Subgroup analysis depending on histology of this network meta-analysis showed neoadjuvant CRT and neoadjuvant CT are effective and superior to adjuvant therapies for improving survival of patients with SCC [47].

14.4 Future Perspective of Adjuvant and Neoadjuvant Therapeutic Modality

The important role of individualized treatment of esophageal cancer has long been emphasized [48]. In the field of surgery, individualization of lymph node dissection, applying the concept of sentinel node navigation has been discussed to rationally reduce the extent of lymphadenectomy [49]. In the field of multimodal treatments, identification of chemo- and radio-responders is an urgent subject based on the evidence that histological complete response is predictive of long disease-free and overall survival outcomes as described in previous subchapters. If it were possible to predict of responders, unnecessary toxicity, and time caused by unnecessary preoperative chemotherapy or chemoradiotherapy could be avoided and rational radical surgery implemented. Therefore current investigations focus on the identification of prognostic and predictive biomarkers as well as the integration of molecular targets into biological therapies [50]. Overexpression of epidermal growth factor receptor (EGFR) is recognized in esophageal cancer, a wide range of 12%–71% of SCC, and is associated with a poor prognosis. In a study from the United States, evaluating pretreatment expression of EGFR, increased levels of EGFR were associated with worse overall survival but not with histological response [51]. A review article summarized to be seven categories of molecules correlating with response and/or prognosis of ESCC patients undergoing nCRT: tumor suppressor (p53, p21), cell cycle regulators (Cyclin D1, CDC25B, 13-3-3sigma), DNA repair molecules (p53R2, ERCC1), drug resistance proteins (metallothionein), angiogenetic factors (VEGF), molecules involved in cell proliferation/invasion/metastasis (Ki-67, COX-2), and hedgehog signaling molecules (Gli-1). Among them tumor suppressor p53 was regarded as a potential biomarker for predicting response and prognosis [52].

Clinical trials incorporating molecularly targeted therapeutics into multimodality treatment for esophageal cancer are being initiated. EGFR inhibitors, e.g., cetuximab and gefitinib, are now incorporated into nCRT [53], and inhibitors of vascular endothelial growth factor receptor (VEGF) are being applied to combination chemotherapy [54]. A randomized phase II/III study investing the addition of cetuximab to CF-based definitive CRT was performed in the United Kingdom. This study recruitment was stopped without continuation to phase III and this study did not show that the addition of cetuximab to standard definitive CRT benefits patients with locally advanced esophageal cancer in not only OS but toxicity [55].

Recent great interest in immune checkpoint inhibitors, that help unleash the body's immune response to cancer, expands to esophageal cancer as well as more cancer types. A multicenter phase II trial of nivolumab in Japan showed a promising activity with a response rate of 17% of 64 patients with ESCC refractory or intolerant to previous chemotherapies [56]. Based on the result of this phase II trial, a feasibility trial of nivolumab with neoadjuvant CF or DCF therapy for locally advanced ESCC has launched in JCOG. Pembrolizumab same as nivolumab demonstrated meaningful antitumor activity and manageable toxicity in patients with heavily pretreated, PD-L1 positive advanced ESCC in phase IB and II trials [57].

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Chemotherapy and Chemoradiotherapy

15

Ken Kato

Abstract

There are various roles of chemotherapy and chemoradiotherapy for the treatment of esophageal squamous cell carcinoma (ESCC). Cytotoxic agents were used as palliative chemotherapy for metastatic or recurrent cases, which consist 5-FU and platinum agents mostly. For failure following the first-line chemotherapy, taxanes are used as the second-line chemotherapy of ESCC. Recently triplet combination with 5-FU, platinum, and taxanes has been evaluated in the first-line chemotherapy. As for chemoradiotherapy, the schedule and dose of radiation, and timing of salvage treatment has been optimized. In earlier line, comparable efficacy of chemoradiotherapy was reported compared to surgery. Immune-checkpoint inhibitor (ICI) showed impact on the survival of patients who failed to the first-line chemotherapy in comparison with chemotherapy. ICI has also been evaluated as first-line chemotherapy, combination with chemoradiotherapy, pre- and postoperative therapy.

Keywords

Chemotherapy · Chemoradiotherapy · Immune-checkpoint inhibitor

15.1 Purpose and Evaluation of Chemotherapy

Chemotherapy has many roles for the treatment of esophageal squamous cell carcinoma (ESCC). It has been used for patients with metastatic or recurrent cancer to prolong survival and/or alleviate the symptoms caused by cancer, and it has also

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been used for preoperative or postoperative therapy combined with surgery to increase the complete resection rate. At the same time, chemotherapy has been used with radiation therapy as definitive chemoradiotherapy (CRT) for localized ESCC. Responses to chemotherapy may be evaluated via endoscopy, computed tomography, magnetic resonance imaging, and other modalities, which are the same modalities used at diagnosis, as described in Chaps. 3, 4, and 5. There are no current consensuses on the optimal follow-up duration, although evaluation frequencies of every 2 or 3 months for metastatic cancer and evaluations at every course for preoperative chemotherapy or CRT are the usual manner.

15.2 Chemotherapeutic Agents Used for Esophageal Squamous Cell Carcinoma

Various agents have been reported as effective for ESCC, but most of these studies were phase I and II studies and included only a small number of patients. While these results were investigational, they provided support for consideration of combination therapy with new drugs. 5-Fluorouracil (5-FU), bleomycin, mitomycin, cisplatin (CDDP), and taxanes have been used most frequently because of their activity and synergistic effect with radiation and other drugs (Table 15.1).

15.2.1 Bleomycin

Bleomycin as a single agent for ESCC has been reported to have a response rate of 15–20% [1–3]. A randomized trial comparing chemotherapy with bleomycin and best supportive care did not show a survival benefit [25]. Bleomycin is no longer used because of its pulmonary toxicity in combination with other drugs or radiotherapy.

15.2.2 Fluoropyrimidine

15.2.2.1 5-Fluorouracil

5-FU, in combination with other drugs and/or radiation therapy, is the most commonly used chemotherapeutic drug for ESCC. Efficacy of 5-FU as a single agent is modest. A response rate of 15% was observed in previously treated patients administered an intermittent bolus of 5-FU in an Eastern Cooperative Oncology Group trial [4].

15.2.2.2 S-1

S-1, an oral fluoropyrimidine preparation combining tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1, has been used for gastric, head and neck, lung, colon, and other cancers. The response rate of S-1 for pretreated patients with ESCC was reported to be 22–25% [5, 6].

Table 15.1 Single-agent chemotherapy for advanced esophageal cancer

Agent	Histology and number of pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Bleomycin	SCC 29	1st	NA	14	NA	NA	[1]
Bleomycin	SCC + AC 20	1st	NA	20	NA	NA	[2]
Bleomycin	SCC 14	1st	NA	0	NA	NA	[3]
5-FU	SCC 26	1st	5-FU 500 mg/m^2 × 5 days/q5wks	15	3.4	NA	[4]
S-1	SCC 20	2nd or 3rd	S-1 40–60 mg × twice daily day 1–28/q6wks	25	3.3	10.8	[5]
S-1	SCC11	2nd or 3rd	S-1 40–60 mg × twice daily day 1–28/q6wks	22.2	3.0	11.7	[6]
Cisplatin	SCC 44	1st	Cisplatin 100 mg/m^2/q3wks	19	4.1	6.4	[7]
Carboplatin	SCC 11	1st	NA	9	NA	NA	[8]
Carboplatin	SCC 18	1st	Carboplatin 130 mg/m^2/day days 1, 3, 5	0	NA	NA	[9]
Nedaplatin	SCC 29	1st or 2nd	Nedaplatin 100 mg/m^2/q4wks	51.7	NA	NA	[10]
Paclitaxel	SCC18 AC32	1st	Paclitaxel 250 mg/m^2/q3wks	SCC28 AC34	3.9	13.2	[11]
Paclitaxel	SCC20 AC66	1st or 2nd	Paclitaxel 80 mg/m^2 Day 1, 8, 15, 22/q4wks	12	3.1	9.0	[12]
Paclitaxel	SCC 52	2nd	Paclitaxel 100 mg/m^2 Day 1, 8, 15, 22, 29, 35/q7wks	44.2	3.9	10.4	[13]
Docetaxel	AC 41	1st	Docetaxel 100 mg/m^2/q3wks	17	NA	NA	[14]
Docetaxel	AC 22	1st or 2nd	Docetaxel 75 mg/m^2/q3wks	1st 18 Second 0	NA	3.4	[15]
Docetaxel	SCC35 AC 3	1st or 2nd	Docetaxel 70 mg/m^2/q3wks	1st 36 Second 16	4.7	8.1	[16]
Vindesine	SCC26	1st	Vindesine 3.0 mg/m^2 weekly	17.3	NA	NA	[17]
Vindesine	SCC 9	1st or 2nd	Vindesine 4.0 mg/m^2/q2wks	22.2	NA	NA	[18]
Vindesine	SCC 52	1st	Vindesine 3 mg/m^2 weekly	27	NA	NA	[19]
Vinorelbine	SCC 46	1st or 2nd	Vinorelbine 25 mg/m^2 weekly	1st 20 Second 6	NA	6.0	[20]
Etoposide	SCC 26	1st	Etoposide 200 mg/m^2 day 1, 2, 3/q3wks	19	4.0	NA	[21]
Irinotecan	SCC10 AC3	1st or 2nd	Irinotecan 125 mg/m^2 Day 1, 8, 15, 22/q6wks	15	3.8	6.1	[22]

(continued)

Table 15.1 (continued)

Agent	Histology and number of pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Methotorexate	SCC 26	1st	Methotrexate 40 mg/m^2 weekly	12	NA	3.2	[4]
Ifosfamide	SCC 32	1st or 2nd	Ifosfamide 1.5 g/m^2 × 5 days	7	NA	NA	[23]
Gemicitabine	SCC6 AC14	1st	Gemicitabine 1250 mg/m^2 Day 1, 8, 15/q4wks	0	2	5	[24]
Doxorubicin	SCC 20	1st	Doxorubicin 60 mg/m^2/q3wks	5	NA	1.8	[4]

Pts patients, *PFS* progression free survival, *MST* median survival time, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *NA* not available, *wks* weeks, *5-FU* 5-fluorouracil

15.2.3 Platinum Agents

15.2.3.1 Cisplatin

Platinum agents have been used mostly in combination with 5-FU, topoisomerase inhibitors, and taxanes. As monotherapy, CDDP is administered at doses of 50–120 mg/m^2 every 3–4 weeks; the cumulative response rate for ESCC was 21% [7, 26, 27]. In a randomized phase II trial, the addition of 5-FU to CDDP was compared to CDDP monotherapy administered at 100 mg/m^2 every 3 weeks in 92 patients with ESCC. Although the response rate was higher in the combination group (35% vs. 19%), survival was similar in both groups (monotherapy vs. combination: 33 vs. 28 weeks) [7].

15.2.3.2 Carboplatin

Carboplatin, a second-generation platinum analogue, was developed to maintain the antitumor activity of CDDP and to reduce toxicity. Carboplatin has also been used mostly in combination; its single-agent activity is limited, with response rates of 0–14% [8, 9].

15.2.3.3 Oxaliplatin

Oxaliplatin, a platinum derivative with less emetogenic, nephrotoxic, and ototoxic effects compared to CDDP, has been evaluated mainly in combination regimens for esophageal cancer.

15.2.3.4 Nedaplatin

Nedaplatin, a second-generation platinum derivative, is 10 times as water soluble as CDDP with less gastrointestinal and renal toxicity. In a phase II study of nedaplatin monotherapy at 100 mg/m^2 via intravenous infusion every 4 weeks, 5 partial responses (55.6%) were observed in 9 patients with ESCC who had received prior chemotherapy, including 2 partial responses in 4 patients previously treated with CDDP [10].

15.2.4 Taxanes

Taxanes have shown activity against not only adenocarcinoma but also squamous cell carcinoma of the esophagus.

15.2.4.1 Paclitaxel

Paclitaxel promotes the stabilization of microtubules, and it is a cell cycle-specific agent affecting cells in the G2/M phase, and showed activity for ESCC by monotherapy [11, 12, 28]. Paclitaxel was evaluated for the patients who failed to previousl chemotherapy in phase II study, at a dose of 100 mg/m^2 once per week for 6 weeks followed by 1 week off (each cycle was 7 weeks). The overall response rate of patients with squamous cell cancer was 43.1%, with 4 patients (7.8%) achieving a complete response. Although grade 3 or 4 neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), and fatigue (9.4%) were observed, weekly paclitaxel was highly active and well-tolerated [13].

15.2.4.2 Docetaxel

Docetaxel at doses of 75–100 mg/m^2 administered every 3 weeks has also shown activity against adenocarcinoma of the esophagus, with a response rate of approximately 20% in previously untreated patients [14, 15]. For squamous cell carcinoma, a phase II trial of docetaxel at a dose of 70 mg/m^2 administered every 3 weeks was conducted. The majority of patients (94%) had squamous cell carcinoma in this trial. The response rate was reported to be 16% for pretreated patients and 36% for untreated patients [16]. However, careful management of infection is needed because grade 3/4 neutropenia (88%) and febrile neutropenia (18%) were observed in this trial.

15.2.5 Vinca Alkaloids

15.2.5.1 Vindesine

The vinca alkaloid vindesine was evaluated in several phase II trials; it demonstrated reproducible antitumor activity, with a response rate of 20% in cases of squamous cell carcinoma [17–19].

15.2.5.2 Vinorelbine

Vinorelbine, which has less neurotoxicity compared with vincristine and vindesine, was evaluated in patients with ESCC in a phase II trial by the European Organization for Research and Treatment of Cancer. Vinorelbine was administered weekly as a 25 mg/m^2 short intravenous infusion. Response rates of 20% and 6% were observed in untreated patients and pretreated patients, respectively [20].

15.2.6 Topoisomerase Inhibitors

There have been reports on the use of topoisomerase inhibitors for the treatment of ESCC.

15.2.6.1 Etoposide

Etoposide, an inhibitor of type II topoisomerase, demonstrated a response rate of 19% in one trial [21]. In contrast, other trials showed response rates of less than 5% [29, 30].

15.2.6.2 Irinotecan

Irinotecan, a type I topoisomerase inhibitor, has shown modest activity in 10 previously treated patients with ESCC, with a 10% response rate [22].

15.2.7 Others

Other drugs have been tested for ESCC as single agents, and they have demonstrated antitumor activity, with response rates of 0–42%; these include methotrexate [4], ifosfamide [23], gemcitabine [24], mitomycin-C [26], and doxorubicin [4].

15.3 Combination Chemotherapy

Because of the limited activity of single-agent chemotherapy, most of the drugs described above have also been tested in combination regimens. Another randomized trial in 24 patients with esophageal cancer, including 19 patients with squamous cell cancer, also failed to show a meaningful survival benefit with cyclophosphamide and doxorubicin combination therapy. Although these randomized trials did not show a survival benefit with combination therapy, combination regimens with 5-FU, CDDP, and newer agents have been used for the treatment of ESCC (Table 15.2).

15.3.1 Combination with Platinum Agents

15.3.1.1 CDDP and Fluoropyrimidine

CDDP-based combinations appear to be the most studied regimen and demonstrate the most favorable response activity. The combination of 5-FU and CDDP is the most frequently used regimen, but the schedules vary. Although a randomized trial did not showed benefit with combination therapy with 5-FU and CDDP than outcomes with CDDP monotherapy [7], CDDP (80–100 mg/m^2 on day 1) and 5-FU (800–1000 mg/m^2/day continuous infusion for 4–5 days) repeated every 3–4 weeks has been the standard regimen for the treatment of patients with ESCC for 2 decades. Other trials with smaller numbers of patients and different treatment schedules showed response rates of 30–35% and median survival times of 5.5–12.0 months [7, 31–35]. Phase II with 60 mg/m^2 CDDP intravenously on day 1 and 1250 mg/m^2 capecitabine orally twice daily on days 1–14, repeated every 3 weeks showed the overall response rate of 57.8%, and the median survival time of 11.2 months [36].

Table 15.2 Combination chemotherapy for esophageal squamous cancer

Agent	Histology and number of Pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
5-FU + cisplatin	SCC 44	1st	Cisplatin 100 mg/m^2 day 1 5-FU 1000 mg/m^2/day day 1–5/q3wks	35	6.2	7.6	[7]
5-FU + cisplatin	SCC 72	1st	Cisplatin 20 mg/m^2 day 1–5 5-FU 1000 mg/m^2/day day 1–5/q4wks	NA	NA	12	[31]
5-FU + cisplatin	SCC 39	1st	Cisplatin 70 mg/m^2 day 1 5-FU 700 mg/m^2/day day 1–5/q3wks	35.9	Responders 3.5	Responders 9.5	[32]
5-FU + cisplatin	SCC 36	1st	Cisplatin 20 mg/m^2 day 1–5 5-FU 800 mg/m^2/day day 1–5/q4wks	33.3	NA	7.5	[33]
5-FU + cisplatin + leucovorin	SCC 5 AC 5	1st	Cisplatin 50 mg/m^2 day 1 5-FU 2000–2600 mg/m^2/day day 1, 8 Leucovorin 500 mg/m^2/day day 1,8/q2wks	40	NA	10.6	[34]
5-FU + cisplatin	SCC 30	1st	Cisplatin 100 mg/m^2 day 1 5-FU 1000 mg/m^2/day day 1–5/q4wks	13	3.6	5.5	[35]
Capecitabine + cisplatin	SCC 45	1st	Capecitabine 1250 mg/m^2 twice day 1–14 Cisplatin 60 mg/m^2/day day 1/q3wks	57.8	4.7	11.2	[36]
Vinorelbine + cisplatin	SCC 71	1at	Vinorelbine 25 mg/m^2/day day 1, 8 Cisplatin 80 mg/m^2/day day 1/q3wks	33.8	3.6	6.8	[37]

(continued)

Table 15.2 (continued)

Agent	Histology and number of Pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Gemcitabine + cisplatin	SCC12 AC 24	1st	Gemcitabine 800 mg/m^2/day day 2, 9, 16 Cisplatin 50 mg/m^2/day day 1, 8/ q4wks	SCC42 AC 41	NA	9.8	[38]
FOLFOX	SCC56	1st	Oxaliplatin 100 mg/m^2 day 1 Leucovorin 400 mg/m^2 day 1 5-FU 400 mg/m^2 day 1 iv 5-FU 2400 mg/m^2 day 1–2 46 h div	23.2	4.4	7.7	[39]
XELOX	SCC 64	1st or 2nd	Capecitabine 1000 mg/m^2 twice daily day 1–14 Oxaliplatin 120 mg/m^2 day 1/ q3wks	43.8	4.0	10.0	[40]
5-FU + nedaplatin	SCC 42	1st	5-FU 800 mg/m^2/day day 1–5 Nedaplatin 90 mg/m^2 day 1/ q4wks	39.5	2.5	8.8	[41]
Paclitaxel + carboplatin	SCC 13 AC 22	1st	Paclitaxel 200 mg/m^2/day day 1 Carboplatin AUC 5 mg/h/ml/ q3wks	SCC 31 AC 50	3.4	8.8	[42]
Paclitaxel + cisplatin	SCC30 AC33	1at	Paclitaxel 100–200 mg/m^2/ day day 1 Cisplatin 60 mg/m^2 day 1/q2wks	SCC 48 AC 59	NA	NA	[43]
Paclitaxel + cisplatin	SCC 14 AC 6		Paclitaxel 90 mg/m^2/day day 1 Cisplatin 50 mg/m^2 day 1/q2wks	SCC 50 AC 17	NA	7	[44]
Paclitaxel + cisplatin	SCC 39	1st	Paclitaxel 175 mg/m^2/day day 1 Cisplatin 75 mg/m^2 day 1/q3wks	48.5	7	13	[45]
Nab-paclitaxel + cisplatin	SCC 33	1st	Nab-paclitaxel 250 mg/m^2/ day day 1 Cisplatin 75 mg/m^2 day 1/q3wks	60.6	6.2	15.5	[46]

Paclitaxel + nedaplatin	SCC 36 AC 3	1st	Paclitaxel 175 mg/m^2/day day 1 Nedaplatin 80 mg/m^2 day 1/ q3wks	SCC 44.5 AC 33.3	6.1	10.3	[47]
Paclitaxel + nedaplatin	SCC 46 AC 2	1st	Paclitaxel 175 mg/m^2/day day 1 Nedaplatin 80 mg/m^2 day 1/ q3wks	41.7	6.1	11.5	[48]
Paclitaxel + nedaplatin	SCC 39	1st	Paclitaxel 175 mg/m^2/day day 1 Nedaplatin 80 mg/m^2 day 1/ q3wks	46.1	7.1	12.4	[49]
Capecitabine + paclitaxel	SCC 32	1st or 2nd	Capecitabine 900 mg/m^2 twice daily day 1–14 Paclitaxel 80 mg/m^2/day day 1, 8/ q3wks	56.3	5.2	11.7	[50]
Docetaxel + cisplatin	SCC 38	2nd	Docetaxel 70 mg/m^2/day day 1 Cisplatin 75 mg/m^2 day 1/q3wks	34.2	4.5	7.4	[51]
Docetaxel + nedaplatin	SCC 12	2nd	Docetaxel 30–40 mg/m^2/day day 1, 15 Nedaplatin 70–90 mg/m^2 day 1/ q4wks	25	NA	NA	[52]
Docetaxel + nedaplatin	SCC 48	2nd	Docetaxel 30 mg/m^2/day day 1 Nedaplatin 50 mg/m^2 day 1/ q2wks	27.1	3.1	5.9	[53]
Docetaxel + nedaplatin	SCC 12	2nd	Docetaxel 50 mg/m^2/day day 1, 8 Nedaplatin 50 mg/m^2 day 8/ q3wks	0	2.0	7.8	[54]

(continued)

Table 15.2 (continued)

Agent	Histology and number of Pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Docetaxel + nedaplatin	SCC 9	2nd	Docetaxel 50-60 mg/m^2/day day 1 Nedaplatin 70 mg/m^2 day 1/q4wks	22	2.1	9.5	[55]
Paclitaxel + 5-FU + cisplatin	SCC 31 AC 30	1st	Paclitaxel 175 mg/m^2/day day 1 5-FU 750–1000 mg/m^2 daily Cisplatin 20 mg/m^2 weekly/q5wks	SCC 50 AC 46	5.7	10.8	[56]
Docetaxel + 5-FU + cisplatin	SCC 39	1st	Docetaxel 50 mg/m^2/day day 1 5-FU 700 mg/m^2/day day 1–5 Cisplatin 70 mg/m^2 day 1/q3wks	66.6	7.0	13.0	[57]
Docetaxel + 5-FU + cisplatin	SCC 18	1st	Docetaxel 30–40 mg/m^2/day day 1 5-FU 400 mg/m^2/day day 1–5 Cisplatin 40 mg/m^2 day 1/q2wks	88.9	NA	NA	[58]
Docetaxel + 5-FU + cisplatin	SCC 30	1st	Docetaxel 60 mg/m^2/day day 1 5-FU 800 mg/m^2/day day 1–5 Cisplatin 60 mg/m^2 day 1/q3–4wks	72	NA	8.9	[59]
Docetaxel + 5-FU + cisplatin	SCC 40	1st	Docetaxel 70 mg/m^2/day day 1 5-FU 700 mg/m^2/day day 1–5 Cisplatin 70 mg/m^2 day 1/q3wks	72.5	14	1-year 74.6	[60]

Docetaxel + 5-FU + cisplatin	SCC 29	1st	Docetaxel 50 mg/m^2/day day 1 5-FU 700 mg/m^2/day day 1–5 Cisplatin 70 mg/m^2 day 1/q3wks	34.5	2.8	10.4	[61]
Docetaxel + 5-FU + cisplatin	SCC 55	1st	Docetaxel 30 mg/m^2/day day 1, 15 5-FU 800 mg/m^2/day day 1–5 Cisplatin 80 mg/m^2 day 1/q4wk	62	5.8	11.1	[62]
Docetaxel + 5-FU + nedaplatin	SCC 43	1st	Docetaxel 75 mg/m^2/day day 1 5-FU 375 mg/m^2/day day 1 5-FU 2600 mg/m^2/day 1–2 46 h div Nedaplatin 100 mg/m^2 day 1/q3wks	62.8	6.6	10.2	[63]
Doxorubicin + 5-FU + cisplatin	SCC 41	1st	Doxorubicin 30 mg/m^2/day day 1 5-FU 700 mg/m^2/day day 1–5 Cisplatin 14 mg/m^2/day day 1–5/q4wks	43.9	5.0	7.6	[64]

Pts patients, *PFS* progression-free survival, *MST* median survival time, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *NA* not available, *wks* weeks, *5-FU* 5-fluorouracil

15.3.1.2 CDDP and Vinorelbine

The combination of CDDP with vinorelbine showed confirmed partial response of 33.8%, and the median survival time of 6.8 months [37].

15.3.1.3 CDDP and Gemcitabine

CDDP (50 mg/m^2; days 1 and 8) followed by gemcitabine (800 mg/m^2; days 2, 9, and 16) was evaluated with 36 untreated patients of esophageal adenocarcinoma (67%) and squamous cell carcinoma (33%), and the response rates for all patients and patients with squamous cell cancer were 41% and 42%, respectively [38].

15.3.1.4 Oxaliplatin and Fluoropyrimidine

Oxaliplatin has been used in combination with 5-FU and leucovorin primarily for colorectal cancer, as the FOLFOX regimen. A response rate of 23.2% and overall survival of 7.7 months was reported in a phase II trial [39, 65]. Capecitabine combined with oxaliplatin (XELOX) was evaluated in a phase II trial with a schedule of 120 mg/m^2 oxaliplatin administered intravenously on day 1 and 1000 mg/m^2 capecitabine administered orally twice daily on days 1–14. Among 64 patients with ESCC, the overall response rate was 43.8% and the median survival time was 10 months [40].

15.3.1.5 Nedaplatin and Fluoropyrimidine

Nedaplatin was also evaluated in combination with 5-FU. JCOG9905-DI, a phase II trial with 42 patients with metastatic ESCC, showed a 39.5% response rate and an 8.8-month median survival time [41].

15.3.2 Combination with Taxanes

15.3.2.1 Paclitaxel and Platinum

As a single agent, paclitaxel is the most active compound against esophageal cancer. Combination regimens have also been evaluated in many trials. Paclitaxel and carboplatin that have been used for many cancers such as lung, ovary, and unknown primary cancers, have been reported to be effective for ESCC. Among 35 patients, an objective response was observed in 43%, and the median survival time was 8 months [42]. A prospective trials which evaluate paclitaxel and CDDP combination therapy with squamous cell cancer reported a response rate of 40.0–57.8% and a median survival time of 7.0–13.0 months [43–45]. Nab-paclitaxel is a novel, solvent-free paclitaxel that uses albumin to deliver paclitaxel, thus avoiding the need for solvents such as polyoxyethylated castor oil and ethanol. Although only 33 patients with ESCC were evaluated, a higher response rate (60.6%) and longer survival time (15.5 months) were reported with the combination of nab-paclitaxel and CDDP [46]. Another platinum combination of nedaplatin and paclitaxel was reported to have response rates of 40–46.1% and a median survival of 10.3–12.4 months [47–49].

15.3.2.2 Paclitaxel and Fluoropyrimidine

The combination of paclitaxel and capecitabine, an oral fluoropyrimidine, was reported that 9 (75%) patients among 32 ESCC patients achieved an objective response, and the median survival time was 14.5 months as the first-line treatment, and 9 (45%) patients achieved an objective response, and the median survival time was 8.5 months as the second-line treatment [50].

15.3.2.3 Docetaxel and CDDP

A phase II trial that included 35 patients with ESCC who were previously treated with 5-FU and CDDP used docetaxel (70 mg/m^2) and CDDP (75 mg/m^2) on day 1, repeated every 3 weeks. The overall response rate was 34.2%, with a 2.6% complete response rate. Progression-free and overall survival times were 4.5 months and 7.4 months, respectively [51]. Many small studies have evaluated nedaplatin and docetaxel combination regimens as second-line treatment in various doses and schedules. The response rates were 0–27.1%, and progression-free and overall survival times were reported to be approximately 2 months and 7 months, respectively [52–55, 66].

15.3.3 Triplet Combinations

15.3.3.1 5-FU, CDDP, and Paclitaxel

Triplet combination regimens have shown relatively higher response rates compared to doublet regimens. The triplet combination of paclitaxel combined with CDDP and 5-FU has been evaluated as first-line therapy in 61 patients with advanced esophageal carcinoma, including 31 patients with ESCC. Although severe stomatitis and neutropenia were seen, the response rate was 54% in patients with squamous cell cancer, with a 20% complete response rate [56].

15.3.3.2 5-FU, CDDP, and Docetaxel

The combination of 5-FU, CDDP, and docetaxel has shown response rates of 44.3–88.9% and median survival times of 8.9–14 months [57–62]. The most common serious adverse events with this regimen are neutropenia and febrile neutropenia. Neutropenia was improved without decreasing efficacy by separating the administration of docetaxel [62]. From the result of JCOG0807, biweekly docetaxel in combination with 5-FU and cisplatin showed a response rate of 62% and an overall survival of 11.1 months. Grade 3–4 neutropenia and febrile neutropenia were reduced to 25.5% and 0% by separated administration of docetaxel. The phase III trial named JCOG1314 which compared biweekly DCF and CF regimen for the ESCC patients as the first-line chemotherapy has been conducted [67]. Nedaplatin may sometimes be used as a substitute for CDDP in patients with renal or cardiac dysfunction. Among 43 patients, including 13 patients with adenocarcinoma, the combination of 5-FU, nedaplatin, and docetaxel resulted in a 62.78% response rate and a median survival time of 10.2 months [63].

15.3.3.3 5-FU, CDDP, and Doxorubicin

Another triplet combination of 5-FU, CDDP, and doxorubicin, which has been used in gastric adenocarcinoma, was as ECF regimen also evaluated in patients with ESCC. Doxorubicin was administered on day 1 at 30 mg/m^2; CDDP, on days 1–5 at 14 mg/m^2; and 5-FU, on days 1–5 at 700 mg/m^2. Among 41 patients with ESCC, the response rate was 43.9% and the median survival time was 10.1 months [64].

15.4 Chemoradiotherapy

The role of chemoradiotherapy (CRT) varies. CRT has proven effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with CDDP, 5-FU, and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T13N01M0 esophageal cancer. The final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the radiation-alone arm [68]. Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment (Table 15.3).

15.4.1 Definitive Chemoradiotherapy for Resectable Esophageal Cancer

15.4.1.1 Chemoradiotherapy with CDDP and 5-FU

CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T13NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a complete response rate of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery [78]. A phase II trial (JCOG9708) was conducted in Japan for stage I esophageal cancer. Among 73 patients, 63 (87.5%) achieved a complete response, and the 5-year survival rate was 75.5% [70]. Residual (12.5%) or recurrent (41%) disease was observed, but curative resection was achieved in most of these cases via endoscopy or surgery. Based on the results of JCOG0502, the parallel-group controlled trial of esophagectomy versus CRT in patients with stage I ESCC, the 5-year survival rate was 86.5% for esophagectomy arm and 85.5% for CRT arm. Though this comparison was not randomized, the adjusted hazard ratio was 1.052 (95% CI: 0.674–1.640) [71]. CRT would be considered as one of the standard care for stage I ESCC.

JCOG9906, a phase II study of CRT for stage II/III ESCC, showed promising activity with a complete response rate of 62.2% and a 5-year survival rate of 36.8% [72]. In JCOG9906, radiotherapy was delivered using megavoltage (≥6 MV) X-rays; a total dose of 60 Gy was administered in 30 fractions with 40 Gy of elective lymph node irradiation. Acute toxicities were mild, but there were 4 treatment-related deaths (5.3%) related to late toxicities. Most of these events occurred several years after CRT. Moreover, a high mortality rate of 8–11% was seen in patients who

Table 15.3 Chemoradiotherapy for esophageal squamous cell cancer

Trial name	Stage histology	Regimen	Radiation dose (Gy)	CRR (%)	Survival (%)	Ref.
RTOG85-01	Stage I/II/III SCC, AC	Radiation alone	64	NA	5-year 0	[68]
		5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	50.4	NA	5-year 26	
RTOG95-04	Stage I/II/III SCC, AC	5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	50.4	NA	2-year 31	[69]
		5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	64.8	NA	2-year 40	
JCOG9708	Stage Ib SCC	5-FU 700 mg/m^2 day 1–4, 29–32 Cisplatin 70 mg/m^2 day 1, 29	60	87.5	5-year 75.5	[70]
JCOG0502	Stage Ib SCC	Esophagectomy + two-three field lymph node dissection	–	–	5-year 86.5	[71]
		5-FU 700 mg/m^2 day 1–4, 29–32 Cisplatin 70 mg/m^2 day 1, 29	60		5-year 85.5	
JCOG9906	Stage II/III SCC	5-FU 400 mg/m^2 day 1–5, 8–12, 36–40, 43–47 Cisplatin 40 mg/m^2 day 1, 8, 36, 43	60	62.2	3-year 44.7	[72]
mRTOG	Stage II/III SCC	5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	50.4	70.6	3-year 63.8	[73]
JCOG0909	Stage II/III SCC	5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	50.4	58.5	3-year 74.2	[74]
PRODIGE5	Stage I–IVA SCC, AC	5-FU 1000 mg/m^2 day 1–4, 29–32 Cisplatin 75 mg/m^2 day 1, 29	50	41.3	3-year 26.9	[75]
		Oxaliplatin 85 mg/m^2 day 1, 15, 29 Leucovorin 200 mg/m^2 day 1, 15, 29 Bolus 5-FU 400 mg/m^2 day 1, 15, 29 Infusional 5-FU 1600 mg/m^2 day 1–3, 15–17, 29–31	50	41.0	3-year 19.9	
JCOG9516	Unresectable Local SCC	5-FU 700 mg/m^2 day 1–4, 29–32 Cisplatin 70 mg/m^2 day 1, 29	60	15	2-year 31.5	[76]
KDOG0501	Unresectable Local SCC	5-FU 400 mg/m^2 day 1–5, 15–19, 29–33 Cisplatin 40 mg/m^2 day 1, 15, 29 Docetaxel 20–40 mg/m^2 day 1, 15, 29	61.2	42.1	1-year 63.2	[77]

SCC squamous cell carcinoma, *AC* adenocarcinoma, *NA* not available, *wks* weeks, *5-FU* 5-fluorouracil, *CRR* complete response rate

underwent "salvage" surgery for residual or recurrent disease after completion of CRT [79–81]. The late toxicities and higher mortality rate might be caused by the extended field of irradiation, which corresponds to the dissected area in an extended radical surgery. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT did not result in improved survival and local control as compared to a standard dose (50.4 Gy) due to lower tolerability and higher toxicity in 64.8 Gy arm [69]. A phase II study of CRT for patients with stage II/III ESCC included 2 courses of 5-FU infusion (1000 mg/m^2) on days 1–4 and a 2-h infusion of CDDP (75 mg/m^2) on day 1, with concurrent radiotherapy at a dose of 50.4 Gy was conducted for Japanese patients [73]. Although the radiation dose was reduced, the efficacy was comparable to the previous report, and late toxicities greater than grade 3 were lower than that of previous reports. In the JCOG0909, among the 94 patients with stage II/III ESCC, salvage endoscopic resection, and surgery were performed in 5 (5%) and 25 patients (27%). R0 resection of salvage surgery was achieved in 19 (76%) without any operative mortality [74].

