Esophageal Squamous Cell Carcinoma

Diagnosis and Treatment

Nobutoshi Ando
Editor

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Foreword

There are about ten histologic types and subtypes of carcinoma of the esophagus, each of which can present a variety of morphologic findings. In Japan, squamous cell carcinomas account for 90 % of all esophageal carcinoma. The latter half of my career, 1980–1995, coincided with the establishment and development of the International Society for Diseases of the Esophagus, and consensus meetings were held frequently. Fortunately, I was provided several chances to present at such meeting as one of the symposiasts. Through the congresses of the Society we were able to recognize many differences of opinion between Western countries and Japan regarding the patterns of development of primary lesions, invasion, and types of lymph node metastasis of esophageal cancer. In particular, great differences were seen concerning the extent of esophageal resection and lymph node dissection, which was probably due in part to different frequencies of various histologic types. For example, adenocarcinoma arising in Barrett's esophagus is much more common in Western countries than in Japan. Optimal treatment for each histologic subtype still has not been established. Although medical science has indeed developed, we need to investigate each histologic subtype.

This book concentrates on squamous cell carcinoma from the aspects of epidemiology, pathology, diagnosis, stage classification, statistics, and so on. In the chapters on treatment, the authors talk about all types of endoscopic resection, minimally invasive esophagectomy, esophagectomy via thoracotomy and/or laparotomy, and esophageal reconstruction as well as all therapeutic aspects, including chemotherapy and radiotherapy. This single volume contains state-of-the-art information on all aspects of squamous cell carcinoma. I am confident this book will be looked on as the bible of esophageal cancer, and it will also be very useful for comparative information for those who deal mainly with adenocarcinoma of the esophagus. Finally, I appreciate the opportunity to introduce this book and strongly hope it will be of great help to the diagnosis and effective treatment of carcinoma of the esophagus worldwide.

Teruo Kakegawa, M.D.
Honorary President of the Japan Esophageal Society

Preface

Esophageal cancer causes an estimated 386,000 deaths worldwide annually and is the sixth most common cause of death for men. The background characteristics of esophageal cancer treatment are markedly different between Asian and Western countries, however. With regard to tumor histology, squamous cell carcinoma, which is associated with smoking and alcohol consumption, is overwhelmingly prevalent in Asia, whereas adenocarcinoma associated with Barrett's esophagus is markedly prevalent in the West. In Asia, especially in Japan, the key persons who play the most vital roles in the management of esophageal cancer patients are surgeons; in the West medical and radiation oncologists as well as surgeons are heavily involved. The approach of surgeons regarding cancer surgery varies from locoregional to local tumor control, particularly focusing on lymph node dissection. The approach of health professionals to surgical adjuvant therapy differs, therefore, between Asia and the West. 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.

Japan has long been taking initiatives in establishing advances in interpreting the pathology, introducing new diagnostic and therapeutic methods for patients with esophageal squamous cell carcinoma. The authors of each chapter in this book are all at the forefront in their field and they present original Japanese knowledge in terms of treatment of esophageal squamous cell carcinoma, expertise developed and accumulated for more than half a century. As this volume contains a wide spectrum of current information and addresses topics surrounding the treatment of patients with esophageal squamous cell carcinoma, 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. I am grateful to Mr. J.P. Barron for his friendly guidance regarding editing this book. Finally, my thanks go to Ms. Yoko Arai and Ms. Makie Kambara at Springer Japan for their efforts to help me make this book a reality.

Yokohama, Japan — Nobutoshi Ando

Contents

Epidemiology of ESCC

1

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 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 two to four times more common among men than women in general; however in Japan it is approximately seven times more common among males. Both incidence and mortality are on the rise since 1960 due to the aging Japanese population, while age-adjusted rates are consistently decreasing with the exception of the increasing male incidence rate. Established risk factors for esophageal squamous carcinoma include tobacco smoking and alcohol consumption, while fruit and vegetable intake show high probability in preventing esophageal cancer. 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 improvement such as refraining from smoking of tobacco and alcohol use, while maintaining sufficient fruit and vegetable intake.

Keywords

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

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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 [1]

Esophageal cancer is the eighth most common cancer worldwide, with 481,000 new cases (3.8 % of the total) estimated in 2008, and the sixth most common cause of death from cancer with 406,000 deaths (5.4 % 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 15-fold in men (age-standardized incidence rate to the world population (ASR) 22.3 per 100,000 in Southern Africa compared to 1.4 in Western Africa) and almost 20-fold in women (ASR 11.7 per 100,000 in Southern Africa compared to 0.6 in Micronesia/Polynesia) (Fig. 1.1). The incidence rate in China is one of the highest (22.9 in men and 10.5 in women), while it is also relatively high in Japan (10.6 in men and 1.5 in women).

Esophageal cancer is two to four times more common among men than women in general; however it is approximately seven times more common among men in Japan and 17 times more common among men in Korea. These differences in sex

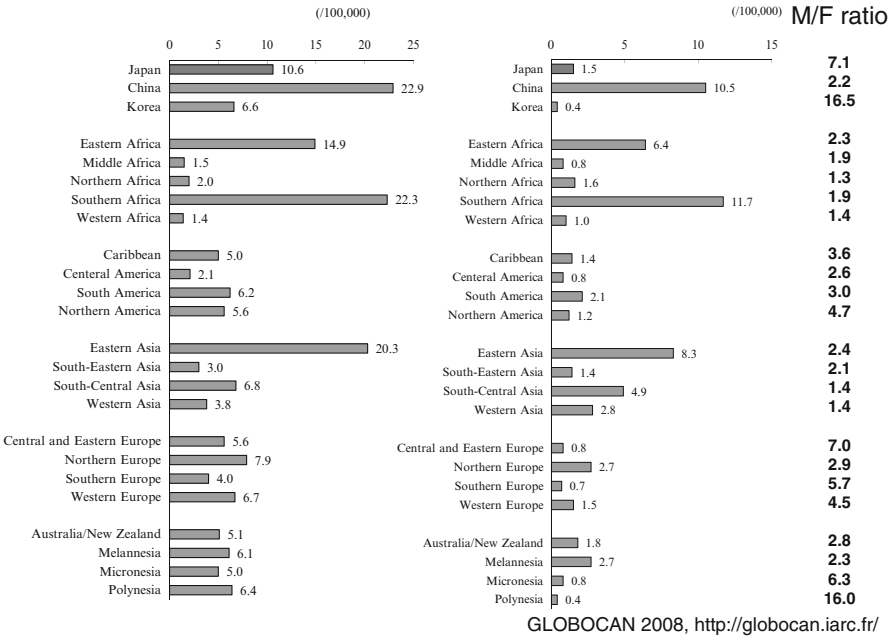
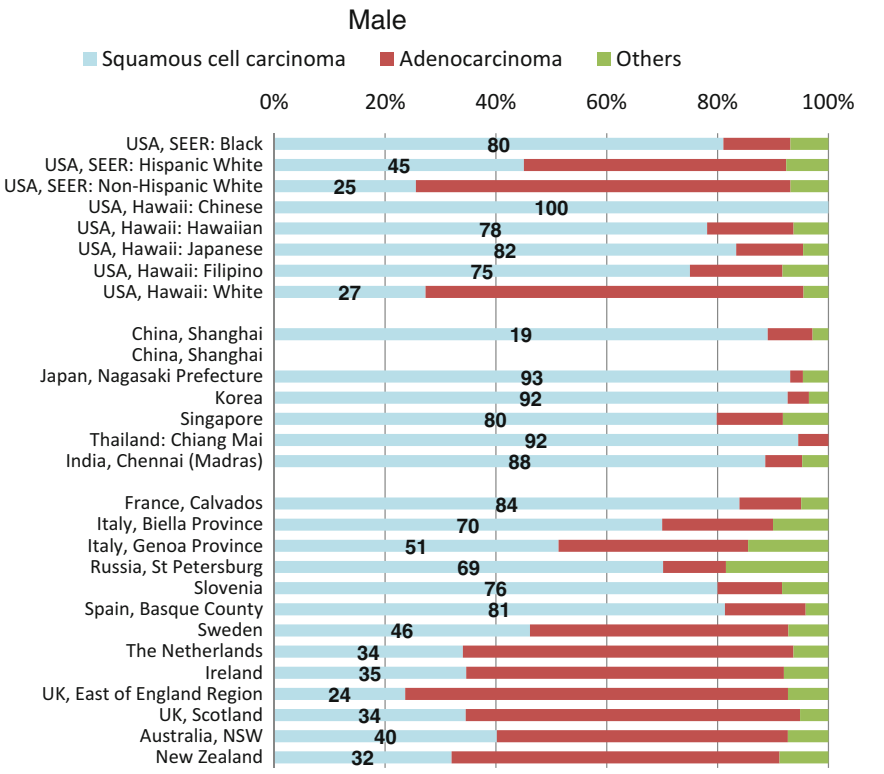


Fig. 1.1 Age-standardized incidence rate (World) of esophageal cancer in the world (2008)



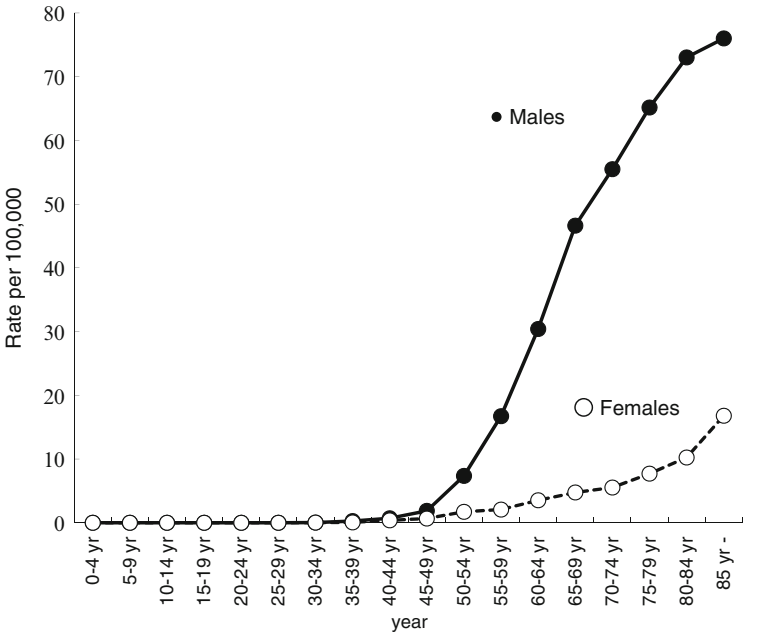
Cancer Incidence in Five Continents Volume IX (2007), http://ci5.iarc.fr/CI5i-ix/ci5i-ix.htm)

Fig. 1.2 Esophageal cancer—histological distribution % (1998–2002)

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 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 of geographic variations is unspecified.

1.1.1.2 Histological Type [2]

In those high-incidence regions that provide information on histological type, approximately 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 USA, SEER (non-Hispanic White) indicated ASR 5.3 in men where 67 % of cases are coded as adenocarcinoma as opposed to 25 % squamous cell carcinoma. In contrast,



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

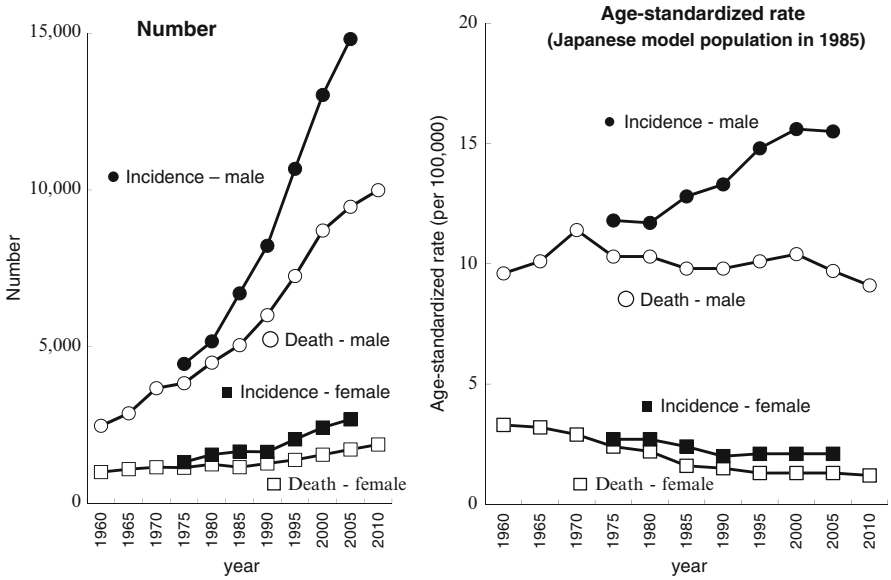
Fig. 1.3 Age-specific mortality rate of esophageal cancer in Japan (2011)

Japan, Nagasaki indicated ASR 9.1 in men where only 2 % of cases are coded as adenocarcinoma as opposed to 93 % squamous cell carcinoma.

1.1.2 Esophageal Cancer in Japan

In 2011, 10,141 men and 1,829 women died from esophageal cancer, representing 4.8 and 1.3 % of the total cancer death in men and women, respectively. Mortality rates increased with age rapidly after 40 years (Fig. 1.3). The mortality rate of esophageal cancer is estimated to be 0.67 % in men and 0.09 % in women up to 75 years, increasing to 1.17 % in men and 0.20 % in women over lifetime. Regarding incidence, 17,004 men and 2.990 women were estimated to be diagnosed with esophageal cancer in 2007 and the probability of esophageal cancer diagnosis was 1.35 % in men and 0.19 % in women up to 75 years, increasing to 2.16 % in men and 0.43 % in women for lifetime. Five-year survival rates were 32.3 % in men and 41.3 % in women who were diagnosed with esophageal cancer in 2003–2005 based on the population-based cancer registry.

Both incidence and mortality rates are observed to have increased in number since 1960 due to the aging of Japanese population, while age-standardized rates are observed to have been consistently decreasing with the exception of the increasing male incidence rate (Fig. 1.4). Histological distribution trends were



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

analyzed using eight population-based cancer registries with high level of reliability from 1993 to 2001 (Table 1.1) [3]. Squamous cell carcinoma remains the predominant type of esophageal cancer in Japan, and a remarkable increase in adenocarcinoma has not been observed before 2001. Disparity in the classification of esophageal and gastric cardia adenocarcinoma may have led to underestimation of esophageal adenocarcinoma incidence.

An increased trend of adenocarcinoma of the esophagogastric 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 esophagogastric junction) [4]. 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 1.2). Tobacco smoking and alcohol consumption are convincing risk factors for esophageal cancer, especially squamous cell carcinoma.

Table 1.1 Trends in incidence of esophageal cancer by histological subtype in Japan[a]

	Males			Females		
	1993–1995	1996–1998	1999–2001	1993–1995	1996–1998	1999–2001
Total number (%)	4,819 (100)	5,734 (100)	6,360 (100)	990 (100)	1,033 (100)	1,157 (100)
Histology						
Squamous cell	3,496 (72.5)	4,277 (74.6)	4,629 (72.8)	661 (66.8)	686 (68.6)	750 (64.8)
[% among specified histology]	[94.3]	[94.1]	[93.3]	[94.3]	[93.1]	[91.0]
Adenocarcinoma	125 (2.6)	146 (2.5)	192 (3.0)	19 (1.9)	28 (2.7)	41 (3.5)
Other types	87 (1.8)	120 (2.1)	140 (2.2)	21 (2.1)	23 (2.2)	33 (2.9)
Unspecified	1,111 (23.1)	1,191 (20.8)	1,399 (22.0)	289 (29.2)	296 (28.7)	333 (28.8)

[a]Shibata et al. [3]

Table 1.2 Established risk and protective factors for esophageal cancer

Evidence	Risk factors	Protective factors
Convincing	Tobacco smoking[a]	–
	Alcohol consumption[b,c] (squamous cell carcinoma)	
	Body fatness[c] (adenocarcinoma only)	
Probable	Mate[c]	Non-starchy vegetables[c]
		Fruits[c]
		Foods containing beta-carotene[c]
		Foods containing vitamin C[c]
Limited–suggestive	Red meat[c]	Foods containing dietary fiber[c]
	Processed meat[c]	Foods containing folate[c]
	High-temperature drinks[c]	Foods containing pyridoxine[c]
		Foods containing vitamin E[c]

[a]IARC monograph on the evaluation of carcinogenic risks to humans, Volume 83 (2003)
[b]IARC monograph on the evaluation of carcinogenic risks to humans, Volume 96 (2007)
[c]Second Expert Report, food, nutrition, physical activity, and the prevention of cancer: a global perspective
World Cancer Research Fund/American Institute for Cancer Research [5]

Mate, a traditional herbal beverage consumed in parts of South America, has been identified as a probable cause of esophageal cancer. Non-starchy vegetables, fruits, and foods containing beta-carotene and/or vitamin C probably prevent esophageal cancer.

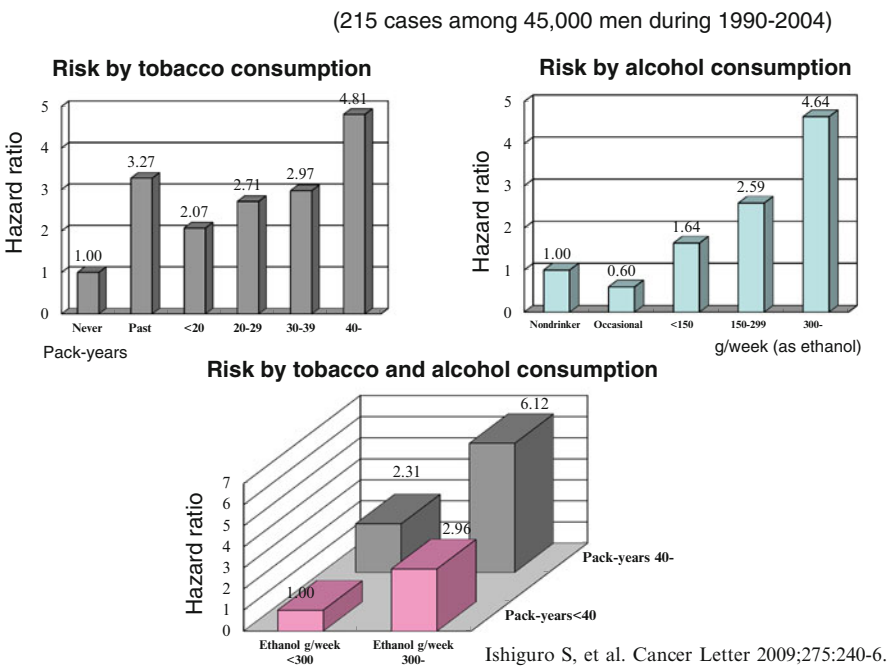


Fig. 1.5 Smoking of tobacco, alcohol consumption, and subsequent risk of esophageal squamous cell carcinoma in men—JPHC study

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 [6]. 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 eleven case–control studies tested the association between tobacco smoking and esophageal cancer risk [7]. 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 % 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 [8]. With the exception of three case–control studies, all cohort studies and case–control studies showed strong positive associations and dose–response relationship. 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 [9] (Fig. 1.5). A total of 44,970

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 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, 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 [10]. The majority of the studies focused on ESCC and was 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 = 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 ALDH1 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 ALDH*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

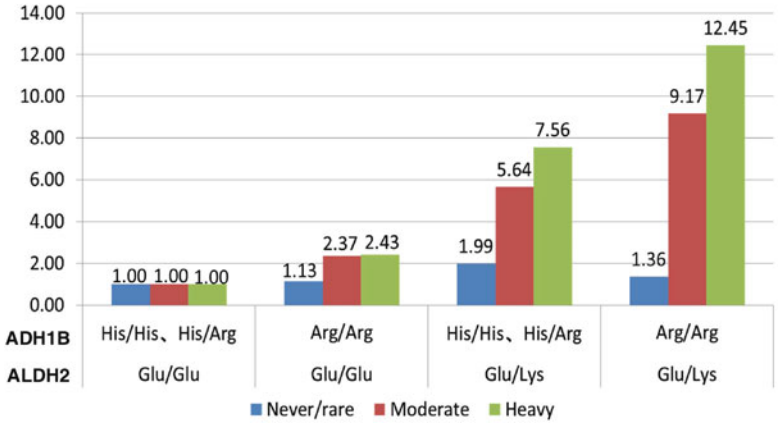


Fig. 1.6 Risk of esophageal cancer associated with combinations of alcohol dehydrogenase (ADH)1B and aldehyde dehydrogenase (ALDH)2 genotypes

with the highest risk of esophageal cancer among heavy drinkers [12.45 (2.9–53.46)] (Fig. 1.6), 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 [11].

1.2.3 Fruit and Vegetable Intake

Although tobacco smoking and alcohol consumption are the primary lifestyle risk factors for esophageal cancer, dietary factors are also likely to be important [5]. Intake of non-starchy vegetables and fruits 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 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 significant relationship between the intake of such vegetables and esophageal cancer prevention. However, residual confounding by tobacco smoking and alcohol consumption cannot be ruled

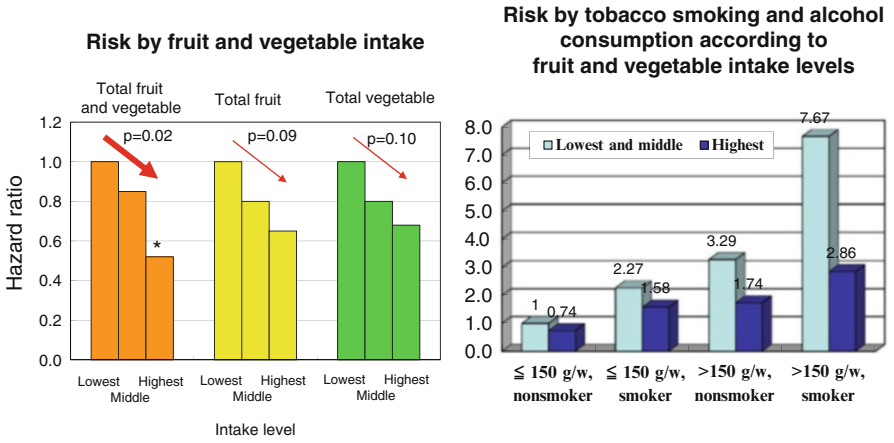


Fig. 1.7 Fruit and vegetable intake and subsequent risk of esophageal squamous cell carcinoma—JPHC study

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 [12] (Fig. 1.7). An increase in consumption of total fruits and vegetables by 100 g 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 (HR 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.

1.2.4 Mate and Hot Beverages

Regarding the intake of hot beverages, 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 cancer. 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.

Although there are several studies that show high-temperature drinks and foods are associated with the increased risk of esophageal cancer in Western populations, this evidence is not consistent and most studies have not adequately adjusted for tobacco smoking and alcohol consumption. In a UK population-based case–control study on ESCC comprising 159 female case–control pairs, tea consumption was identified as a risk factor, demonstrating a significant positive correlation with the temperature at which the tea was consumed ($p = 0.03$) [13].

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 systematic review of epidemiologic evidence (two cohort and three case–control studies) among the Japanese population (unpublished data, 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 consumption of hot tea (drinking green tea at high temperatures) in comparison with not-hot tea (drinking green tea at moderate temperatures) [14], while another cohort showed that green tea consumption was significantly associated with an increased risk of esophageal cancer [15].

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 [16]. PAFs of tobacco smoking, alcohol consumption, and insufficient intake of vegetables and fruits 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 carcinoma, carcinosarcoma, adenosquamous carcinoma, verrucous carcinoma, and lymphoepithelioma-like carcinoma.

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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 of regional lymph node metastases [1–4].

Superficial esophageal cancer: an esophageal cancer whose invasion is limited to the mucosa or the submucosa irrespective of the presence of regional lymph node metastases [1–4].

Advanced esophageal cancer: an esophageal cancer whose invasion extends into or beyond the muscularis propria irrespective of the presence of regional lymph node metastases [1, 2].

Mucosal cancer and submucosal cancer are subclassified into three categories, respectively, based on the depth of cancer invasion [1–3]: "EP (M1)" for intraepithelial carcinomas (carcinoma in situ), "LPM (M2)" for tumors invading the lamina propria, "MM (M3)" for tumors in contact with or invading the muscularis mucosae, "SM1" for tumors invading the upper third of the submucosa, "SM2" for tumors invading the middle third of the submucosa, and "SM3" for tumors invading the lower third of the submucosa (Fig. 2.1). In the endoscopically resected specimens "SM1" is defined as a carcinoma that infiltrates the submucosa up to 200 μm below the lower border of the muscularis mucosa, and "SM2" is defined as a carcinoma that infiltrates more than a depth of 200 μm in the submucosa [1–3]. Superficial esophageal squamous cell carcinoma is classified into *Tis* (carcinoma in situ/high-grade dysplasia), *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].

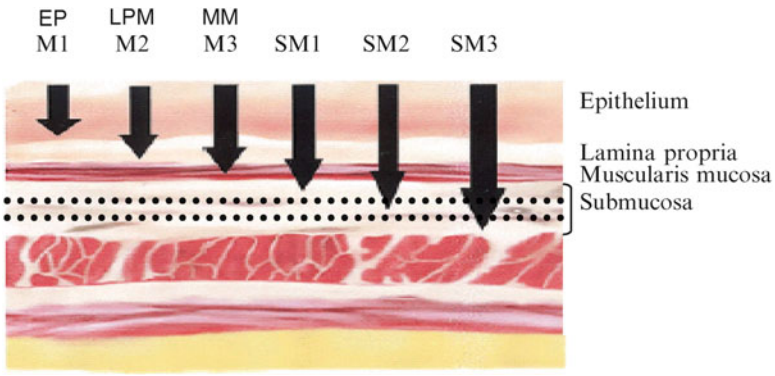

Fig. 2.1 Classification of the depth of invasion

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 characterize 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 flat boards 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 specimen 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 dysplasia, squamous cell carcinoma, atrophy, keratinization, 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 [10].