15.4.1.2 Chemoradiotherapy with Carboplatin and Paclitaxel

Other combination regimens with concurrent irradiation have been evaluated. Stomatitis or esophagitis caused by 5-FU may sometimes occur during CRT with 5-FU and CDDP. The combination of paclitaxel and carboplatin has also been used as neoadjuvant CRT or definitive CRT [82, 83]. Although there is no robust evidence, this regimen has shown non-inferior antitumor activity and reduced non-hematologic toxicity [84].

15.4.1.3 Chemoradiotherapy with Oxaliplatin and 5-FU

The combination regimen of 5-FU and oxaliplatin (FOLFOX) was evaluated in PRODIGE5, a phase III study that included 85% of patients with ESCC. FOLFOX with radiation therapy did not show superiority compared to 5-FU and CDDP combination CRT, but a lower frequency of renal toxicity and treatment-related death was observed in the FOLFOX radiation arm [75]. Despite the increased incidence of peripheral neuropathy, the FOLFOX radiation regimen is considered as a standard regimen for ESCC because of its convenience.

15.4.2 Chemoradiotherapy for Unresectable Locally Advanced Esophageal Cancer

15.4.2.1 Chemoradiotherapy with CDDP and 5-FU

For patients with local but unresectable lesions, CRT is the only treatment modality with a potentially curative intent. From the results of prospective trial, 15–33% of complete response rate and approximately 20% of 3-year survival rate was reported in the patients with clinical T4 and/or M1 only in cervical lymph node who received CDDP/5-FU with concurrent 60-Gy irradiation [76, 85, 86].

15.4.2.2 Chemoradiotherapy with Triplet of CDDP, 5-FU, and Docetaxel

The triplet combination of 5-FU, CDDP, and docetaxel which consisted of 400 mg/m^2 5-FU on days 1–5, 40 mg/m^2 CDDP on day 1, and 20–40 mg/m^2 docetaxel on day 1 repeated every 2 weeks, with concurrent irradiation of 61.2 Gy for T4 ESCC was conducted as a phase I study [77]. The overall response rate was 89.5%, including a complete response rate of 42.1%. Docetaxel, CDDP, and 5-FU with radiation showed promising efficacy, but a relatively larger number of severe adverse events, for example, esophagitis and febrile neutropenia, are critical for practical use.

15.4.2.3 Induction Chemotherapy Followed by Definitive Chemoradiotherapy

Fistula formation between the esophagus and the neighboring structures such as the aorta or the airway is highly associated with death and termination of treatment. Esophageal fistulas were observed in 22% of patients who enrolled in JCOG0303 trial, which related to poor survival [87]. Induction chemotherapy with DCF before CRT may reduce the risk of fistula formation even in T4 disease. A phase II study of induction DCF followed by CRT, revealed no fistula formation among 48 ESCC patients with T4 and/or unresectable supraclavicular lymph node metastasis. Conversion surgery was performed in 41.7% of patients and R0 resection was achieved in 39.6% of patients [88]. Phase III trial that compared CRT with induction DCF followed by surgery or CRT has started [89].

15.5 Chemotherapy or Chemoradiotherapy with Targeted Agents

Since the 2000s, many targeted agents have been approved for the treatment of lung, colorectal, breast, and other cancers. Results from preclinical or translational studies may help identify optimal targets related to cancer invasion, proliferation, and oncogenesis. Recently, many molecular targets have been evaluated for clinical use on the basis of the genetic findings of ESCC (Table 15.4).

15.5.1 Antihuman Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor (EGFR) is one of the therapeutic targets of ESCC. High levels of EGFR protein expression have been detected in 50–70% of ESCC cases via immunohistochemical analysis, and gene amplification of *EGFR* has been observed in 7–31% of ESCC cases [95–97]. Overexpression of EGFR may correlate to invasion and poor prognosis [98]. Rare mutations in *EGFR* and *KRAS* have also been reported [99, 100].

Table 15.4 Targeted agents for esophageal squamous cell cancer

Agent	Histology and number of pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Gefitinib	SCC 27 AC 9	2nd	Gefitinib 500 mg/day	2.8	2	5.5	[90]
Erlotinib	SCC 13 AC 17	2nd	Erlotinib 150 mg/day	SCC 15 AC 0	SCC 3.3 AC 1.6	SCC 8.2 AC 11.2	[91]
Gefitinib	SCC 107 AC 340	2nd	Placebo	0.4	1.17	3.60	[92]
			Gefitinib 500 mg/day	3.1	1.60	3.73	
Cetuximab	SCC 30	1st	5-FU 1000 mg/m^2 day 1–5 Cisplatin 100 mg/m^2 day 1/q4wks	30%	3.9	5.5	[35]
	SCC 32		5-FU 1000 mg/m^2 day 1–5 Cisplatin 100 mg/m^2 day 1/q4wks Cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2)	34%	5.9	9.5	
Cetuximab SCOPE1	SCC 96 AC 32	cT1–4 N0-1 M0 1st	Capecitabine 625 mg/m^2 twice daily day 1–84 Cisplatin 60 mg/m^2 day 1, 22, 43, 64 Radiation 50 Gy	NA	21.6	25.4	[93]
	SCC 92 AC 33		Capecitabine 625 mg/m^2 twice daily day 1–84 Cisplatin 60 mg/m^2 day 1, 22, 43, 64 Radiation 50 Gy Cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2)	NA	15.9	22.1	

Table 15.4 (continued)

Agent	Histology and number of pts.	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Cetuximab RTOG0436	SCC 59 AC 79	cT1N1M0 cT2-4NanyM0 cTanyNanyM1a 1st	Paclitaxel 25 mg/m^2 day 1, 8, 15, 22, 29, 36 Cisplatin 50 mg/m^2 day 1, 8, 15, 22, 29, 36 Radiation 50.4 Gy	CRR SCC 64 AC 54	NA	2-year survival SCC 43% AC 41%	[94]
	SCC 54 AC 74		Paclitaxel 25 mg/m^2 day 1, 8, 15, 22, 29, 36 Cisplatin 50 mg/m^2 day 1, 8, 15, 22, 29, 36 Radiation 50.4 Gy Cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2)	CRR SCC 59 AC 53	NA	2-year survival SCC 46% AC 43%	

Pts patients, *PFS* progression free survival, *MST* median survival time, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *NA* not available, *wks* weeks, *5-FU* 5-fluorouracil, *CRR* complete response rate

15.5.1.1 Gefitinib and Erlotinib

Two types of EGFR inhibitory therapy, an antibody and tyrosine kinase inhibitors (TKI), were evaluated in patients with ESCC. Gefitinib, an orally active EGFR TKI, showed 2.8% of partial response and 27.8% of stable disease among ESCC patients. Progression-free and overall survival times were 2 and 5.5 months, respectively [90]. Erlotinib, another oral EGFR TKI, showed 15% of partial response and 13.3% of stable disease in ESCC patients. The median time to progression was 3.3 months [101]. No correlation of the EGFR status and the degree of expression with erlotinib efficacy could be established, possibly because of the small number of patients. A large phase III trial that compared the effect of gefitinib alone to placebo in patients with esophageal cancer by considering disease progression following standard chemotherapy was conducted in England. Totally, there were no significant differences between two groups, indicated gefitinib does not work for ESCC. Although the subgroup of patients with ESCC showed a trend of better progression-free survival, this was not statistically significant [92]. Totally, the efficacy of EGFR TKIs is modest and limited to ESCC. The patients with copy number gain of EGFR were reported to have benefited from EGF TKI by TRANS-COS study [101].

15.5.1.2 Anti-EGFR Antibody

Cetuximab, an anti-EGFR monoclonal chimeric antibody, was evaluated for the treatment of metastatic ESCC in combination with CDDP and 5-FU as the first-line treatment. From the result of randomized phase II trial compared daily 5-FU and CDDP with or without 250 mg/m^2 cetuximab administered weekly for metastatic ESCC as first-line treatment, there was no adding effect of cetuximab significantly, though a trend toward longer progression-free survival (5.9 months vs. 3.9 months) and overall survival (9.5 months vs. 5.5 months) was observed in the cetuximab arm [35]. The SCOPE1 trial was a phase II/III trial that compared capecitabine and CDDP with radiotherapy, with or without cetuximab. Overall survival was significantly worse in the CRT plus cetuximab group than in the CRT only group (hazard ratio = 1.53; $p = 0.035$) [93] due to toxicities in cetuximab group. In the RTOG0436 phase III trial weekly concurrent paclitaxel and CDDP plus radiotherapy at a dose of 50.4 Gy with cetuximab was compared to which without cetuximab. The superiority of cetuximab group was not shown with the 1- and 2-year survival rates of 64% and 44% in the cetuximab group and 65% and 42% in the non-cetuximab group, respectively. These tendencies were the same among patients in both histologic groups, SCC and AC [94].

Panitumumab is a fully human immunoglobulin (IgG) 2 monoclonal antibody targeting EGFR. Moehler et al. reported the results of a phase 3 trial (POWER) comparing CF versus CF plus panitumumab as the first-line chemotherapy in patients with ESCC [102]. The trial was terminated because of potential safety concerns with regard to the addition of panitumumab. Treatment-related deaths occurred more frequently in the CF plus panitumumab group (23.6% versus 4.3%, $p = 0.0012$). No improvement of OS was observed in the CF plus panitumumab group (median OS: 9.4 months in the CF plus panitumumab group versus 10.2 months in the CF group, HR = 1.17; $p = 0.43$).

15.5.1.3 Other Antihuman Epidermal Growth Factor Receptor Inhibitors

Sym004 is a 1:1 mixture of two antibodies targeting nonoverlapping epitopes of the epidermal growth factor receptor that antagonizes ligand binding and induces receptor downregulation, and have greater growth inhibition than cetuximab in the preclinical model. From the result of expansion cohort of Sym004 phase I trial, 16.7% of 30 patients achieved objective response and disease control rate was 56.7% for refractory ESCC patients [103]. The incidence of grade 3/4 dermatitis acneiform was 23.5% in the total population, which is comparable to cetuximab.

Nimotuzumab, a humanized antibody directed against epidermal growth factor receptor, evaluated adding effect with concurrent CRT for locally advanced ESCC patients. Nimotuzumab is less likely to induce skin toxicities because nimotuzumab has a relatively low affinity and bivalent binding is required for stable attachment of nimotuzumab to cellular surface. Randomized phase II named NICE trial showed a tendency for survival benefit of nimotuzumab with CRT arm with MST of 15.9 months compared to CRT arm with MST of 11.5 months, and HR for OS was 0.68 (95% CI; 0.44–1.07) [104]. Safety of 5-FU, CDDP and Nimotuzumab with radiation was confirmed in Japanese patients [105].

15.5.2 Immune-Checkpoint Inhibitors

Immune-checkpoint inhibitors became the key drug for most cancer types, including esophageal, lung, gastric, renal, and other cancer. Inhibitory immune-checkpoint molecules (e.g., programmed cell death ligand 1 [PD-L1], cytotoxic T lymphocyte-associated antigen 4 [CTLA-4], lymphocyte activation gene-3 [LAG-3]), and stimulatory immune-checkpoint molecules (e.g., CD40L, OX40, inducible T-cell costimulatory [ICOS]) play a role in maintaining immunological homeostasis. In ESCC tumors, PD-L1 expression is observed in 18.4%–82.8%, associated with poor survival [106] (Table 15.5).

15.5.2.1 Nivolumab

Nivolumab, a human IgG4 monoclonal antibody against PD-1 was approved for patients with non-small cell lung cancer, melanoma, renal cell carcinoma, etc. As for ESCC, a single-arm, multicenter phase 2 trial (ONO-4538-07) was undertaken to assess the activity of nivolumab to ESCC patients who failed to fluoropyrimidine-, platinum-, and taxane-based chemotherapies without patient selection according to tumor PD-L1 expression [107]. Nivolumab showed a promising antitumor efficacy with an objective response rate of 17%. As same as other cancer types, the durable response in some patients cause discrepancy between the longer OS (10.8 m) and the shorter median PFS (1.5 m). A phase 3 trial (ONO-4538-24/CA209-473_ATTRACTION-3 trial) which compares nivolumab versus docetaxel or paclitaxel in patients with ESCC refractory to fluoropyrimidine and platinum (NCT02569242) was conducted as a global study. It was reported that nivolumab demonstrated a significant improvement in OS compared to chemotherapy in the final analysis [108].

15.5.2.2 Pembrolizumab

Pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1, also demonstrated a promising efficacy in esophageal cancer in the multicohort phase 1b trial (KEYNOTE-028) in patients with PD-L1 positive (with ≥1% of tumor or inflammatory cells or positive stromal band) advanced solid tumors [111]. In the esophageal cancer cohort, 78% of 23 patients had ESCC, and 87% of patients had received at least two previous chemotherapeutic regimens. The objective response rate was 30% (28% in patients with ESCC). Additionally, a phase 2 trial (KEYNOTE-180) was conducted in order to evaluate the efficacy of pembrolizumab according to histology and PD-L1 positivity in heavily treated patients with SCC or AC of the esophagus or the EGJ [109]. PD-L1 positivity was determined by using the combined positive score (CPS) which was defined as the number of PD-L1–staining cells (tumor cells, macrophages, lymphocytes). In total, 121 patients were enrolled, and a meaningful antitumor activity of pembrolizumab in heavily treated esophageal cancer regardless of histology or PD-L1 expression. A phase 3 trial (KEYNOTE-181) was conducted to compare pembrolizumab versus the investigator's choice chemotherapy (paclitaxel, docetaxel, or irinotecan) as second-line treatment in patients with esophageal and EGJ cancer, including ESCC [110]. There

Table 15.5 Immune-checkpoint inhibitors for esophageal squamous cell cancer

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	Ref.
Nivolumab	SCC 65	3rd	Nivolumab 3 mg/kg/q2wks	17.2	1.5	10.78	[107]
Nivolumab	SCC419	2nd	Nivolumab 3 mg/kg/q2wks	19	1.7	10.9	[108]
			Paclitaxel or Docetaxel	22	3.4	8.4	
Pembrolizumab	SCC 63 AC 58	3rd	Pembrolizumab 200 mg/q3wks	SCC 14 AC 5	SCC 2.1 AC 1.9	SCC 6.8 AC 3.9	[109]
Pembrolizumab	CPS ≥ 10,107 CPS < 10,201	2nd	Pembrolizumab 200 mg/q3wks	CPS ≥ 10 23	CPS ≥ 10 2.6	CPS ≥ 10 9.3	[110]
	CPS ≥ 10,115 CPS < 10,196		Paclitaxel 80–100 mg/m^2 day 1, 8, 15/q4wks Docetaxel 75 mg/m^2/q3wks Irinotecan 180 mg/m^2/q2wks	CPS ≥ 10 7	CPS ≥ 10 3.0	CPS ≥ 10 6.7	

CPS Combined Positive Score of PD-L1

were three primary endpoints including OS in patients with PD-L1–positive tumor (CPS ≥ 10), patients with ESCC, and in intent to treat cohort. The superiority of pembrolizumab over chemotherapy in terms of OS was demonstrated in patients with PD-L1–positive tumors. The median OS in the pembrolizumab group was 9.3 months compared with 6.7 months in the chemotherapy group (HR = 0.69; $p = 0.0074$), in PD-L1 positive patients. A phase 3 trial (KEYNOTE-590) is comparing CF plus pembrolizumab with CF as first-line chemotherapy in patients with adenocarcinoma of esophageal or EGJ cancer and ESCC (NCT03189719) [112].

15.5.2.3 Combination of Immune-Checkpoint Inhibitors

Dual immune-checkpoint inhibition and the combination of immunotherapy with cytotoxic agents have also been investigated to enhance the efficacy of immunotherapy. In the ESCC cohort in a phase 1b trial (NCT02658214), dose-limiting toxicities (DLTs) for durvalumab (PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody) in combination with CF were evaluated in first-line setting [113]. No DLT occurred for this combined treatment in six patients. Early evidence of antitumor activity was observed; two of the six patients had a confirmed partial response. A phase 3 trial (ONO-4358-50/CheckMate 648) has been initiated to compare nivolumab plus ipilimumab (anti-CTLA-4 antibody) or CF plus nivolumab versus CF as first-line chemotherapy in patients with ESCC (NCT03143153).

15.5.3 Other Potential Molecular Targets

Antiangiogeneses are also a potential therapeutic target. Vascular endothelial growth factor-A expression is seen in 24–93% of ESCC cases [114]. The overexpression of vascular endothelial growth factor isoforms has been shown to correlate significantly with poor prognosis in ESCC [114–116]. Apatinib is an oral multi-kinase inhibitor including antiangiogenetic pathway that showed a survival benefit for a later line of gastric cancer. Phase II trial of apatinib for ESCC showed efficacy with a response rate of 24.2% and a disease control rate of 74.2% [117].

BKM120, an oral pan-class I PI3K inhibitor, showed modest activity for ESCC patients with DCR of 51.2% and PFS of 2.3 months. PI3K pathway activation was observed in patients with good clinical response [118].

15.6 Future Directions

While many aspects regarding ESCC have been reported, there is limited clinical evidence for ESCC treatment options. Comprehensive analysis of ESCC by genomic, immunogenic, proteomic, and others have revealed recently [119]. Biological analysis of ESCC based on robust preclinical data with clinical outcomes may accelerate the development of new drugs, and trans-Asian clinical trial groups, which include biobanks or translational study teams, will result in definitive clinical evidence. International collaboration will be expected.

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Radiation Therapy for Esophageal Squamous Cell Carcinoma

16

Yoshinori Ito

Abstract

Radiotherapy is indicated for the treatment of esophageal cancer both with curative intent and with palliative intent. Concurrent chemoradiotherapy is the standard treatment for patients in good condition who can receive chemotherapy, based on the results of randomized trial compared chemoradiotherapy with radiotherapy alone. For locally advanced unresectable esophageal cancer, definitive chemoradiotherapy is standard therapy with potentially curative intent. And for resectable esophageal cancer, definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus from favorable results of clinical trials. These results are supported by salvage treatment in cases of residual or recurrent disease after chemoradiotherapy. However, high mortality rate of salvage surgery and high incidence of late toxicities after chemoradiotherapy with higher radiation dose are important problems to be solved. Neoadjuvant chemoradiotherapy is the standard treatment for locally advanced esophageal cancer in Western countries, however, it is investigational in Japan. Recently, prophylactic chemoradiotherapy for patients with pT1b or pT1a involving lymphovascular invasion after endoscopic resection could be a treatment option from favorable result of a clinical trial. Combination chemotherapy of new agents and new radiotherapy techniques such as intensity-modulated radiation therapy, proton-beam therapy, and heavy-particle radiotherapy have been evaluated in clinical trials to improve the treatment results including efficacy and toxicity.

Keywords

Esophageal cancer · Radiotherapy · Chemoradiotherapy · Brachytherapy · Treatment planning

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16.1 Indications of Radiotherapy

Although surgery is the principal curative therapy for resectable esophageal cancer, definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus since favorable treatment results were reported from clinical trials [1–5]. And resection of a cervical esophageal cancer would require a laryngoesophagectomy, so definitive chemoradiotherapy is also a treatment option in an attempt to preserve the larynx in addition to the esophagus. For locally advanced unresectable esophageal cancer (T4 cases), definitive chemoradiotherapy is a standard therapy from favorable results [6–8]. Recently, prophylactic chemoradiotherapy for patients with pT1b or pT1a involving lymphovascular invasion after endoscopic resection could be a treatment option from favorable result of clinical trial [9]. And radiotherapy alone is a treatment option since many patients with esophageal cancer are elderly, of poor PS or have metastases at presentation. Radiotherapy is also useful to palliate dysphagia or pain.

16.2 Radiation Therapy Techniques

16.2.1 Simulation

During simulation, the patient lies supine with arms by their sides or with arms above their head in the case of considering to use the lateral or oblique beam arrangements. For cervical esophageal tumor, an immobilization mask should be used to minimize variation in daily setup. Computed tomography (CT)-based planning is recommended. The patient is placed on the CT simulator in the treatment position, and a scan of the entire area of interest with margin is obtained. At minimum, 3–5-mm slices should be used, allowing accurate tumor characterization, as well as improved quality of digitally reconstructed radiographs. The tumor and normal tissue structures are then outlined on each slice on the treatment planning system, enabling a three-dimensional treatment plan to be generated. Four-dimensional (4D) CT scan may be appropriate to assess tumoral motion, facilitating appropriate margin placement on the target volumes.

16.2.2 Treatment Planning

16.2.2.1 Target Volume Delineation

Gross Tumor Volumes (GTV)

The primary tumor in the esophagus is defined as GTVp based on the examinations including barium swallow, upper esophagogastroduodenoscopy (EGD), endoscopic ultrasonography (EUS), and CT scan. The endoscopic diagnosis with iodine staining is essential for detecting the superficial cancer and intraepithelial spread of the advanced cancer. In the treatment of the superficial cancer, endoscopic metal

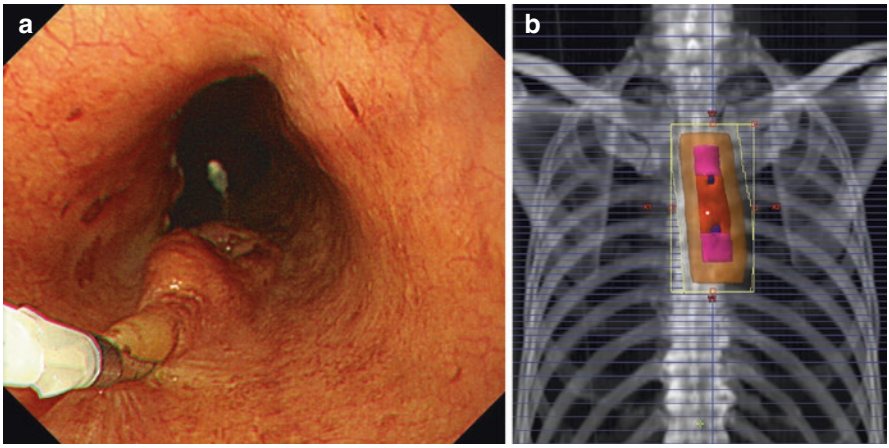


Fig. 16.1 (**a**, **b**) Example 3D-treatment planning for a cT1bN0 middle thoracic esophagus tumor. (**a**) Endoscopic insertion of metal clips in the esophageal wall near the proximal and distal end of the primary tumor. (**b**) Target volume of local radiotherapy planning. Metal clips (blue), GTV of primary tumor (red), CTV of primary tumor (pink); GTV plus 2-cm margin proximally and distally along the length of the esophagus, PTV (orange)

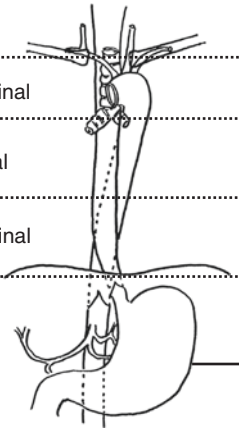
clips are inserted in the esophageal wall near the proximal and distal end of the primary tumor as fiducial markers before radiotherapy treatment planning (Fig. 16.1a). Diagnostic PET/CT has more recently been integrated into radiation treatment planning of esophageal cancer and definition of GTV [10]. The metastatic lymph nodes are defined as GTVn mainly based on the CT scan and palpitation. Similarly, EUS may detect enlarged nodes that need to be included. It is difficult to evaluate the metastatic lymph nodes accurately by the tumor size. In a study from Kyoto University, the optimal size criterion for both CT and MR in the detection of cervical and mediastinal lymph node metastases is 5 mm for short-axis diameter [11].

Clinical Target Volume (CTV)

CTVp is defined as the GTVp with 2–4 cm expansion proximally and distally along the length of the esophagus. The intent is to extend the margin along the length of the esophagus to provide a margin for coverage of the submucosal extension of the tumor. One pathological analysis of 34 surgical specimens of ESCC showed the mean microscopic spread beyond the gross tumor was 10.5 ± 13.5 mm proximally and 10.6 ± 8.1 mm distally and placement of a 3-cm margin proximally and distally on the primary tumor would cover microscopic disease extension in 94% of cases [12].

CTVn is defined as the GTVn with 0–0.5 cm margin in all directions.

The regional lymph nodes are defined as CTVsubclinical (CTVs) for each primary site in the treatment of elective nodal irradiation. Several pathological analyses of surgical specimens of ESCC reported that the rate of positive lymph nodes per number of cases were 47–70% and patterns of involved nodal spread were



	Primary site		
	Upper thoracic tumor	Middle thoracic tumor	Lower thoracic tumor
Cervical	46.3%	29.2%	27.2%
Upper mediastinal	46.3%	35.7%	29.6%
Mid-mediastinal	22.0%	32.7%	39.5%
Lower mediastinal	7.3%	16.1%	35.8%
Abdominal	12.2%	39.9%	74.1%

Fig. 16.2 Location and frequency of nodal involvement (%) by ESCC according to the site of primary site (From Akiyama H, et al. [13])

Table 16.1 Regional lymph nodes defined as CTVs for each primary site

Primary site	Regional lymph nodes
Cervical esophagus	Mid jugular lymph nodes, supraclavicular lymph nodes, superior mediastinal lymph nodes, subcarinal lymph nodes
Upper thoracic esophagus	Supraclavicular lymph nodes, superior mediastinal lymph nodes, subcarinal lymph nodes
Middle thoracic esophagus	Superior mediastinal lymph nodes, middle mediastinal lymph nodes, lower mediastinal lymph nodes, perigastric lymph nodes
Lower thoracic esophagus	Superior mediastinal lymph nodes, middle mediastinal lymph nodes, lower mediastinal lymph nodes, perigastric lymph nodes, celiac lymph nodes

different from each primary site [13–15] (Fig. 16.2). Even if clinical T1bN0 cases, the rate of positive lymph node was 27.0% based on the pathological analysis of surgical specimens of ESCC [16]. Retrospective analysis from Japan showed that elective nodal irradiation was effective for regional lymph node failure [17]. Guidelines 2016 for the treatment of esophageal cancer in Japan show the inclusion of regional lymph nodes in CTVs for each primary site (Table 16.1) (Fig. 16.3a–d). Typically, the regional lymph nodes include bilateral supraclavicular fossae, superior mediastinal, and subcarinal lymph nodes for carcinoma of the cervical esophagus and upper thoracic esophagus (Fig. 16.4a). Mid jugular lymph nodes are also included for carcinoma of the cervical esophagus. And the regional lymph nodes include superior mediastinal, subcarinal, middle mediastinal, lower mediastinal, and perigastric lymph nodes for carcinoma of the middle or lower thoracic esophagus (Fig. 16.4b). Celiac axis lymph nodes are also included for carcinoma of the

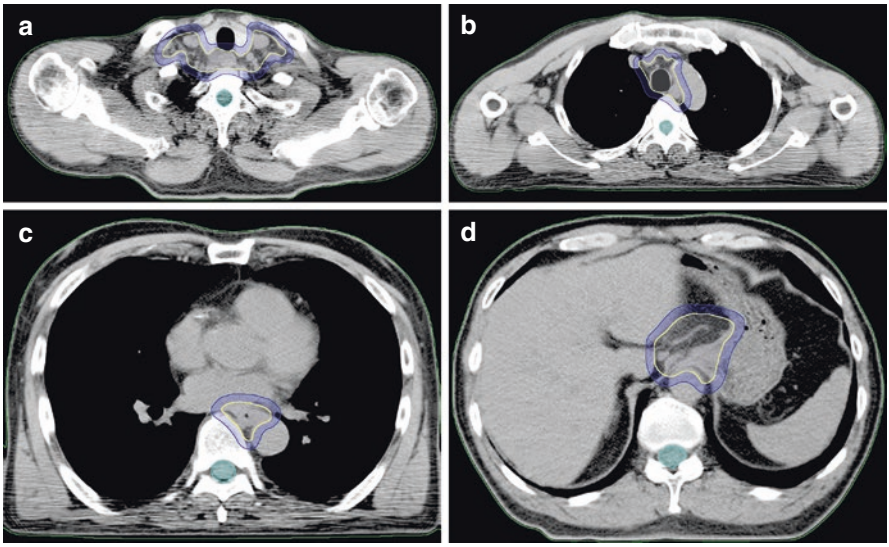


Fig. 16.3 Example of target volume delineation of CTV of the elective nodal region. CTVs (yellow) and PTVs (blue)

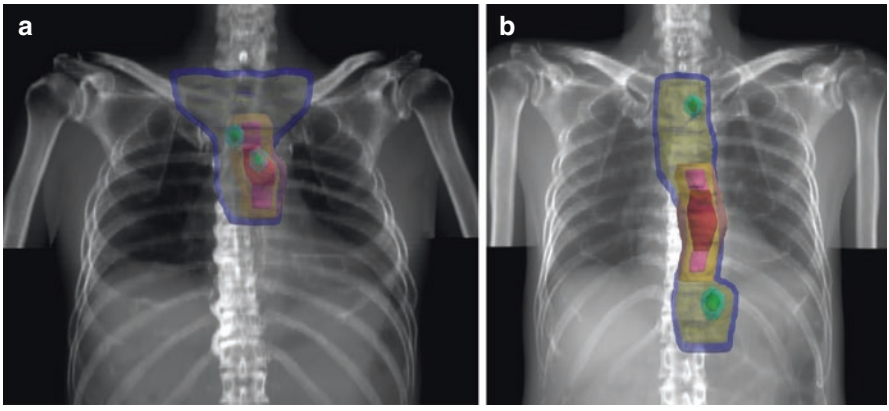


Fig. 16.4 (**a**, **b**) Examples of the target volume with the elective nodal region in the 3D-treatment planning for cT3N1 thoracic esophagus tumor. (**a**) For cancer of the upper thoracic esophagus. (**b**) For cancer of the middle or lower thoracic esophagus. GTV of primary tumor (red), GTV of metastatic lymph nodes (green), CTV of primary tumor (pink), CTV of elective nodal region (yellow), and Initial PTV (blue), boost PTV (orange and cyan)

lower thoracic esophagus. There is no consensus about inclusion of regional lymph nodes in CTVs for each primary site. Although elective nodal irradiation yields to prevent or delay regional node failure, a recent review reported that its impact on survival remains less clear [18].

Planning Target Volume (PTV)

Planning Target Volume (PTV) is defined as Clinical Target Volume (CTV) with 1–2 cm margin in craniocaudal direction and 0.5–1 cm margin in the lateral direction to account for respiratory organ motion and daily setup error. Report of evaluating the respiratory motion of distal esophageal tumor using 4D-CT showed that a radical margin of 0.8 cm and an axial margin of ±1.8 cm would provide tumor motion coverage for 95% of the cases [19].

16.2.2.2 Field Design

In the treatment of target to the primary tumor and involved lymph nodes only, beam arrangement in 3D-CRT uses a multi-field technique such as a three- to six-field arrangement (Fig. 16.1b). By contrast in the treatment including the elective nodal irradiation, anteroposterior (AP)/posteroanterior (PA) fields is used up to 40–45 Gy followed by off-cord boost fields. For cervical esophageal tumor, right anterior oblique (RAO) and left anterior oblique (LAO) with wedged pairs is usually used as off-cord boost fields. For upper, middle, and lower esophageal tumor, RAO and left posterior oblique (LPO) is usually used as off-cord boost fields. At the beginning of initial treatment for a middle or lower thoracic esophagus tumor, a multi-field technique such as a four-field arrangement (AP/PA/RAO/LPO) is recommended considering the cardiac toxicity (Fig. 16.5). However, it is necessary to minimize the volume of the irradiated lung (beam weight; AP/PA >> obliques) as to the lung toxicity. In the case of exist of hot spot such as >110% of the prescribed radiation dose, the field-in-field technique is considered to improve the conformity of the dose distribution. More recently, intensity-modulated radiotherapy (IMRT) has been considered, particularly cervical lesions. IMRT can further improve the conformity of the dose distribution by sparing the adjacent normal strictures such as spinal cord to help meet dose constraints (Fig. 16.6). Diametric comparisons of IMRT versus 3D conformal therapy in cervical esophageal cancer have demonstrated superior target volume coverage and conformality with decreased normal tissue dose [20]. A potential disadvantage of IMRT is the possibility of delivering

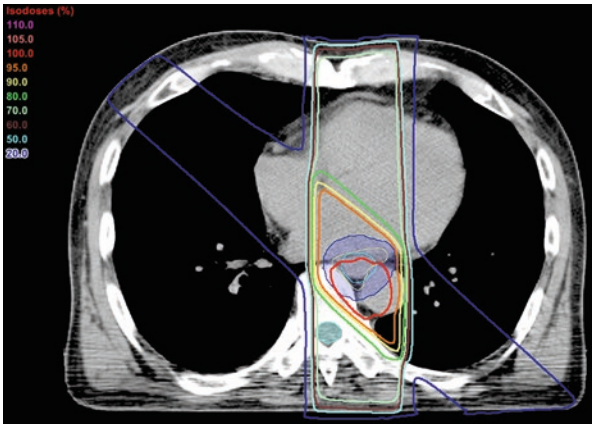


Fig. 16.5 Example of dose distribution treated with a four-field technique for a middle thoracic esophagus tumor (beam weights arrangement of 180 cGy per fraction; anterior 60 cGy, posterior 70 cGy, obliques 25 cGy). Daily heart dose: <80% of the prescribed dose, Daily lung dose: <30% of the prescribed dose

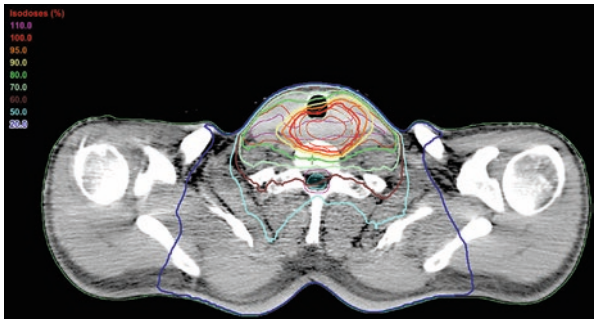


Fig. 16.6 Dose distribution of IMRT plan for a cervical esophagus tumor

low doses of radiation therapy to normal tissue areas. The influence of this on toxicity (low-dose pulmonary irradiation and development of lung toxicity) remains uncertain. Several clinical trials of definitive chemoradiotherapy using IMRT for cervical or thoracic esophageal cancer are now ongoing.