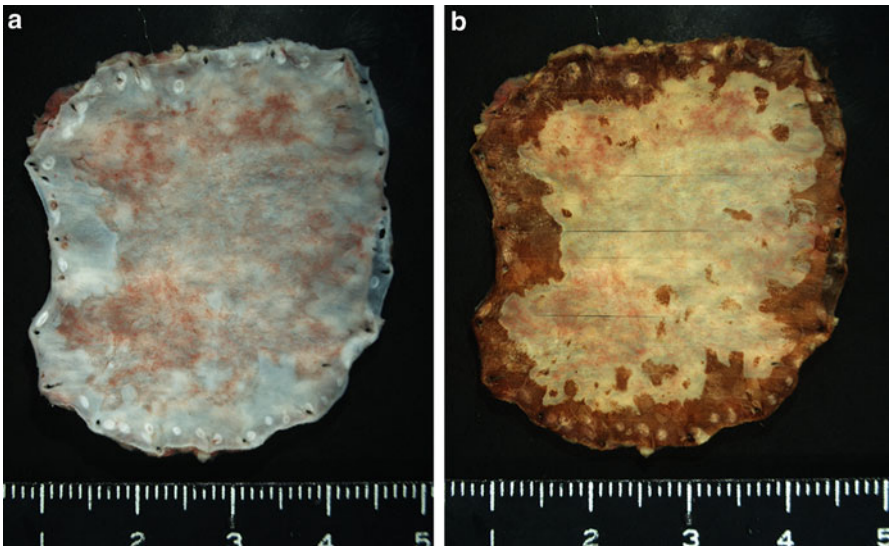

Fig. 2.2 (**a**) A 0-IIc type superficial esophageal carcinoma resected by endoscopic submucosal dissection (ESD). (Courtesy of Dr. Tateishi (Department of Pathology, Yokohama City University, Yokohama) and Dr. Hishima (Department of Pathology, Tokyo Metropolitan Komagome Hospital, Tokyo). (**b**) After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

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.

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 [1–3] (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.

The 0-Ip cancer is most typically seen in esophageal carcinosarcoma (sarcomatoid carcinoma) (Fig. 2.5) [15]. The 0-IIc cancer is most common in

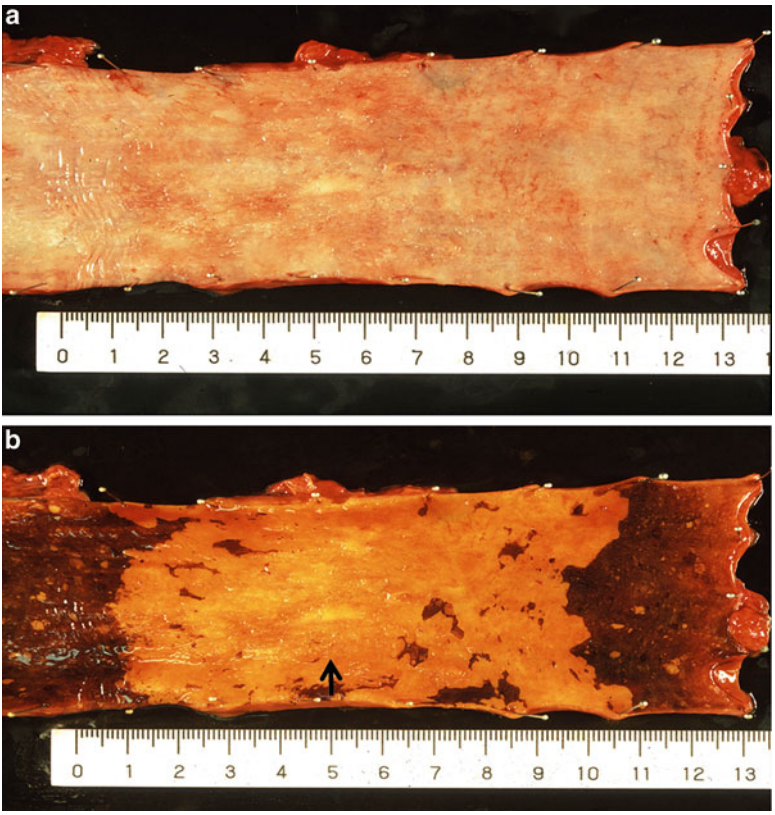

Fig. 2.3 (**a**) A shallow depressed lesion (0-IIc type) resected by esophagectomy. (**b**) Iodine staining clearly revealed an unstained area. This 0-IIc type cancer showed submucosal invasion in the whitish discolored area (*arrow*). This cancer can be also classified as a superficial spreading type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

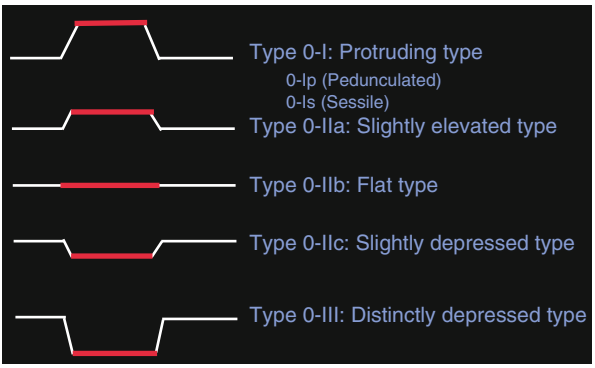

Fig. 2.4 Macroscopic classification of superficial esophageal carcinoma

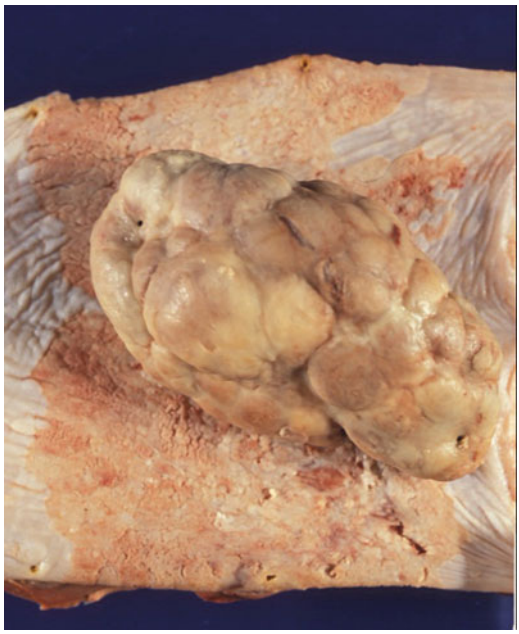

Fig. 2.5 A typical 0-Ip type superficial esophageal carcinoma (carcinosarcoma), which appears as a large polypoid tumor with a smooth surface and prominent lobulation. The stalk is very small and narrow, and not visible in this picture. Erosive superficial squamous cell carcinoma surrounding the polypoid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

superficial esophageal cancers [16, 17]. Type 0-IIb cancer is almost always mucosal cancer, whereas type 0-IIc 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 [1–3]. A type 1 tumor is defined as a protruding tumor (Fig. 2.7a). A type 2 tumor is defined as an ulcerated tumor with a sharply demarcated raised border (Fig. 2.7b). A type 3 tumor is also an ulcerated tumor, but shows infiltration into the 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

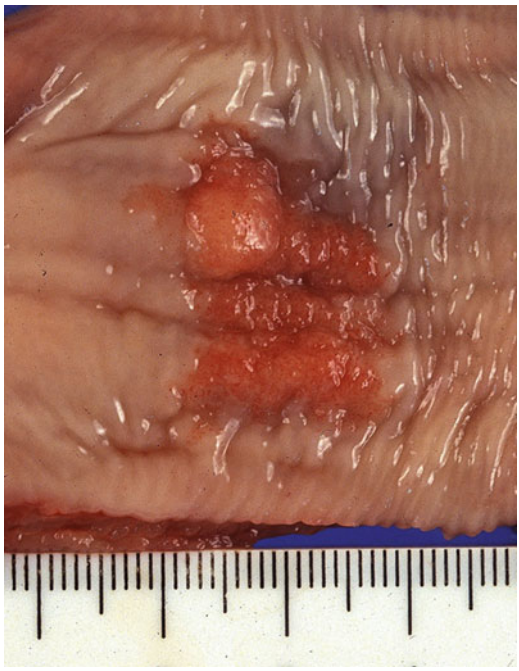

Fig. 2.6 A 0-IIc + "Is" type superficial esophageal cancer. The sessile portion (0-Is type) showed a deepest cancer invasion

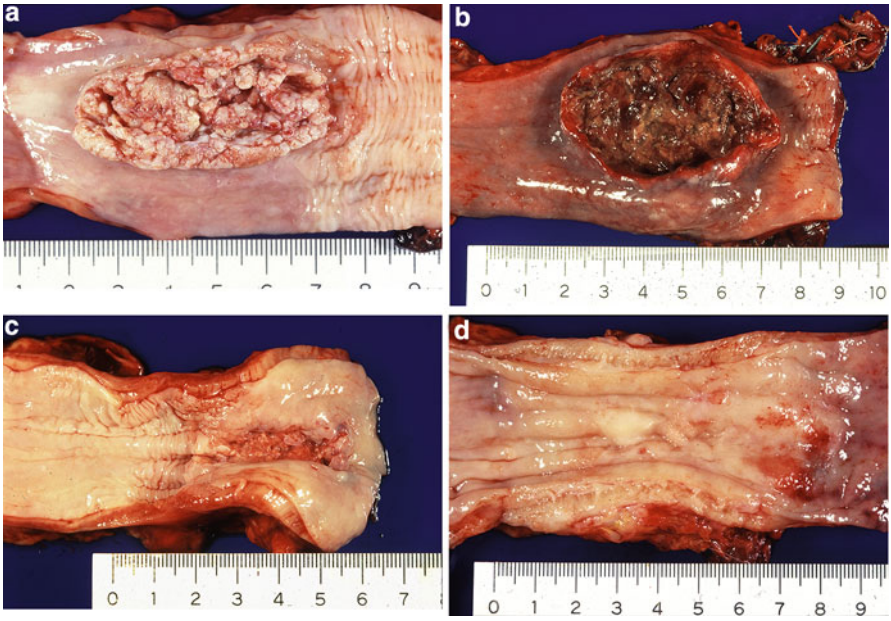

Fig. 2.7 (**a**) A type 1 tumor (protruding tumor). (**b**) A type 2 tumor (an ulcerated tumor with a sharply demarcated raised border). (**c**) A type 3 tumor (an ulcerated tumor with an unclear border). (**d**) A type 4 tumor (a diffusely infiltrating tumor)

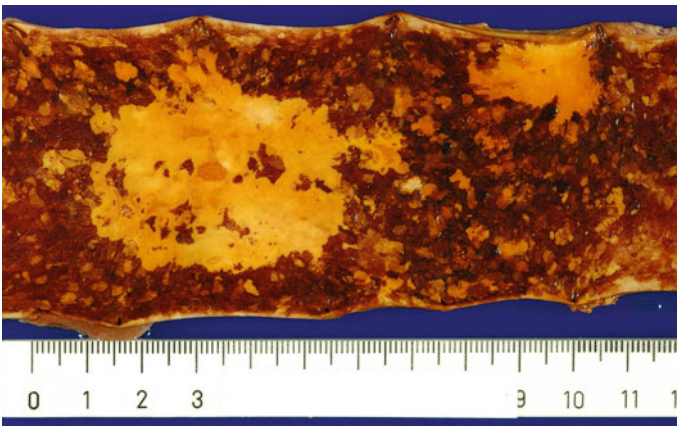

Fig. 2.8 Iodine staining clearly reveals two unstained cancerous areas. In addition to the cancerous areas, there are multiple small iodine-unstained areas in the mucosa surrounding the cancerous lesions

advanced tumor. When an advanced tumor shows a combined type, the most advanced type is described first and double quotation marks are unnecessary according to the Japanese classification of esophageal cancer [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]. Protruding type tumors are usually found to be carcinosarcomas (sarcomatoid carcinoma), squamous cell carcinomas, or malignant melanomas [19]. Protruding type tumors, especially showing a subepithelial growth, are small cell neuroendocrine carcinomas, basaloid squamous carcinomas, and lymphoepithelioma-like carcinomas (esophageal carcinomas 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 registry of esophageal cancer in Japan, up to 47 % of patients with esophageal carcinoma had synchronous or metachronous carcinoma at another 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) [8]. 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 [8, 20, 21]. The incidence of multiple small areas unstained with iodine has been reported to be associated with the development of multiple primary

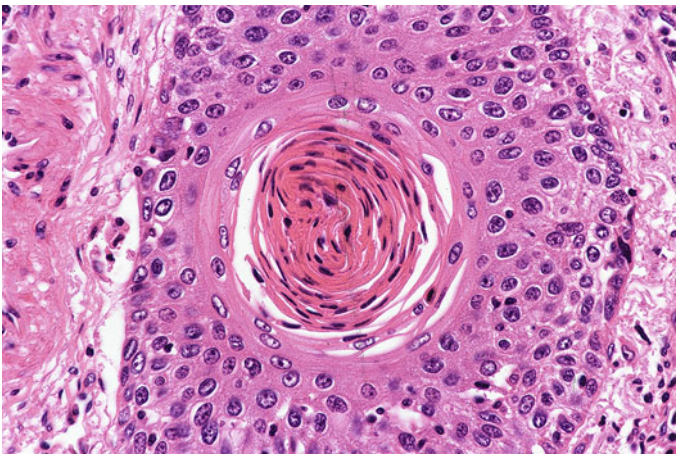

Fig. 2.9 Well-differentiated squamous cell carcinoma is characterized by stratified squamous differentiation and prominent keratinization

cancers in the upper aerodigestive tract and the patients' tobacco and alcohol consumption [8]. Also, male sex and presence of the aldehyde dehydrogenase type 2 (ALDH2) 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], nonepidermolytic 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].

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/or stratified squamous

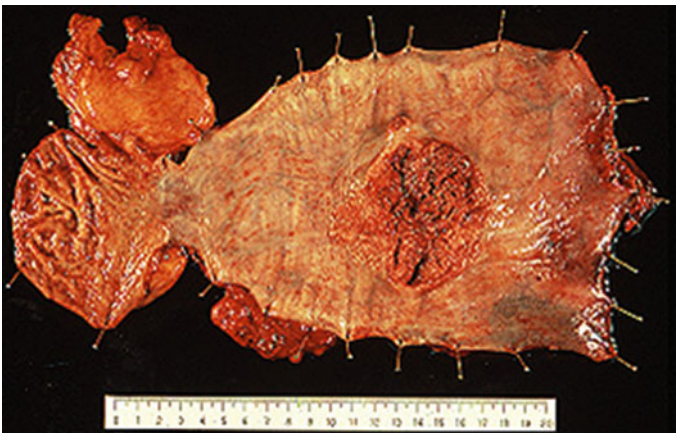

Fig. 2.10 A type 2 advanced esophageal cancer developed in Achalasia

differentiation are observed depending on tumor differentiation grade. The neoplastic cells form variably sized irregular tumor nests with variable amount of desmoplastic reaction and inflammatory response. 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, accounting for more than three quarters of the tumor area (Fig. 2.10), whereas poorly differentiated squamous cell carcinoma has such keratinization accounting for less than one quarter of the tumor area. Moderately differentiated squamous cell carcinoma lies between these two. The WHO classification states that grading is traditionally based on mitotic activity, nuclear atypia, and degree of squamous differentiation, with no special reference to the ratio of keratinization [4]. No widely accepted, well-tested grading system is not established. 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 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 [30]), radiation effect, hyperplastic polyp of the esophagogastric junction [31], malignant melanoma, and metastatic tumor. The main differential diagnosis of squamous cell carcinoma in a biopsy specimen is usually a reactive squamous epithelium. Immunohistochemistry (e.g., p63 and cytokeratin 5/6) can provide assistance in the differential diagnosis, as well as review of imaging studies.

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 the uterine cervix and nipple.

2.4.1 Superficial Esophageal Cancer

ESCC begins as an in situ carcinoma and spreads both horizontally and vertically. Initial invasion into the lamina propria is characterized by the proliferation of downward growth of neoplastic squamous epithelium. It is a distinctive feature of ESCC that lymph node metastases occur 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 [32, 33]. All submucosal tumors have a substantial risk of lymph node metastases [17, 18].

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 21.3–22.3 % [34, 35]. Maximum tumor size has been reported to correlate with the presence of ductal/glandular involvement by multivariate analysis, indicating that ductal/glandular involvement develops in association with horizontal tumor growth [34]. 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, 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 [36, 37]. 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, 38, 39]. 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, 38, 39]. 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 [38, 39].

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 [14, 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 % [40, 41]. 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 [40].

2.4.3.2 Prognostic Factors

Clinicopathologic prognostic factors include TNM stage [1–3], lymph node metastasis [42, 43], tumor invasion depth [42, 43], lympho-vascular invasion [43], intramural metastasis [40, 43], tumor vascularity [44], infiltrating growth pattern [45], inflammatory response [45, 46], tumor budding [47], tumor nest configuration [48], extranodal spreading [49], epithelial-mesenchymal transition phenotype [50], pathologic response to neoadjuvant therapy [51], completeness of surgical resection [42], and the patient's general health condition [52]. 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 [53, 54]. In patients with tumor 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 [55]. Isolated distant lymph node involvement from superficial esophageal carcinoma is thus not necessarily a sign of advanced disease [55]. The most predictive factor for patient's survival is not the area of involved nodes, but the number of involved nodes [56, 57]. Numerous genes, proteins, and microRNAs are involved in the development of ESCC [58–60]. Most of them are involved in signal transduction, regulation of transcription, cell cycle, or cell apoptosis [58]. Such markers may have potential implications in early detection of tumorigenesis and prediction of metastasis and survival. Among those, cyclin D1, p53, E-cadherin, and VEGF have been reported to be most potential markers in ESCC according to the review of protein alterations in ESCC and clinical implications [58].

2.5 Precursor Lesion (Squamous Dysplasia/Intraepithelial Neoplasia)

Two different terms are used to describe precursor lesions of invasive neoplasia, i.e., dysplasia and intraepithelial neoplasia. Dysplasia is almost synonymous with intraepithelial neoplasia. Dysplastic epithelium is defined as intraepithelial neoplasia with architectural and cytological abnormalities (Fig. 2.11) [1–4]. According to the WHO classification of tumors of the digestive system [4], intraepithelial neoplasia is classified as low-grade intraepithelial neoplasia or high-grade intraepithelial neoplasia. In low-grade intraepithelial neoplasia, the architectural and cytological abnormalities are confined to the lower half of the epithelium. In high-grade intraepithelial neoplasia, the abnormalities involve the upper half of the epithelium, and cytological alterations are greater than those in low-grade intraepithelial neoplasia. 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, 61]. Japanese pathologists diagnose carcinoma solely on the basis of the architectural and cytological changes observed without requiring

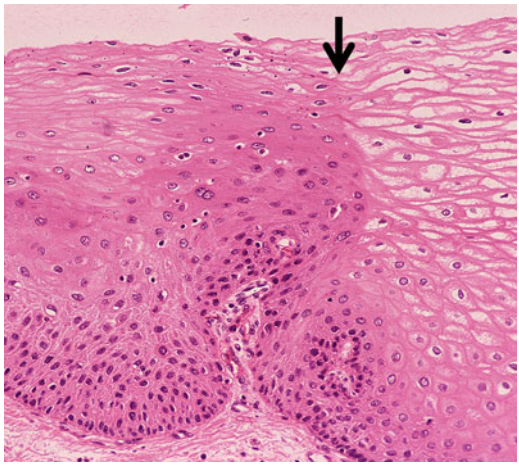

Fig. 2.11 Increased cellularity, mild nuclear atypia, and hyperchromasia are evident, which can be regarded as dysplasia (low-grade intraepithelial neoplasia). The abrupt transition of squamous cells (*right*) to atypical squamous cells (*left*) is noted. *Arrow* indicates the border between normal squamous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

histological evidence of invasive growth, whereas pathologists in North America and Europe define carcinoma as one that has histological evidence of invasive growth [4, 62].

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 dysplasia (intraepithelial neoplasia) (Fig. 2.11). Immunohistochemistry for Ki-67 and p53 is also adjunctively available in the diagnosis of squamous dysplasia (intraepithelial neoplasia) [63].

2.6 Variants

The subtypes of ESCC include basaloid squamous carcinoma, carcinosarcoma (sarcomatoid carcinoma), adenosquamous carcinoma, verrucous carcinoma, and lymphoepithelioma-like carcinoma (esophageal carcinoma with lymphoid stroma).

2.6.1 Basaloid Squamous Carcinoma

Basaloid squamous carcinoma is an uncommon variant of squamous cell carcinoma, accounting for approximately 3 % of primary esophageal malignancies [64, 65]. It is histopathologically distinct from squamous cell carcinoma and is characterized by a poor degree of differentiation and high proliferative activity [66]. Histologically, typical basaloid squamous 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 carcinoma has been reported to have a wide variation of

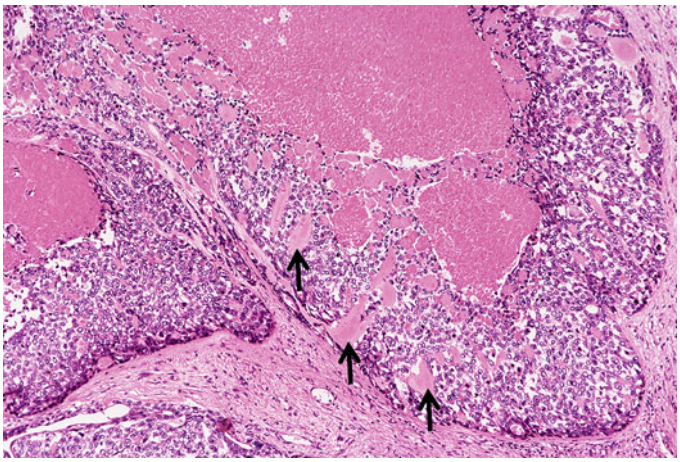

Fig. 2.12 Typical histologic features of basaloid squamous carcinoma. Relatively uniform neoplastic cells with scant cytoplasm form a large solid tumor nest with comedo-like necrosis. The tumor nest contains eosinophilic hyaline material, suggesting a basement membrane-like substance (*arrows*)

histologic features including solid nest, cribriform pattern, microcyst, trabecular nest, and ductal differentiation [64]. Basaloid squamous carcinoma with salivary-type differentiation, mimicking the histologic features of epithelial-myoepithelial carcinoma of the salivary gland, has also been reported [67]. Areas of squamous intraepithelial neoplasia or invasive squamous cell carcinoma are often observed [64, 66]. Biospy specimens are taken from superficial areas of a tumor. Therefore, many cases of basaloid squamous carcinoma of the esophagus are reportedly diagnosed as squamous cell carcinoma preoperatively. Basaloid squamous 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, solid nest, or trabecular nest.

2.6.2 Carcinosarcoma (Sarcomatoid Carcinoma)

Histologically, carcinosarcoma (sarcomatoid carcinoma) is composed of a proliferation of spindle-shaped sarcomatous tumor cells and squamous cell carcinoma forming tumor nests. The spindle-cell component may show osseous, cartilaginous, and skeletal-muscle differentiation. Therefore, this tumor can be regarded as carcinosarcoma. Immunohistochemically, spindle-shaped sarcomatous tumor cells may display various degrees of epithelial differentiation. Almost all reported cases of esophageal carcinosarcoma (sarcomatoid carcinoma) have been macroscopically polypoid and rarely show an ulcerated appearance [15]. Grossly, esophageal carcinosarcoma (sarcomatoid carcinoma) shows a typical 0-Ip type superficial

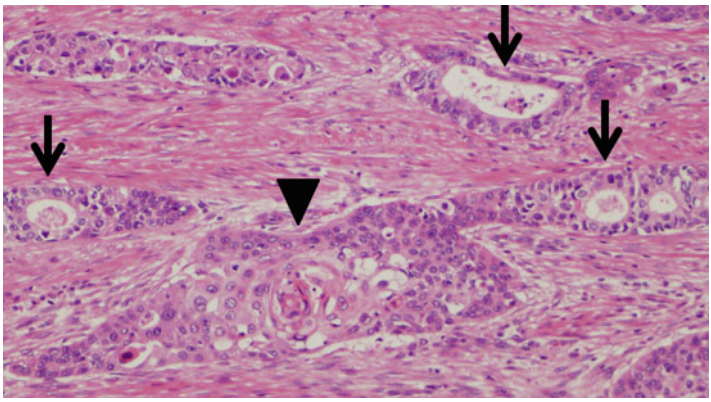

Fig. 2.13 Adenosquamous carcinoma containing coexisting elements of infiltrating squamous cell carcinoma (*arrow head*) and adenocarcinoma (*arrows*)

esophageal carcinoma, which appears as a large polypoid tumor with a smooth surface and prominent lobulation (Fig. 2.5). The stalk is 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 (sarcomatoid carcinoma) (Fig. 2.5).

2.6.3 Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare variant of squamous cell carcinoma. According to our previous reports, only 1.0 % of resected esophageal cancers are diagnosed pathologically as adenosquamous carcinoma [68]. Microscopically, it consists of coexisting elements of infiltrating squamous cell carcinoma and adenocarcinoma (Fig. 2.13). 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 case reports of esophageal adenosquamous carcinoma have indicated that these tumors show highly aggressive biological behavior [69, 70], our own data showed that such patients had a significantly better outcome than patients with squamous cell carcinomas or adenocarcinomas [68]. The location and macroscopic type of adenosquamous carcinomas were similar to those of squamous cell carcinomas, but the former were significantly smaller than the latter [68].

2.6.4 Verrucous Carcinoma

Verrucous carcinoma is a rare, highly differentiated variant of squamous cell carcinoma. Verrucous carcinoma grows slowly and locally and only rarely metastasizes [1–3, 71]. 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.

2.6.5 Lymphoepithelioma-Like Carcinoma (Esophageal Carcinoma with Lymphoid Stroma)

Lymphoepithelioma-like carcinoma, best known to occur in the nasopharynx, reveals striking morphological similarity to nasopharyngeal carcinoma (lymphoepithelioma). Histologically, the tumor is predominantly composed of a subepithelial growth of poorly differentiated carcinoma with prominent lymphoid stroma [72, 73]. The tumor cells are characterized by large vesicular nuclei and prominent nucleoli with scant cytoplasm. Epstein-Barr virus genomes have been identified in lymphoepithelioma-like carcinoma of the esophagus [74]. Lymphoepithelioma-like carcinoma of the esophagus (esophageal carcinoma with lymphoid stroma) seems to represent a relatively good prognosis [72].