16.2.2.3 Dose and Fractionation

Conventional daily dosing at 1.8–2.0 Gy fraction is standard. In the treatment of radiotherapy alone, 60–70 Gy at 1.8–2 Gy per fraction is standard radiation dose. In the treatment of chemoradiotherapy, based on the result of a randomized trial intergroup (INT) 0123 demonstrated that no significant difference in overall survival and local/regional control between the 50.4 Gy arm and the 64.8 Gy arm among patients (85% SCC) treated with concurrent 5-FU and cisplatin chemotherapy for nonsurgical therapy [21], standard dose of radiotherapy for esophageal cancer is usually 50–50.4 Gy at 1.8–2 Gy per fraction in the definitive setting. Meanwhile, the Pattern of Care Study reported that median total dose of external radiotherapy was 60 Gy for definitive chemoradiotherapy patients in Japan [22]. In the neoadjuvant setting, 40–50.4 Gy at 1.8–2 Gy per fraction is standard radiation dose. And in the prophylactic setting, 41.4 Gy at 1.8 Gy per fraction is used in clinical trial [9].

16.2.2.4 Dose Constraints

In radiotherapy treatment planning of esophageal cancer, normal-tissue tolerance should always be considered. Accurate delineation of adjacent organs, including lungs, spinal cord, heart, kidneys, and liver is important. And it is necessary to evaluate the dose-volume histogram (DVH) analyses for each organ (Fig. 16.7). Max dose of the spinal cord is generally limited to 45 Gy using 1.8 Gy fractions. Several studies have demonstrated that dosimetric parameters derived from DVH are associated with organ toxicity after treatment of esophageal cancer [23–27]. In the treatment of esophageal cancer using a neoadjuvant regimen of 45 Gy with concurrent chemoradiotherapy, a lung V10 (a percentage of lung volume receiving at least 10 Gy) of 40% or greater, and a V15 of 30% or greater, was shown to be predictive of significantly greater pulmonary complications (pneumonia and acute respiratory distress syndrome [ARDS]) [26]. Investigators from the United States reported that the volume of lung spared from doses of 5 Gy or higher (VS5) was the factor most strongly associated with postoperative pulmonary complications

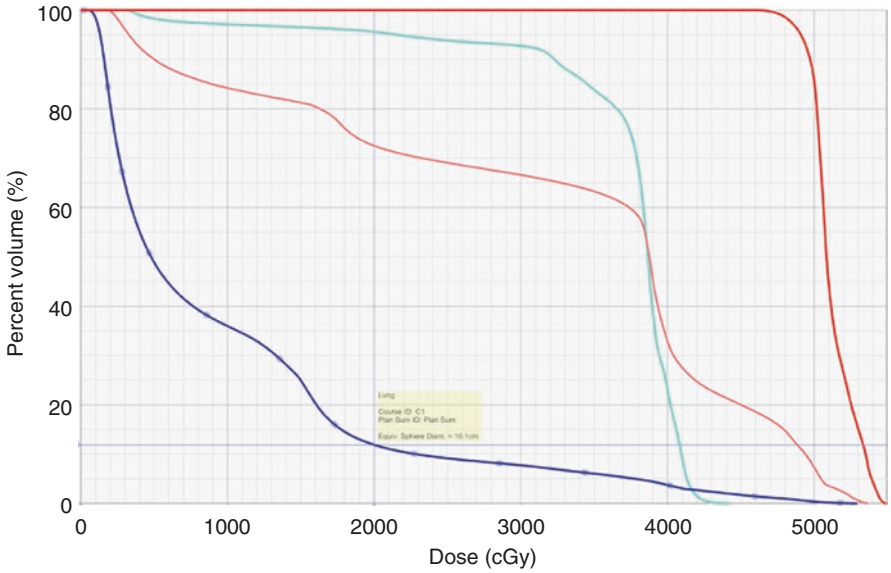


Fig. 16.7 DVH analysis of a four-field technique for a middle thoracic esophagus tumor (50.4 Gy in 28 fraction with elective nodal irradiation of 41.4 Gy). Boost PTV (red), Total lung (blue), Heart (pink), and Spinal cord (cyan)

(pneumonia and ARDS) for esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery [27]. In the treatment of esophageal cancer using definitive regimen of 60 Gy with concurrent chemoradiotherapy, investigators from Japan reported that the optimal V20 threshold to predict symptomatic radiation pneumonitis (grade2) was 30.5% [23]. Konski and colleagues proposed thresholds for symptomatic cardiac toxicities (pericardial effusion, myocardial infarction, and sick sinus syndrome) for whole-heart V20 of 70%, V30 of 65%, and V40 of 60% [25]. Fukada and colleagues reported that mean pericardial doses of 36.5 Gy and V45 of 58% were selected as optimal cutoff values for predicting symptomatic pericardial effusion [24]. For lower esophageal cancers, it is recommended that mean liver dose should be limited to less than 28 Gy, and mean dose of bilateral whole kidneys should be limited to less than 15–18 Gy [28].

16.2.3 Brachytherapy

Brachytherapy involves intraluminal placement of a radioactive source into the esophagus with an intraorally or intranasally inserted applicator and permits treatment of a localized area of the esophagus to high radiation doses with relative sparing of surrounding structures. This technique may be used alone or in combination with external beam radiotherapy with or without chemotherapy. The indication of brachytherapy is the treatment of superficial esophageal cancer for curative intent in

Japan (local control rate: 79–85%) [29–35], on the other hand it is used to relief symptom such as dysphagia for palliative intent in the treatment of advanced esophageal cancer in Western countries [36, 37]. Brachytherapy can be administered by two general methods; Low-dose rate (LDR) brachytherapy, High-dose rate (HDR) brachytherapy. Modern HDR brachytherapy equipment delivers radiation much faster than 12 Gy/h, permitting the delivery of a planned dose within minutes compared with LDR sources, which require many hours or days. As a general rule of HDR brachytherapy, the diameter of the balloon applicator should be 15–20 mm. The whole length of the tumor and 2 cm above and below the lesion are included in the target volume. The reference dose point is set at a depth of 5 mm of the esophageal submucosa (5 mm beyond the wall of the balloon surface). There is no definite consensus about the optimal dose of intraluminal brachytherapy for esophageal cancer. In Japan, 50–60 Gy external beam radiotherapy followed by 8–12 Gy in two-four fractions (3–4 Gy per fraction) HDR brachytherapy is generally used. It was reported that a higher dose per fraction associated with the risk of esophageal ulcer and perforation [29]. Dose of 4 Gy or less per fraction by HDR brachytherapy and dose of 6 Gy or less per fraction by LDR brachytherapy once or twice a week is recommended in Japan [31]. The American brachytherapy society (ABS) recommends an HDR dose of 10 Gy in two fractions, prescribed at 1 cm from the source, to boost 50 Gy EBRT [38]. Figure 16.8 illustrates the dose distribution and 3D-view in the treatment planning of HDR-brachytherapy.

16.3 Treatment Results

16.3.1 Radiotherapy Alone

Radiation therapy alone has been usually delivered when lesions are deemed inoperable because of tumor extent or medical contraindications. In general, patients receiving radiation as a sole treatment modality have a median survival of 6–12 months and 5-year survival of <10%. In a review of 49 early series involving more than 8400 patients (100% SCC) treated with radiation therapy alone, overall survival rates at 1, 2, and 5 years were 18%, 8%, and 6%, respectively [39]. Okawa and colleagues reported 5-year survival rates by stage (100% SCC) [40]. For patients with stage I disease, the 5-year survival rate was 20%; stage II, 10%; stage III, 3%; and stage IV, 0%. Five-year overall survival rate (OS) was 9%. For cervical esophageal lesions treated with radiation alone, the cure rates are comparable with those in patients treated with surgery alone. As a result of clinical trial, Radiation Therapy Oncology Group (RTOG) trial (RTOG8501) comparing combined chemotherapy with 5-FU and cisplatin with radiotherapy (50 Gy) versus radiotherapy alone (64 Gy) showed that 3-year survival with radiotherapy alone was 0% [1–3]. In a prospective trial of radiotherapy alone (66 Gy) for patients older than 80 years old with T1-3N0M0 squamous cell carcinoma of the thoracic esophagus, median survival time and 3-year overall survival rate were 30 months

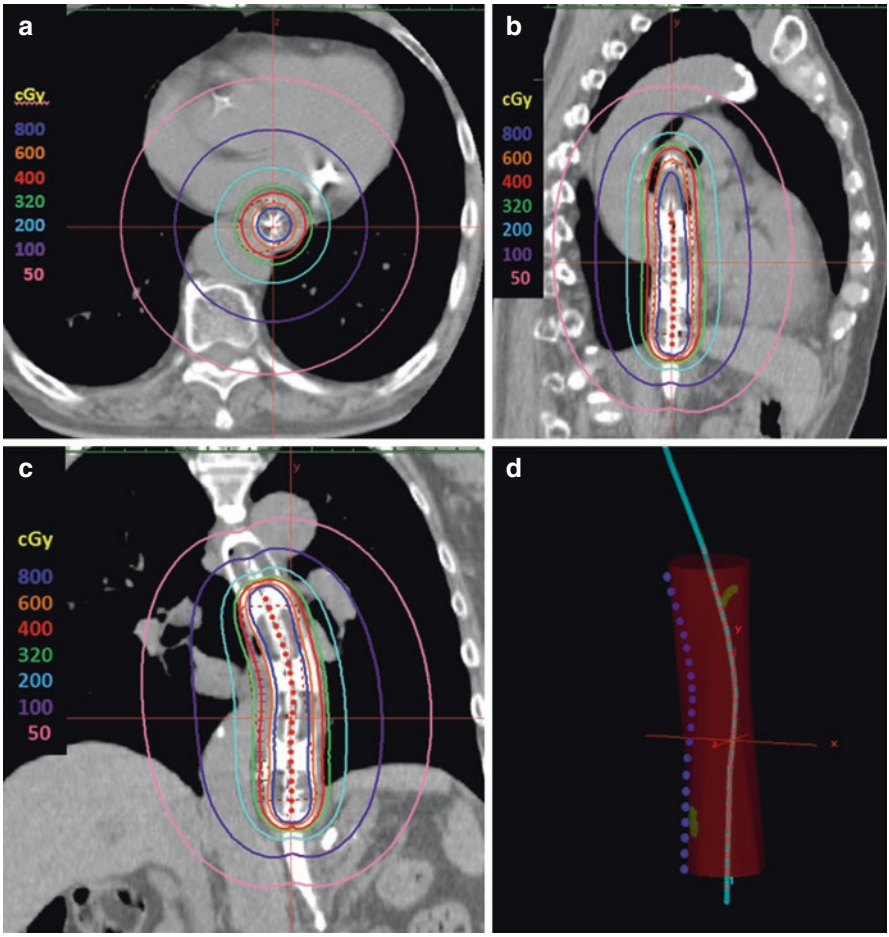


Fig. 16.8 (**a–d**) Dose distribution of intraluminal brachytherapy for a cT1bN0 middle thoracic esophagus tumor. Prescription dose: 400 cGy at a depth of 5 mm of the esophageal submucosa as the reference dose point. (**a**) axial view. (**b**) Sagittal view. (**c**) Coronal view, (**d**) 3D-view. Metal clips (green), High-risk CTV (red): GTV plus 2 cm margin proximally and distally along the length of the esophagus, reference dose point (blue), catheter (cyan), and dwell points (red)

and 39%, respectively [41]. This favorable results were due to patient selection including earlier stage (non-T4N0; 35% T1N0) compared to RTOG8501.

16.3.2 Chemoradiotherapy

The landmark trial establishing the superiority of concurrent chemoradiotherapy to radiation therapy alone was RTOG8501. Herskovic and colleagues reported the results of this randomized trial comparing combined chemotherapy with 5-FU and

cisplatin with radiotherapy (50 Gy) versus radiotherapy alone (64 Gy) for esophageal cancer (88% SCC) [3]. The median survival in patients treated by radiation alone was 8.9 months compared with 12.5 months for those treated with combined therapy, with 2-year survival rate 10% versus 38%; the incidence of local recurrence decreased from 24% to 16%, and the 2-year distant metastasis rate decreased from 26% to 12%. Updated results showed that at 5 years, survival rates were 26% and 0%, respectively, for chemoradiotherapy and radiation therapy alone [1, 2].

16.3.2.1 Chemoradiotherapy for Unresectable Locally Advanced Esophageal Cancer

For locally advanced unresectable esophageal cancer, chemoradiotherapy is standard treatment with potentially curative intent. Results of clinical trials of definitive chemoradiotherapy for T4 tumor is shown in Table 16.2 [6–8, 21, 42–52]. INT0123, a randomized clinical trial compared standard-dose 50.4 Gy to high-dose 64.8 Gy with both concurrent 5-FU and cisplatin chemotherapy for patients with clinical T1-4N0-1M0 esophageal cancer [21]. This study was closed after an interim analysis showed no probability of superiority in the high-dose arm. No significant difference in median survival (18.1 vs. 13 months), 2-year survival (40% vs. 31%), or local-regional failure/persistence of disease (52% vs. 56%) was seen between the standard-dose and high-dose arms. In a single institute phase II trial of chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation for patients with clinical T4 and/or M1 lymph node ESCC, complete response (CR) rate was 33% and median survival time and 3-year survival rate was 9 month and 23%, respectively [8]. Another clinical trials of 5-FU and cisplatin and 60 Gy irradiation for patients including clinical T4 showed that CR rate was 15–33% and 2-year, 3 year survival rates were 27%–46% and 23%–30%, respectively [6, 7, 42–44]. Other combination regimens using new drugs (paclitaxel, docetaxel, oxaliplatin, S-1, capecitabine, cetuximab, and nimotuzumab) with concurrent radiotherapy have been evaluated [46–54]. Recently, another treatment strategy including intensive induction chemotherapy (docetaxel, cisplatin, and 5-FU) have been evaluated [55, 56]. Multidisciplinary treatment in which surgery or chemoradiotherapy was performed after intensive induction chemotherapy has been shown to yield good short-term results with a 1-year overall survival rate of 67.9% [52]. JCOG1510, randomized control trial compared this multidisciplinary treatment to definitive chemoradiotherapy is now ongoing.

16.3.2.2 Chemoradiotherapy for Resectable Esophageal Cancer

Definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus for resectable esophageal cancer. Results of clinical trials of definitive chemoradiotherapy for resectable esophageal cancer is shown in Table 16.3 [1–5, 55–60]. For stage I esophageal cancer, Japan Clinical Oncology Group (JCOG) 9708, a phase II trial of chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation against primary tumor only was conducted (Fig. 16.1b). CR rate was 87.5% and the 5-year overall survival rate was 75.5% [4]. Recently, results of the parallel group controlled trial of esophagectomy versus chemoradiotherapy for stage I (T1b)

Table 16.2 Results of clinical trials of definitive CRT for ESCC including T4

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate (%)	Survival
INT0123 [21] (USA)	T1-4N0-1 (T4: 8%)	86	109 109	FP + 50.4 Gy FP + 64.8 Gy	NR NR	2y: 31% 2y: 40%
Ohtsu [8] (Japan)	T4/M1Lym (T4: 67%)	100	54	FP + 60 Gy	33%	1y: 41% 3y: 23%
JCOG9516 [6] (Japan)	T4/M1lym (T4: 100%)	100	60	FP + 60 Gy	15	2y: 31.5%
Nishimura [7] (Japan)	T4/M1Lym (T4: 100%)	100	28	FP + 60 Gy	32	Stage III; 2y: 27% Stage IV; 1y: 23%
JCOG0303 [42] (Japan)	T4/M1lym (T4: 75%)	100	71 71	FP + 60 Gy Low dose FP + 60 Gy	0[a] 1.4[a]	3y: 30% 3y: 26%
KROSG0101/JROSG021 [43, 44] (Japan)	Stage II–IVA (T4: 44%)	100	46 45	FP + 60 Gy Low dose FP + 60 Gy	NR NR	2y: 46%, 5y: 35% 2y: 44%, 5y: 22%
Shahl [45] (Germany)	T3-4N0-1 (T4: 17%)	100	86 86	FLEP → EP + 60 Gy FLEP → EP + 40 Gy + S	NR NR	3y: 55% 3y: 58%
PRODIGE5/ACCORD17 [46] (France)	Stage I–IVA (T4: NR)	86	133 134	FP + 50 Gy FOLFOX + 50 Gy	43 43	3y: 26.9% 3y: 19.9%
SCOPE1 [47] (UK)	Stage I–III (T4: NR)	73	129 129	CP + 50 Gy CP + Cetuximab + 50 Gy		2y: 56.0% 2y: 41.3%
RTOG0436 [48] (USA)	T1N1/ T2-4N0-1/ M1a (T4: 18%)	37	169 159	Cisplatin + PTX + 50.4 Gy Cisplatin + PTX + Cetuximab + 50.4 Gy	57.9 56.3	2y: 44.0%, 3y: 27.9% 2y: 44.9%, 3y: 33.8%

KDOG0501 [49] (Japan)	T4/M1lym (T4: 69%)	100	42	DCF + 50.4 Gy, 61.2 Gy	52.4	1y: 66.1%, 3y: 43.9%
NICE trial [50] (Brazil)	T3-4N0-1/ M1a (T4: 33%)	93	107	FP + 50.4 Gy FP + Nimotuzumab + 50.4 Gy	33.3[b] 47.2[b]	MST: 11.5 months MST: 15.9 months
Sateke [51] (Japan)	T4/M1lym (T4: 61%)	100	33	DCF → FP + 60 Gy	39.4	1y: 78.8%, 3y: 40.4%
Yokota [52] (Japan)	T4/M1lym (T4: 90%)	98	48	DCF →CS if resectable →FP + 60 Gy → CS if resectable	23.5 (no CS group)	1y: 67.9%

[a]Only one point assessment of tumor response

[b]Endoscopic complete response

CRT chemoradiotherapy, *SCC* squamous cell carcinoma, *CR* complete response, *INT* intergroup, *JCOG* Japan Clinical Oncology Group, *KROSG* Kyoto Radiation Oncology Study Group, *JROSG* Japanese Radiation Oncology Study Group, *PRODIGE* Partenariat de Recherche en Oncologie Digestive, *ACCORD* Actions Concertées dans les Cancers Colo-Rectaux et Digestifs, *SCOPE* Study of Chemoradiotherapy in OesoPhageal cancer with Erbitux, *KDOG* Kitasato digestive disease & oncology group, *S* surgery, *FP* 5-FU + cisplatin, *FLEP* 5-FU + leucovorin + etoposide + cisplatin, *FOLFOX* 5-FU + oxaliplatin + leucovorin, *EP* etoposide + cisplatin, *CP* capecitabine + cisplatin, *DCF* docetaxel + cisplatin + 5-FU, *NR* not reported, *MST* median survival time, *CS* conversion surgery

Table 16.3 Results of clinical trials of definitive CRT for resectable ESCC

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate (%)	Survival
RTOG8501 [1–3] (USA)	T1-3N0-1	88	62 134	64 Gy FP + 50 Gy	NR NR	2y: 10%, 5y: 0% 2y: 38%, 5y: 26%
Bedenne [55] (France)	T3N0-1	89	130	FP + 30 Gy or 46 Gy →FP + 15 Gy or 20 Gy	NR	3y: 34%
			129	FP + 30 Gy or 46 Gy →S	NR	3y: 29%
JCOG9708 [4] (Japan)	Stage I	100	72	FP + 60 Gy	87.5	4y: 80.5%
JCOG0502 [56] (Japan)	Stage I (T1b)	100	159	FP + 60 Gy	87.3	3y: 93.1% 5y: 85.5%
JCOG9906 [5] (Japan)	Stage II/III	100	76	FP + 60 Gy	62.2	3y: 44.7% 5y: 36.8%
Kato [57] (Japan)	Stage II/III	98	51	FP + 50.4 Gy	70.6	1y: 88.2% 3y: 63.8%
JCOG0604 [54] (Japan)	Stage II/III	100	44	S-1 + cisplatin + 50.4 Gy	59.5	3y: 61.9%
RTOG0246 [58, 59] (USA)	Stage II/III	27	41	TPF → FR + 50.4 Gy + selective S	36.6	1y: 71% 5y: 36.6%
JCOG0909 [60] (Japan)	Stage II/III	100	94	FP + 50.4 Gy ± salvage treatment	58.5	3y: 74.2%

CRT chemoradiotherapy, *SCC* squamous cell carcinoma, *CR* complete response, *RTOG* Radiation Therapy Oncology Group, *JCOG* Japan Clinical Oncology Group, *FP* 5-FU + cisplatin, *S* surgery, *TPF* Paclitaxel + cisplatin + 5-FU, *NR* not reported

esophageal cancer (JCOG0502) were reported [56]. Chemoradiotherapy consisted of 5-FU and cisplatin and 60 Gy irradiation against primary tumor only the same as JCOG9708 regimen. The 3- and 5-year overall survival rates were 94.7% and 86.5% in esophagectomy arm (209 patients), and 93.1% and 85.5% in chemoradiotherapy arm (159 patients) which results were comparable with esophagectomy. CR rate was 87.3% and 3- and 5-year esophagectomy-free survival rates were 88.7% and 80.4% in chemoradiotherapy arm. Most of residual or recurrent diseases after chemoradiotherapy were curatively resected by endoscopy or surgery. Several reports showed the efficacy of these salvage treatment after definitive chemoradiotherapy [61–64]. For stage II/III esophageal cancer, JCOG9906, a phase II trial of

chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation with elective lymph nodal irradiation showed promising activity with 62.2% of CR rate and 36.8% of 5-year overall survival rate [5]. Acute toxicities were mild, but there were four treatment-related death (5.3%) caused by late toxicities. Moreover, 8–15% of high mortality rate was seen in patients who underwent salvage surgery to residual or recurrent disease after chemoradiotherapy [62, 63]. Late toxicity and higher mortality rate might be caused by the extensive radiation field and daily treatment of AP/PA opposite fields. Therefore, a phase II trial of chemoradiotherapy with 5-FU and cisplatin and concurrent radiotherapy 50.4 Gy using of multiple field technique with reducing both the radiation dose and the volume of heart within the radiation field for stage II/III esophageal cancer was conducted [57]. At a median follow up of 29.4 months, late toxicities which were greater than grade 3 were observed in 5.9% of pneumonitis only. And CR rate was 70.6% and 3-year overall survival rate was 63.8%. As a development of the esophagus-preserving approach, a phase II study of induction chemotherapy followed by definitive chemoradiotherapy with selective salvage surgery for stage II/III esophageal cancer (27% SCC) was conducted (RTOG0246) [58, 59]. CR rate was 36.6%. Salvage surgery was performed in 44%. Treatment-related death after surgery occurred in 4.8%. The 1- and 5-year overall survival rates were 71% and 36.6%. Recently, a single-arm confirmatory study of definitive chemoradiotherapy including salvage treatment for stage II/III esophageal carcinoma (JCOG0909) was reported [60]. Chemoradiotherapy consisted of 5-FU and cisplatin and 50.4 Gy irradiation with elective nodal irradiation of 41.4 Gy. For residual or recurrent disease after chemoradiotherapy, salvage endoscopic resection or surgery was performed based on the prespecified criteria. CR rate was 58.8%. Salvage endoscopic resection and surgery were performed in 5% and 27%. R0 resection of salvage surgery was achieved in 76%. Treatment-related death after surgery occurred in 4.0%. 3-year overall survival rate and 3-year esophagectomy-free survival rates were 74.2% and 63.6%, respectively. Grade 3 late toxicities were observed in 9.6% only.

16.3.2.3 Prophylactic Chemoradiotherapy

Recently, a single-arm confirmatory study of endoscopic resection followed by selective chemoradiotherapy for stage I esophageal carcinoma (JCOG0508) was reported [9]. Patients with cT1bN0 (SM1-2) esophageal cancer, which was estimated to be treatable endoscopically, were treated with endoscopic resection, and prophylactic chemoradiotherapy was performed for patients with pathologically confirmed complete resection who had pT1a with positive vascular invasion or pT1b. Chemoradiotherapy consisted of 5-FU and cisplatin and 41.4 Gy irradiation for regional lymph nodes. The 3-year overall survival rate of 90.7%. Grade 3 late toxicities were observed in 3.1% only.

16.3.2.4 Neoadjuvant Chemoradiotherapy

Several randomized trials comparing surgery alone to neoadjuvant chemoradiotherapy were conducted and the results were conflicting (Table 16.4) [65–72]. Bosset and colleagues reported an European Organisation for Research and Treatment of

Table 16.4 Results of clinical trials of neoadjuvant chemoradiotherapy for ESCC

Author	Pathology: rate of SCC (%)	Regimen	No. of patients	MST (months)	*p*-value
Bosset [65] (France)	100	S FP + 37 Gy + S	139 143	18.6 18.6	N.S.
Urba [66] (USA)	25	S FP + VBL + 40 Gy + S	50 50	17.6 16.9	N.S.
Lee [67] (Korea)	100	S FP + 45.6 Gy (HF) + S	51 50	27.3 28.2	N.S.
Burmeister [68] (Trans-Tasman)	38	S FP + 35 Gy + S	128 128	19.3 22.2	N.S.
Tepper [69] (USA)	25	S FP + 50.4 Gy + S	30 26	21.6 54	0.002
Van Hagen [70, 71] (Netherland)	23	S PTX + CBDCA + 41.4 Gy + S	188 178	24.0 48.6	0.003
Hashimoto [72] (Japan)	100	FP + 41.4 Gy + S	31	3y OAS: 70.8%	–

SCC Squamous cell carcinoma, *MST* median survival time, *S* surgery, *FP* 5-FU + cisplatin, *VBL* vinblastine, *HF* hyperfraction, *PTX* paclitaxel, *CBDCA* carboplatin, *OAS* overall survival, *NS* not significant

Cancer (EORTC) trial randomizing 282 patients with squamous cell carcinoma of the esophagus to either surgery alone or preoperative therapy using concurrent cisplatin chemotherapy with radiation therapy [65]. Outcomes showed patients receiving neoadjuvant therapy experienced a significant improvement in disease-free survival, cancer-related mortality, margin-negative resection, and local control; however, no improvement in overall survival was seen versus patients undergoing surgery alone. Recently, results of the largest randomized trial assessing neoadjuvant chemoradiotherapy in the treatment of esophageal cancer (23% SCC) showed a significant survival benefit in patients receiving preoperative chemoradiotherapy [71]. A pathologic complete response rate was 29% in patients receiving preoperative therapy. Median survival was 49.4 months in patients receiving chemoradiotherapy versus 24.0 months in surgery alone, with a significant improvement in 3-year survival (58% vs. 44%). Updated results showed that at 5 years, survival rates were 47% and 33%, respectively, for neoadjuvant chemoradiotherapy and surgery alone [70]. Several meta-analyses have been performed concerning neoadjuvant therapy for esophageal cancer. Gebski and colleagues demonstrated an absolute 2-year overall survival benefit of 13% with the use of neoadjuvant chemoradiotherapy when compared to surgery alone [73]. Sjoquist and colleagues performed an updated meta-analysis of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy [74]. All-cause mortality for neoadjuvant chemoradiotherapy trials estimated an absolute survival benefit at 2 years of 8.7%, with survival benefits similar between squamous cell carcinoma and adenocarcinoma patients. Recently, another

meta-analysis demonstrated that neoadjuvant chemoradiotherapy significantly increased rates of pathologic complete response/R0 resection rates in both adenocarcinoma and squamous cell carcinoma patients compared to neoadjuvant chemotherapy alone. A significant increase in 3-year survival was seen only in squamous cell carcinoma patients (56.8% vs. 42.8%), whereas in adenocarcinoma patients, no significant difference was seen (46.3% vs. 41%) [75]. Currently, neoadjuvant chemoradiotherapy is accepted as the standard treatment for locally advanced esophageal cancer in Western countries. However, there is no randomized trial performed compared neoadjuvant chemoradiotherapy to surgery alone or neoadjuvant chemotherapy in Japan. Therefore, neoadjuvant chemoradiotherapy for resectable esophageal cancer is investigational in Japan. Hashimoto and colleagues conducted a first mutli-institutional phase II trial of neoadjuvant chemoradiotherapy for stage II/III esophageal cancer in Japan and reported promising activity with 41% of pathological CR rate and 77.4% of 2-year overall survival [72]. JCOG1109, three-arm randomized control trial compared neoadjuvant 5-FU and cisplatin to neoadjuvant 5-FU and cisplatin and radiotherapy or neoadjuvant docetaxel and cisplatin and 5-FU is now ongoing [76].

16.3.3 Palliative Therapy

Palliative radiotherapy is also useful for the purpose of relief of symptoms such as dysphagia and pain, and impair of the patient's quality of life. Palliative treatment regimens range from 30 Gy over 2 weeks to 50 Gy over 5 weeks or up to 60 Gy over 6 weeks, with up to 80% relief of pain and dysphagia [77]. Many studies report a 60% to >80% rate of relief from dysphagia with radiation. Coia and colleagues reported that nearly half of patients with baseline dysphagia experienced an improvement in swallowing within 2 weeks of treatment initiation [78]. By the completion of the sixth week, 80% or more of patients experienced improvement. A median time to maximal improvement was approximately 1 month. Palliative chemoradiotherapy is likely preferable to radiation alone for patients with advanced-stage esophageal carcinoma who have a good performance status. Retrospective analysis showed that 75% of stage IVB patients treated with 5-FU and cisplatin and 40 Gy irradiation improved dysphagia score [79]. Recently, Penniment and colleagues reported a Trans-Tasman Radiation Oncology Group (TROG) trial (TROG 03.01) randomizing 220 patients with advanced/metastatic esophageal cancer (26% SCC) to receive 35 Gy in 15 fractions (or alternatively 30 Gy in 10 fractions) with or without the addition of concurrent cisplatin and fluorouracil [80]. No significant differences in dysphagia relief (45% vs. 35%) and median overall survival (6.9 vs. 6.7 months) were seen between the chemoradiotherapy group and the radiotherapy group. As to toxicity, there were significant differences in grade 3–4 acute toxicity (36% vs. 16%) between the chemoradiotherapy group and the radiotherapy group. Intraluminal brachytherapy has also been used for palliation of dysphagia [38]. The previously described randomized trial from the Netherlands comparing intraluminal brachytherapy to stent placement showed that although patients undergoing stenting

experienced a more rapid improvement in dysphagia, long-term palliation was significantly improved in patients treated with brachytherapy [37]. A meta-analysis of prospective studies of brachytherapy encompassing 623 patients concluded that brachytherapy was a highly effective and relatively safe treatment option that was currently underused. However, the severe adverse event rate was 23% (stenosis 12%, fistula development 8%) [81].

16.4 Toxicity of Radiotherapy

Acute adverse events are esophagitis, dermatitis, weight loss, fatigue, and anorexia. Nausea and vomiting are relatively common, particularly in patients with lower esophageal tumor. Most patients experience esophagitis and dysphagia. Many symptoms resolve within 1–2 weeks of treatment completion. Radiation pneumonitis is subacute, generally occurs 2–6 months after radiation therapy completion. Usually, most patients have no symptoms. Common symptoms include nonproductive cough, fever, dyspnea, and, more uncommonly, respiratory distress. Late adverse events are pericardial effusion, pleural effusion, esophageal strictures, fistula formation, and hemorrhage [82]. And hypothyroidism may occur in case of including the thyroid within radiation field [44]. In a Japanese study, long-term analysis of 78 patients with complete remission treated with definitive chemoradiotherapy (cisplatin and 5-FU with 60 Gy) for squamous cell carcinoma revealed grade 2, 3, and 4 late pericarditis occurring in 6%, 5%, and 1% of patients, respectively; grade 4 heart failure in 2 patients; grade 2, 3, and 4 pleural effusion development in 5%, 6%, and 0% of patients, respectively; and grade 2, 3, and 4 radiation pneumonitis development in 1%, 2%, and 0% of patients, respectively [83]. Another analysis from Japan using fields inclusive of supraclavicular, mediastinal, and celiac regions up to a dose of 60 Gy with concurrent cisplatin and 5-FU showed a 2-year cumulative incidence of late, high-grade cardiopulmonary toxicities for patients ≥75 years of 29% versus 3% in younger patients. They concluded that older patients may not tolerate extensive radiation fields [84]. In JCOG9906, late toxicities included grade 3/4 esophagitis (13%), pericardial (16%), and pleural (9%) effusions, and radiation pneumonitis (4%), which caused 4 deaths [5]. These high incidences of late toxicities might be caused by extensive radiation field and daily treatment of AP/PA opposite fields. Recently, to reduce the late cardiac toxicity, use of multiple field technique with reducing both the radiation dose and the volume of heart within the radiation field is recommended while keeping the volume of the irradiated lung at a lower percentage [9, 57, 60]. About half of the esophageal strictures are due to local persistent or local recurrence. For benign strictures, dilation results in palliation in the majority of patients. Tumor involvement of the trachea or aorta or lung can lead to fistula formation during or after radiotherapy. In regard to brachytherapy, combination chemoradiotherapy with HDR-brachytherapy was associated with a high risk of life-threatening toxicities including esophageal ulcer, fistula, and perforation [34, 85–87]. And intubation with metallic stents before or during radiotherapy was associated with a high risk of life-threatening complications (Grade 3–5: 51%, Grade 5:

21%) such as hematemesis, esophageal fistula, and pneumonitis [88]. Samual and colleagues reported the outcome of patients with and without esophageal stenting before radiotherapy treated with concurrent chemoradiotherapy at a median dose of 50.4 Gy [89]. Of the 103 patients, there were significant differences in grade 3 or higher acute toxicities including esophagitis, dehydration, and anorexia between the stent group and no-stent group (71% vs. 27%). And after propensity score matching, the stent patients had a worse median overall survival compared with the no-stent patients (11.5 vs. 22.0 months).