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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 is 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

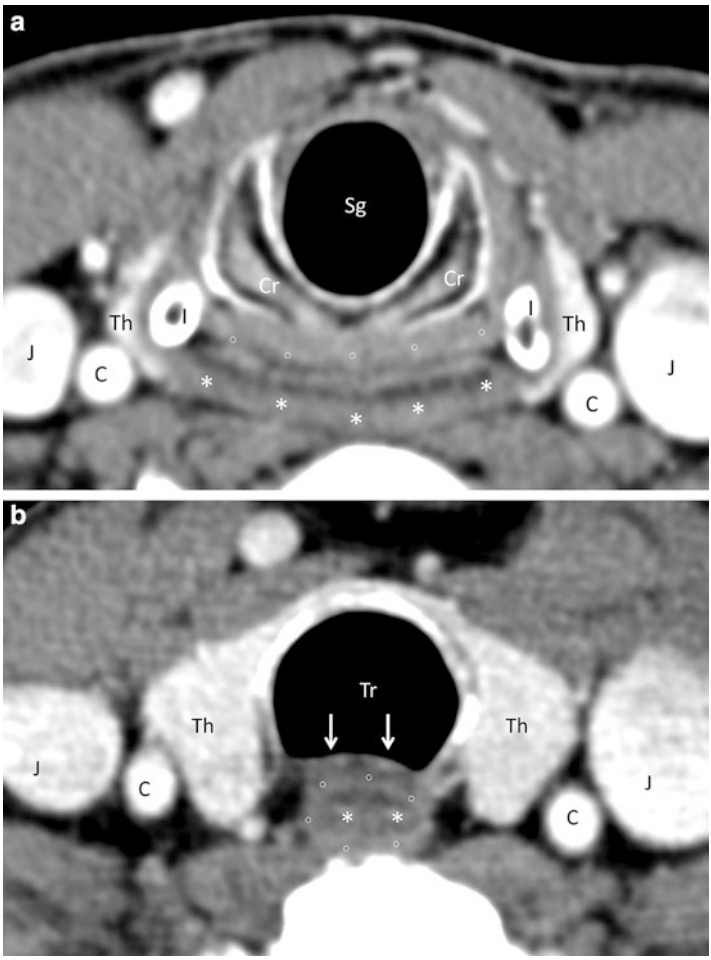

Fig. 3.1 Normal CT anatomy of the hypopharynx and cervical esophagus. (**a**) Contrast-enhanced axial CT image obtained at the level of the hypopharynx. The ossified cricoid cartilage (Cr) is identified as a "U-shaped" structure at this level because the anterior arch is lower than the posterior lamina 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 cirlce*) 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

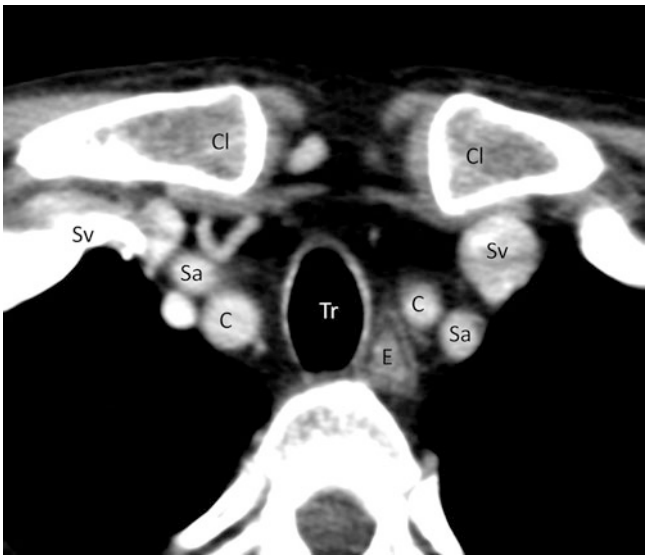

Fig. 3.2 Normal CT anatomy of the thoracic inlet. Contrast-enhanced axial CT image. The esophagus (E) deviates to the *left,* whereas the trachea (Tr) stays in the *middle*. *C* common carotid artery, *Cl* clavicle (sternal end), *Sa* subclavian artery, *Sv* subclavian vein

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 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.

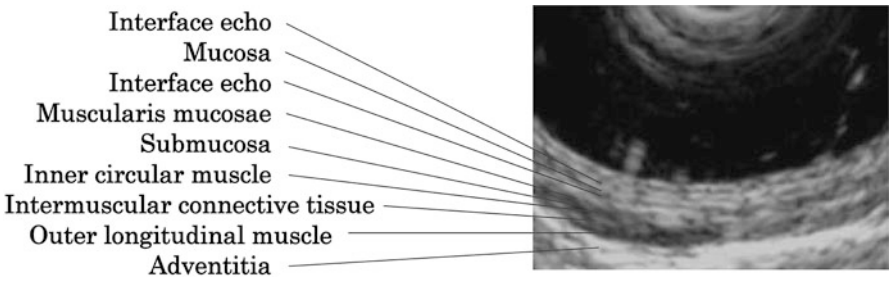

Fig. 3.3 EUS of the normal esophagus (by courtesy of Dr. Gohda, Department of Endoscopy, The Jikei University School of Medicine). EUS differentiates nine layers of the esophageal wall

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 is 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.

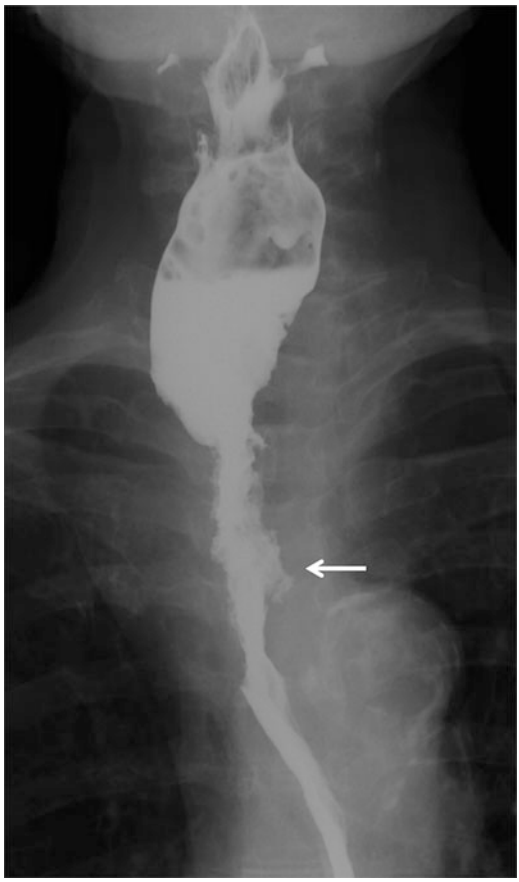

Fig. 3.4 Esophageal cancer (upper thoracic esophagus). On single-contrast barium esophagography there is an irregular stricture of the esophagus (Ut) associated with ulceration (*arrow*)

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 plaquelike 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].

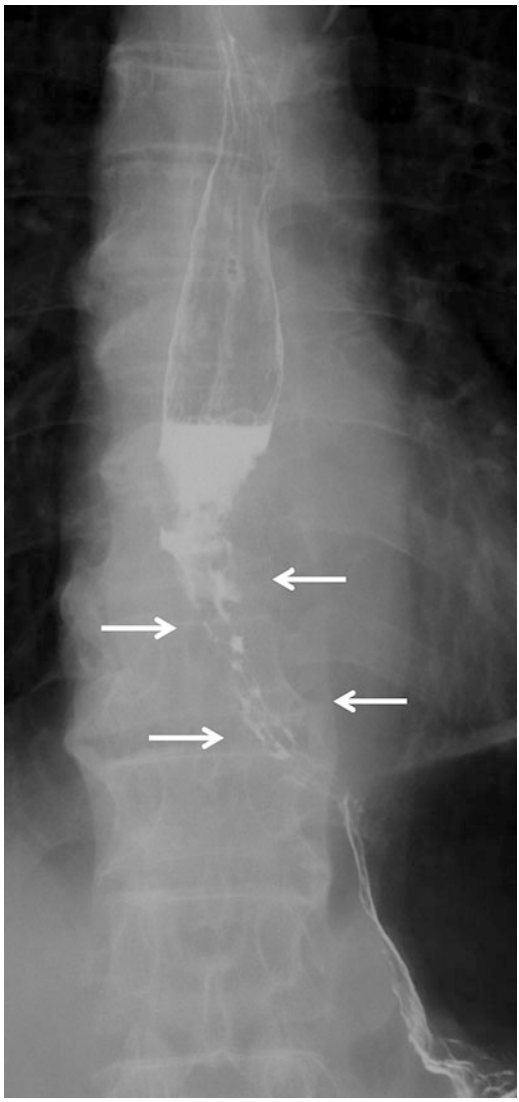

Fig. 3.5 Esophageal cancer (lower thoracic esophagus). Barium esophagography shows an irregular stenosis and varicoid appearance of the lower thoracic esophagus (*arrows*)

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].

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

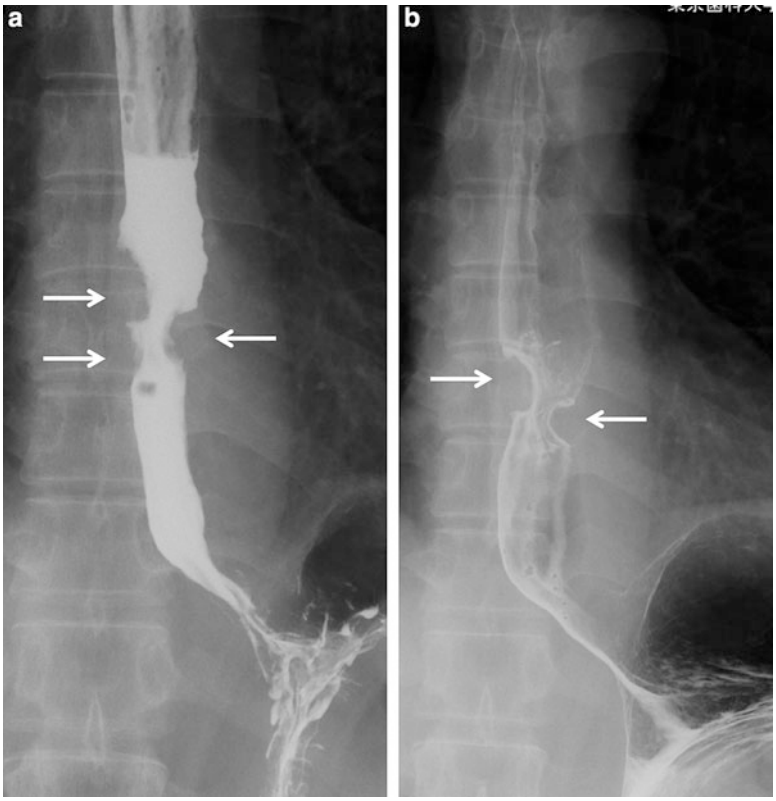

Fig. 3.6 Esophageal cancer (middle thoracic esophagus). Single-contrast image (**a**) and double-contrast image (**b**) of barium esophagography reveal an irregular stricture and abrupt caliber change of the middle thoracic esophagus (*arrows*)

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.

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].

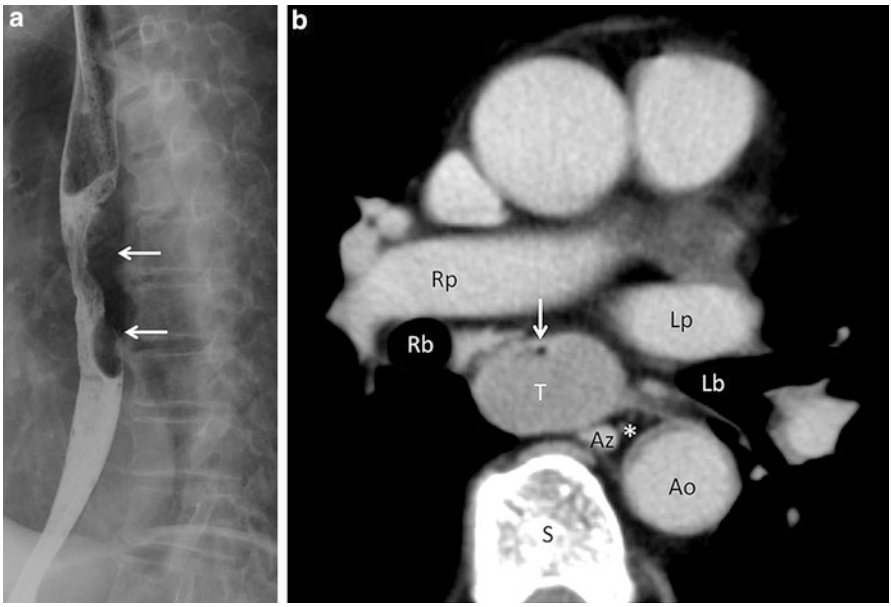

Fig. 3.7 Esophageal cancer (middle thoracic esophagus). (**a**) Barium esophagography shows an irregularly shaped, mass-like filling defect (*arrows*) in the lower thoracic esophagus. (**b**) Contrast-enhanced axial CT image at the level of the middle thoracic esophagus. Asymmetrical wall thickening 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.

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).