16.5 New Radiation Treatment Modalities

New radiotherapy techniques such as IMRT, proton-beam therapy, and heavy-particle radiotherapy permit concentration of the radiation dose on the tumor with avoidance of critical organs such as the heart, lung, and spinal cord. These techniques may allow dose escalation in the treatment of esophageal cancer. Proton-beam treatment and heavy-particle radiotherapy take advantage of Bragg peak property to allow dose localization at the tumor while avoiding critical organs. In addition, carbon-ion radiotherapy that utilizes heavy-ion beams has a high relative biological effectiveness (RBE) with high linear transfer. Report from Japan using protons with or without photons to a median total dose of 76 GyE for 46 patients with ESCC showed the 5-year local control rate was T1: 83%; T2–4: 29%; and survival T1: 55%; T2–4: 13% [90]. Mizumoto and colleagues reported the results of locally advanced ESCC using protons with or without photons to a total dose of 70–98 GyE [91]. Of 51 patients, 40 (78%) showed a complete response (T1, T2: 100%; T3: 77%; T4: 38%). And the 5-year local control rate was 38.0% and 5-year overall survival rate was 21.1%. As a late toxicity, one patient died due to hemorrhage from an esophageal ulcer at the site of irradiation without recurrence. However, there were no other non-hematologic toxicities of grade ≥3 including lung and heart toxicity. Lin and colleagues reported the toxicities and outcomes of 62 patients treated with proton-beam therapy to a median total dose of 50.4 Gy with concurrent chemotherapy for esophageal cancer (22.6%SCC) [92]. A total of 29 patients (46.8%) received preoperative CRT. The pathologic complete response rate for surgical cohort was 28%, and the CR and near CR rates (0%–1% residual cells) were 50%. The 3-year overall survival rate was 51.7% and local-regional control rates were 56.5%. There was one case each of grade 2, 3, 5 radiation pneumonitis and another one patient died due to cardiac toxicity. Ishikawa and colleagues also reported the toxicities and outcomes of 40 patients treated with proton-beam therapy concurrently combined with chemotherapy consisting of cisplatin and 5-FU for esophageal cancer [93]. A total dose of 60 GyE was delivered and an additional boost of 4–10 GyE was given when residual tumors were suspected. Of 40 patients, 31 (78%) showed a complete response (stage I: 88%; stage II: 89%; stage III: 56%). And the 2-year local control rate was 66.4% and 2-year overall survival rate was 75.1%. As a late toxicity, no cardiopulmonary toxicities of grade 3 or higher were observed. Akutsu and colleagues conducted a phase I/II clinical trial of preoperative

carbon-ion radiotherapy for ESCC [94]. Thirty-one patients were enrolled and the radiation dose was escalated from 28.8 GyE up to 36.8 GyE. 12 (38.7%) patients achieved a pathological CR. The overall 3- and 5-year survival rates in the stage I cases were 81% and 61%, and were 85% and 77% for the stage II, and 43% and 29% for the stage III cases, respectively. One case (3.2%) in 35.2 GyE presented Grade 3 of postoperative acute respiratory distress syndrome (ARDS), and there were no late toxicities. However, these new approaches remain investigational, so further research is necessary to evaluate the efficacy and safety of new techniques and technology in a prospective trial.

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Hong Kong Experiences of the Treatment of Esophageal Squamous Cell Carcinoma

17

Claudia Wong and Simon Law

Abstract

Treatment of squamous cell carcinoma of the esophagus (ESCC) has evolved over the years. In the past, surgery was performed for patients with potential for cure as well as those for palliation only. Endoscopic placement of plastic prosthesis was used for those unfit for surgery, and the results of radiotherapy were suboptimal. Management of ESCC has become more individualized. Early mucosal/submucosal cancers can be resected by endoscopic methods. For more advanced cancers, results of surgery have improved. Through better patient selection, refinement of anesthetic, perioperative care, and surgical technique, esophagectomy can be carried out with minimal mortality. Minimally invasive approaches have replaced traditional open surgery and result in fewer morbidities. Enhanced Recovery After Surgery (ERAS) programs have led to better recovery experiences after esophagectomy. Integration of multimodality treatment strategies is routine, with improved in long-term outcome. For palliation, better endoscopic methods such as insertion of self-expanding metallic stents (SEMS), chemotherapy, radiotherapy, and even immunotherapy are utilized. The changes in treatment strategies at The University of Hong Kong over the past decades are outlined. However, many issues remain unanswered in treating ESCC and it is hoped that through research, the prognosis of these unfortunate patients will continue to improve.

Keywords

Esophageal carcinoma · Diagnosis · Treatment experience

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17.1 Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer deaths in the world [1]. There has been a divergence of histological cell type between the East and West. In Western countries, adenocarcinoma has increased dramatically in incidence in the past 30 years, closely related to the rising prevalence of obesity, gastro–esophageal reflux disease, and Barrett's esophagus. In Asia, esophageal squamous cell carcinoma (ESCC) remains the predominant cell type; more than 80% of esophageal cancer is a squamous cell in origin. There has not been a convincing rise in the incidence of true adenocarcinoma of the esophagus (Siewert type I) in Asia. In Hong Kong, ESCC accounts for more than 90% of all esophageal cancers.

There has been advancement of technology in diagnosis, staging, and treatment of this highly lethal disease in the last few decades. In Hong Kong, more than 70% of esophageal cancer patients are diagnosed at stage III/IV. Diagnosis at an earlier stage can improve the outcome and prognosis. Accurate staging allows optimal stage-directed therapeutic strategy. Multimodality treatment methods such as neoadjuvant chemotherapy or chemoradiation with surgery have gained popularity and outcomes have improved compared with surgical resection alone. The authors will summarize the treatment strategies and experience at The University of Hong Kong.

17.2 Diagnosis

When diagnosed at an early stage, the prognosis of ESCC is significantly better. The rate of detection of early tumor is higher in countries where uptake of endoscopy for early cancer diagnosis and screening is high, such as in Japan. In Hong Kong, there is no screening program but at the authors' institution high-risk patients are offered screening endoscopy, in particular those with a history of head and neck cancers [2, 3]. Chromoendoscopy with Lugol's iodine solution and optical chromoendoscopy such as narrow-band imaging with magnifying endoscopy are routinely utilized for screening. Since 2011, the authors' institution has been performing surveillance endoscopy for patients who had a history of head and neck cancers. Among these patients, 6.3% had screening-detected neoplastic lesions, and 3.9% had ESCC or dysplastic lesions amendable to endoscopic treatment (unpublished data).

17.3 Investigations

Once the diagnosis is confirmed, investigations are directed to [1] accurate staging of disease, and [2] assessment of co-morbidities and operative risk. Based on the information obtained, an appropriate therapeutic strategy can be formulated for each individual. The algorithm in patient evaluation is shown in Fig. 17.1.

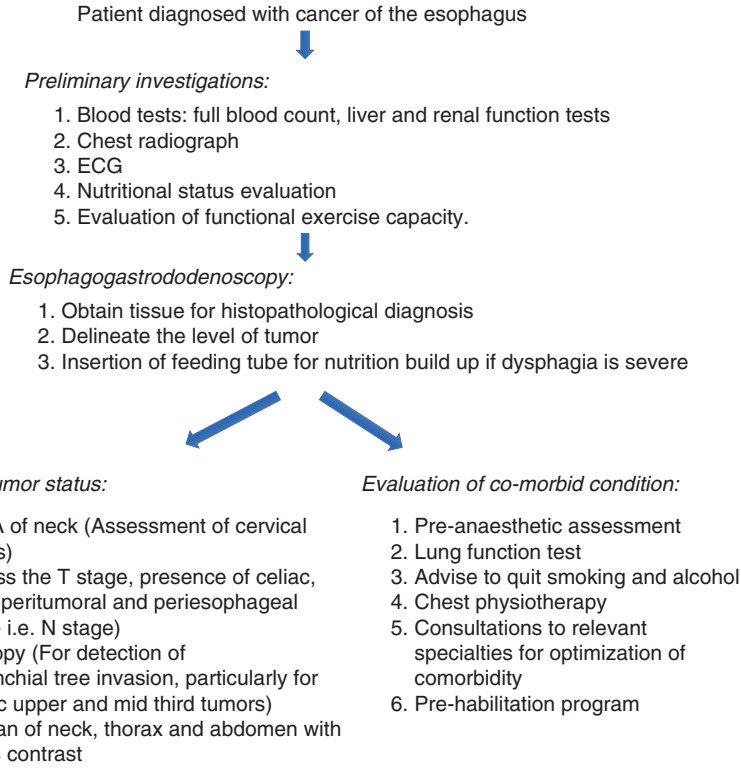


Fig. 17.1 Evaluation of patients suffering from cancer of the esophagus

17.3.1 Staging

Clinical staging follows the American Joint Committee on Cancer Staging (AJCC) TNM classification system. In addition to endoscopy, bronchoscopy [4] percutaneous ultrasound of the neck with or without fine-needle aspiration (FNA) cytology, endoscopic ultrasonography (EUS) with or without fine-needle aspiration [5], 2-(^{18}F) fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan are routinely employed.

Since the 1960s, bronchoscopic examination has been routine practice for patients with esophageal cancer at the authors' institution, initially by rigid, and later with flexible bronchoscope [6, 7]. This is especially important for tumors that are located in the middle and upper portions of the esophagus. In one study, the reported complications rate was 0.95% (4 out of 525 patients). Airway involvement by tumor contraindicates surgical resection. In a handful of anecdotal cases, response to chemoradiation therapy resulted in disappearance of tumor involvement, leading to subsequent successful resection, but this is an exception rather than the rule.

Percutaneous ultrasonography with or without fine-needle aspiration is crucial to delineate the nodal status of the cervical region, and this is routinely performed. Diagnosis of cervical nodal metastases is important from a therapy point of view. Prior to the seventh edition of the AJCC staging classification, cervical nodal metastases were regarded as stage IV disease, although our policies have been in line with the Japanese guidelines to treat them as regional nodal metastases [8]. Chemotherapy or chemoradiation is usually given and followed by surgery if restaging demonstrates potentially, curatively resectable disease.

We have been using endoscopic ultrasound (EUS) for staging since the 1990s [5]. The sensitivity and specificity of EUS in detecting the depth of esophageal involvement are 89% and 96%, respectively, whereas the respective figures for nodal status are 85% and 86% [5]; results that are comparable with other reports [9–11]. In recent years, we have been using the miniaturized ultrasound catheter probes (12.5 MHz mini probe), mainly because a substantial proportion of our patients have un-traversable tumor stenosis for conventional dedicated radial endo-ultrasonic endoscope.

In Hong Kong, FDG-PET is a routine investigation for ESCC; it is used in most of our patients although one limitation is that the scan is not publicly funded and is self-financed. In those who could not afford a PET scan, only contrast CT scans are used. In an early study, we found that the maximum standard uptake value of the primary tumor (SUVmax) correlated with nodal status (N+ vs. N− disease) on PET scan, the T stage measured by EUS, the pathological T stage after surgical resection, the pathological overall stage as well as the chance of a R0 resection [12].

In a more recent series of 244 patients from 2007 to 2012, we found that the SUVmax correlated with the T stage of disease; the mean SUVmax values for T1, 2, 3, and 4 tumors were 2.74, 4.55, 12.9, and 13.6, respectively. In addition, a SUVmax of 7.3 or more predicted a T3/4 tumor with a sensitivity of 90.1% and specificity of 95%. For nodal metastases, our experience with PET scan has an accuracy of diagnosing positive nodal spread of 70.3%. The tendency, however, is to underestimate false-negative nodes, while the predictive value of a metabolically active node is generally high. For patients who undergo neoadjuvant chemoradiotherapy, our policy is to repeat a PET/CT at 4 weeks post therapy before a decision is made for surgical resection.

17.3.2 Patient Pre-treatment Evaluation

Accurate tumor staging provides guidance for stage-directed therapy. In addition to tumor stage, careful pre-treatment risk evaluation is important in selecting the appropriate patients for surgery.

The physiological reserve is an important factor to evaluate for potential surgical candidates. The assessment is generally based on surgeons' experience and intuition rather than an exact science. Objective score systems are available to help the assessment of operative risk and patient selection [13, 14]. In our multivariate analysis of predictive factors for morbidity and mortality after esophagectomy, advanced

age was predictive of both pulmonary complications and postoperative death. Patients with tumor location in the superior mediastinal segment were also at risk of pulmonary complications [15]. In addition to routine blood tests for work-up, specific tests would include a pulmonary spirometric function test, and in selected patients, an echocardiogram and coronary angiography or stress thallium test. In our experience, there is not much in general that can be done to improve the existing physiological fitness of patients, with perhaps the exception of cardiorevascularization by angioplasty or stenting in those with critical coronary artery stenosis. In such patients, double antiplatelet agents such as aspirin and Clopidogrel may be required after coronary intervention. Neoadjuvant therapy is often given in these patients, aiming to downstage tumor. It would also allow the patient to recover from the cardiac procedure. Modern coronary intervention often allows the stopping of Clopidogrel at 1 month post procedure. Aspirin can be continued in the perioperative period.

17.3.3 Patient Pre-habilitation and Preparation for Surgery

Postoperative management starts with preoperative evaluation and optimization. Enhanced Recovery After Surgery (ERAS) programs have been employed successfully in many institutions and are shown to improve outcome. Major guidelines are published for its adoption [16–18]. The protocol used at the authors' institution is shown in Table 17.1. Many of the ERAS principles are adopted.

The following preoperative measures should be instituted:

- Cessation of smoking and alcohol intake.
- Incentive spirometry and chest physiotherapy +/− pre-habilitation program.
- Optimization of bronchodilator therapy in patients with asthma or significant chronic obstructive airway disease.
- In patients with high-grade esophageal tumor stenosis, a fine-bore nasogastric tube can be placed for nutritional support while workup is performed and is preferable over parenteral nutrition, gastrostomy, or jejunostomy feeding. Oral nutritional supplementation is given [19].
- Diabetic control should be optimized.
- Immediate preoperative preparations include prophylactic antibiotics to be given at anesthesia induction and deep vein thrombosis prophylaxis. Bowel preparation is not necessary, unless a colonic interposition is intended.
- Preoperative patient education and counselling.

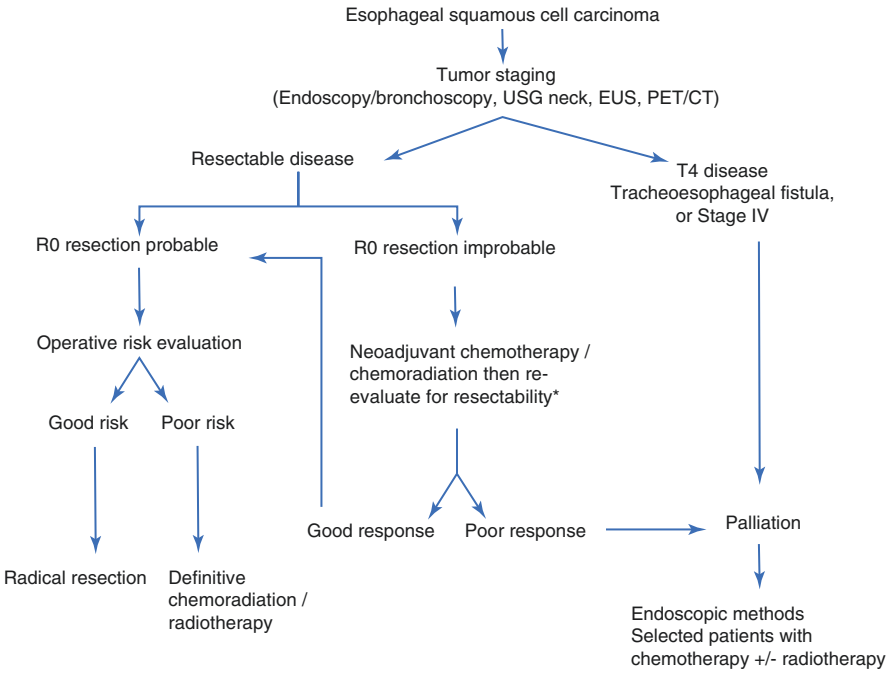
17.4 Treatment

Surgical resection and radical radiotherapy used to be the only two treatment options for esophageal cancer. Advancement in endoscopic technology has made endoscopic treatment for early cancer possible. Improvement in chemotherapy and

Table 17.1 Perioperative management

Preoperative	
• Preoperative counseling	
• Nutritional assessment	Nasogastric tube feeding for those with significant stenosis of the esophagus, and oral supplement in those at risk of malnutrition
• Preoperative exercise	General and incentive spirometry + pre-habilitation program
• Stop smoking and alcohol intake	
• Chest physiotherapy	
• Carbohydrate loading on day of surgery	No solid food 6 h before and fluid 2 h before surgery. Carbohydrate loading night before and finishes 2 h before surgery
• No need for bowel preparation unless colonic interposition is planned	
Intraoperative	
• Prophylactic antibiotics	
• DVT prophylaxis	Mechanical ± pharmacological
• Judicious use of intraoperative fluids	
• Avoid hypothermia	
• Minimally invasive surgery if possible	
• Epidural analgesia	
Postoperative	
• Nutrition	POD1 carbohydrate drink, gradual advancement to soft diet by POD5 (if no vocal cord palsy and assessment by speech therapist shows no risk of aspiration) PPN/TPN in those at nutritional risk and oral intake insufficient
• Nasogastric tube	Removal on POD 1 (if no vocal cord palsy and assessment by speech therapist shows no risk of aspiration)
• Analgesia	Epidural analgesia/patient-controlled analgesia/ multimodal analgesia
• Chest drain	Single closed small caliber drain (19Fr Blake drain, which does not require underwater seal), removal POD 3–4 when output <200–300 ml per day
• Early mobilization	From POD1, supervised by physiotherapist
• Urinary catheter	Early removal as soon as close monitoring of urine output is not essential
• Intravenous fluid	Balanced intravenous fluid to avoid over- and under-hydration
• DVT prophylaxis	

DVT deep vein thrombosis, *POD* post-operation day, *PPN/TPN* peripheral parenteral nutrition/ total parenteral nutrition



* The choice of neoadjuvant chemotherapy or chemoradiation depends on the likely resectability of the primary tumor, location and number of suspected nodal metastases, the applicability of the radiation field, and tolerance of patients. Each patient will be discussed at a multidisciplinary meeting comprising surgeons, oncologist, radiation oncologist, and radiologist.

Fig. 17.2 Management protocol of patients with cancer of the esophagus at The University

radiotherapy also increases the choice of therapeutic options. The management algorithm for ESCC at The University of Hong Kong is shown in Fig. 17.2.

17.4.1 Endoscopic Treatment for Early Cancer

Early ESCC is defined as tumor that is limited to the mucosa or submucosa. In Hong Kong, most ESCC patients are diagnosed at an advanced stage. The number of patients suitable for endoscopic treatment is therefore small. The indications for endoscopic treatment generally follow the guidelines from Japan [20]. Distinguishing m1/2 disease (where the chance of nodal metastases is negligible) from deeper

lesions is often difficult. Deep invasions are not uncommonly missed with superficial biopsies and careful endoscopic examination. We practice endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) to assess the lesions in detail pathologically before deciding on further treatments. Radiofrequency Ablation (RFA) is also advocated over EMR/ESD especially in treating long segments and circumferential early cancers/neoplastic lesions. Studies have boasted lower stricture rates and complete response rates of up to 80–97% [21–24]. The safety of radiofrequency ablation (RFA) remains debatable in the context of treating ESCC. Compared to other endoscopic methods, RFA does not allow detailed histological assessment of depth of neoplastic lesions hence harbors risk of undertreatment.

17.4.2 Neoadjuvant or Adjuvant Treatment

Neoadjuvant and adjuvant therapy for esophageal cancer has been controversial. Policies on their use vary widely in different countries. Preoperative chemotherapy is the standard-of-care in Japan and is commonly used in the United Kingdom [25–27], while in the United States chemoradiation is more widely practiced [28–30]. With the published ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) from Europe, neoadjuvant chemoradiation is liberally adopted at the authors' unit [31].

Historically in Hong Kong, we have investigated different treatment strategies in treating esophageal cancer in addition to surgical resection alone. An early randomized trial looked at the impact of postoperative radiotherapy after esophagectomy. It was found that while postoperative radiotherapy did not lead to an overall improvement in survival, in those with palliative resections, the addition of radiotherapy reduced the chance of death from local–regional recurrence, especially from tracheobronchial recurrence [32]. The technique of radiotherapy was suboptimal by modern standard, the fractionation was high (3 Gy per fraction), and a few deaths resulted from the deleterious effects on the gastric conduit, even including perforation. This might have affected the overall survival results. Postoperative radiotherapy is not widely practiced worldwide, perhaps with the exception of some centers in China, where improved survival can be shown in selected patient populations [33, 34].

In the early 1990s, our focus shifted to preoperative chemotherapy. A randomized trial compared esophagectomy alone and two courses of preoperative cisplatin and 5-FU was carried out. Again overall survival benefit could not be demonstrated. A pathological complete response rate of 7% was achieved, and in those who responded well to chemotherapy, survival was superior to those who had surgery alone. Unfortunately, this was offset by those who responded poorly, whose survival was worse than the controls [35]. Attempts were made to identify predictors of response but none was found to be reliable [36].

Chemoradiotherapy as neoadjuvant therapy has been investigated since the mid-1990s. A historical cohort comparison on patients treated with surgery alone

and surgery with neoadjuvant chemoradiation demonstrated that the strategy of including chemoradiotherapy improved outcome. The adoption of chemoradiation allowed better patient selection for curative surgery, and resulted in more R0 resection by tumor downstaging [37]. The technique of radiotherapy has also improved over the years. Often Intensity-Modulated Radiation Therapy (IMRT) and 3-D conformal radiotherapy planning are used replacing the traditional AP opposing radiation field.

In our earliest experience with chemoradiation, the most common chemotherapy regime was cisplatin at 100 mg/m^2 on day 1 and then day 22 and continuous infusion of 5-fluorouracil at 500 mg/m^2 per day for 5 days from days 1 to 5 and days 22 to 26. Radiotherapy was given concurrently with a dose of 40 Gy at 2 Gy per fraction. With this approach, tumor downstaging of 75% could be achieved. Pathological complete response rate in the primary tumor was up to 45% and overall pathological complete response rate (including negative nodes) 31% [38].

In response to the positive results of the CROSS trial [31, 39], our choice of chemotherapeutic agents has widened to include taxanes since 2012. In a recent review of our own experience of treating ESCC with the CROSS regimen, pathological complete response rate was 33.3%. Median survival was 24.2 months. This is inferior to the original Dutch data in the CROSS trial, which reported a complete response rate of 49% in ESCC. Inclusion of patients with more advanced disease could have explained the discrepancy in results [40].

Patient selection seems essential to ensure good response and outcome. We conducted another study looking at a group of 40 patients with advanced nodal disease (stage M1a/M1b according to sixth edition of the AJCC—cervical and celiac lymph nodes, but considered loco-regional disease according to seventh edition of AJCC) and still considered a potentially resectable disease. Chemoradiotherapy according to the CROSS regimen was given. Five (25%) patients developed distant metastases upon post-chemoradiation assessment, three patients were not operated on because of death before surgery, tracheoesophageal fistula, and patient refusal. Therefore only 60% underwent esophagectomy and R0 resection was achieved in 75% and pathological complete response in 15%. Median survival of the group was 11.1 months and even for those who underwent esophagectomy was only 14 months [41]. It highlights the fact that promising trial results may not be reproducible in the real-world setting when it is more widely and less stringently applied. Certainly better defining how chemoradiotherapy such as CROSS impacts treatment strategy is important [42, 43]. A project is underway to compare results of CROSS in Dutch and Chinese patients with participating centers in Hong Kong, mainland China and Taiwan.

Research is still ongoing in Asia to find the optimal neoadjuvant therapy for ESCC. Reinforcement of conventional neoadjuvant chemotherapy with the addition of Docetaxel (such as triplet therapy with Docetaxel, Cisplatin, and 5-FU) is being tested in Japan [44]. At the authors' institution, this combination is selectively applied in patients whose suspected nodal metastases are distributed in more than two-fields for which the radiation field would be too extensive. This strategy has been adopted since early 2018. It is, however, the authors' impression that in those with bulky, clinically staged cT4 lesions, radiotherapy is probably still more

effective in bringing about an R0 resection. This depends more on the primary tumor than nodal metastases. The triplet regimen is also more toxic compared to the usual doublet regimens, and routinely G-CSF are given. Much awaited is the results of an ongoing three-arm trial that compares neoadjuvant triplet chemotherapy and neoadjuvant radiation with doublet chemotherapy over doublet chemotherapy alone that is conducted in Japan [45]. The results are expected to be available in 2021.

The timing of surgery after chemoradiation is an important consideration; when the interval between chemoradiation and surgery is short, the resultant pathological response rate may be affected because the tumor has not had a chance to degenerate, tissue inflammation may still be severe and patients often need some time to recover physically from the treatment. On the other hand, if the interval is left too long, fibrosis may ensure which may make dissection more difficult. More importantly, tumor may have more chance to regrow and metastasize. Our policy is to restage the patients at 4 weeks post therapy, including endoscopy and PET/CT scan. Surgery is then performed around 6–10 weeks post therapy.

At the authors' institution, the impact of time interval between neoadjuvant chemoradiation and surgery was studied in 107 ESCC patients. Patients were divided into two groups using 64 days from the completion of neoadjuvant therapy (median interval). When an R0 resection could be performed, the 3- and 5-year survivals were better in the early surgery group than the delayed surgery group (3-year: 71.7% vs. 56.5%, $p = 0.023$; 5-year: 71.7% vs. 51%, $p = 0.032$).

On further analysis by reclassifying the patients into 3 interval groups, patients who underwent surgery within 40 days from completion of therapy had significantly lower R0 resection rate than those who had a longer wait till surgery ($\leq$40 days: 56.3%, 41–80 days: 90%, >80 days: 74.2%, $p = 0.006$) [46]. Postoperative morbidity and mortality rates were not affected by the timing of surgery. Our previous data had also demonstrated the safety of neoadjuvant chemoradiation with regards to postoperative morbidity rates [15, 37].

The relationship between survival and interval to surgery after neoadjuvant therapy is an interesting observation but the data require confirmation in a larger cohort. This factor needs consideration when surgery is planned.

The applicability of the AJCC staging system in the post-neoadjuvant chemoradiation setting has also been questioned. In one study, we showed that in patients without neoadjuvant therapy, there was an orderly relationship between the chance of finding nodal metastases with advancing pT stage. This was no longer true after chemoradiation. Applying the same TNM staging system may not be accurate enough to provide prognostic information [47]. Survival tends to be much poorer in post neoadjuvant therapy early-stage ESCC compared to the corresponding pathological stage groups without neoadjuvant therapy [48]. The latest eighth edition of the AJCC staging system addresses the dissimilarity in survival between treatment naïve and post chemoradiation or chemotherapy ESCC [49].

The percent of residual viable cells in the primary tumor together with nodal status were independent prognostic factors [38], while ypT stage was not. The cut-off point on the percent of residual viable cells and the interplay between other prognostic factors for better prognosis stratification warrant further investigation.

One major consideration of neoadjuvant therapy is how best to predict response. Much evidence has shown that those with pathological complete response had a better survival [38, 50]. Chemotherapy and radiotherapy are not without morbidities, and subjecting patients to such treatments without significant effect will potentially cause harm, delay surgery, and increase the chance of tumor metastases while waiting for definitive treatment. However, no reliable clinical, biochemical or molecular predictor exists. At the author's institution, using PET scans, SUVmax values were found to correlate with pathological complete response (pCR). In 52 patients who had undergone neoadjuvant chemoradiation and then resection, 21 (40.4%) achieved pCR. SUVmax of the primary tumor at 1 month post neoadjuvant therapy was independently predictive of pCR. However the predictive value was only modest, sensitivity was 71%, specific was 66.7%, positive predictive value was 75.9% and negative predictive value 60.9% [51]. PET scans were also only performed after completion of therapy and therefore limited their application. The use of PET scans to assess response during the early part of neoadjuvant therapy has some promise. Nonetheless, most of these reports to date studied chemotherapy-treated patients with a substantial number being adenocarcinomas [52–54].

At the authors' institution, molecular pathways and blood-based assays are actively being studied to see if prediction of response is possible [55–59]. For example, specific microRNAs such as miR-193b, are significantly elevated in good responders to chemoradiation with Cisplastin/5-FU [60]. It is hoped that assays can be developed that have significant predictive value to guide treatment in the future, and even developing potential therapeutic targets to enhance sensitivity to chemotherapy [61].

In the event of a complete clinical response, is surgery still indicated? This is one of the latest areas of research. The concept of esophageal preservation, active surveillance, and salvage surgery only in the event of recurrence after a clinical complete response to neoadjuvant therapy is attractive [62, 63]. The Dutch Pre-SANO study has been published. It evaluated the accuracy of clinical response evaluation. Patients with potential complete response after chemoradiation underwent postponed surgery at 12–14 weeks with a pre-surgery second-stage clinical response evaluation, comprising fine-needle aspiration of suspicious local–regional lymph nodes in addition to repeat endoscopic ultrasonography, bite-on-bite tumor biopsy and PET-CT scan. The overall false-negative rate of this approach to response evaluation was 10% for Chirieac modified tumor regression grades 3 and 4 tumors (more than 10% residual carcinoma) [63]. This has led to a randomized SANO trial, to test whether surgery can be omitted after clinical complete response. However, these studies focuses on adenocarcinomas only. The authors are participating in a multicenter trial similar to the Pre-SANO trial but in squamous cell carcinoma (Pre-SINO trial) [64].

17.4.3 Surgery

Most patients seen at the authors' institution have advanced disease with comorbidities. Early cancers are uncommon and therefore most who come to surgery

will have had neoadjuvant chemotherapy +/− radiotherapy. This has to be taken into account when operative strategies are planned.

17.4.3.1 Cervical Esophageal Cancer

Cervical ESCC justifies separate consideration. It accounts for 2–10% of all esophageal carcinomas, and by convention, this cancer is treated by pharyngo–laryngo–esophagectomy (PLE) with or without adjuvant radiotherapy. PLE with one-stage gastric pull-up was first described by GB Ong in 1960 from the authors' institution [65]. The original description of PLE involved a thoracotomy for esophageal mobilization. This was later modified so that a transhiatal approach was used without a thoracotomy. This was again changed when videoscopic-assisted thoracoscopy (VATS) became available [66, 67].

In recent years, laryngeal preservation has been the aim of treatment and definitive chemoradiotherapy is generally preferred; surgery is reserved for those who respond suboptimally or when recurrence develops. While definitive chemoradiation is widely practiced, our data show that this type of strategy is not without drawbacks. Chemoradiation-related complications include mucositis, vocal cord palsies, esophageal stricture, carotid blow out, hypothyroidism, and hypoparathyroidism. Persistent dysphagia affects 29% of patients and 38% eventually require surgery as salvage. Salvage surgery has suboptimal results, disease status, and prior heavy irradiation increases morbidities. In patients with locally advanced disease, especially in those with extra-esophageal extension, upfront surgery with postoperative radiotherapy as the preferred therapy should be carefully considered, in particular the outcomes of PLE have also significantly improved over the last few decades [68–71]. Both the anastomotic leak and mortality rates were reduced to 9% [71]. Improvements in surgical technique including thoracoscopic esophageal mobilization, better perioperative care, and patient selection all contributed to better results [66, 67, 72].

To reduce morbidity further, in patients with limited tumor extension into the intrathoracic esophagus, availability of the technique of free jejunal graft to replace the cervical esophagus has reduced the need for PLE with total esophageal extirpation [72]. Less morbidity is expected as no thoracic phase and mediastinal dissection is needed. A significant number of patients with primary hypopharyngeal cancer or those with limited involvement of the cervical esophagus can undergo pharyngo–laryngo–cervical esophagectomy. Free jejunal graft is the preferred organ for reconstruction; it has a failure rate of 2% and anastomotic leak rate of 4.6% [73–75].

17.4.3.2 Intra-thoracic Esophageal Cancer

The Approach to Resection

Our preferred surgical approach is a transthoracic one. In the past, a randomized trial comparing transthoracic and transhiatal approach for lower third tumors was conducted at the authors' institution [76]. No significant difference was found, the trial sample size was too small to be able to demonstrate any difference. The study

was terminated because our focus then shifted to minimally invasive esophagectomy.

In Hong Kong, the application of minimally invasive surgical technology in esophagectomy commenced in the mid-1990s [77]. At the initial stage, thoracoscopic esophageal dissection was applied in lieu of open thoracotomy or transhiatal mobilization of the esophagus in PLE [67]. Then it was applied to intrathoracic esophageal cancers as well. Thoracoscopic esophageal mobilization with lymphadenectomy was carried out combined with open laparotomy for gastric conduit preparation for cervical esophago–gastrostomy [78]. Our early hypothesis was that minimally invasive methods had its maximum benefits in those with high risk of surgery and such patients were preferentially selected. The early results though acceptable were not impressive [77]. This was because of the combination of high-risk patients, immature techniques and suboptimal instrumentation. The uptake of minimally invasive esophagectomy was thus slow. It was not until 2006 that we changed our policy and applied the operation more unselectively. In addition, laparoscopic gastric mobilization was introduced so that the whole procedure became totally minimally invasive (MIE). Our techniques have also improved together with better instruments.

To date, we have performed such procedures in nearly 300 patients. MIE is the approach in about 67% of our patients; in nearly 57% of these patients prior neoadjuvant therapy has been applied (and in recent years, over 80% of these patients have had neoadjuvant chemoradiation). VATS esophagectomy with laparotomy was performed in 100 patients, totally MIE in 199. The median thoracoscopy time was 190 min, blood loss of 200 ml. Our conversion rate (VATS) was 13%, reflecting our policy of unselected choice of patients. In one patient conversion was due to hemorrhage, while most were related to extensive lung adhesions or advanced post chemoradiated tumors that were found to be unsafe to dissect. In a propensity score-matched analysis of VATS/MIE and conventional open esophagectomies, thoracoscopic approach improved lymph node yield. The median number of lymph nodes harvested was 35, compared to a significantly lower median of 21 nodes in open esophagectomies. It may be explained by better visualization, especially at the apex of the thoracic cavity, by thoracoscopy. There was also a significant difference in pulmonary complication rate of 29% in the VATS/MIE group and 55.1% in the open esophagectomy group. Long-term survival was not compromised [79]. Results from other trials across the world concur with our findings [80, 81]. Postoperative quality of life has also been demonstrated to be superior. It is anticipated that the uptake of MIE will become more widespread.