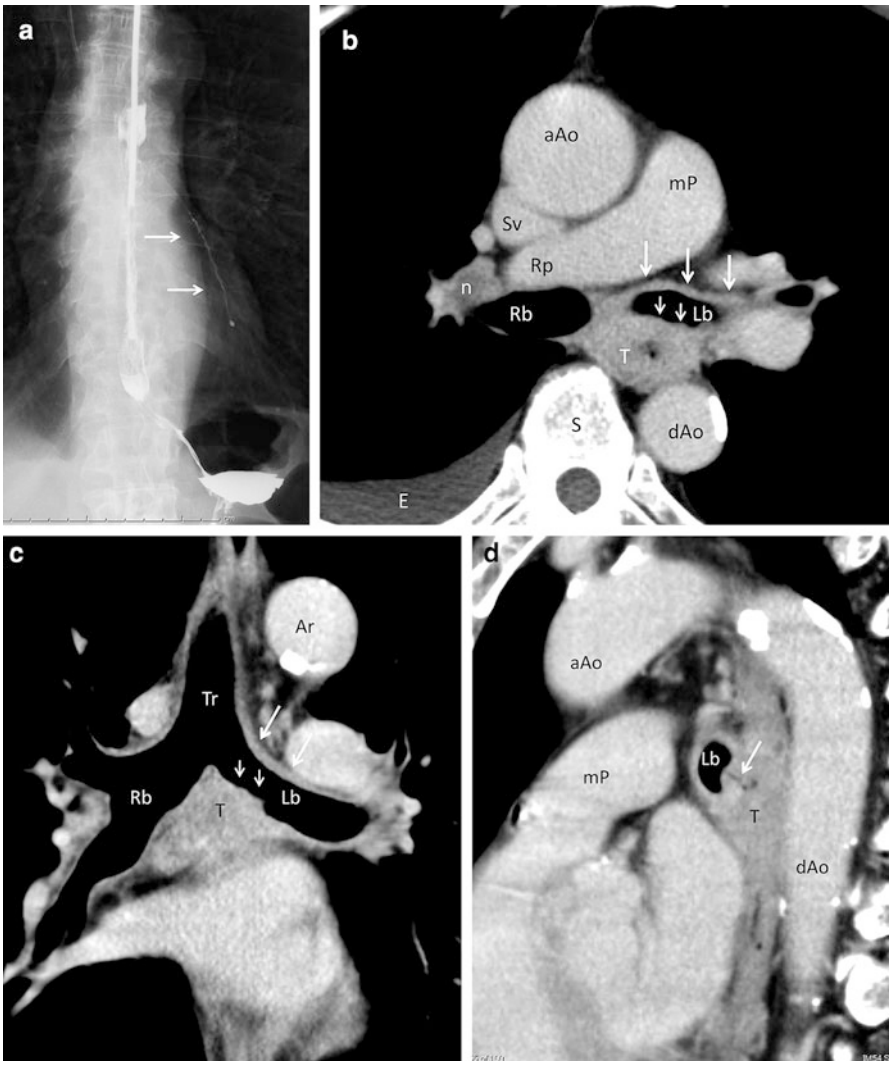

Fig. 3.8 Esophageal cancer (middle thoracic esophagus). Esophagography (**a**) shows contrast material leaking into the left main bronchus and lower lobe bronchi (*arrows*). Contrast-enhanced axial CT image at the level just below the tracheal bifurcation (**b**) and coronal image at the level of the 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* arotic arch, *dAo* descending aorta, *mP* main pulmonary artery, *Rb* right main bronchus, *Rp* right pulmonary artery, *S* spine, *Sv* superior vena cava

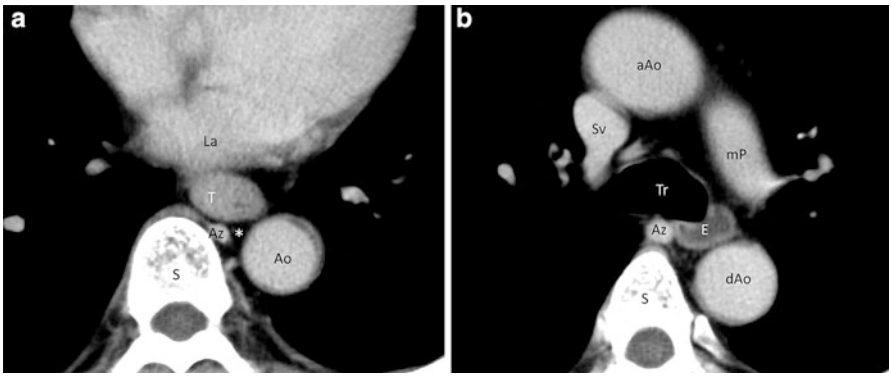

Fig. 3.9 Esophageal cancer (lower thoracic esophagus). (**a**) Contrast-enhanced axial CT image at the level of Lt shows asymmetrical wall thickening of the lower thoracic esophagus (*T*). Integrity both of an entire fat plane around the esophagus and of a triangular fat space (*asterisk*) among the 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

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 2nd arterial phase of dynamic CT (35 sec 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 (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

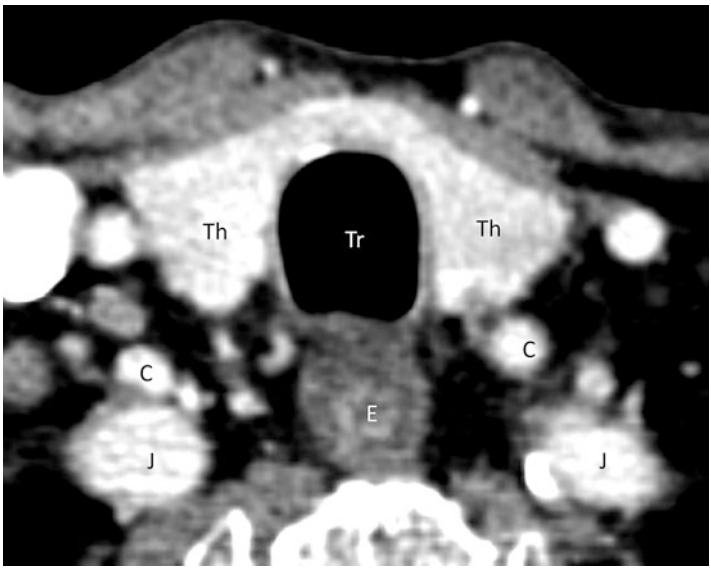

Fig. 3.10 Zonal anatomy of the esophageal wall on CT. Contrast-enhanced axial CT image of the cervical esophagus reveals three different layers of the esophageal (*E*) wall: the inner enhancing layer, middle fatty layer, and outer soft tissue density layer representing the mucosa, submucosal fat, and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

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).

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, 27–29].

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

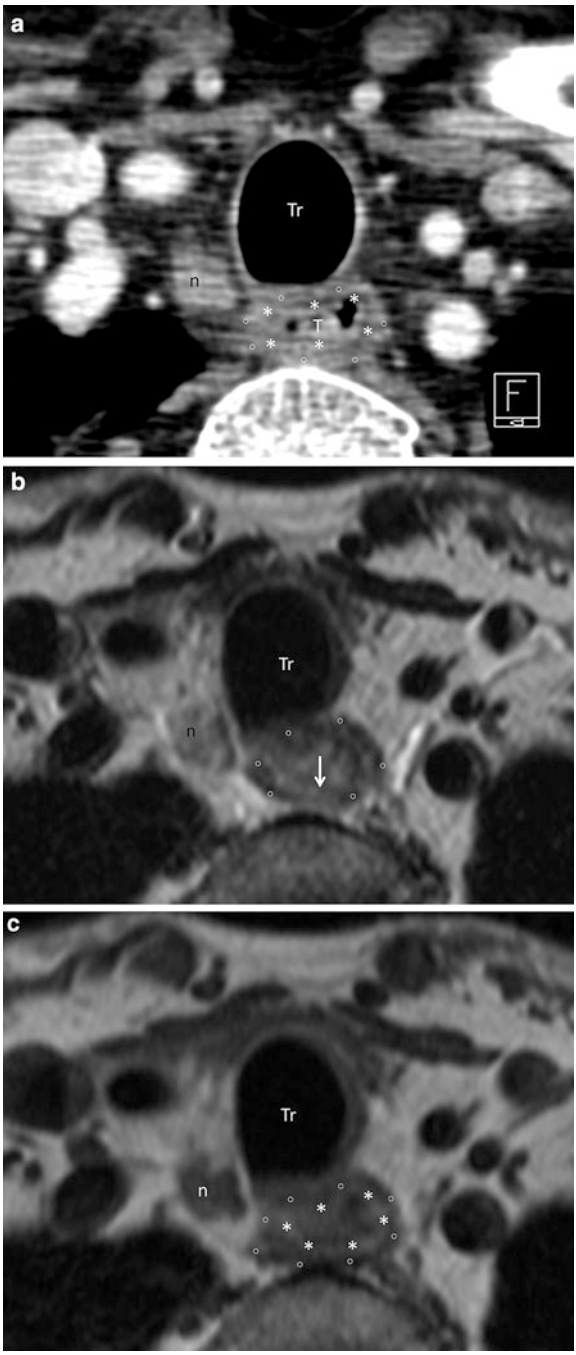

Fig. 3.11 Esophageal cancer (cervical esophagus; T1). Contrast-enhanced axial CT image of the level of the cervical esophagus (**a**) shows a nodular lesion (*T*) arising from the posterior aspect of esophageal wall. A fatty submucosal layer (*asterisk*) and soft tissue muscular layer (*open circle*) 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

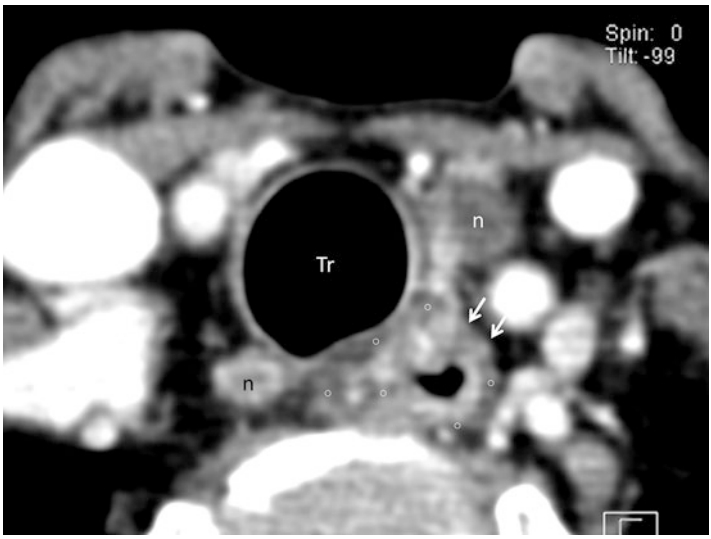

Fig. 3.12 Esophageal cancer (cervical esophagus; T3). Contrast-enhanced axial CT image at the level of the cervical esophagus differentiates the inner enhancing mucosal layer and outer poorly enhancing muscular layer (*open circle*). The relatively thickened inner layer at the anterior aspect represents 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

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 [30]. Ruf et al. reported that esophageal cancer was unresectable when 4 contiguous CT sections demonstrated periesophageal infiltration [13, 31].

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) [28].

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°

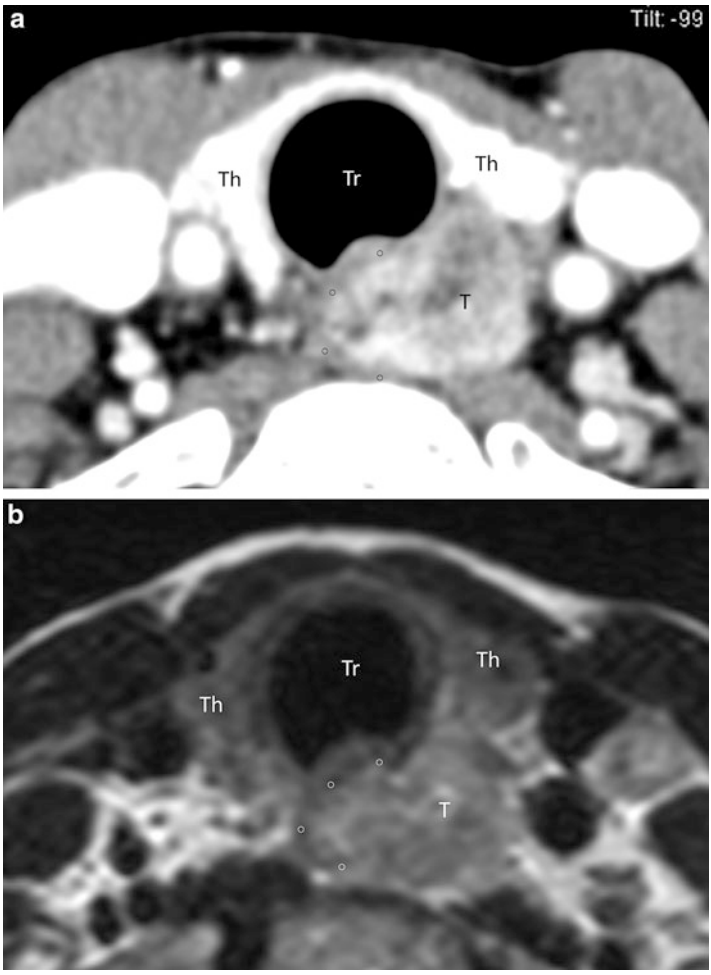

Fig. 3.13 Esophageal cancer (cervical esophagus; T3). Contrast-enhanced axial CT image (**a**) and T2-weighted axial image (**b**) at the level of the cervical esophagus show an infiltrative tumor (*T*). No detectable muscular layer (*open circle*) on the *left side* without loss of tissue planes among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

(Fig. 3.15a). 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) [28]. Ogawa et al. reported that the second criteria