Extent of Resection and Lymphadenectomy

A curative (R0) resection implies histological clear proximal, distal and lateral margins. There is a propensity of ESCC to have intramural and submucosal spread. Increasing the length of resection margin reduces the chance of a histologically positive resection margin. We advocate an in-situ proximal resection margin length of 10 cm to allow a less than 5% chance of anastomotic recurrence [82]. In our study, 28 (5.3%) out of 524 patients developed anastomotic recurrence; the length

of the axial resection margin correlated with the chance of anastomotic recurrence [83]. A negative margin, however, may not totally preclude anastomotic recurrence. In our experience, anastomotic recurrence occurred in 10.2% of patients with positive resection margin compared to 4.9% in those with negative margin [82].

On lymphadenectomy, although extended mediastinal lymphadenectomy is practiced, cervical nodal dissection is not routinely performed at our institution. In patients with overt cervical nodal metastases, our policy is, in general, to treat with upfront chemoradiation before surgical resection. In a study of 109 patients with cervical nodal metastases proven on ultrasound guided-FNA, survival was compared among those with stage IV disease by virtue of cervical nodal disease (AJCC sixth edition) and those with systemic metastases. The former group had significantly longer survival compared to the latter group; median survival was 9.8 months vs. 3 months. More importantly, in those with upfront chemoradiation and then esophagectomy, a median survival of 35 months was achieved [84]. In our experience, cervical lymphadenectomy after neoadjuvant chemoradiation often yields negative nodes on histological examination, but dissection around the recurrent laryngeal nerve may lead to a higher rate of vocal cord palsy. However, nodal dissection should still be performed because of the unreliable means of confirming the absence of metastases after chemoradiation.

In patients with no evidence of cervical nodal metastases on preoperative workup including PET/CT scan and ultrasound, routine cervical lymphadenectomy is not performed. Neck dissection can still be performed later should recurrence occurs locally in the cervical region. In our study of recurrence pattern after esophagectomy without routine cervical lymphadenectomy, isolated recurrence in the neck was uncommon. We studied 108 patients who underwent curative resection for ESCC, 56 (52%) of them developed recurrence. There were 12 patients who had cervical nodal recurrence, only four of whom had isolated recurrence in the neck. This implies that cervical nodal recurrence, if present, tends to be found together with other sites of recurrences, thus reducing the benefits of cervical lymphadenectomy [83].

Mediastinal dissection, however, is important, especially when future resection for nodal recurrence in the mediastinum is generally not possible after esophagectomy. Therefore disease control at the time of esophagectomy must be maximized. In the era of neoadjuvant chemoradiation, dissection, especially around the recurrent laryngeal nerve is difficult with increased risk of nerve injury. And again, prediction of residual positive disease is often unreliable. These factors have to be taken into account when lymph node dissection is considered. For each patient, the risk and benefits should be carefully balanced. As far as surgical technique is concerned, we do not limit MIE to patients without prior neoadjuvant chemoradiation. As stated above, over 60% of our patients would have had chemoradiation before esophagectomy. From a technical standpoint, judicious use of energy dissection devices is important to achieve the required lymphadenectomy without risking recurrent laryngeal nerve as well as airway injury.

Since 2014, intraoperative recurrent nerve conduction study is routinely carried out in esophagectomies at the authors' institution (Fig. 17.3). Both intermittent

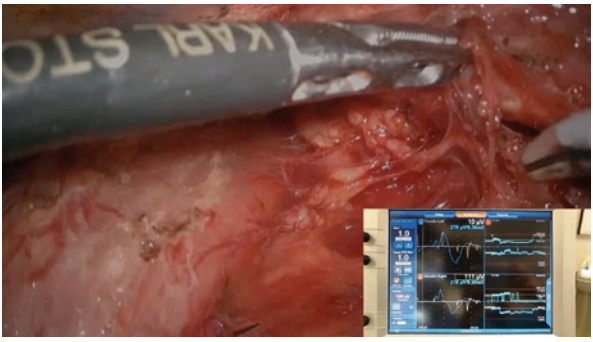


Fig. 17.3 Recurrent laryngeal nerve lymphadenectomy showing the effect on intraoperative continual nerve monitoring. Traction of the left recurrent laryngeal nerve results in an increase of the latency of nerve conduction (insert top tracing in red)

nerve stimulation for mapping and continuous nerve monitoring are routinely used [85, 86]. Overall recurrent laryngeal nerve palsy rate was 22.2%, but only 5.5% persisted at 1 year [87]. Although there has not been an apparent reduction of nerve palsy rate since the implementation of this technique compared to our previous data, it might have been contributed by the more extensive lymphadenectomy along the recurrent laryngeal nerves since the use of intraoperative nerve monitoring. The use of this technology to safeguard recurrent laryngeal nerve injury is still investigational.

Reconstruction

Restoration of the gastrointestinal tract continuity after esophagectomy has a significant impact on immediate postoperative morbidity and long-term quality of life. The authors' institution has performed many studies on reconstructive techniques and their relationship to morbidity and mortality after esophagectomy.

A pyloric drainage procedure remains controversial. Pyloroplasty is a routine procedure during esophagectomy by the authors. In a randomized trial comparing outcome after a Lewis-Tanner esophagectomy with or without a pyloroplasty, 13% of patients who did not have the drainage procedure had delayed gastric emptying [88]. A pyloromyotomy was shown to be as effective [89, 90]. Although meta-analyses have not proven the role of pyloroplasty and other factors are probably contributory to gastric emptying, based on our own experience, we perform pyloroplasty for all patients, except in those whose stomach length is short and foregoing the pyloroplasty could preserve more length of the gastric conduit.

Our preferred conduit is the gastric tube because of its ease of preparation and reliability. Right ileo–colonic interposition is our second choice for esophageal replacement. Colonic interposition reconstruction is associated with higher morbidity rates, such as more blood loss, longer operating duration and higher anastomotic leak rate [91]. In 57 patients who had colonic interpositions, the reasons of using the colon as the esophageal substitute were prior gastrectomy in 34 (59.6%), tumor involvement of the stomach in 18 (31.6%), presence of peptic ulcer in 3 (5.3%) and for other reasons: 2 (3.5%). Four patients (7%) developed ischemia and required re-exploration, nine (15.8%) had anastomotic leak and two patients (3.5%) died within 30 days of surgery [92].

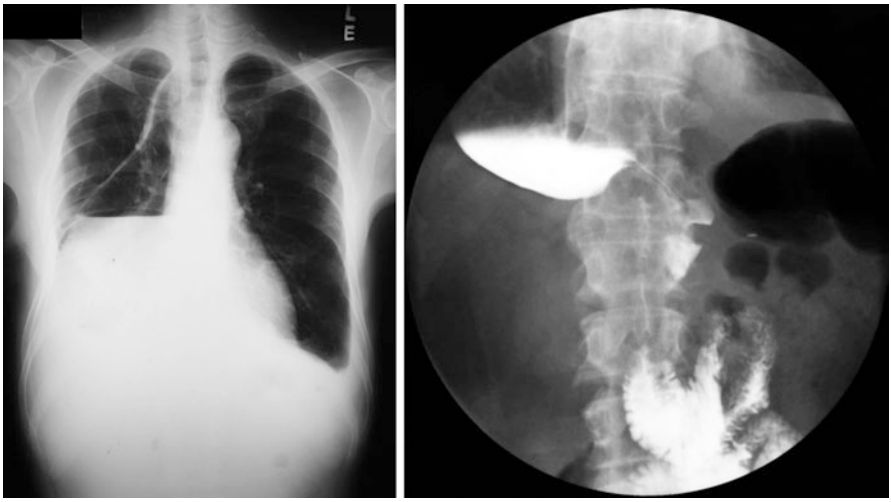


Fig. 17.4 Distended intrathoracic stomach as a result of a wide gastric tube rotated and flopping into the right paravertebral space. Right panel: Dilated stomach with the fluid level. Left panel: A contrast study showing the hold-up of contrast in the dilated stomach. This is not the site of the pyloroplasty

Our preferred route of reconstruction when cervical anastomosis is performed is the retrosternal route. We see several advantages over the posterior mediastinum as the route of reconstruction. Compared to the posterior mediastinal route, longer gastric conduit transit time in the retrosternal route has been described, which did not translate into difference in dysphagic symptoms and quality of life of patients [93]. In our own experience, the use of retrosternal route is in fact associated with less frequency of delayed gastric emptying. It contrasts with the posterior mediastinal route where the gastric conduit could flop into the right paravertebral space resulting in distension or twisting (Fig. 17.4). In case of residual tumor left in the posterior mediastinum after resection, reconstruction via the retrosternal route prevents tumor ingrowth from recurrent disease. Postoperative radiotherapy can also be given to the tumor bed, avoiding injury to the gastric conduit. Another application of retrosternal route is when the reconstructive phase of the surgery precedes the resection phase. The conduit is brought up to the neck via the new surgical plane (retrosternal route) before the thoracotomy for tumor resection. This is a routine practice by the authors when a colonic interposition is planned.

It has been reported that the retrosternal route is associated with increased cardiopulmonary morbidity [93], but in a meta-analysis it was not associated with increased perioperative morbidity compared to reconstruction through the posterior mediastinum [94]. In our experience, no difference was found comparing the posterior mediastinal and retrosternal routes of reconstruction in intraoperative blood loss, operative duration, cardiopulmonary complications, leak and mortality rates [95].

Much effort was made in studying the optimal esophageal anastomosis after esophagectomy. Anastomotic leak and stricture remain problematic areas in many centers around the world. The location and technique of anastomosis affect the outcomes of esophagectomy [96]. Anastomosis can be located in the neck or in the thoracic cavity. It is generally believed that cervical anastomosis is associated with a higher leak rate but it is more easily managed and results in lower mortality rate [97]. However, in our experience, a cervical anastomosis is no more likely to leak compared to its intra-thoracic counterpart, both occurring at around 4%. Mortality rates were also similar. If hand-sewn method is used, the stricture rate is also similar at around 10%.

The technique of anastomosis was studied in a randomized controlled trial comparing a circular stapling device and a hand-sewn method. Similar leak rates were found; 1.8% for hand-sewn and 5% for circular stapler [98]. The stricture rate, however, was fourfold with the stapling technique 9.1% vs. 40% [98]. Our preferred way of anastomosis thus remains a one-layer hand-sewn method with a fine monofilament suture. The exception being a low mediastinal anastomosis performed via the abdomen for a gastric cardia lesion where exposure for a hand-sewn method is generally inadequate. For these lesions, our experience has evolved from using a circular stapler to linear stapling which involves side-to-side anastomosis of the esophageal stump to the gastric conduit and stapled closure of the defect.

The authors' institution has previously reported the leak rate of below 5% and that most of the leaks were related to technical faults [14, 99] such as the tension between the conduit and esophageal stump or conduit ischemia. The principles of management of leak are early detection, maintenance of nutrition and treatment of sepsis. Depending on the severity, the general condition of the patient and the location of the anastomosis, approaches to manage anastomotic leak vary. Most leaks from cervical anastomoses can be managed conservatively by drainage via cervical wound and nasogastric tube drainage and enteral nutrition. Our practice has been to deploy a negative pressure dressing system to the cervical surgical bed to facilitate drainage and promote healing by granulation. Surgical exploration for drainage is reserved for large-sized defects and leaks that do not respond to the strategy aforementioned. In patients with frank conduit ischemia, it is important to diagnose and explore early before actual leakage occurs and sepsis ensures. Immediate re-anastomosis is sometimes possible in stable patients with limited necrosis. Historically take-down of the ischemic stomach is necessary for most and staged reconstruction is later carried out. In selected patients whose extent of conduit necrosis does not allow immediate re-anastomosis, intervening free jejunal flap reconstruction with manubrial resection to facilitate exposure may be performed. The use of indocyanine green fluorescent angiography is an increasingly useful adjunct in assessing conduit vascularity intraoperatively (Fig. 17.5a and b). This should reduce the incidence of ischaemic conduits and may be anastomotic leak rates as well [100].

Management of leaks has improved, so that most patients are successfully salvaged. In the 1960s and 1970s, our leakage rate was 16%, and 61% of patients died,

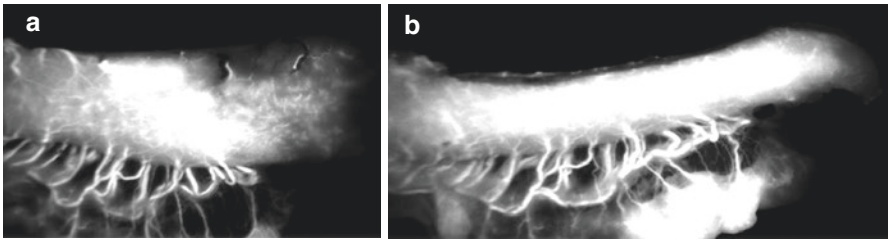


Fig. 17.5 (**a**) Indocyanine green fluorescence showing poor perfusion at the tip of the gastric conduit. (**b**) Indocyanine green fluorescence showing good perfusion at the new tip of the gastric conduit after resection of the poorly perfused segment

making a leak-related mortality of 9.8%, in the 1980s and 1990s, leakage rate was 3.5%, 35% of whom died, making a leak-related mortality rate of 1.2%. This subsequently improved to 3.2%, and there was no mortality [37, 99, 101].

17.4.4 Postoperaive Management

The appropriate selection of surgical procedures, its meticulous execution, and perioperative care have a causal relationship with morbidity and mortality. For most patients, a standardized clinical pathway is helpful, along the lines of ERAS protocol (Table 17.1):

- Most patients have endotracheal tube extubation in the recovery room, unless the surgery has been prolonged, complicated, or performed in high-risk patients.
- Epidural analgesia is most important in postoperative pain relief. It is continued for the first 4–5 days after surgery and can be replaced by patient-controlled analgesia or oral medications. Recently, a propensity score-matched analysis revealed postoperative scheduled intravenous acetaminophen decreased the rate of opioid use and may contribute to ERAS program for esophagectomy [102].
- At the author's unit, the nasogastric tube is usually removed the day after surgery. Early removal of the tube results in more comfort and facilitates coughing. There is no need to replace the tube unless progressive dilatation of the gastroplasty is seen, but this is uncommon with a narrow gastric tube with a drainage procedure.
- All patients have a bronchoscopic examination on the first postoperative day to check for recurrent laryngeal nerve injury although this is unusual in the absence of superior mediastinal or cervical lymphadenectomy. Judicious use of intravenous fluid is also important to avoid over-hydration and pulmonary edema.
- Chest physiotherapy is instituted and early ambulation encouraged.
- Deep vein thrombosis prophylaxis is continued.
- Chest drain is removed on day 4–5 post operation, the daily output should be less than 200–300 ml per day.

- Liquid by mouth is started on day 1 post operation; usually, a carbohydrate drink can be taken as sips of fluid. Generally, by day 3–4 patients can take a liquid diet freely. A soft diet is started on day 5 post operation. The early oral intake does not increase the incidence of anastomotic leak and pneumonia [103]. An oral contrast study is not routine unless leakage is suspected or if there is evidence of delayed gastric emptying. The author does not place feeding jejunostomy as a routine because early oral alimentation is successful in most patients, and most do not need supplementary nutritional support. Should oral intake is delayed, such as when anastomotic leak occurs; endoscopic placement of a naso-duodenal tube for feeding will suffice.

17.4.5 Other Morbidities and Mortality

In our experience, the commonest medical complications are atrial fibrillation and pulmonary morbidities (pneumonia, atelectasis, sputum retention, and respiratory failure). Atrial fibrillation affects about 20% of our patients. Although it is relatively benign and is easily controlled with appropriate anti-arrhythmic medications, it may be reflective of underlying more serious events, such as pneumonia, anastomotic leak, or conduit ischemia [104]. Among a cohort of 921 patients, 198 (22%) developed postoperative atrial fibrillation; pulmonary complications affected 42% of patients in the atrial fibrillation group compared to only 17% among the controls. Similarly, anastomotic leak was more common (6.9% vs. 1.4%, $p = 0.035$); surgical sepsis was also four times more frequent ($p = 0.001$). Occurrence of atrial fibrillation should prompt a search for an underlying cause. It is our policy to have a low threshold of performing endoscopy to look for complications with the anastomosis or conduit whenever such arrhythmia occurs, so that we can intervene early if required.

Pneumonia and respiratory failure occur in 15.9% of our patients and are responsible for 55% of the hospital mortality. A cohort study from our institution demonstrated that advanced age, tumor location above the tracheal bifurcation, and long operative duration were independent risk factors for pulmonary complications [15]. The chance of developing a major respiratory complication was twice in those older than 70 years, and the death rate was fourfold higher. Patients with a supra-carinal tumor had a 3.5 times risk of developing pulmonary complications when compared to tumors located more distally. The measures to reduce pulmonary complications include cessation of smoking preoperatively, early institution of chest physiotherapy, avoidance of recurrent laryngeal nerve injury; avoidance of fluid overload, use of smaller-sized chest tube, early ambulation, regular bronchoscopic toileting, and early tracheostomy should sputum retention be severe. Postoperative pain control with epidural analgesia is invaluable [105].

The hospital mortality rate in the 1980s in the authors' institution was 11–15.5% [14, 106]. The respective figures reduced to 3.2% in early 1990s and 1.1% in late 1990s, respectively [15, 106]. Mortality rate since 2000 has remained below 3%. Surgical volume and experience have an obvious positive impact on the outcome.

17.5 Palliation

Various treatment modalities are available for palliation. Radiotherapy +/− chemotherapy is used in selected patients. Pain and dysphagia are the most frequent symptoms that needed palliation in our patients. Pain anesthesiologists are often an integral part of our management. To palliate dysphagia, our preferred choice of endoscopic treatment is the placement of self-expanding metallic stents (SEMS) [107]. Palliative resections and bypass procedures such as the Kirschner bypass using gastric or colonic conduits are seldom necessary nowadays [108, 109].

17.6 Summary

In Hong Kong, ESCC remains one of the most challenging cancers. Steady advances have been made in the last three decades in staging methods, surgery, and multimodality strategies. Like many centers in the world, a low mortality rate after esophagectomy has been achieved. Morbidity rates, however, remain substantial. Our results are commensurate with international standards and benchmarking [110]. Although progress has been made in prolonging long-term survival, there is still much room for improvement. Owing to positive results from neoadjuvant therapy, watchful waiting after neoadjuvant therapy, and salvage surgery on an as-needed basis in selected patients with good clinical response is being tested. Results from such research may allow finer individualization of treatment strategy in patients suffering from this highly lethal cancer, so that survival and quality of life can be optimized.

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Squamous Cell Carcinoma of the Esophagus: The Indian Experience

18

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Abstract

Esophageal cancer is a relatively common cancer among both men and women and is the fourth commonest cause of cancer-related deaths in India. Squamous cell carcinoma is the most frequent histology (80%) although there has been a recent relative increase in the incidence of adenocarcinoma. Etiological factors for esophageal squamous cell carcinoma (ESCC) in India are unique and include alternative forms of tobacco consumption, alcohol, tea drinking, nutritional and dietary factors, and possibly human papilloma virus (HPV) infection. Most patients present with advanced stage of disease and in poor general health at the time of diagnosis. Diagnostic and staging workup of ESCC in India is similar to other countries although the use of PET-CT and endoscopic ultrasonography is not universal. Treatment of early stage disease (T1/T2 and N0) is primarily surgery alone, while patients with more advanced, resectable disease (T3/T4a or N+) is usually neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. Unresectable or metastatic disease is treated with palliative radiotherapy or esophageal stenting. Surgical technique is widely variant with both transthoracic and trans-hiatal esophagectomy being performed along with minimally invasive esophagectomy depending on the specialization and expertise of the surgeon. Research on esophageal cancer has focused on epidemiology, etiological factors, primary treatment options, neoadjuvant and adjuvant therapy, surgical techniques, perioperative care, and palliative treatment. The formation of the Indian Society for Diseases of the Esophagus and Stomach (ISES) is expected to

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promote collaborative research and standardization of treatment across the country.

Keywords

Esophagus · Esophageal cancer · Squamous cell carcinoma

18.1 Introduction

Esophageal cancer is a morbid disease and globally is a major cause of cancer-related deaths [1]. Worldwide, *squamous cell carcinoma* is the commonest type of esophageal cancer although there has been an exponential increase in the incidence of adenocarcinoma in the western world in the past three decades [2–5]. The overall disease spectrum has unique geographic distribution with squamous cancers being common in Asia (countries like China, Iran, India, Japan, and Korea) and adenocarcinomas of the gastroesophageal junction and lower esophagus in North America and Europe [2, 4, 5].

18.2 Epidemiology, Etiology, Diagnosis, and Staging of Squamous Esophageal Cancer in India

18.2.1 *Epidemiology* of Esophageal Cancer in India

In India, esophageal cancer is the fourth commonest cancer in males and the fifth commonest cancer in females, with an estimated incidence of over 48,000 new cases in 2008 [3]. It is also the fourth commonest cause of cancer-related deaths in India [3]. As in most parts of Asia, the majority of esophageal cancers in India are squamous cell carcinoma [6, 7] although there has been a recent increase in the incidence of adenocarcinoma [8]. In a retrospective study [9] involving 1000 esophageal cancer patients over a 16-year period, patients were divided into four cohorts of 4 years each. Lower esophageal cancers outnumbered the mid-esophageal cancers in the fourth cohort though mid-esophageal cancers represented the most common site of malignancy overall. However, there have been no systematic prospective studies on the changing epidemiology and histopathological profile of esophageal cancer in India. Regional variations in the incidence of esophageal squamous cancer have been observed in India with markedly higher rates seen in the Kashmir valley [10] and north-eastern India [11]. Overall, approximately 80% of all esophageal cancers in India are squamous cancers with 20% being adenocarcinomas.

18.2.2 Etiology

The common risk factors for esophageal squamous cell carcinoma (ESCC) in India include smoking, alcohol consumption, combination of both, low socioeconomic status, deficiency of micronutrients, dietary factors, and intake of hot beverages. Various case control and other studies from certain areas of high incidence in India, such as the Kashmir valley demonstrate that there are unique risk factors in these areas for the development of esophageal squamous carcinoma [12–17]. There have been several other studies from virtually all parts of the country evaluating various risk factors including tobacco, alcohol, tea drinking, and other nutritional factors [11, 18–26].

18.2.2.1 Tobacco Consumption

Tobacco consumption in India is peculiar in the sense that smokeless tobacco use is far more prevalent than smoked tobacco. A number of smokeless tobacco products are popular and freely consumed across all age groups in India [27]. In a survey of over 300,000 adults, 30% used tobacco in some form with over 20% using chewed tobacco or pan masala. Chewed tobacco is considered to be one of the important risk factors for squamous esophageal cancer [11, 18, 19, 22, 23]. In a case–control study of 702 cases and over 1600 controls, Dar and colleagues found that cigarette smoking was not a major risk factor for esophageal cancer in the Kashmir valley [12]. However, the consumption of smokeless tobacco (nass) and hookah smoking were associated with a significantly increased risk [12]. Nass chewing had an increased risk of esophageal squamous cancer with an OR of 2.88. Ever-hookah smoking was associated with an increased risk of ESCC (OR 1.85; 95% CI-1.41–2.44). They also found association between the intensity, duration, and cumulative amount of hookah smoking [12].

A study conducted in South India identified both smoked and chewed tobacco to be associated with an increased risk of squamous esophageal cancer with risk ratios of 2.8 and 2.5, respectively [18]. Another study found a risk of 3.16 times associated with consumption of betel leaf with tobacco and 1.95 times with bidi smoking [23]. In a case–control study of 343 cases and 686 controls, Nandakumar and colleagues [22] found that chewing areca preparations was associated with an increased risk of developing cancer in the middle third of the esophagus; in contrast, chewing tobacco was associated with lesions in the lower third [22]. A study from the northeastern state of Assam (which has among the highest rates of esophageal cancer in India) found betel nut chewing to be associated with higher risks of developing esophageal cancer when compared to smoking and alcohol consumption [11]. The adjusted odds ratios for persons who chewed betel nut more than 20 times a day in comparison with non-chewers were 13.3 for males and 8.4 for females [11]. A meta-analysis of case–control studies evaluating areca nut as a causative factor in esophageal squamous carcinoma reported areca nut use to be a significant and independent risk

factor with an odds ratio of 3.05. Areca nut chewing with smoked tobacco had an additive effect that increased the risk of esophageal cancer by a factor of 6.79 [28]. A case–control study conducted at the authors' institute included 442 cases of esophageal cancer and 1628 hospital controls [19]. Data was collected on chewing, smoking, alcohol habits, and dietary habits. The results indicated a moderate 1.1 times excess risk for chewers of pan (betel-leaf) with tobacco, 1.8-fold excess risk for bidi smokers and two-fold for cigarette smokers [19].

18.2.2.2 Alcohol

Alcohol consumption is not as common in India as it is in other parts of the world, both in frequency as well as quantity of consumption [29, 30]; however, it is one of the known etiological factors for esophageal cancer in India. In a case–control study conducted in South India with more than 500 esophageal cancer patients and over 1700 controls, alcohol consumption was shown to increase the risk by more than three times [26]. A significant dose–response relationship was observed for the duration of drinking and average daily amount of alcohol consumption with ESCC. Among all types of alcohol analyzed, arrack, a locally brewed preparation, showed the highest risk-4.5 times that of the controls [26]. The intake of other types of alcohol (gin, rum, whisky, or brandy) did not show a significant increase of risk, but this might be related to the amount of alcohol consumed rather than the type, as these types of alcohol cost much more than arrack. In another study conducted in South India, the risk was found to be 3.5 times higher with alcohol consumption [18]. In the study conducted in the authors' institute [19], alcohol use was found to be associated with an increased risk of 1.8 times while a case–control study carried out in Kerala showed an increased risk of 2.33 times for regular alcohol use [24]. Almost all studies that have evaluated the role of tobacco, smoking, and alcohol consumption have found an elevated risk of esophageal cancer with the use of alcohol increasing the risk by 1.8–3.5 times.

18.2.2.3 Dietary Factors

It is widely recognized that a diet high in vegetables, fruits, and other plant-based foods and low in animal fats can reduce the risk of cancer [31]. In a case–control study conducted at the All India Institute of Medical Sciences, low consumption of green leafy vegetables, other vegetables, and consumption of alcohol were the three factors that are associated with increased risk for esophageal cancer [25]. Other researchers also found an increased risk with less consumption of green and leafy vegetables and fruits and consuming more of spicy, fried, and hot food and beverages [21, 23]. A case–control study done in Assam found a positive association between increased risk of esophageal cancer and consumption of spicy food, hot foods and beverages while green leafy vegetables and fruits were protective for esophageal cancer [11]. The risk associated with consumption of locally prepared food items, e.g., kalakhar (a food additive) was found to be eight times.

Consumption of salt tea has been associated with increased risk of esophageal cancer in Kashmir, where 90% of the cases had history of salt tea consumption [15]. The mechanism of carcinogenic activity of salt tea has been attributed to the

presence of nitroso compounds, which get activated due its peculiar method of brewing and presence of salt. Hyperthermic injury to the esophageal mucosa due to consumption at high temperatures may also be responsible [16]. Presence of higher levels of nitrosamines was found in the sun-dried vegetables and chilies, which are commonly consumed in Kashmir [32]. A study conducted in the authors' institute showed a four-fold higher risk with tea drinking [19]. They also found that consumption of fresh fish was associated with a 20% reduction in the risk.

A study conducted in Jammu with 200 case–control pairs, evaluated the role of dietary characteristics as risk factors for esophageal cancer [17]. Among the dietary and lifestyle risk factors, snuff was highest (OR = 3.86, 95% CI = 2.46–6.08) followed by salt tea (OR = 2.53, 95% CI = 1.49–4.29), smoking (OR = 1.97, 95% CI = 1.18–3.30), sun-dried food (OR = 1.77, 95% CI = 1.10–2.85), and red chili (OR = 1.76, 95% CI = 1.07–2.89) [17]. Pickle consumption was associated with an odds ratio of 2.5 in a study conducted in South India [18].

18.2.2.4 Low Socio-economic Status

Studies have associated esophageal squamous cell carcinoma risk with low *socio-economic status*. A case–control study was conducted to assess the association of multiple indicators of socio-economic status and esophageal squamous carcinoma risk in the Kashmir valley [13]. A total number of 703 histologically confirmed ESCC cases were matched with 1664 controls with respect to age, sex, and district of residence. Composite wealth scores were constructed based on the ownership of several appliances using multiple correspondence analyses. Higher education, living in a constructed house, use of liquefied petroleum gas and electricity for cooking, and higher wealth scores showed an inverse association with esophageal cancer risk. Compared to farmers, individuals who had government jobs or worked in the business sector were at lower risk of esophageal squamous cancer. They also found an inverse association between poor oral hygiene and increased risk of esophageal cancer, suggesting that oral hygiene could be used as a surrogate marker for socio-economic status [13, 14].

18.2.2.5 Genetic Factors

A study from Kashmir [33] which analyzed TP53 mutations in esophageal SCC in 55patients revealed the presence of mutations in 36.4% (20/55) tumors. Another study analyzed the interaction of various habit-related factors and polymorphism of GSTM1/GSTT1 genes toward inducing promoter hypermethylation of multiple tumor suppressor genes [34]. In 112 cases with 130 matched controls, significantly higher methylation frequencies were observed in tobacco chewers than non-chewers for the genes under study ($p < 0.01$) [34].

Other studies have also found a high rate of protein over-expression and alterations in p53 gene expression in subjects with esophageal squamous cancer and correlated a higher expression with increased intake of chilies [35]. These results have been corroborated by other workers who showed that somatic chromosomal mutations, especially in exon 6 of Tp53 gene, among esophageal cancer patients of an ethnically homogenous population of Kashmir valley are closely related to

continued exposure to various common dietary risk factors, especially hot salty tea, meat, baked bread, and 'Hakh' (a preparation of greens), that are rich in nitrosamines and familial cancer history [36].

18.2.2.6 Role of Human Papilloma Virus (HPV)

The role of *Human papilloma virus* as a causative factor for esophageal cancer is unclear. Various studies have demonstrated the presence of HPV in esophageal cancer specimens in the range of 15–80% [37, 38]. Few studies in India have also demonstrated moderate to high HPV positivity rate, although the results are conflicting and the etiological role of this virus remains unclear. One small study evaluated the prevalence of HPV infection in ESCC tumor and adjoining mucosa in 23 patients with paired samples [39]. They found an HPV positivity rate of 87% in esophageal cancer patients and higher rates were seen in smokers [39]. Another study identified HPV DNA in 46% of non-keratinizing squamous cell carcinomas of the esophagus and in none of the keratinizing squamous cell carcinomas or adenocarcinomas postulating an etiological association with this subtype of ESCC [40].

A 2014 meta-analysis of 132 studies evaluating HPV infection in the context of esophageal SCC showed an increased risk associated, especially with HPV-16 infection in Asian countries [41].

18.2.3 Diagnosis

Most patients in India present at advanced stages of disease [42, 43]. The available investigations for diagnosis and staging of esophageal cancer in India include a double contrast barium swallow, upper gastrointestinal endoscopy and biopsy, contrast enhanced computed tomography (CECT) scan of the thorax and upper abdomen, fused positron emission tomography-CT (PET-CT) scan, endoscopic ultrasonography (EUS), and fiberoptic bronchoscopy. The usual workup followed in India in the diagnostic and staging process of a patient suspected to have esophageal cancer include endoscopic mapping of the disease, histopathological confirmation and staging using contrast enhanced computed tomography (CECT) of the thorax and abdomen. Additional diagnostic methods such as endoscopic ultrasound and positron emission tomography with or without computed tomography (PET/PET-CT) are used only in select institutions where the infrastructure and expertise is available. Fiber-optic bronchoscopy is used to rule out involvement of the trachea-bronchial tree in patients with upper and middle third tumors planned for curative treatment.

18.2.3.1 Barium Swallow

Barium swallow is the initial diagnostic investigation in many patients in India presenting with dysphagia. Although it gives information regarding the site, length, and extent of the disease, it is not useful in obtaining a tissue diagnosis and a normal barium swallow can be misleading. Therefore, in the authors' institution, barium swallow is rarely performed in the diagnostic evaluation of patients with suspected

esophageal cancer. However, it is conventionally performed at a primary health center level prior to an endoscopic diagnostic procedure.

18.2.3.2 Endoscopy

Flexible upper gastrointestinal endoscopy visualizing the esophagus from the cricopharynx to the gastroesophageal junction, the stomach and the duodenum is essential to map the extent of the disease, aids in planning the treatment (surgery/*intraluminal brachytherapy*) and is helpful in obtaining a tissue diagnosis by biopsy of the abnormal areas and tumor. In the authors' institute and in several other centers, this is also used to simultaneously introduce a nasogastric tube for *enteral feeding* in patients with grade 3 or more dysphagia.

A number of studies have been done in India on cytological and histological diagnosis of esophageal cancer on endoscopy. One study evaluated the utility of *brush cytology* and its correlation with biopsy in 100 patients with upper gastrointestinal symptoms [44]. Cytohistopathological correlation was found in more than 80% of the cases and the study concluded that brush cytology was an effective method for evaluation and screening of upper gastrointestinal lesions and could be utilized for rapid diagnosis with minimal discomfort to the patient [44]. Two other studies compared the sensitivity and specificity of cytology and biopsy in establishing the diagnosis of esophageal cancer [45, 46]. Both the studies concluded that cytology increases the diagnostic efficacy but also emphasized that cytology alone cannot be used instead of histology due to a high false positive rate [45, 46]. A small study evaluated 48 patients with carcinoma of the esophagus to assess the optimal number of biopsy specimens required to obtain the highest yield [47]. Eight specimens were obtained from each patient; the first two specimens provided a positive diagnosis in 95.8% of cases, and the fifth and sixth specimens increased the positive yield to 100% [47].

18.2.3.3 Endoscopic Ultrasonography

Accurate staging of esophageal cancer is essential to plan the treatment. EUS helps to delineate the different layers of the esophageal wall and it is a useful staging modality in combination with CT and or PET. EUS guided FNA is useful to get a tissue diagnosis from suspicious lymph nodes such as the celiac. Complete EUS, however may not be possible in patients with obstructive growths. Endoscopic mucosal resection can be performed for superficial esophageal cancers restricted to the mucosa without involvement of the lamina propria. Loco-regional staging of the tumor invasion and lymph node involvement done by EUS has shown to be superior to that by CT. The utility of EUS is not well established in evaluation of the residual esophageal disease after neoadjuvant chemotherapy or chemoradiation, as it cannot reliably differentiate between fibrosis due to inflammation or residual/recurrent disease. However, the use of routine EUS in all patients diagnosed with esophageal cancer is debatable as the ability to influence treatment decisions in all cases is unproven. Moreover, due to limited availability of equipment and infrastructure, it is not performed in many centers.

18.2.3.4 Contrast Enhanced Computed Tomography (CECT) Scan of the Thorax and Upper Abdomen

A CECT scan of the thorax and upper abdomen is widely accepted to be the minimum staging investigation for esophageal cancer. CECT scanning in the pretreatment assessment of esophageal cancer in the Indian setting was found to be highly accurate in determination of the tumor "T" stage, invasion of surrounding structures, and distant metastases but not effective in determination of the nodal involvement [48]. The diagnosis of invasion of the tracheobronchial tree was 96% accurate, whereas the invasion of the aorta and pericardium could be predicted in more than 85% of the cases. Previous studies also indicated the utility of computed tomography in patients undergoing surgery for esophageal cancer [49, 50].

18.2.3.5 Positron Emission Tomography (PET/PET-CT)

The addition of CT to PET has resulted in better specificity and sensitivity than either of the modalities alone, as the combined approach gives functional and morphological details in a single investigation. The treatment algorithm for locally advanced esophageal cancer includes neoadjuvant therapy, either chemotherapy alone or in combination with radiotherapy, followed by surgery. Accurate staging is important to avoid unnecessary morbidity due to treatment and futile thoracotomies in metastatic disease. A small study evaluated 28 patients with esophageal carcinoma with contrast enhanced computed tomography followed by PET/CT after two weeks [51]. Nine patients were upstaged by PET/CT compared to CECT, out of which 7 (25%) were correctly upstaged and 2 (7.14%) were falsely upstaged. They concluded that PET/CT improved their ability to detect distant metastases in 25% of patients that were missed by CECT [51]. Unusual sites of metastases, such as muscular metastases have been detected without any morphological evidence of disease [52]. In a study of 156 patients conducted at the authors' institution, 16% of patients with esophageal cancer were found to have distant metastases on evaluation with FDG PET/CT. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for detecting distant metastases were 83.3, 98.4, 92.5, 96.1, and 95.3%, respectively [53]. This study established the incorporation of PET/CT in the staging work up of all patients of esophageal carcinoma fit for curative intent therapy in the authors' institution.

The clinical utility and accuracy of various imaging modalities in the diagnosis of esophageal cancer are summarized in Table 18.1.

18.2.4 Staging

TNM staging is one of the most important and reliable prognostic variables. Standardized and accurate staging of cancer is important for uniform reporting and comparison of results from various centers. It also determines whether the intent of treatment is curative or palliative. It is based on clinical examination and information obtained by imaging: CT scan/PET-CT and/or endoscopic ultrasonography (EUS).

Table 18.1 Clinical usefulness and accuracy of modalities used in staging of esophageal cancer

Modality	Clinical utility	Overall accuracy (%)
Computed tomography (chest, abdomen)	Invasion of local structures (airways, aorta)	≥90
	Metastatic disease	≥90
Endoscopy	Local tumor (T) staging (operator dependent)	80–90
Ultrasonography (with or without fine-needle aspiration of lymph nodes)	Local nodal (N) staging (operator dependent)	70–90
Positron emission tomography	Metastatic disease, assessing response to neoadjuvant therapy	≥90

The eighth edition of the AJCC TNM classification came into effect from January 2017 [54].

The key changes in the eighth edition compared to the seventh edition are as follows:

1. The definition of cancer location made during esophagoscopy has changed from the upper edge (seventh edition) to the epicenter of the tumor (eight edition), both referenced to distance from the incisors.
2. Carcinomas with epicenters no more than 2 cm beyond the GE junction are classified as esophageal cancers, those with epicenters beyond 2 cm are classified as stomach cancers.
3. Includes clinical stage groups before any treatment (cTNM) and pathological stage groups post neoadjuvant therapy (ypTNM) that has significant prognostic implications [54].

18.2.5 The Tata Memorial Centre Experience

The authors' institution, the Tata Memorial Centre, is the largest tertiary-level cancer center in the country and is a high volume center for treatment of esophageal cancer. Between 1200 and 1300 new patients with esophageal cancer are seen every year, most of them presenting in advanced stage of disease or in an emaciated condition, precluding potentially curative treatment. Squamous esophageal cancers predominate in a ratio of 80:20 and the commonest location of tumors are in the lower third of the esophagus. The typical diagnostic workup of patients with a good performance status includes a detailed flexible fiber-optic upper gastrointestinal endoscopy with mapping of the disease and biopsy, PET-CT scan with contrast, pulmonary function tests with diffusion coefficient of carbon monoxide (DLCO) and cardiac evaluation. Flexible fiber-optic bronchoscopy is performed in patients with upper and middle third lesions and those with an obvious change of voice; endoscopic ultrasonography is done selectively for patients with low volume disease on CECT scan (to confirm early disease amenable for upfront surgery) or in borderline

resectable disease after neoadjuvant therapy. This diagnostic workup is curtailed in patients who are emaciated and not fit for radical therapy and in patients with obviously metastatic disease. Patients who are high risk for surgery due to co-existing comorbidities undergo a thorough cardio-pulmonary evaluation and are discussed in a special "high-risk multidisciplinary team" meeting by surgeons, intensivists and critical care specialists, anesthesiologists, and pulmonary physicians to optimize them prior to surgery. The preferred therapeutic approach is discussed in a subsequent section of the chapter.

18.3 Treatment of Squamous Esophageal Cancer in India

18.3.1 Treatment

India is a vast and populous country with significant resource constraints. The wide variation in availability of facilities and technical expertise across different regions has made standardization of treatment a difficult process. While the establishment of 27 Regional Cancer Centres across the country has partially addressed the issue, the urban–rural divide and between-center variability of care is still considerable. Efforts by the authors' institute and the National Cancer Grid (NCG) have culminated in the establishment of uniform esophageal cancer treatment guidelines tailored to the country's varied levels of expertise and availability of infrastructure (Fig. 18.1). One of the core recommendations of the guidelines is establishment of multi-disciplinary teams for management of esophageal cancer. While some major cancer centers in India have a multi-disciplinary team including a surgical, medical, and radiation oncologist in place, several others do not, and one of the biggest challenges has been to ensure the same standards of care and decision-making regardless of whether the patient initially presents to a surgeon, gastroenterologist, medical, or radiation oncologist.

18.3.1.1 Patient Evaluation

The initial evaluation of the patient includes assessment of physical (ECOG performance) status, oral hygiene, nutrition, and cardiopulmonary status. This is particularly important in the Indian scenario, where patients generally present in an advanced stage and in poor general health. Generally, only patients who are ECOG performance score (PS) 0 or 1 are selected for radical treatment. Assessment of oral hygiene is necessary because of the high prevalence of tobacco chewing in India [27, 30] and the possibility of co-existing oropharyngeal malignancy. Since most patients present with significant dysphagia and some degree of nutritional impairment, assessment of nutritional status, and early institution of rehabilitation is key. Malnutrition is found to be an independent risk factor for severe morbidity after esophageal surgery (HR 3.07) [55]. The enteral route is the preferred route of nutritional rehabilitation due to its inherent advantages of keeping the gut in use, as well as the ease of administration and relatively low complication rate compared to parenteral nutrition [56]. All patients considered for radical treatment undergo

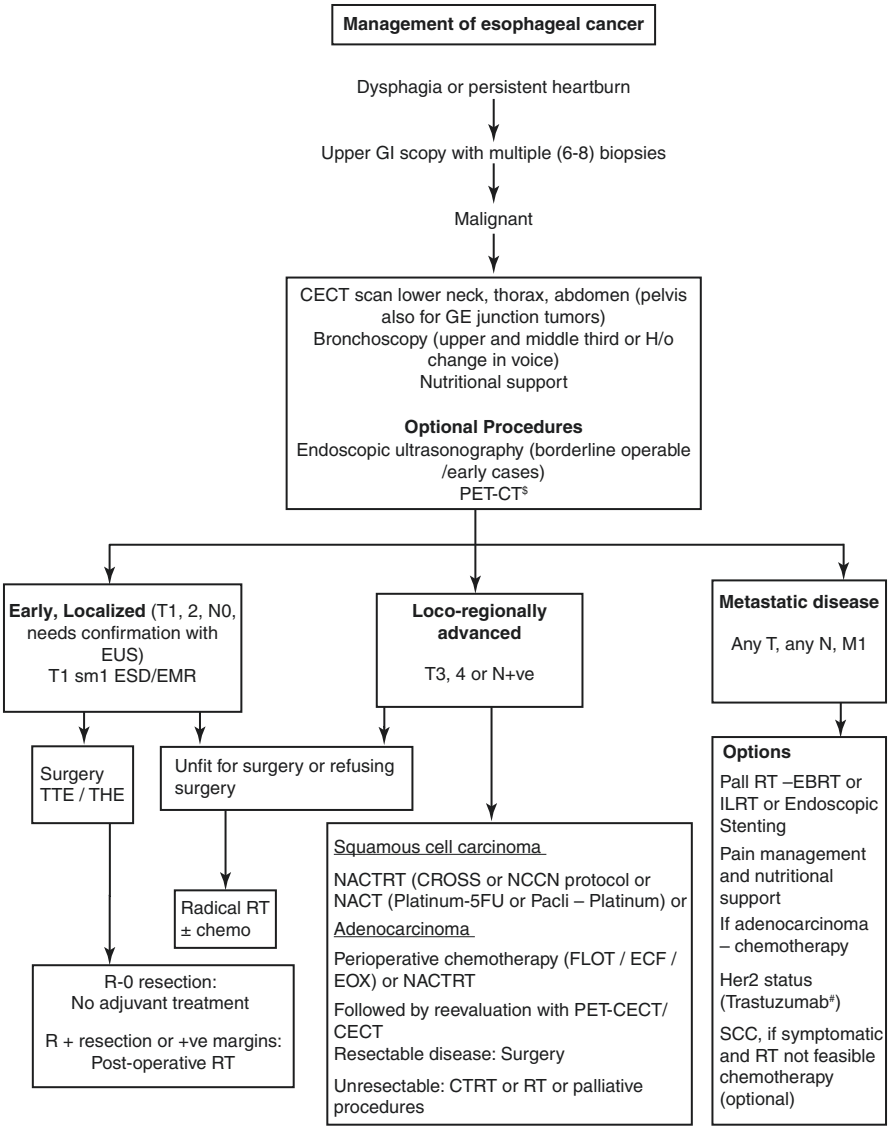

Fig. 18.1 Management of esophageal cancer

extensive evaluation of cardio-pulmonary status including pulmonary function tests (PFT), 2D Echocardiography and in select cases, stress cardiac testing. Pulmonary rehabilitation is started at the outset for all patients planned for radical treatment with the active involvement of the chest physician and physiotherapists. A Japanese study showed that institution of chest physiotherapy at least 7 days prior to surgery decreased the rate of post-esophagectomy pulmonary complications from 24.3% to

6.4% [57]. Early institution of chest physiotherapy, and tobacco and alcohol cessation are routinely advocated as soon as a diagnosis of esophageal cancer is made.

18.3.1.2 Principles of Management

Broadly, decisions regarding treatment are based on the anatomical location and stage of disease and the performance status of the patient. The authors' repeated emphasis on the performance status of the patient is primarily because poor general health precludes potentially curative treatment in a considerable proportion of patients in India. Concurrent radical chemoradiation is the preferred therapeutic strategy for lesions in the upper third of the esophagus, i.e., within 5 cm of the cricopharynx while surgery is the preferred treatment for lesions in the middle and lower third esophagus. Early stage lesions (T1/T2, N0) are usually treated by surgery alone for middle and lower third lesions. Endoscopic mucosal resection (EMR), though a less morbid procedure is not widely practiced in India primarily due to the fact that very few patients present at a stage amenable to the procedure and also due to limited availability of expertise in select centers across the country. Patients with locally advanced disease (T3/T4, N+) undergo multi-modality treatment, generally with neoadjuvant chemotherapy [58, 59] or neoadjuvant chemoradiotherapy followed by surgery. Patients with metastatic disease are usually treated with palliative radiotherapy or esophageal stenting or a combination of the two and rarely with palliative chemotherapy.

18.3.2 Surgery

Surgery is the preferred modality of treatment for middle and lower third esophageal cancer [60–63]. Most patients in India with early stage disease (T1/T2, N0) are considered for upfront surgery while patients with locally advanced disease undergo surgery after neoadjuvant therapy. Rarely, patients with residual disease after radical chemoradiotherapy are taken up for esophagectomy albeit at the cost of significantly higher post-operative morbidity. In spite of the established role of surgery in the radical treatment of esophageal cancer, there is very little consensus on what constitutes a standard esophagectomy in terms of approach, extent, and template for lymph node dissection. This may, in part be, because there is no organ-specific surgical training program in India. Esophageal resections in India are performed by surgeons from varied surgical specialties including general surgery, gastrointestinal surgery, thoracic surgery, and surgical oncology.

18.3.2.1 Approach

Trans-thoracic esophagectomy predominantly by a modified McKeown three stage procedure is considered to be the standard approach by most thoracic surgeons and surgical oncologists while most general and gastrointestinal surgeons prefer a transhiatal approach particularly for lower third tumors [60–64]. In a large series of 367 trans-hiatal esophagectomies performed over a period of 18 years at the All India Institute of Medical Sciences, the five-year overall survival was 38% with a

post-operative mortality rate of 12% [63]. Since there is no strong evidence favoring one approach over the other, both approaches are widely practiced in India with a bias toward trans-thoracic approach in high-volume oncology centers. In these centers, trans-hiatal resection is performed in limited numbers as a compromise surgery in patients with poor pulmonary function or extensive pulmonary fibrosis precluding trans-thoracic resection.

18.3.2.2 Lymphadenectomy

Lymphadenectomy for esophageal cancer is a controversial topic in India, as in many other parts of the world [65]. Surgical oncologists who predominantly perform trans-thoracic esophagectomies place more emphasis on extensive lymph nodal clearance. Infra-carinal nodal dissection or a standard two-field dissection is considered to be the standard template for dissection by most surgeons performing a trans-thoracic esophagectomy. In India, very few centers with high volumes of esophageal surgery practice three-field lymphadenectomy routinely. The increase in lymph node yield with more radical lymphadenectomy needs to be balanced against an increased post-operative morbidity, primarily with recurrent laryngeal paresis and pulmonary complications. In contrast, the lymph node yield achieved by a trans-hiatal resection is low and is usually limited to the peri-esophageal lymph nodes. However, as mentioned in the previous section, trans-hiatal resections are usually performed only as a compromise surgery in high-volume centers.

18.3.2.3 Minimally Invasive Surgery

Surgeons in India were early to adopt minimally invasive esophagectomy. A few high volume centers have published data showing better results with a minimally invasive approach with respect to pulmonary morbidity and operative blood loss [62, 64, 66–68]. A prospective study comparing minimally invasive esophagectomy with open esophagectomy [66] demonstrated comparable results in terms of lymph node yield (9.5 vs. 7.3), duration of surgery (312 min vs. 262 min), average blood loss (276 ml vs. 313 ml), and morbidity (26.5% vs. 28.6%). A larger series [62] of 463 thoracoscopic esophagectomies demonstrated a lower morbidity rate (16%) and postoperative mortality rate (0.9%). The results of the TIME trial and the more recent MIRO trial have reiterated the benefit of minimally invasive esophageal surgery on short-term postoperative outcomes [69, 70]. The 3-year follow-up of the TIME trial showed a trend toward improved overall and disease-free survival with the minimally invasive approach [70]. With this evidence, the superiority of minimally invasive esophagectomy with respect to short-term outcomes and equivalence, if not superiority in long-term oncological outcomes, has been established. This has reflected in the evolving trend of esophageal surgery in India, with most centers offering the minimally invasive approach. The safety of thoraco-laparoscopic esophagectomy has also been established in the older patient population in India [71].

Different surgical groups in India use different patient positions for thoracoscopic esophagectomy with lateral, prone and more recently, semi-prone positions being utilized based on surgeon preference. The prone or semi-prone position offers

the advantage of not requiring lung isolation for thoracoscopy, whereas the lateral position offers better exposure to the superior mediastinum for radical lymph node dissection. The authors' preference is to perform MIS esophagectomy through the lateral approach.

Robotic surgery for esophageal cancer has just started in India and is confined to few centers currently. A series of 83 robotic esophageal resections showed comparable post-operative outcomes to thoracoscopic esophagectomy with no conversion. The docking and operating time decreased significantly as experience increased [72]. Equivalent long-term oncological outcomes with robotic resections as compared to open surgery have been shown in recent reports [73]. However, no distinct advantage over thoracoscopic esophagectomy has been demonstrated. Specially in the Indian scenario, where the cost of robotic instruments and other consumables may exceed that of any benefit in terms of hospital stay, the advantages of robotic esophagectomy over thoraco-laparoscopy need careful consideration.

18.3.2.4 Reconstruction

The stomach is the preferred conduit for reconstruction and in cases where the stomach is not available, the colon, either right or left side, is the preferred alternative. The posterior mediastinum is the most commonly used route of reconstruction, the retrosternal route being used only when the patient is being considered for post-operative radiotherapy to the mediastinum or when the surgeon adopts an abdomen-first approach to a trans-thoracic esophagectomy. A small randomized study of 49 patients comparing posterior mediastinal versus retrosternal conduit placement [74] found both routes to have comparable outcomes. The anastomosis is usually performed in the neck either by a stapled or handsewn technique [75]. Both techniques are widely practiced in India depending upon the surgeon's preference and cost constraints. Some clinical trials on anastomotic technique are described in a subsequent section of the chapter.

18.3.3 Multi-modality Management

India was late to embrace multi-modality management in esophageal cancer. This may have been primarily because of the delayed establishment of multi-disciplinary teams and also the fear that multiple modalities of treatment may not be well tolerated by the generally frailer Indian patients. In view of the strength of evidence supporting neoadjuvant therapy currently, patients with locally advanced potentially operable esophageal cancer are treated with either neoadjuvant chemotherapy [58, 59] or neoadjuvant chemoradiotherapy. The common chemotherapy regimens include doublets consisting of cisplatin with 5-fluorouracil or cisplatin with paclitaxel, while few centers use triplets of cisplatin, 5-fluorouracil and either paclitaxel or docetaxel, which have superior response rates at the cost of higher morbidity. The commonly followed schedule is to administer three cycles at three weekly intervals followed by reassessment with CT scan imaging and surgery between 4 and 6 weeks after the last cycle of chemotherapy. The results with neoadjuvant chemotherapy

have been encouraging in terms of tolerability and completion of planned treatment; however, no long-term outcome data is available. The CROSS and the NEOCRTEC trials have established the role of neoadjuvant chemoradiation in esophageal SCC. Both trials have shown advantage with this approach in terms of survival, pathological complete response, and R0 resection rates [76, 77]. In light of this evidence, neoadjuvant chemoradiotherapy is also rapidly gaining popularity in India. The most commonly used protocol is the CROSS protocol, i.e., radiation 41.4 Gy in 23 fractions of 1.8 Gy over 5 weeks with concurrent weekly chemotherapy, paclitaxel 50 mg/m^2, and carboplatin at AUC 2. Most centers are stringent in patient selection for this regimen and the early results have been very encouraging. However, despite improved cancer-specific outcomes, this approach has shown an increase in severity of postoperative complications and 1 year mortality as elucidated in the recent NeoRes trial, which needs to be kept in mind while adopting this approach [78].

Postoperative radiotherapy or chemoradiotherapy is not practiced as a routine after esophagectomy. The use of adjuvant radiotherapy is restricted to patients with positive resection margins and occasionally, patients with significant residual metastatic lymphadenopathy after neoadjuvant chemotherapy.

18.3.4 Chemoradiotherapy

Chemoradiotherapy is the primary modality of treatment of upper third esophageal cancers and locally advanced middle and lower third cancers that are unresectable. It is also the treatment of choice in patients who are medically inoperable or unwilling to undergo surgery. The most widely practiced and well-tolerated regimen includes radiotherapy to 66 Gy in 33# in 6.5 weeks with concurrent weekly cisplatin 35 mg/m^2, 5–6 cycles [79]. In institutes with facilities for intra-luminal brachytherapy, the radiation regimen may be changed to teletherapy 50 Gy in 25# in 5 weeks followed by 2# of high dose rate intra-luminal brachytherapy of 12 Gy after 2 weeks, with the chemotherapy regimen remaining the same. Several concurrent chemotherapy regimens are practiced including 3-weekly cisplatin and 5-fluorouracil and 3-weekly paclitaxel and cisplatin along with standard doses of radiation. Pretherapy fiber-optic bronchoscopy in cancers of the upper and middle third are mandatory to rule out airway involvement.

18.3.5 Palliative Therapy

The emphasis of management in patients presenting with metastatic esophageal cancer is on early palliation of dysphagia. Patients with metastatic disease but grade 3 or less dysphagia are treated with palliative radiotherapy with or without stenting [80]. Patients with absolute dysphagia who need immediate palliation are treated with esophageal stents, most commonly self-expanding metal stents [81]. A few centers offer intra-luminal radiotherapy for metastatic and locally advanced

esophageal cancer, which has been found to offer faster and sustained palliation of dysphagia [82]. Rarely patients with bulky disease obstructing the tracheobronchial tree as well as the esophagus are treated with double stents, i.e., tracheal and esophageal stents.

18.3.6 The Tata Memorial Centre Experience

At the authors' institute, patients with early (T1 or T2 with N0) disease are treated with primary surgery while those with more advanced (T3 or T4a or N+) disease are treated with neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACTRT) followed by surgical resection. While the default option is NACT for most patients, eligible patients are currently getting randomized in a phase II trial comparing the two strategies. Over 2500 surgeries have been performed for esophageal cancer over the last 15 years. The preferred choice of surgery is a trans-thoracic three-stage esophagectomy while trans-hiatal esophagectomy is occasionally performed as a compromise procedure in patients with borderline fitness or extensive pulmonary fibrosis. Elective three-field lymphadenectomy is done in all patients with supracarinal disease and those with radiologically or metabolically metastatic supracarinal lymphadenopathy. Patients without these features are considered for randomization to a trial comparing standard two-field with elective radical three-field lymphadenectomy. Minimally invasive esophagectomy (thoracoscopy and/or laparoscopy) is performed in approximately half the patients undergoing trans-thoracic esophagectomy. The preferred conduit is the stomach and the posterior mediastinum, the most common route of reconstruction. Esophago-gastric anastomosis is performed in the neck by a triangulated stapled anastomosis. A nasojejunal tube is placed intra-operatively for post-operative enteral feeding.

Pre-operative evaluation includes a detailed history and examination, assessment of functional capacity by stair climbing or a 6-minute walk test and blood investigations including a complete blood count, coagulation profile, and renal and liver function tests. All patients undergo pulmonary function testing in the form of spirometry and diffusion capacity for carbon monoxide, and cardiac evaluation with an electrocardiogram and resting echocardiography. Patients with cardio-pulmonary risk factors (ischemic heart disease, limited functional capacity, or poor performance on spirometry) may be considered for either stress echocardiography or a formal cardio-pulmonary exercise test to determine peak oxygen consumption and anaerobic threshold. Patients considered high risk for post-operative complications are discussed in a multi-disciplinary clinic consisting of anesthesiologists, surgeons, and pulmonary physicians, for optimization prior to surgery.

Pre-operative preparation includes chest physiotherapy, incentive spirometry, and nutritional rehabilitation along with smoking cessation. Deep vein thrombosis (DVT) prophylaxis is started 12 hours prior to surgery and continued postoperatively. Prophylactic antibiotics are given pre-operatively and repeated once after 3 hours intra-operatively and are not continued routinely in the post-operative period.

Anesthesia management: All patients receive thoracic epidural analgesia (unless contra-indicated). For minimally invasive surgery, we use either double-lumen tubes or bronchial blockers for lung isolation. In addition to standard monitors, we use invasive arterial pressure monitoring for all cases. Fluid therapy is restrictive and is guided by hemodynamic parameters, urine output, and serial arterial lactate measurements.

Most patients are extubated immediate post-operatively on table and shifted to a recovery ward rather than the intensive care unit. Physiotherapy and active mobilization are started soon after shifting to the recovery ward. Post-operative analgesia is multi-modal and combines epidural local anesthetics with systemic paracetamol and non-steroidal anti-inflammatory agents. Enteral (naso-jejunal) feeding is started on the morning after surgery and stepped up gradually to full enteral feeds by the evening of the second post-operative day. The naso-gastric tube is clamped on the second post-operative day and removed by the same evening if the chest radiograph shows no gastric tube dilatation. Routine laryngoscopy examination is done to check the vocal cord status on the fifth postoperative day and oral liquids started on the sixth post-operative day. Contrast swallows are not done prior to starting orals and patients are on full solid feeds by the eighth post-operative day. Uncomplicated patients are discharged by the tenth post-operative day. The post-operative major morbidity and mortality are 19.9% and 5.9%, respectively. Common post-operative complications include pulmonary complications (27.1%), anastomotic leaks (8.8%), vocal cord paresis (31.4%, of which 6.3% have permanent palsy), and thoracic duct injuries (1.3%). The 5-year survival (Fig. 18.2) of patients undergoing total esophagectomy was 44% with a median survival of 42 months (95% confidence interval, 25.5–60.5 months).

18.4 Research in Esophageal Cancer in India

Research on esophageal cancer in India has a long history. The main areas of focus in esophageal cancer research have been the possible etiological factors and associations with squamous esophageal cancer, the choice of primary treatment for the disease, modifications in surgical technique, the role of neoadjuvant and adjuvant treatment and palliative treatment options.

18.4.1 Epidemiology Research

Epidemiological research from the Kashmir valley, which is a high incidence area for squamous esophageal cancer, established that low socio-economic status was an independent risk factor [13]. A large case–control study, matched for age, sex, and geographic area showed a strong inverse association between higher education and wealth status and ESCC risk. The same study also established the probable etiological role of “hookah” smoking and “nass chewing” on esophageal squamous cell cancer with odds ratios of 1.85 and 2.88, respectively [12]. In a

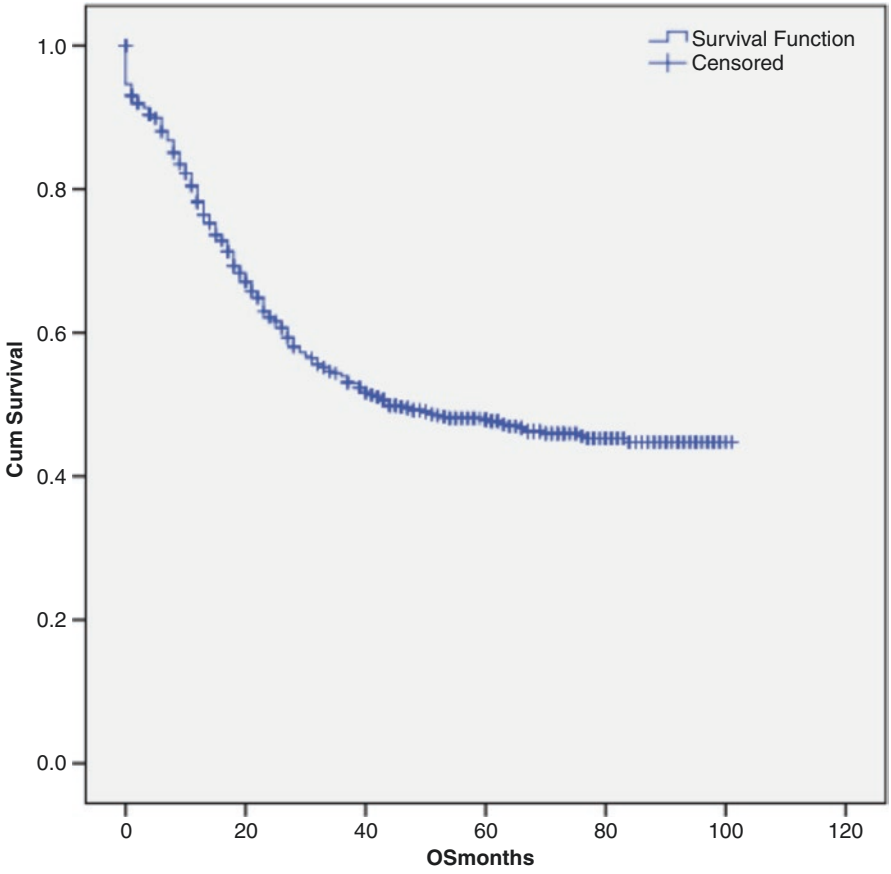

Fig. 18.2 Kaplan–Meier survival curve for patients operated at the Tata Memorial Centre

small study evaluating the prevalence of human papilloma virus (HPV) strains in ESCC, researchers found that a high proportion (87%) of patients with ESCC harbored high risk HPV strains [39]. While association between HPV strains and ESCC is already established and the study supported the hypothesis of persistent oncogenic viruses in cancer development, a larger study would be required to firmly establish causation. In a study of epigenetic, genetic, and environmental interactions in ESCC, significantly higher methylation frequencies were noted in tobacco chewers compared to non-tobacco users for all the four genes (p16, DAPK, BRCA1, and GSTP1) studied [34]. Betel quid chewing, alcohol consumption, and a null GSTT1 genotype had maximum risk for ESCC without promoter hypermethylation whereas tobacco chewing, smoking, and null GSTT1 variants were found to be associated with ESCC with promoter hypermethylation on logistic regression analysis [34].

18.4.2 Primary Treatment

One of the two randomized trials [83, 84] comparing surgery with radical radiotherapy for localized esophageal cancer was conducted in the authors' institute. Although this trial was primarily designed to evaluate quality of life in patients treated with surgery or radiotherapy, it established that surgery was far superior to radiotherapy even for overall survival [83]. The study randomized 99 patients to either surgery alone ($n = 47$) or radiotherapy alone ($n = 52$). Outcomes with respect to disease specific symptoms, which was the primary outcome, were consistently superior in the surgery arm; specifically, the quality of swallowing, which is an important endpoint of treatment of esophageal cancer was superior in the surgery arm compared to radiotherapy. The secondary endpoint of survival was vastly superior in the surgery arm compared to the radiotherapy arm ($p = 0.002$) [83]. To date, this is one of only two randomized trials [83, 84] performed so far to address this important question.

18.4.3 *Neoadjuvant* Therapy

A small randomized trial compared quality of life (QOL) outcomes after transhiatal esophagectomy with or without neoadjuvant chemotherapy [58]. Utilizing the validated EORTC QLQ C-30 and OES-18 questionnaires, the authors showed that quality of life (QOL) improved after surgery in all patients in functional, global health and symptom scales; in addition, the results showed an improved QOL in patients treated with neoadjuvant chemotherapy and surgery compared to those with surgery alone [58]. In another series reporting on outcomes following neoadjuvant chemoradiation for esophageal cancer, 76.6% patients completed neoadjuvant treatment and proceeded to surgery. Of these, 93.4% underwent R0 resection with a pathological complete response in 37.2%. One and two-year survival was reported to be 76% and 62.8%, respectively [85]. In a series from Chennai, 64% patients undergoing neoadjuvant chemoradiation came up for surgery, of which 38% had a pathological complete response. There were no mortalities in the 90-day period [86]. Similar outcomes were reported from Hyderabad and Lucknow [87, 88]. All these centers used radiation doses between 41.4 and 45 Gy. This data clearly shows a trend toward preference for neoadjuvant chemoradiation in esophageal SCC in India. Currently, there is an ongoing phase II randomized trial comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy (both followed by radical surgery) in the authors' institution.

18.4.4 Surgical Trials

A number of trials have been conducted on surgical techniques and variations therein. These include the use of pedicled omentum to reinforce esophago-gastric anastomosis [89], modifications of the anastomotic technique [90], and the route of

reconstruction [74]. In addition, observational studies on minimally invasive esophagectomy [62, 64, 66–71] and robotic esophagectomy [72, 73] have also been performed.

A small randomized trial [74] was performed on 49 patients to compare outcomes between the anterior mediastinal (retrosternal) (n = 24) with the posterior mediastinal (n = 25) routes of reconstruction. The duration (235 vs. 225 min) and blood loss (531 vs. 538 ml) of surgery were similar in the two groups. Similarly, there were no significant differences between the retrosternal and posterior mediastinal routes, respectively, in immediate postoperative pulmonary (45.8% vs. 48%) or cardiac (25% vs. 20%) complication rates, anastomotic leaks (16.7% vs. 16%), hospital stay (15 vs. 17 days), and mortality (12.5% vs. 4%) [74]. Long-term outcomes including stricture rate, dysphagia, aspiration, reflux, and weight loss were also similar in the two groups [74]. In a small study involving patients who underwent esophagectomy with a cervical anastomosis, patients were randomized into either no pyloric drainage or pyloroplasty with gastric emptying as the primary endpoint [91]. The study demonstrated significant delay in gastric emptying in both the groups though it was less pronounced in the pyloroplasty group. The sequelae of delayed gastric emptying were seen in both groups and the authors concluded that the intra-thoracic stomach causes delayed gastric emptying and pyloroplasty failed to prevent its occurrence [91].