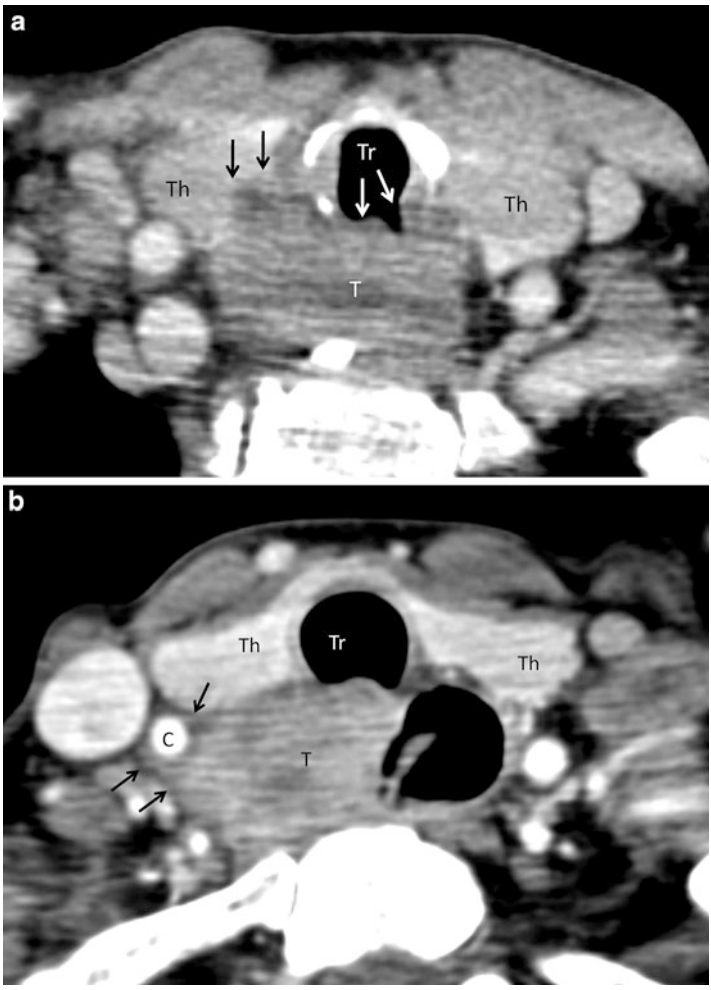

Fig. 3.14 Esophageal cancer (cervical esophagus; T4). Contrast-enhanced axial CT image at the level of the cervical esophagus (**a**) shows an irregularly shaped mass (*T*). The mass anteriorly invades to the trachea (Tr) (*white arrows*) and right lobe of the thyroid gland (*Th*) (*black arrows*). Contrast-enhanced 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

(obliteration of the triangular fat space) were 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 [32].

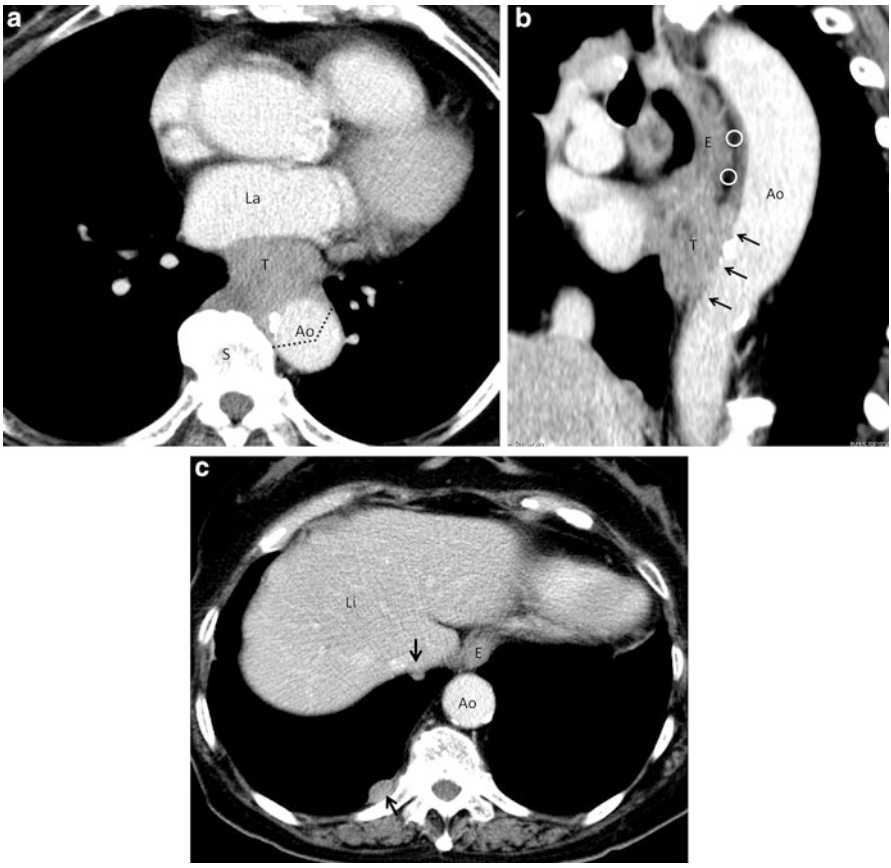

Fig. 3.15 Esophageal cancer (middle and lower thoracic esophagus; T4). (**a**) Contrast-enhanced axial CT image at the level of the left atrium (*La*). There is an infiltrative tumor (*T*) of the esophagus in the posterior mediastinum. The tumor directly abuts upon the anterior aspect of the descending 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 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].

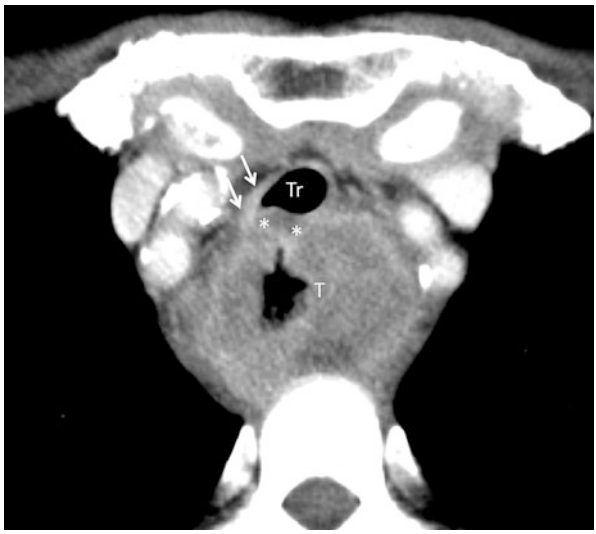

Fig. 3.16 Esophageal cancer (upper thoracic esophagus; T4). Contrast-enhanced axial CT image at the level of superior mediastinum shows irregular thickening of the esophageal wall (*T*). The tumor (*T*) indents the membranous portion (*asterisk*) and infiltrates along the right lateral wall (*arrows*)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

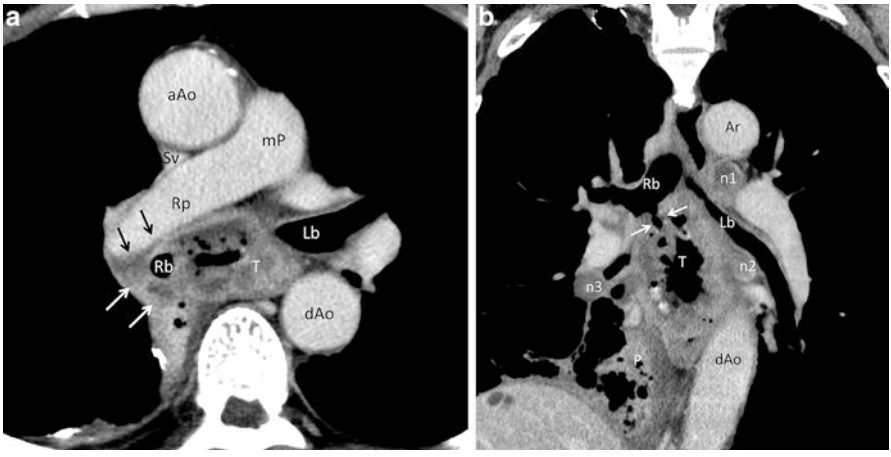

Fig. 3.17 Esophageal cancer (middle thoracic esophagus; T4). (**a**) Contrast-enhanced axial CT image at the level of middle thoracic esophagus. A necrotic tumor (*T*) arising from the middle thoracic esophagus encompasses the right main bronchus (*Rb*) (*arrows*). *aAo* ascending aorta, *dAo* descending 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

Invasion to the Other Structures

Gastric invasion is manifested by a soft tissue mass extending from the primary esophageal tumor into the gastric fundus [28].

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 [28]. 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 % [33].

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 [33]. 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 disease although size is known to be an insensitive parameter for determining nodal spread because tumor can be present in subcentimeter nodes [35]. Generally, mediastinal and abdominal nodes are abnormal when a maximum axial diameter is greater than 1 cm [28]. 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 [36, 37]. We must recognize that enlargement of lymph nodes is nonspecific and can easily be reactive

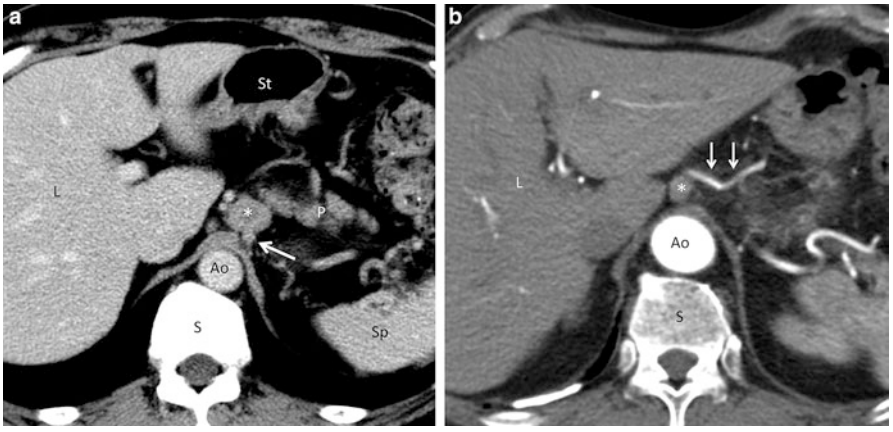

Fig. 3.18 Metastatic adenopathy of the abdominal nodes. Contrast-enhanced axial CT image (**a**) of the upper abdomen shows an enlarged lymph node (*asterisk*) adjacent to the celiac trunk (*arrow*). The node contains low attenuation within it. *Ao* aorta, *L* liver, *P* pancreas, *S* spine, *Sp* spleen, *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

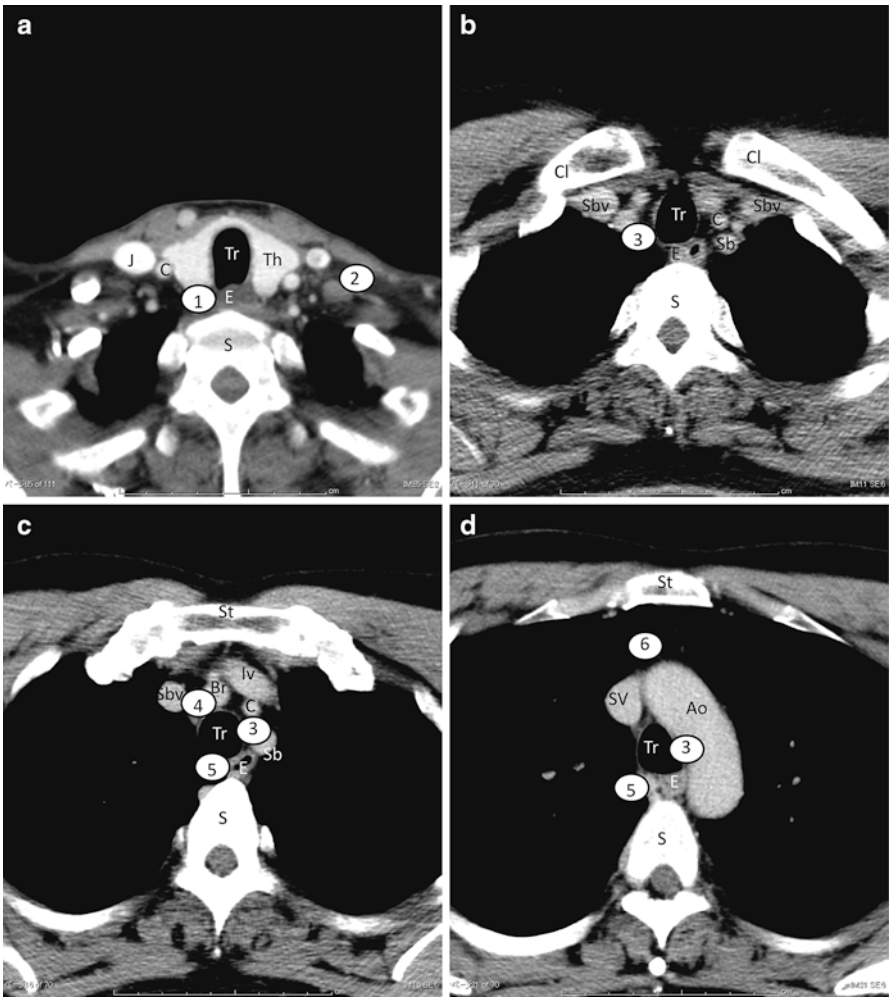

Fig. 3.19 Representative nodal groups in the lower neck and mediastinum on CT. (**a**) CT image at the level of the lower neck. (1) cervical paraesophageal node; (2) supraclavicular node. (**b**) CT image at the level of the thoracic inlet. (3) right recurrent nerve node. (**c**) CT image at the level 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 imagea 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. (**i**) CT image at the level just above the diaphragm. (10) lower thoracic paraesophageal node; (11) posterior mediatinal 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