18.4.4.1 Anastomotic Technique

A randomized trial [89] was performed to evaluate whether the addition of a pedicled omental wrap on the esophago-gastric anastomosis would decrease the incidence of anastomotic leaks. Patients undergoing radical esophagectomy (63% Ivor Lewis and 37% trans-hiatal esophagectomy) were randomized to conventional anastomosis (manual end to side esophago-gastric) with (n = 97) or without an omental wrap (n = 97). The anastomotic leak rate was significantly lower (3.1% vs. 14.4%, p = 0.005) in patients who had the omental wrap [89]. This difference was seen in both the Ivor Lewis as well as the trans-hiatal esophagectomy groups. Another randomized trial was conducted to evaluate whether a wide cross-sectional area at the anastomotic site would lead to lower rates of anastomotic leaks and strictures [90]. One hundred patients were randomized to the control arm (end-to-side esophago-gastric anastomosis on the anterior gastric wall without removal of the crescent) or the experimental arm (end-to-side anastomosis after removal of a crescent from the anterior gastric wall). Anastomotic leak rates (4.3% vs. 20.8%, p = 0.03) and strictures (8.5% vs. 29.2%, p = 0.02) were significantly lower with the modified (wider anastomotic) technique [90]. Another randomized trial was done comparing a side-to-side stapled anastomosis to a hand-sewn technique with anastomotic leaks and strictures as the primary and secondary endpoints, respectively [75]. Out of 174 patients randomized, anastomotic leak rates were similar in the two groups (14/87 vs. 16/87, p = 0.33); however, post-operative strictures were significantly lower (17/82 vs. 7/81, p = 0.045) in the stapled anastomosis [75].

18.4.4.2 Peri-operative Management

Two relatively large randomized trials of peri-operative management were conducted in the authors' institute. The first, a randomized trial evaluated whether it was safe to shorten the duration of naso-gastric drainage after esophagectomy [92]. One hundred and fifty patients undergoing modified McKeown three-stage or trans-hiatal esophagectomy with gastric tube reconstruction were randomly allocated to either conventional (6–10 days) or shortened (2 days) naso-gastric drainage. The primary composite endpoint was anastomotic leaks and/or pulmonary complications and was found to be similar (18.7% vs. 21.3%) in the two groups; patient discomfort scores were significantly lower in the early removal arm [92]. The trial established that it was feasible and safe to remove the naso-gastric drainage tube 2 days after esophagectomy and a neck anastomosis without any adverse effects [92]. The authors performed another randomized trial to evaluate the impact of restricted intra-operative and post-operative fluid administration on major post-operative pulmonary complications [93]. The study initially planned to recruit 320 patients, was prematurely terminated after 183 patients were accrued on the advice of an independent data monitoring committee. Eligible patients were randomized to either conventional (liberal) fluid administration or restricted fluids intra- and post-operatively. At the planned interim analysis after 183 patients were accrued, the major post-operative complication rates were identical and the DSMC felt that continuing the trial would be futile as the likelihood of demonstrating an important difference between the two groups was very low [93]. Another randomized trial from the authors' institution evaluating the role of peri-operative erythromycin (a motilin agonist) in reducing the immediate post-operative and medium-term occurrence of delayed gastric emptying is completed and awaiting data analysis. Enhanced Recovery After Surgery (ERAS) protocols have shown improved short-term outcomes after esophagectomy like in other major gastrointestinal surgery. Guidelines for peri-operative management in esophageal surgery have been given by the ERAS society [94].

18.4.5 Palliative Treatment

A randomized trial was conducted to evaluate whether the combined treatment of esophageal stenting followed by radiotherapy was superior to stenting alone in advanced inoperable esophageal cancer [80]. The study, which randomized 84 patients concluded that the combination of self-expandable metal stenting followed by 30 Gray radiation (10 fractions, over 2 weeks) offered longer dysphagia relief (7 vs. 3 months, $p = 0.002$), and prolonged survival (median 180 vs. 120 days, $p = 0.009$) compared to stenting alone [80].

18.4.6 Ongoing Research

There are several ongoing trials on various aspects of esophageal cancer screening and treatment. The authors' institute, along with a rural hospital is currently

conducting a large community-based screening trial in Ratnagiri, one of the rural districts of Western India where 110,000 individuals are being randomized in a cluster randomized design to either health education alone or health education with screening for upper aero-digestive tract (oral, hypopharyngeal, and esophageal) cancers. Trained health workers go to individual villages and screen high-risk individuals (tobacco and alcohol users) by visual examination of the oral cavity and a double-contrast barium swallow for early detection of oral and hypopharyngeal/esophageal cancers, respectively. Results are expected in about 8 years. Another large randomized trial is underway in the authors' institution evaluating the role of radical lymphadenectomy in operable esophageal cancer [95]. Patients with operable esophageal cancer are randomized intra-operatively (after confirming operability and absence of gross supra-carinal lymphadenopathy) to either standard two-field or radical three-field lymphadenectomy—682 out of a target 700 patients have been accrued so far [95].

18.5 Future Directions

Treatment for esophageal cancer in India has so far been carried out in institutions with wide range of experience in managing this disease without an organizational framework. Challenges to improve overall patient outcomes in esophageal cancer include the wide disparity in quality of cancer care provision, availability of qualified, trained experts in all parts of the country, and the relative lack of infrastructure. Healthcare provision in India is multi-tiered, with only basic medical facilities at a primary health center level while tertiary-level treatment centers have state-of-the-art infrastructure and highly qualified medical and paramedical staff, especially in apex government and private institutions. Future efforts will include widespread dissemination of evidence-based treatment guidelines for management of esophageal cancer, training adequate manpower, centralization of treatment, wider adoption of multi-disciplinary treatment teams and multi-modality treatment protocols, creation of a collaborative network, and standardized data capture.

The lack of a cooperative working group to meet the above challenges was felt to be a lacuna in the system. The Indian Society for Diseases of the Esophagus (ISES) was recently formed to address this gap. The mandate for the ISES includes formulation and adoption of uniform guidelines for management of esophageal diseases, more systematic data collection, and collaborative multi-centric research studies. It is expected that this society will also provide a forum for discussion among surgeons and oncologists treating esophageal cancers and help identifying specific problems and questions to be answered in the Asian context. The authors also agree on the need for collaborative research in squamous esophageal cancers among countries like Japan, China, Iran, and India where they are far more common that adenocarcinomas. Possible questions to answer include the dilemma of neoadjuvant chemotherapy or chemoradiotherapy, personalized therapy to guide the choice of neoadjuvant treatment, the ideal surgical approach and the extent of lymphadenectomy and quality of life issues.

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Korean Experiences of the Treatment of Esophageal Squamous Cell Carcinoma

19

Dae Joon Kim, Seong Yong Park, and Min Hee Hong

Abstract

According to the Cancer Central Registry, there were 2499 new cases of esophageal cancer in Korea in 2016, and the crude incidence rate of esophageal cancer was 4.9 cases per 100,000 population. Histologically, 95.2% of esophageal cancer cases were carcinoma, 89.9% of which were squamous cell carcinoma, followed by adenocarcinoma at 2.8%.

Over the past 15 years, the incidence of esophageal cancer in Korea has decreased, with an annual percent change of −2.6% in men and −2.2% in women. In this review, we have aimed to summarize the current status of esophageal cancer in terms of its incidence, treatment strategies, and outcomes after the introduction of a nationwide screening program in Korea. Owing to a nationwide screening program, the proportion of early-stage cancer increased and the 5-year relative survival improved from 12.1% (1993–1995) to 34.6% (2009–2013). Positron emission tomography and endoscopic ultrasound are routinely employed for accurate staging. Treatment of early-stage disease primarily involves surgery alone, but endoscopic submucosal dissection is also applied in selected patients. The Ivor Lewis operation with two-field lymphadenectomy is most commonly performed, and the stomach is the preferred esophageal substitute. By 2016, minimally invasive esophagectomy was performed in approximately 30% of patients; interestingly, 27% of these patients underwent robotic esophagectomy. In Korea, 16 hospitals performed 73.7% of esophagectomy procedures,

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indicating the predominance of the centralization phenomenon. Based on favorable reports from other countries, in locally advanced cancers, many centers have actively adopted neoadjuvant chemoradiation. Recently, collaborative work to collect nationwide data was initiated, and a national registry for esophageal cancer is expected to be set up in the near future.

Keywords

Esophageal cancer · Squamous · Korea

19.1 Esophageal Cancer in Korea

According to the Cancer Central Registry, there were 229,180 new cases of cancer in Korea in 2016, and 2499 cases (1.1% of all cancers) were esophageal cancer. The crude incidence rate of esophageal cancer was 4.9 cases per 100,000 population. The male-to-female ratio was 8.8:1, and the incidence was highest at age 60–69 years (33.7%), followed by age 70–79 years (29.8%). Histologically, 95.2% of esophageal cancer cases were carcinoma, 89.9% of which were squamous cell carcinoma, followed by adenocarcinoma at 2.8%.

The incidence of esophageal cancer in Korea is relatively low in comparison with that in Japan and China, but the reasons for this have not yet been elucidated. In addition, Shin et al. reported that the incidence of esophageal cancer has decreased in Korea over the past 15 years [1]. The age-standardized incidence rates decreased from 8.8 per 100,000 population in 1999 to 5.9 in 2013, with an annual percent change of −2.6% in men and −2.2% in women. The proportion of localized and regional cancer tended to increase compared with that of distant cancer, and the 5-year relative survival rate of esophageal squamous cell carcinoma (ESCC) improved from 12.1% (1993–1995) to 34.6% (2009–2013).

Several papers have reported regarding the epidemiology of esophageal cancer in Korea. For instance, Choi et al. reported that light drinking of just one alcoholic drink a day is associated with increased risks of esophageal, gastric, and colorectal cancer [2]. They also reported that underweight was a risk factor for ESCC and that alcohol consumption raised the risk synergistically with low body mass index [3]. After analyzing the Kanghwa cohort, Jung et al. reported that there was a strong dose–response relationship between volume of alcohol drinking and development of esophageal cancer [4]. Another study reported that alcohol, smoking, and the aspartate aminotransferase to alanine aminotransferase ratio were independently associated with increased risk of esophageal cancer [5].

19.2 Diagnosis and Staging

Since the introduction of a nationwide screening program to detect gastric cancer, esophageal cancer has been diagnosed at earlier stages. Moreover, the proportion of localized and regional diseases tended to increase, contributing to

improved survival over the past two decades. In addition to the nationwide screening program, we recommend routine screening using esophagogastroduodenoscopy (EGD) for high-risk patients who have a history of head and neck cancer. One single-institution study reported that synchronous esophageal cancer was detected in 25.5% (12/47) of hypopharyngeal cancer cases and in 27.8% (15/54) of head and neck cancer cases involving the pyriform sinus. They suggested that patients with head and neck squamous cell carcinoma, especially those who are current smokers, have a history of cancer, or have pyriform sinus involvement, should undergo intensive endoscopic screening to detect synchronous esophageal cancer [6].

For the staging work-up, EGD, endoscopic ultrasound sonography (EUS), chest computed tomography (CT), abdomen CT, and positron emission tomography (PET)-CT are routinely performed. Bronchoscopic examination is indicated only when airway invasion is suspected. Jung et al. reported the diagnostic accuracy of EUS by analyzing 126 patients with superficial esophageal cancer [7]. In their report, EUS using a high-frequency catheter probe generally provides highly accurate assessments of invasion depth (78.9%), but its accuracy decreases for tumors ≥3 cm. Nonetheless, PET-CT scan is used in almost all patients because it is reimbursed by the National Health Insurance System. Although many studies have reported that PET-CT is useful for diagnosis, staging, evaluating treatment, and predicting prognosis, it has several limitations, especially in nodal staging. We reported that a significant proportion of nodal metastases were too small to be detected by PET-CT scan [8]. In 85 patients who underwent preoperative PET-CT, nodal upstaging was evident in 29 (34.1 %) patients postoperatively due to small metastatic foci (4.47 ± 0.35 mm) in metastatic lymph nodes (6.60 ± 0.39 mm). Although lymph node dissection has been regarded as the most accurate nodal staging method, PET-CT scan in addition to EUS is the most important and efficient way to establish a treatment strategy.

The American Joint Committee on Cancer (AJCC) staging system and the corresponding lymph node map are usually used in most institutions [9, 10]. Some institutions have used their own lymph node map, which is a mixture of the AJCC staging system and Japanese classification, because the AJCC lymph node map has no accurate description concerning recurrent laryngeal nerve lymph nodes or cervical lymph nodes. Currently, we use the lymph node map described in the 11th edition of the Japanese classification. Another issue is whether to accept the eight edition of AJCC staging system. In case of supraclavicular lymph node metastasis, the seventh edition defines it as locoregional metastasis, whereas the eight edition defines it as distant metastasis [9, 10]. Many institutions still classify the supraclavicular lymph node as a regional lymph node, even if they use the AJCC map for staging. Cho et al. reported treatment outcomes in patients with supraclavicular lymph node metastasis [11], and they suggested that supraclavicular lymph node metastasis was not a risk factor for progression-free or overall survival. In our institute, the supraclavicular lymph nodes are regarded as regional lymph nodes, and we routinely perform bilateral neck dissection in all patients.

19.3 Endoscopic Treatment for Superficial Esophageal Cancer

In superficial esophageal cancer patients, endoscopic submucosal dissection (ESD) has been regarded as a useful treatment option. Many studies showed acceptable early and long-term outcomes after ESD, with a complete resection rate of 75–100%, complication rate of 0–25%, and recurrence rate of 0–13% (Table 19.1). Usually, T1a lesions are indicated for ESD, and T1b lesions are usually indicated for surgical resection.

Song et al. reported that applying general anesthesia for esophageal ESD could improve clinical outcomes of ESD such as a low complication rate and higher complete resection rate in patients with superficial ESCC [13]. Moreover, they reported that esophageal ESD could be performed safely in elderly patients (more than 70 years old) [18]. Esophagectomy is recommended if the resection margin is positive or if there is lymphovascular invasion in the specimen. In patients who are medically unfit for surgery, adjuvant chemoradiation or radiation alone could be employed. In our institute, we routinely perform esophagectomy for T1b lesions. Based on our data, we believe that aggressive mediastinal lymphadenectomy should be employed because of the high incidence of nodal metastasis (>50% in T1b); furthermore, aggressive mediastinal lymphadenectomy resulted in better long-term survival [19].

Table 19.1 Clinical and oncologic outcomes after endoscopic submucosal dissection, Korean Series

Author	Year	No. of lesions	Indication (T stage)	Complete resection rate (%)	Complication rate (%)	Recurrence rate (%)	Long-term outcome
Yang et al. [12]	2018	62	T1a	100	0	7	5-year OS; 86.0%
Song et al. [13]	2018	175	T1a	75	25	3	5-year OS; 93.8%
Min et al. [14]	2018	240	T1a	100	19	–	5-year OS; 93.9%
Park et al. [15]	2016	225	T1	90	13	13	5-year OS; 89.7%
Park et al. [16]	2016	32	T1a	92	25	0	–
Lee et al. [17]	2014	37	T1	80	13	0	–

OS overall survival

19.4 Surgery

19.4.1 Analysis of Surgical Treatment Based on Health Insurance Review and Assessment Service Data

Medical treatments for all Korean citizens are supported by the National Health Insurance System. All practices are evaluated by the Health Insurance Review and Assessment Service (HIRA), which is a suborganization of the National Health Insurance System. The volume–outcome relationship has been demonstrated for some surgical procedures, and high-volume centers are expected to show better postoperative outcomes such as lower mortality and morbidity, shorter hospital stay, and lower cost of care. Because the HIRA has been monitoring and managing the process in relation with the National Health Insurance System, almost all data are collected by the HIRA. However, in Korea, until 2007, there were no reported results regarding the volume–outcome relationship in esophagectomy until it was reported by the HIRA, which also reported the hospital volume and the surgical outcome in Korean hospitals in 2007 and 2013.

In 2007, they analyzed the esophagectomy cases performed from 2005 to 2006. For 2 years, 1272 patients underwent esophagectomy for esophageal cancer, and the operative mortality (30-day mortality plus in-hospital mortality) was 3.38%. The risk factors for operative mortality included age, emergent admission, Charlson index score, and hospital type (teaching hospital or not). They calculated the minimum requirement of surgical volume to achieve acceptable mortality, and 21 cases (per 2 years) was the cutoff value. The volume–outcome model revealed that this cutoff value was the only significant variable to predict operative mortality. Higher volume centers showed lower operative mortality compared to that of lower volume centers (2.07% vs. 6.20%, $p = 0.0001$), and the odds ratio was 0.345 (95% confidence interval 0.182–0.653, $p < 0.05$). In higher volume centers, the overall complication rates were lower (62.95% vs. 69.98%, $p = 0.0144$), and the hospital stay was shorter (26.30 days vs. 30.55 days, $p < 0.001$) as compared to that in lower volume hospitals. Thirteen hospitals (17.1%) were higher volume centers and performed 869 esophagectomies (68.2%) during the study period.

In 2013, the HIRA reported the result of esophagectomies performed from 2011 to 2012. The number of esophagectomies was 1751, and the operative mortality was 4.68%. The cutoff value was calculated based on the previous model, and it was 21 cases per 2 years. The higher volume centers showed lower operative mortality (3.26% vs. 8.68%), shorter hospital stay (25.68 days vs. 37.97 days), and lower cost of care (16,100,000 KRW vs. 20,060,000 KRW). Sixteen (19.5%) hospitals were higher volume centers and performed 1290 esophagectomies (73.7%). In 16 higher volume centers, 14 hospitals showed an operative mortality lower than 5%; these hospitals were located mainly in the Seoul metropolitan area. In comparison with other surgical procedures at higher volume centers, esophagectomy comprised the

lowest proportion in 16 hospitals (19.5%); gastrectomy in 71 hospitals (34.1%), pancreatic cancer surgery in 49 hospitals (43.4%), and liver cancer surgery in 65 hospitals (59.6%).

19.4.2 Approach, Extent of Resection, and Lymphadenectomy

Although a nationwide treatment protocol has not yet been established, most centers prefer the Ivor Lewis operation and actively employ neoadjuvant concurrent chemoradiation therapy. Although most surgeons agree that the lymph node dissection along bilateral recurrent laryngeal nerves is mandatory, there has been no consensus concerning routine three-field lymph node dissection. A few hospitals have performed the McKeown operation, whereas transhiatal esophagectomy or the Sweet operation is rarely performed.

19.4.2.1 Extent of Resection and Lymphadenectomy

Most institutions prefer the Ivor Lewis operation for mid-to-lower thoracic esophageal cancer, and the McKeown operation is performed for upper thoracic esophageal cancer; in contrast, Japanese surgeons prefer the McKeown procedure regardless of tumor location. Trends in Korea might be influenced by Western esophageal surgeons, who usually operate on esophageal adenocarcinomas. Based on HIRA data published in 2013, 69.3% of esophagectomy cases was the Ivor Lewis operation, and 26.2% was the McKeown operation.

Kang et al. reported that local recurrence after esophagectomy is related to lymphatic metastasis rather than to proximal margin status [6]. In their data, the length of proximal margin (LPM) after esophagectomy was not related to local recurrence in N0, but 5-year freedom from local recurrence was higher for LPM of 5 cm or greater in N+ esophageal cancer (72% in LPM less than 5 cm vs. 93% in LPM of 5 cm or greater, $p = 0.040$). They proposed the possibility that the main mechanism of local recurrence is submucosal lymphatic metastasis.

Although most surgeons are aware of the importance of total mediastinal lymphadenectomy, there have been controversies regarding neck node dissection, even in patients with upper thoracic esophageal cancer. Jang et al. analyzed the patterns of lymph node metastasis in 497 patients who underwent esophagectomy and three-field lymph node dissection for upper thoracic ESCC [20]. Metastasis was found in recurrent laryngeal lymph nodes in 43.3%, in cervical lymph nodes in 46.2%, and in abdominal lymph nodes in 24.7%. In their data, the recurrent laryngeal lymph node chains were those most commonly affected by nodal metastasis; this advocates neck node dissection because of the high prevalence of cervical lymph node involvement. On the other hand, Shim et al. analyzed 91 patients with upper thoracic ESCC; 57 patients received three-field lymphadenectomy (3-FL), whereas 34 received two-field lymphadenectomy (2-FL) [21]. There were no differences in long-term survival; the 5-year overall survival was 52% in the 2-FL group and 44% in the 3-FL group ($p = 0.65$), and the 5-year disease-free survival rate was 39% in the 2-FL group and 38% in the 3-FL group ($p = 0.97$). They suggested no survival benefit

from the addition of neck node dissection if there was no evidence of cervical lymph node metastasis in preoperative examinations and testing. Unlike most hospitals in Korea, we routinely perform bilateral neck dissection in all patients, regardless of the tumor location and clinical stage.

19.4.3 Reconstruction

The gastric conduit is the preferred esophageal substitute after esophagectomy. Because the Ivor Lewis operation is the most common procedure in Korea, the whole stomach is commonly used. According to our institutional data, 96.2% of patients underwent the reconstruction procedure using the stomach. When the stomach is not available due to synchronous gastric cancer or previous history of gastrectomy, the colon can be used. Lee et al. reported the outcomes of colon interposition after esophagectomy; the rate of anastomotic leakage and graft failure were 16.4% and 6.0%, respectively [22]. Additionally, neoadjuvant chemoradiation was related to conduit-related complications in their data. Finally, supercharged jejunal grafting has been rarely used, and free jejunal graft is used in selected cases with cervical esophageal cancer or head and neck cancer [23].

19.4.4 Minimally Invasive Esophagectomy (MIE) Series in Korea

Since its introduction in 2006, robotic surgery has been a unique mainstay of MIE in Korea. According to unpublished data from 2016, robotic esophagectomy was used in 21.7% of patients, and conventional MIE was used in 7.5%. However, even with video-assisted thoracic surgery esophagectomy (VATS-E), many surgeons prefer intrathoracic anastomosis to cervical anastomosis. Kim et al. reported their extracorporeal anastomosis technique in an Ivor Lewis operation using VATS [24]. They made an intrathoracic anastomosis through the utility incision made during segmental rib resection to enhance the extracorporeal insertion of the circular stapler. In 31 cases, no anastomotic complications such as leakage or stricture were observed. Jeon et al. reported a similar technique [25], and they reported that the level of anastomoses was 22.3 ± 1.8 cm from the incisor using the thoracoscopic intrathoracic anastomosis technique in 58 consecutive patients; only two patients showed contained leakage. Moon et al. compared VATS-E with open esophagectomy [26] and reported that the overall incidence of postoperative complications was lower (38.1% vs. 57.1%, $p = 0.088$) and the incidence of pulmonary complications was lower (9.5% vs. 40.5%, $p = 0.004$) in the VATS-E group. Because thoracic surgeons are familiar with the lateral decubitus position, most surgeons employ the lateral decubitus position in VATS-E.

Since the first robotic esophagectomy was performed by the authors in 2006, it has been popular among high-volume centers in Korea. In our institution, of 112 esophagectomies in 2018, 48.1% were conducted using robotic esophagectomy, while 23.5% were performed using VATS. The first case series for robotic

esophagectomy in Korea was published by Kim et al. in Yonsei University; the authors suggested that robotic esophagectomy was technically feasible and safe [27]. The authors also reported the benefits of robotic esophagectomy by emphasizing the feasibility of dissecting the recurrent laryngeal nerve node with a robotic system [28]. In the same group, Park et al. reported surgical outcomes of 114 consecutive patients who underwent robotic esophagectomy for intrathoracic esophageal cancer; this study comprised one of the largest case series after robotic esophagectomy [29]. In the report, R0 resection was achieved in 111 patients (97.4%), and the mean numbers of total, mediastinal, and RLN nodes were 43.5 ± 1.4, 24.5 ± 1.0, and 9.7 ± 0.7, respectively. The most common complication was recurrent laryngeal nerve palsy (30, 26.3%), followed by anastomotic leakage (17, 14.9%) and pulmonary complications (11, 9.6%). The median hospital stay was 16 days, and 90-day mortality was observed in three patients (2.5%).

We reported oncologic outcomes of robot esophagectomy in ESCC by analyzing 115 patients who underwent robotic esophagectomy with total mediastinal lymphadenectomy without neoadjuvant therapy [30]. In this report, the 3-year overall survival and the 3-year recurrence-free interval were 86.0% and 79.4%, respectively (Fig. 19.1a and b). The 3-year overall survival and recurrence-free interval were 94.4% and 96.2% in patients with stage I disease, 86.2% and 80.1% in stage II disease, and 77.8% and 79.5% in stage IIIA disease, respectively (Fig. 19.1c and d). This was the first report on oncologic outcomes after robotic esophagectomy for ESCC, and the findings suggested acceptable or even favorable outcomes after robotic esophagectomy.

To date, there has been only one report comparing robotic esophagectomy with VATS-E in Korea. Park et al. retrospectively compared 62 cases of robotic esophagectomy with 43 cases of VATS-E [31]. The numbers of dissected lymph nodes in the upper mediastinum was significantly higher in robotic esophagectomy (10.7 ± 9.7 vs. 6.3 ± 9.3, $p = 0.032$), and they concluded that a higher quality of upper mediastinal lymphadenectomy could be achieved with robotic surgery. MIE is still in its infancy period in Korea, and the majority are performed in only a few high-volume centers. However, with the rapid increase of MIE in up to 30% of all esophagectomies in recent years, there is a need to standardize and improve MIE skills through mutual collaborations and education programs.

19.5 Definitive Chemoradiation and Other Treatments

As described earlier, Korea has a unique health care system that covers all citizens universally [32]. It also means that the government is the only health care payer. This situation indicates that out-of-pocket costs are minimal, but off-label prescriptions are strictly banned by the government, and doctors follow the approved indications and conduct medical practice according to the reimbursement system.

Generally, based on the global guideline and various guidelines (Table 19.2), a combination of 5-fluorouracil (5-FU) and cisplatin is most widely used and has

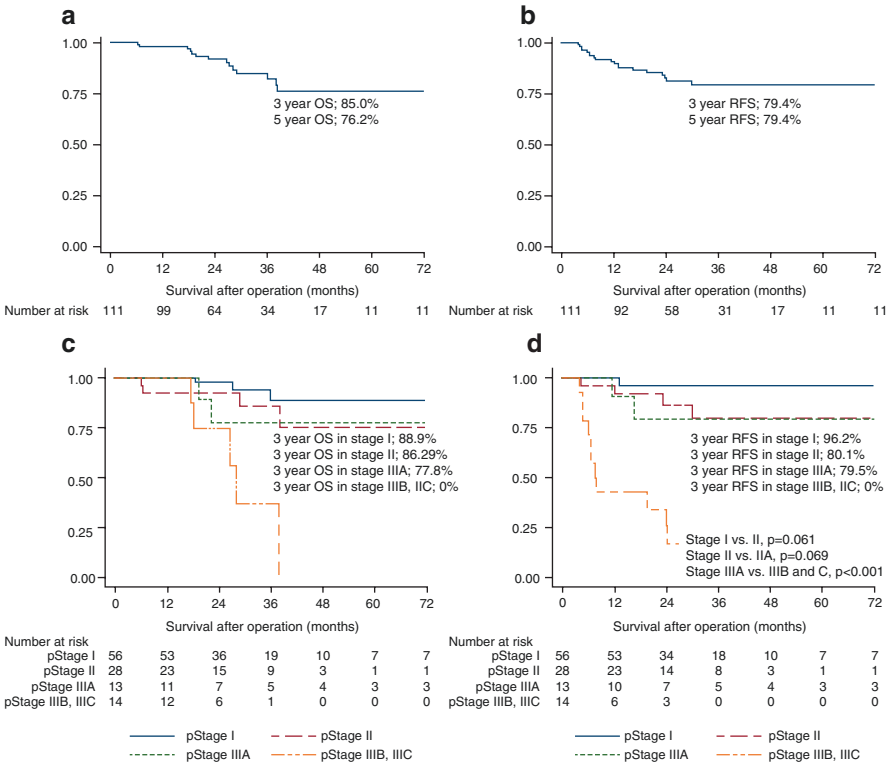

Fig. 19.1 Institutional outcomes after robotic esophagectomy in esophageal squamous cell carcinoma. (**a**) Overall survival in all patients. (**b**) Recurrence-free interval in all patients. (**c**) Overall survival according to stage. (**d**) Recurrence-free interval according to stage

Table 19.2 Results of clinical trials of definitive chemoradiotherapy for esophageal squamous cell cancer in Korea

Study	Regimen	*N*	Outcome
Cho et al. [33] Phase II study	S-1: 70 mg/m^2 for 14 days Cisplatin: 70 mg/m^2 at day 1 Every 3 week Radiotherapy: 200 cGy/day, up to 5400 cGy	30	ORR: 74.1% CR: 18.5% mPFS: 10.6 months mOS: 23.0 months
Shim et al. [34] Phase II study	Docetaxel 20 mg/m^2 weekly Cisplatin 25 mg/m^2 weekly Radiotherapy: 200 cGy/day, up to 5400 cGy	36	ORR: 85.7% CR: 22.9% mPFS: 13.5 months mOS: 26.9 months
Suh et al. [35] Retrospective study	Arm A: Radiation dose <60 Gy Arm B: Radiation dose ≥60 Gy	126	mOS: 28 and 18 months 2-year OS rate: 52.4% and 45.2%

ORR objective response rate, *CR* complete response, *PR* partial response, *mPFS* median progression-free survival, *mOS* median overall survival, *OS* overall survival

been considered as a standard regimen for concurrent chemoradiation therapy [36, 37]. Cho et al. reported the efficacy and safety of the combination regimen with S-1 and cisplatin, and the objective response rate was approximately 75% [33]. In addition, Shim et al. evaluated the feasibility of a weekly docetaxel and cisplatin regimen for concurrent chemoradiation [34].

19.6 Neoadjuvant and Adjuvant Therapy

Similar to definitive treatment, a combination of 5-FU and cisplatin has been widely used for neoadjuvant concurrent chemoradiation therapy (Table 19.3). Researchers have assessed other agents rather than 5-FU without changing the backbone—platinum. The efficacy of different dosing schedules in radiation has been evaluated.

Based on Japanese trials [43–45], some centers are adopting neoadjuvant chemotherapy without radiation. The HIRA approved neoadjuvant chemoradiotherapy with capecitabine and cisplatin for locally advanced ESCC. With ease of administration and tolerable toxicity profile, the usage of this regimen is expected to increase.

Table 19.3 Results of clinical trials of neoadjuvant treatment for esophageal squamous cell carcinoma in Korea

Study	Regimen	*N*	Outcome
Lee et al. [38] Phase II	Two courses of induction: Cisplatin 60 mg/m^2 day 1 and 5-FU 1000 mg/m^2 days 2–6 Radiotherapy: 48 Gy/4 weeks	88	Esophagectomy rate: 79% mOS: 18 months 5-year OS rate: 23%
Lee et al. [39] Phase III	Arm A: Surgery alone Arm B: Chemoradiation then surgery Cisplatin 60 mg/m^2 day 1 and 5-FU 1000 mg/m^2 days 2–6, Radiation: 45.6 Gy/1.2 Gy twice a day	101	mOS: 27.3 and 28.2 months ($p = 0.69$) ORR: 86%, CR: 21%, pathologic CR: 43% in CRT group
Chang et al. [41] Phase II	S-1: 70 mg/m^2 days 1–14 and days 22–35 Cisplatin: 75 mg/m^2 days 1 and 22 Radiotherapy: 50.4 Gy, 1.8 Gy/fraction	60	Esophagectomy rate: 42% Pathologic CR: 60% (in resected patients) 2-year PFS and OS rate: 48% and 65%
Yoon et al. [42] Phase II	Arm A: ICT then CRT followed by surgery Arm B: CRT alone followed by surgery ICT: Oxaliplatin 130 mg/m^2 day 1 and S-1 40 mg/m^2 twice daily days 1–14, every 3 weeks, total 2 cycles CRT: Oxaliplatin 130 mg/m^2 day 1 and S-1 30 mg/m^2 twice daily 5 days/week, radiotherapy: 46 Gy, 2 Gy/day	97	Esophagectomy rate: 72.1% Pathologic CR: 23.4% and 38% (in intended patients) 2-year PFS rate: 58.4% and 58.6% 2-year OS rate: 60.7% and 63.7%

ORR objective response rate, *CR* complete response, *PR* partial response, *mPFS* median progression-free survival, *mOS* median overall survival, *OS* overall survival, *CRT* chemoradiotherapy, *ICT* induction chemotherapy, *PFS* progression-free survival

Table 19.4 Results of clinical trials of adjuvant treatment for esophageal squamous cell cancer in Korea

Study	Study population and regimen	*N*	Outcome
Lee et al. [47] Phase II study	Node-positive, resected ESCC 5-FU: 1000 mg/m^2 days 1–4 Cisplatin: 60 mg/m^2 day 1 Total 3 cycles every 3 weeks	40	3-year DFS rate: 47.6% 5-year OS rate: 50.7%
Kim et al. [48] Retrospective study	Four groups (no adjuvant, chemotherapy, radiotherapy, and CRT group) Chemotherapy: 5-FU and cisplatin every 3 weeks Radiotherapy: 34.8–59.4 Gy	195	5-year OS rate: 37.7, 41.1, 31.1, and 41.8% 5-year DFS rate: 32.2, 31.3, 27.5, and 24.9%
Lim et al. [49] Phase II study	Node-positive, resected ESCC Arm A: leucovorin and 5-FU Arm B: leucovorin, 5-FU, and oxaliplatin	62	1-year DFS rate: 67% and 63% (Hazard ratio: 1.3) Median DFS: 29.6 and 16.8 mon ($p = 0.428$)

DFS disease-free survival, *ORR* objective response rate, *CR* complete response, *PR* partial response, *mPFS* median progression-free survival, *mOS* median overall survival, *OS* overall survival, *CRT* chemoradiotherapy, *ICT* induction chemotherapy

Even though strong evidence does not support the value of adjuvant treatment, postoperative chemotherapy is the preferential treatment of choice in Korea [46]. Esophageal cancer physicians may take advantage of lessons from gastric or colorectal cancers, and the only regimen covered by the government is the combination of 5-FU and cisplatin for 4–6 cycles (Table 19.4).

19.7 Summary

In Korea, the incidence of esophageal cancer is not as high as in Japan and China. The 5-year survival rate has improved because of early detection following implementation of the nationwide screening program. More than 70% of esophagectomy procedures are performed in a few high-volume centers. The Ivor Lewis operation with two-field lymphadenectomy has been the most commonly performed procedure, even in MIE. Although there is increased interest concerning neoadjuvant therapy, treatment modalities as well as surgical policies differ across institutions. Efforts to collect nationwide data are under way, and there are plans to establish a national registry for esophageal cancer in Korea.

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Chinese Experiences of the Treatment of Esophageal Squamous Cell Carcinoma

20

Lijie Tan and Han Tang

Abstract

Esophageal cancer, ranking sixth in the incidence and fourth in mortality of all cancers with 258,000 new cases and 193,000 deaths, is a severe disease in China. Over the last decades, the treatment of esophageal cancer has evolved into a multidisciplinary process, and surgeons, medical oncologists, and radiation oncologists are essential for treatment to be successful. The trend of multidisciplinary treatment is also taking place in China. In this chapter, we introduce the current situation of esophageal squamous cell carcinoma treatment in China, mainly focusing on topics of hot spot, such as epidemiology, endoscopic treatment, surgical approach, anastomotic technique, extent of lymphadenectomy, perioperative therapy, targeted therapy, and immunotherapy.

Keywords

Endoscopic resection · Surgical approach · Anastomotic techniques · Lymphadenectomy · Perioperative therapy · Targeted therapy · Immunotherapy

20.1 Introduction

Esophageal cancer has a poor prognosis, leading to about 200,000 deaths in China annually, and most of them are esophageal squamous cell carcinoma (ESCC) [1]. In 1940, Dr. Wu performed the first esophageal resection, pioneering the surgical treatment for esophageal cancer in China, and since then, Chinese doctors have been investigating and exploring the optimal strategy for treatment of esophageal cancer.

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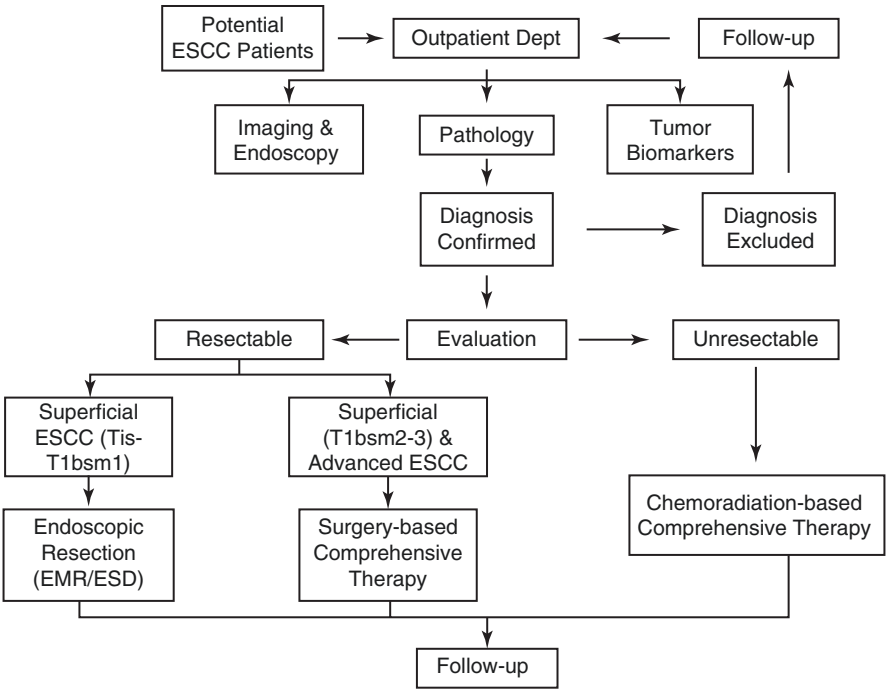

Fig. 20.1 Flowchart of diagnosis and therapy for ESCC. *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *T1bsm1* submucosa invasion less than depth of 200 μm, *T1bsm2-3* submucosa invasion more than depth of 200 μm. Download from clinical practice guidelines for the diagnosis and treatment of esophageal cancer in China (2018 Edition) in the official website of National Health Commission of the People's Republic of China

Over the past decades, multimodality treatment for esophageal cancer, showing a survival benefit, is increasingly applied in China, and individualized comprehensive therapy is recommended by Clinical Practice Guidelines for the Diagnosis and Treatment of Esophageal Cancer [2]. The diagnostic and therapeutic flow in China is shown in Fig. 20.1. In this chapter, we summarize the experiences and advances in the treatment of ESCC in the era of multimodality management in China. In the first section, we provide an overview of endoscopic treatment of ESCC. In the second section, we address commonly used surgical techniques for ESCC, with a particular focus on surgical approach, anastomotic techniques, and extent of lymphadenectomy. In the third section, we discuss perioperative therapy for ESCC, including neoadjuvant and adjuvant therapy. Finally, we introduce the targeted therapy and immunotherapy for ESCC.

20.2 Epidemiology

Esophageal cancer, an estimate of approximately 572,000 new cases and 509,000 deaths, ranks seventh in the incidence and sixth in mortality of all cancers in 2018 globally [3]. Notably, more than half of such cases occurs in China. According to

reports from National Central Cancer Registry of China (NCCRC), this disease ranks as the sixth most frequently diagnosed cancer and the fourth leading cause of cancer death with 258,000 new cases and 193,000 deaths in China in 2014 [4]. Approximately 70% of cases occur in men, resulting in two- to threefold mortality in men than that in women. The highest esophageal cancer incidence rates are found in dispersedly distributed regions, including Fujian Province, Sichuan Province, Chaozhou-Shantou region as well as regions along the Taihang Mountains, such as Henan Province, Shanxi Province, and Shandong Province; in addition, the incidence rate in rural areas is far more than that in urban areas. As for the prognosis, it is reported that the age-standardized 5-year relative survival increased to 30.3% by 9.4% from 2003–2005 to 2012–2015 for esophageal cancer in China with multidisciplinary treatment increasingly applied [5].

In China, esophageal squamous cell carcinoma (ESCC), comprising over more than 90% of all cases, is the predominant pathological type, mainly located in the middle of the esophagus. It is demonstrated that heavy drinking and smoking and their synergistic effects are the major risk factors for SCC; besides, hot meal, poor hygiene, nutritional deficiency, nitrosamines in pickled foods also play a role. In the past decade, screening program for esophageal cancer has been carried out for the high-risk population living in high-prevalence area of over 45-year-old with family tumor history, especially esophageal or other digestive tract malignancy. And this program has yielded significant benefits in achieving early detection and treatment of esophageal cancer, and improved the survival. Therefore, most recently, Chinese government released the blueprint guide of "Healthy China 2030," in which an official goal was set to reduce premature mortality of major noncommunicable diseases by 30% from 2015 to 2030. Esophageal cancer, as one of noncommunicable diseases, also plays a crucial role in achieving this health life indicator.

20.3 Endoscopic Resection

Endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is increasingly propagated and has become an important approach for treatment of superficial esophageal cancer in China. Superficial esophageal cancer is categorized as intraepithelial (high-grade dysplasia, Tis), mucosal (T1a), and submucosal (T1b) cancer. Lesions diagnosed as Tis or T1a ESCC without muscularis mucosae invasion are absolute indications for ER, which are extremely rarely associated with lymph node metastasis, and those as T1a ESCC with muscularis mucosae invasion or T1b ESCC invading less than 200 μm within submucosa are also preferred to be treated via ER; however, due to an increasing risk of lymph nodes metastasis, these represent relative indications for ER [6]. For a superficial lesion involving ≥3/4th of the esophageal circumference, ER should be considered deliberately as such lesion is associated with a high risk of development of stenosis after such resection [7, 8]. Decisions on ER approach are based on preoperative evaluation, including endoscopic examination, computed tomography (CT) of the neck, chest, and abdomen, positron emission tomography–CT (PET-CT) [9, 10]. For superficial lesions, endoscopic ultrasound (EUS) plays a

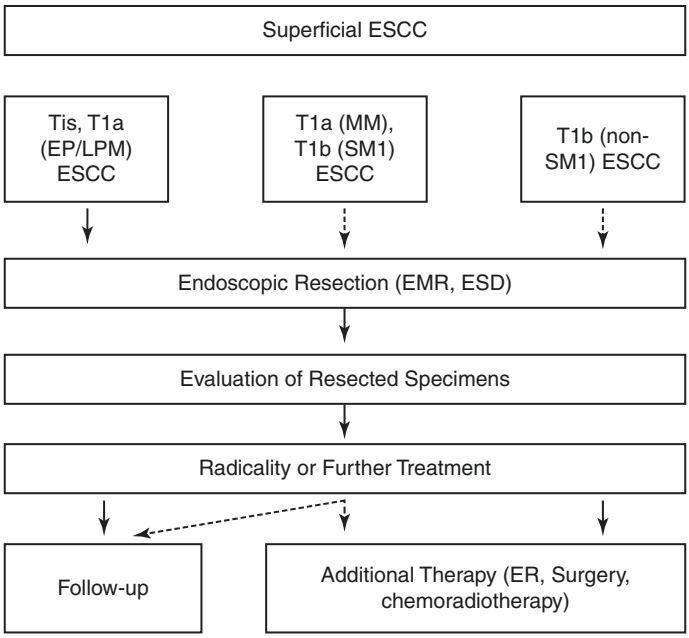

Fig. 20.2 Flowchart of endoscopic resection. *EP* epithelium, *LPM* lamina propria mucosae, *MM* muscularis mucosae, *SM1* submucosa invasion less than depth of 200 μm, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *ER* endoscopic resection. Download from clinical practice guidelines for the diagnosis and treatment of esophageal cancer in China (2018 Edition) in the official website of National Health Commission of the People's Republic of China

key role in determining whether ER is suitable or not, owing to its relatively high accuracy in detecting depth of invasion as well as positive nodes [11, 12]. In addition to preoperative examinations, endoscopic resected specimen also reveals crucial information, and several histopathological parameters of the resected specimen, such as irradicality, the presence of lymphovascular invasion, deeper submucosal tumor invasion, and poor differentiation, determine the necessity of additional treatments, including surgery, chemotherapy, or chemoradiotherapy [13, 14]. The selection among additional treatments should be made after assessing the patient's surgical tolerability. The detailed procedure of ER is shown in Fig. 20.2. If ER is considered radically for superficial lesion, follow-up is carried out every 3 months in the first year, and one time per year in the following years. In addition to endoscopy, other examinations, including CT of neck, thorax, and abdomen, and tumor biomarkers should be also routinely performed.

20.4 Surgery

Esophagectomy remains the most crucial approach for treatment of esophageal cancer in spite of its relatively high perioperative complications. The eligibility of a patient for surgical resection strongly depends on the extent of the disease as long

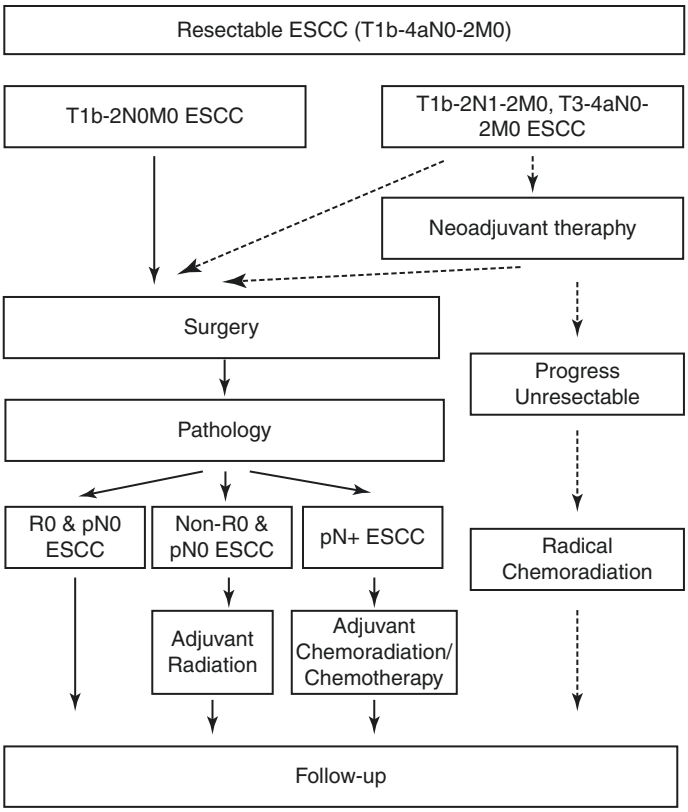

Fig. 20.3 Flowchart of resectable ESCC. Download from clinical practice guidelines for the diagnosis and treatment of esophageal cancer in China (2018 Edition) in the official website of National Health Commission of the People's Republic of China

as the general condition of the patient is tolerable of surgery. In China, patients with early stage, not suitable for ER, or locally advanced, non-distant metastatic ESCC (stage $T_{1b–4a}N_{0–2}M_0$) are considered for surgical resection. Usually, radical resection alone is sufficient for early tumors, and neoadjuvant/adjuvant therapy should be added for locally advanced tumors. The treatment algorithm is shown in Fig. 20.3. Some issues about surgery deserve special attentions. This section is divided into three parts to clarify the current status and tendency of esophagectomy in China, including surgical approach, anastomotic techniques, and extent of lymphadenectomy.

20.4.1 Surgical Approach

Several approaches for the resection of esophageal cancer exist, including Sweet, Ivor Lewis, McKeown, and transhiatal esophagectomy. In China, before 2000, the Sweet approach was the most popular modality, and the 5-year overall survival (OS)

remained 30–40% [15] because of incapability of lymph nodes dissection of upper mediastinum. Nowadays, with the spread and popularization of standardized treatment of esophageal cancer, the Ivor Lewis or McKeown approach through right thoracotomy has become the mainstream in large medical centers; however, the Sweet approach remains the common practice in some hospitals in the North. In recent years, it is reported the 5-year OS raised to 50% [16, 17] after the application of right thoracotomy owing to advantages of dissection of upper mediastinal nodes. Li et al. [18, 19] reported that the right thoracic approach was associated with increased survival in ESCC patients without increasing postoperative complications compared with the left thoracic approach (Sweet approach) in a single central, prospective, randomized trial. Therefore, it is of great significance to spread and expand the usage of Ivor Lewis or McKeown approach to take the place of Sweet approach in the whole nation by the Committee. As for the issue of the selection between Ivor Lewis and McKeown approaches, surgeons make the personalized operative plan and choose the most suitable procedure for individuals according to preoperative evaluation of primary tumor and potential metastatic lymph node locations. Generally, McKeown procedure is used for upper or middle esophageal tumors, and Ivor Lewis procedure for middle or lower tumors in China.

Open esophagectomy (OE) and thoracoscopic-laparoscopic esophagectomy (TLE) are both common procedures in China. As is known to all, minimally invasive esophagectomy (MIE) has great advantages in reducing postoperative complication, especially pulmonary complications, without compromised long-term survival [20, 21]; therefore, it is introduced and adopted in more and more hospitals in China. Mu et al. [22] launched a multicenter, prospective, randomized trial regarding outcomes of OE versus TLE for esophageal cancer involving 13 Chinese academic centers or hospitals in 2014, whose results are highly expected. As the thoracoscopic part is particularly difficult to master, especially when performing an intrathoracic anastomosis, hybrid esophagectomy with laparoscopic gastric mobilization and open right thoracotomy is also performed by surgeons in some low-volume centers, who avoid the challenges in completing their thoracoscopic learning phase owing to insufficient caseload. The MIRO trial demonstrated the hybrid esophagectomy resulted in a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complication, than OE without compromising survival [23], so hybrid esophagectomy could be an option for surgeons in the low-volume centers.

In the past few years, robot assisted minimally invasive esophagectomy (RAMIE) was emerging as a novel optional approach for patients, but it was performed mainly in large medical centers due to the constraints of devices and the high cost in China. Robotic assistance allows for stable three-dimensional, magnified view and articulated instruments enabling precise dissection with 7 degrees of freedom of movement. Since its introduction, RAMIE has shown to be a safe and oncologically adequate alternative to OE and conventional MIE in a series of retrospective studies [24–26]. Chinese surgeons also revealed that RAMIE was a safe and feasible alternative surgical approach for ESCC and was associated with a large yield of lymph nodes, especially along the recurrent laryngeal nerve [27]. Besides, the plateau of

RAMIE was 25 cases of operative duration and 50 cases of lymphadenectomy [27]. Multicenter, prospective, randomized trials are needed to illustrate the clinical merits and possibly extended operability criteria of RAMIE. In China, Dr. Li is carrying out a prospective, randomized trial aiming at assessing the safety and efficacy of RAMIE compared to TLE, hoping the outcomes to come soon.

20.4.2 Anastomotic Techniques

After resection of the tumor, gastrointestinal continuity is commonly restored by gastric tube reconstruction with an esophagogastric anastomosis. Both intrathoracic and cervical anastomoses are commonly performed in China, whose adoption is determined by the primary tumor site as well as metastatic nodes locations. For patients with ESCC, located in the upper or middle of esophagus, or along with upper mediastinal or cervical nodes metastasis, cervical anastomosis is obligatory and important to keep resection margins negative and dissect metastatic nodes radically. The leakage of cervical anastomosis is claimed to be significantly higher compared with the intrathoracic anastomosis [28, 29], but it is usually less severe as it can be easily diverted by opening the neck wound, thus preventing mediastinal contamination. Therefore, the cervical anastomosis is preferred by Chinese surgeons. Besides, the complexity of intrathoracic anastomosis under thoracoscopy hinders its wide application.

Anastomotic leakage is a concerning issue of esophageal cancer. Chinese surgeons have been working on this issue of improving anastomotic techniques to lower leakage rate. Li et al. [30] reported that cervical triangulating stapled esophagogastric anastomosis was a safe and effective procedure, which might lower the incidence of leakage and stenosis. In addition, the embedded three-layer esophagogastric anastomosis named as Li's anastomosis showed excellent short-term outcomes, as it reduced the incidence of anastomotic leakage, stricture, and gastroesophageal reflux [31], and promoted enhanced recovery after surgery (ERAS) with early oral intake [32]. In order to find less challenging techniques and shorten the time of intrathoracic anastomosis under thoracoscopy, several techniques were also developed, including reverse-puncture anastomotic technique [33] and modified overlap anastomosis. The overlap method [34] was initiated in esophagojejunostomy anastomosis, and Dr. Tan made some modifications so that it could be used in esophagogastric anastomosis. Dr. Tan named it as "Self-Pulling and Latter Transection (SPLT)", and it reduced anastomotic time significantly. Specifically, gastric tube was constructed in abdominal cavity, then was inserted into thorax through esophageal hiatus. In the thorax, anastomosis was performed. Firstly, the puncture was made in gastric and esophageal wall, respectively, then stapler could be inserted into the holes to make esophagogastric anastomosis. After checking the anastomotic line, the opening was closed. The detailed procedure is shown in Fig. 20.4.

Nowadays, hand-sewn anastomosis and stapled anastomosis with a mechanical device are the most commonly used methods to construct an esophagogastric

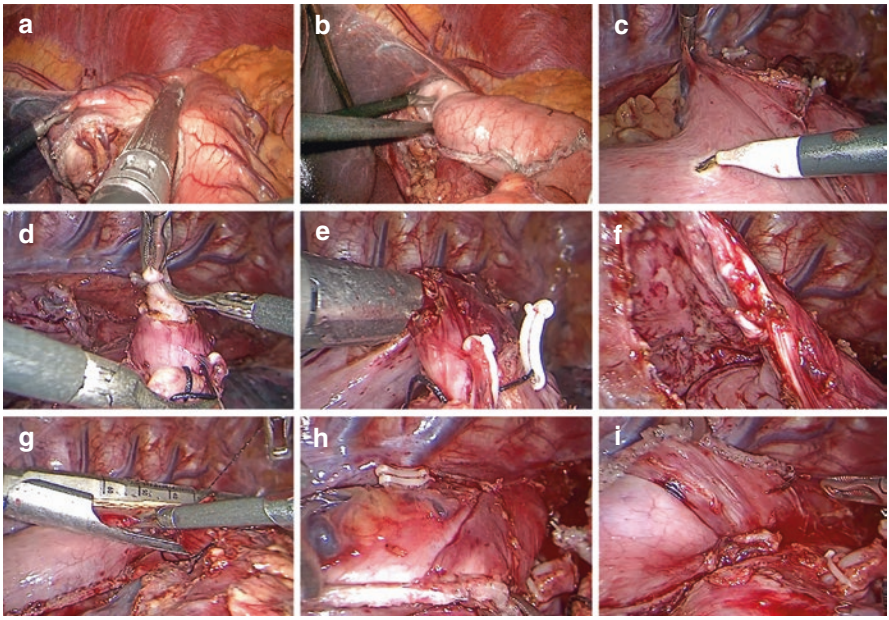

Fig. 20.4 "Self-Pulling and Latter Transection" method in esophagogastric anastomosis. (**a**) Gastric tube construction; (**b**) Put gastric tube into the thorax through esophageal hiatus; (**c**) Puncture in gastric wall; (**d**) Puncture in esophageal wall; (**e**) Esophagogastric anastomosis; (**f**) Anastomotic stoma; (**g**) Closing the opening by stapler; (**h**, **i**) Good anastomosis

anastomosis. There are no differences in leakage rates, other complications, and postoperative mortality [35–37]. So the choice of a hand-sewn or stapled anastomosis depends on the preference of the surgeon in China.

20.4.3 Extent of Lymphadenectomy

Lymph node status is an important prognostic factor in esophageal carcinoma, and radical lymphadenectomy may help determine precise postoperative pathological staging, ensure the integrity and radicality of surgery, and more importantly, improve the survival of patients after surgery. Therefore, lymphadenectomy is an essential part of radical surgery for esophageal cancer. In order to guide the clinical practice in China, a consensus on thoracic lymphadenectomy was reached by the Esophageal Cancer Committee of the Chinese Anti-Cancer Association with a group of experienced experts in 2017 [38]. The Committee made the consensus taking into consideration the experts' clinical experiences and existing evidences mostly from Chinese thoracic surgeons. And on the basis of the consistency with the AJCC/UICC and the JES systems, significant modifications have been made taking clinical practice into account in China. This consensus is easy to use and will facilitate standardization and unification of mediastinal lymph node dissection in China. The Chinese version

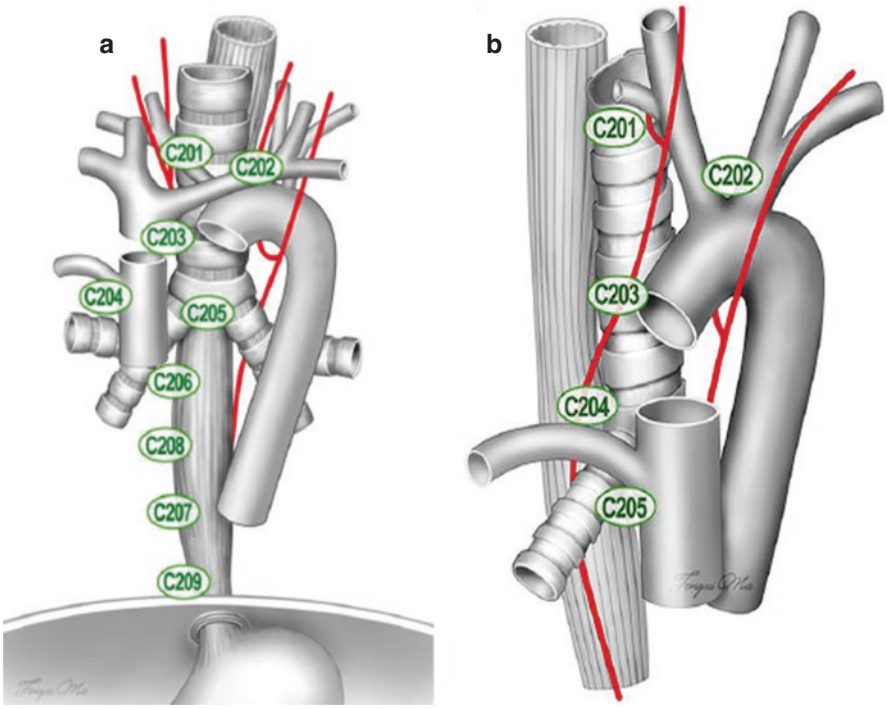

Fig. 20.5 Diagram of the Chinese version of naming and grouping of mediastinal lymph nodes in esophageal cancer: (**a**) anterior view; (**b**) right side view. "C" represents Chinese nomenclature, and "2-" represents thoracic lymph nodes. Station C201, right recurrent laryngeal nerve nodes; Station C202, left recurrent laryngeal nerve nodes; Station C203, upper thoracic para-esophageal lymph nodes; Station C204, right thoracic paratracheal lymph nodes; Station C205, subcarinal lymph nodes; Station C206, middle thoracic para-esophageal lymph nodes; Station C207, lower thoracic para-esophageal lymph nodes; Station C208, inferior pulmonary ligament lymph nodes; Station C209, para-diaphragmatic lymph nodes. Adapted with permission from Dr. Li of REF. [34], AME

of the mediastinal lymph node map and its differences with the AJCC/UICC and JES systems are shown in Figs. 20.5 and 20.6, respectively. In the consensus, it emphasized all nine stations of mediastinal lymph nodes (C201–C209) should be en bloc dissected during radical surgery, especially the left and right para-recurrent laryngeal nerve nodes and para-esophageal nodes. With regard to cervical and abdominal lymph node dissection for esophageal cancer, the abdominal lymph node dissection comprises para-cardial lymph nodes, as well as those located along the lesser gastric curvature, the origin of the left gastric artery, the common hepatic artery, the splenic artery, and the celiac trunk; and the cervical lymph node dissection included bilateral cervical para-recurrent laryngeal nerve nodes, bilateral inferior deep cervical nodes, and bilateral supraclavicular nodes.

There is fierce debate over the issue whether cervical lymph node dissection should be routinely performed in all patients with esophageal cancer all over the

Region	Chinese system	AJCC/UICC system (18)	JES system (19,20)
Upper mediastinum	Station C201*: Right recurrent laryngeal nerve nodes	Station 2R: Upper right paratracheal lymph nodes	Station 106recR: Right recurrent laryngeal nerve nodes
	Station C202: Left recurrent laryngeal nerve nodes	Station 2L: Upper left paratracheal lymph nodes	Station 106recL: Left recurrent laryngeal nerve nodes
	Station C203: Upper thoracic paraesophageal lymph nodes	Station 8U: Upper thoracic paraesophageal lymph nodes	Station 105: Upper thoracic paraesophageal lymph nodes
	Station C204: Right paratracheal lymph nodes	Station 4R: Right lower paratracheal lymph nodes	Station 106: Thoracic paratracheal lymph nodes ❖ Station 106pre: Pretracheal lymph nodes ❖ Station 106tbR: Right tracheobronchial lymph nodes
	N/A	Station 4L: Left lower paratracheal lymph nodes	Station 106tbL: Left tracheobronchial lymph nodes
		N/A	Station 113: Ligamentum arteriosum lymph nodes
		N/A	Station 114: Anterior mediastinal lymph nodes
	Station C205: Subcarinal lymph nodes	Station 7: Subcarinal lymph nodes	Station 107: Subcarinal lymph nodes
Lower mediastinum	Station C206: Middle thoracic paraesophageal lymph nodes	Station 8M: Middle thoracic paraesophageal lymph nodes	Station 108: Middle thoracic paraesophageal lymph nodes
	Station C207: Lower thoracic paraesophageal lymph nodes	Station 8Lo: Lower thoracic paraesophageal lymph nodes	Station 110: Lower thoracic paraesophageal lymph nodes
	Station C208: Inferior pulmonary ligament lymph nodes	Station 9L:Left lower pulmonary ligamnet lymph nodes	Station 112L: Posterior mediastinal lymph nodes
		Station 9R: Right inferior pulmonary ligand lymph nodes	Station 112R: Posterior mediastinal lymph nodes
	N/A	N/A	Station 109L: Left main bronchus lymph nodes
			Station 109R: Right main bronchus lymph nodes
	Station C209: Paradiaphragmatic lymph nodes	Station 15: Paradiaphragmatic lymph nodes	Station 111: Supradiaphragmatic lymph nodes

Fig. 20.6 Comparison of the Chinese version of naming and grouping mediastinal lymph nodes with the AJCC/UICC and the JES systems for esophageal cancer. ∗, "C" represents Chinese standards and "2-" represents thoracic lymph nodes. AJCC, American Joint Committee of Cancer; UICC, Union for International Cancer Control; JES, Japan Esophageal Society. Adapted with permission from Dr. Li of REF. [34], AME

world, which is also an important topic in China. It was recommended by the Committee that all patients received at least two-field lymphadenectomy with 15 or more lymph nodes harvested, if tumors located in the upper third of esophagus, three-field lymphadenectomy, including cervical lymph nodes, must be performed. The three-field lymphadenectomy was not a routine procedure in China due to the intensive trauma; however, several surgeons insisted performing three-field lymphadenectomy in some hospitals [39, 40]. In order to achieve radical lymph nodes dissection as well as avoid unnecessary dissection, Cancer Hospital Chinese Academy of Medical Sciences launched a nationwide trial to find the sentinel lymph node predict the necessity of cervical nodes dissection. The results revealed the status of right para-recurrent laryngeal nerve lymph nodes had certain value in predicting cervical nodes status, that is to say, if right para-recurrent laryngeal nerve nodes positive, cervical node dissection should be performed, especially for patients with middle and lower ESCC [41]. Besides, Dr. Chen proposed 2.5-field

lymphadenectomy [42] for all patients with ESCC, the concept of which was to clean up the cervical nodes along the bilateral para-recurrent laryngeal nerve and cervical esophagus through thorax under the thoracoscope, thus avoiding cervical lymphadenectomy. Indeed, it is of great importance that surgeons make the personalized operative plan and modify the extent of lymphadenectomy for individuals according to preoperative evaluation of primary tumor and potential metastatic lymph node location, achieving the utmost benefits for patients.

20.5 Perioperative Therapy

Neoadjuvant therapy was introduced and recommended for patients with locally advanced resectable ESCC ($cT_{1b-2}N_{1-2}$ or $cT_{3-4a}N_{0-2}$) in China with the publication of CROSS trial [43] and JCOG9907 trial [44]. The strategy of neoadjuvant therapy has not unified among medical centers. Some medical centers adopt neoadjuvant chemoradiotherapy (nCRT), while others prefer neoadjuvant chemotherapy (nCT). Considering no conclusion reached about the issue of which strategy is better, neoadjuvant chemoradiotherapy and chemotherapy are both acceptable. In order to solve the problem, the Chinese CMISG1701 study was launched in 2017 comparing overall survival between neoadjuvant chemotherapy (cisplatin/paclitaxel) with neoadjuvant chemoradiotherapy (cisplatin/paclitaxel with 40 Gy radiation) for locally advanced resectable ESCC [45]. Recently, NEOCRTEC5010 trial demonstrated nCRT plus surgery improved survival over surgery alone among patients with locally advanced ESCC, with acceptable and manageable adverse events [46], which may promote the implementation of nCRT in China. The platinum-based combination chemotherapy is the standard regimen of nCT, and other agents such as paclitaxel or 5-FU could be added to the regimen according to the clinician's experience in China. Usually, the nCRT regimen is composed of the drugs of nCT with reduced dosages and radiation varying from 40 to 50 Gy. Notably, neoadjuvant therapy is mostly applied in large-volume medical centers, and its generalization need a gradual process, so many hospitals in China remain performing surgery directly even for the locally advanced disease. For these patients, adjuvant therapy may play an important role in improving prognosis although a network meta-analysis showed no survival benefits [47]. In China, non-R0 resection is the indication of postoperative radiation and pN+ is the indication of postoperative chemotherapy. In addition, patients with multi-station lymph nodes metastases are recommended taking adjuvant chemoradiotherapy [48, 49]. Up to now, there is no high-level evidence on the value and significance of adjuvant therapy for ESCC. Consequently, two multicenter, prospective, randomized trials comparing different strategies of adjuvant therapy after surgery, including chemoradiotherapy, chemotherapy and non-postoperative therapy, are being carried out in China, one focusing on pN0 patients, while the other enrolling pN+ patients, which are complementary, hoping these outcomes to come out.

For patients with distant metastatic diseases, radical chemoradiotherapy is the first-line treatment, and surgery is not taken into account. As for the locally advanced

non-resectable ($T_{4b}N_xM_0$) tumors, induction chemoradiotherapy with reduced doses (40–50 Gy) is given first; after finishing, take resection if operable, or else, continue chemoradiotherapy. The commonly used concurrent chemoradiotherapy are platinum-based chemotherapy, including DDP/5-FU, DDP/PTX, EPI/DDP/5-FU combined with radiation of 60 Gy [50].

In China, the treatment compliance of patients is far from satisfactory, especially in patients with neoadjuvant therapy [46]. A small part of these patients are likely to take radical chemoradiotherapy instead of surgery after symptoms improvement. There were no conclusions about the issue whether good-response (clinical complete response, cCR) cases should take operation or not. And this is a crucial issue of great concern.

20.6 Targeted Therapy and Immunotherapy

The targeted therapy and immunotherapy are emerging and alternatives for recurrent, metastatic diseases, especially for those with poor control by traditional chemoradiotherapy, but they are not regarded as routine regimens for ESCC in China, as no high-level evidences supporting their usage. Usually, cases are considered and recommended to take targeted therapy or immunotherapy only when the tumor cells show resistance to other treatments.

It is reported that EGFR-TKIs as the second-line regimen for treatment of metastatic esophageal cancer could slightly longer the progression-free survival (PFS) [51], while it had no significant difference in overall survival (OS) [51, 52]. And further researches suggested that EGFR gene amplification may be a biomarker of EGFR-TKIs [53, 54]. However, most of the researches enrolled esophageal adenocarcinoma [51, 52], it has limited value in making decisions on ESCC; therefore, further research is needed before routine application in clinical practice.

In the past few years, immunotherapy targeting immune checkpoints and immune cells has shown encouraging results in many kinds of tumors in plenty of studies [55–58], including esophageal cancer. Recently, it is reported that pembrolizumab demonstrated manageable toxicity and durable antitumor activity in patients with heavily pretreated, PD-L1-positive advanced esophageal carcinoma [59]. Additionally, in the ASCO-GI Congress, the KEYNOTE-181 study assess the efficacy and safety of pembrolizumab in treating advanced or metastatic esophageal or esophagogastric junctional cancer, most of which are ESCC. It showed pembrolizumab did improve median OS compared with the single-agent chemotherapy for ESCC from 7.1 to 8.2 months; in addition, PD-L1-positive (combined positive score, CPS > 100) may be an important marker for pembrolizumab. The results may also adapt to Chinese patients with ESCC, and anti-PD-L1 therapy could spread out widely in China.

In China, surgical comprehensive traditional therapy for esophageal cancer is widely adopted; in the meantime, newly emerging therapy, such as targeted therapy and immunotherapy, is also increasingly applied. The diagnosis and therapy of ESCC will be more standardized and individualized, under the guidance of Clinical Practice Guidelines for the Diagnosis and Treatment of Esophageal Cancer.

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