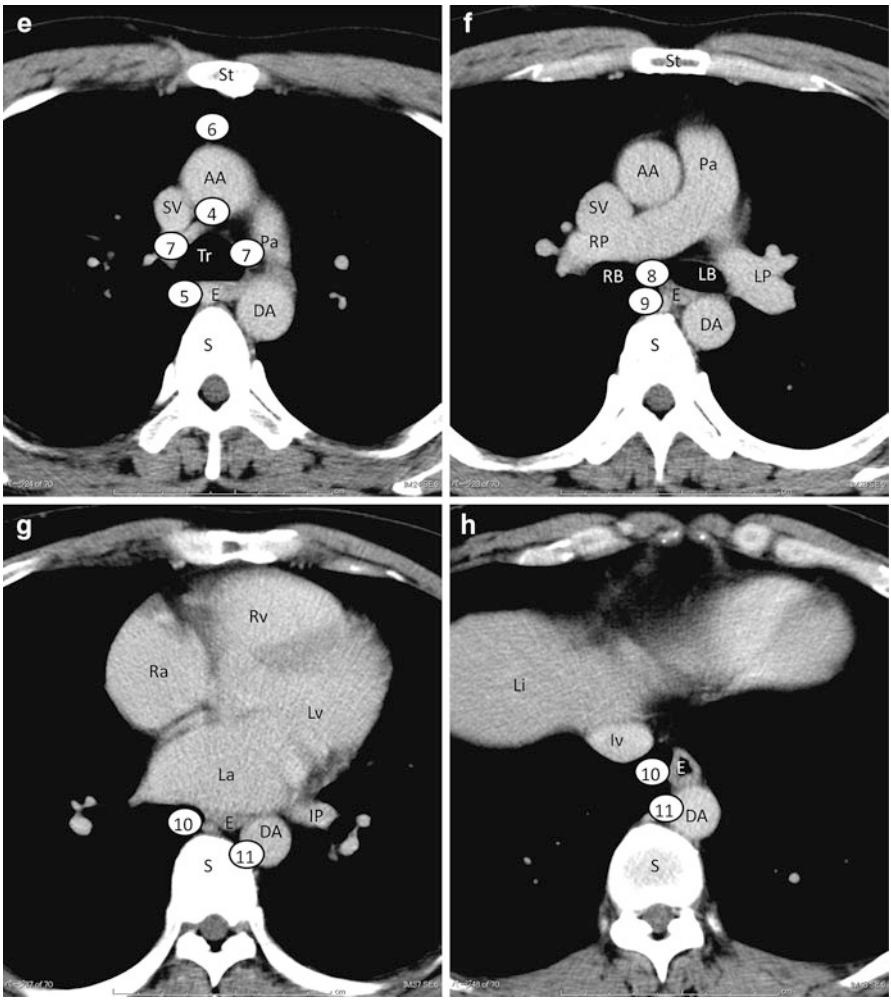

Fig. 3.19 (continued)

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 %

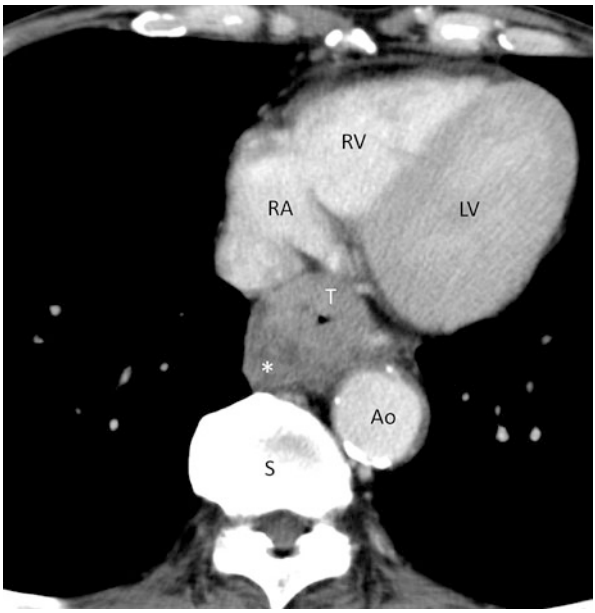

Fig. 3.20 Esophageal cancer (lower thoracic esophagus). Contrast-enhanced axial CT image at the level of the lower thoracic esophagus shows an irregularly shaped tumor (*T*). The tumor (*T*) is indistinguishable from enlarged paraesophageal node (*asterisk*) with extranodal spread. *Ao* aorta, *LV* left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

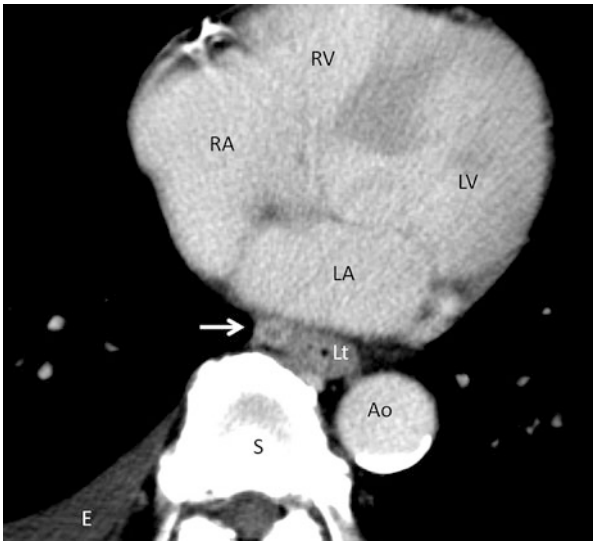

Fig. 3.21 Esophageal cancer (same patient as Fig. 3.8). Contrast-enhanced axial CT image at the level of the lower thoracic esophagus (*Lt*) shows metastatic adenopathy of the paraesophageal node (*arrow*). Metastatic deposit in the node is manifested by focal defect (intranodal low attenuation). The 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

[38, 39]. 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 [27].

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

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) [39]. Hematogenous metastases, often found in patients with esophageal cancer, commonly involve the liver (Fig. 3.22a), lung (Fig. 3.22b),

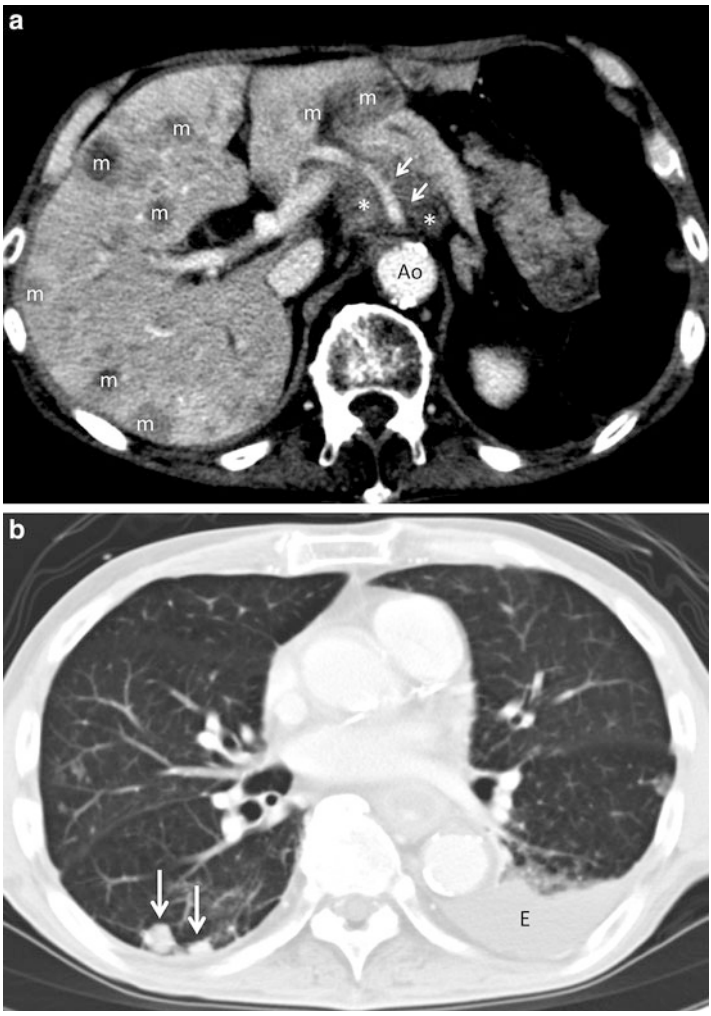

Fig. 3.22 Distant metastases to the liver and lungs. (**a**) Contrast-enhanced axial CT image of the liver on delayed/portal phase. There are numerous metastatic deposits (*m*) in the liver. Enlarged abdominal nodes (*asterisk*) encase the celiac artery (*arrows*). (**b**) Axial CT image in lung window 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*

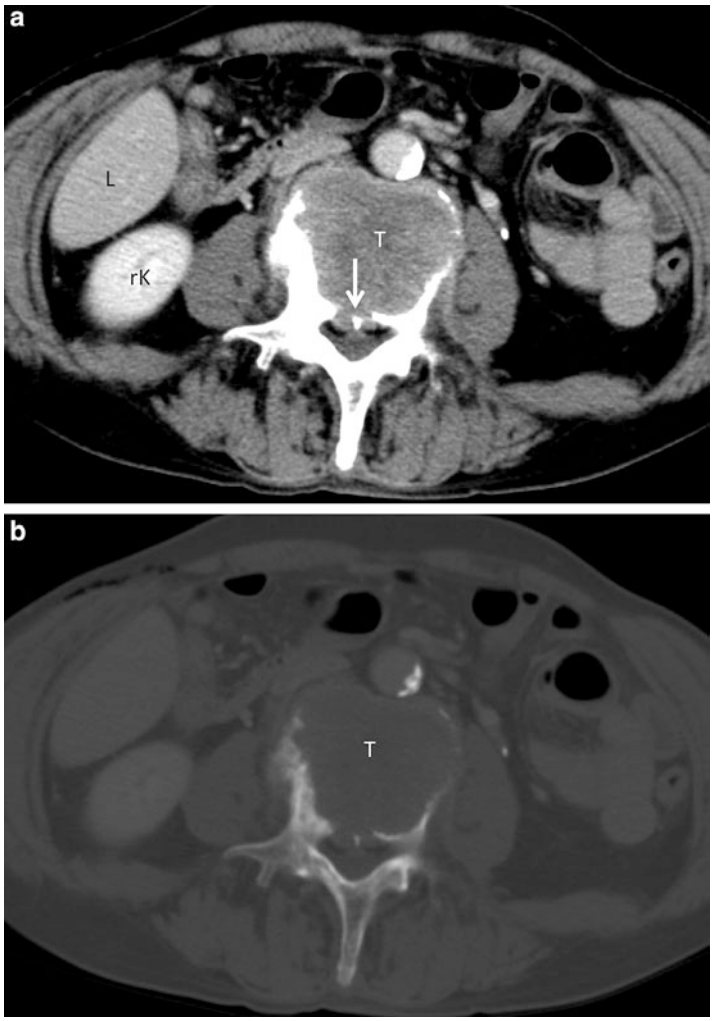

Fig. 3.23 Distant metastasis to the 4th lumbar spine. Axial CT image in soft tissue window (**a**) and bone window (**b**) shows a destructive lesion (*T*) of the 4th lumbar spine. Posteriorly, the lesion protrudes into the anterior aspect of the spinal canal (*arrows*) with impingement upon the anterior aspect of dural sac. *L* liver, *rK* right kidney

bone (Fig. 3.23), adrenal gland, kidney, and brain in descending order of frequency of occurrence [5, 40, 41].

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 specificity is high [28]. 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 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 [42]. 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 [43, 44]. 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 [45].

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 [35]. 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 [35]. 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 % [46].

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Endoscopic Diagnosis of Squamous Cell Carcinoma of the Esophagus

4

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 image (WLI) and Lugol chromoendoscopy. Especially, magnifying endoscopy and equipment-based image-enhanced endoscopy (IEE) [1] including narrow-band imaging (NBI) opened a brand new door of the endoscopic diagnostic field. Magnifying endoscopy combined with IEE can visualize the microstructure of the epithelial surface and microvasculature. Based on the morphological changes in these structures, we can make diagnosis 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 squamous cell carcinoma of the esophagus.

Keywords

Endoscopic diagnosis • EUS • IEE • Lugol chromoendoscopy • NBI

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4.1 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 and other gastrointestinal cancers. Endoscopic imaging technology has dramatically improved, and in particular, magnifying endoscopy and equipment-based IEE [1] have provided dramatic breakthroughs in the endoscopic diagnosis of ESCC.

In an endoscopic image, nonneoplastic and noninflammatory squamous epithelia appear as a flat surface, with a pink-colored mucosa and an irregular vascular network (Fig. 4.1a). In contrast, superficial cancerous lesions show an irregular surface (Fig. 4.1b) and a reddish or whitish color change, while advanced cancerous lesions show clearly apparent irregular elevations or irregular ulceration (Fig. 4.1c). In the most advanced ESCC, the esophageal lumen is obstructed by tumor and the endoscope cannot pass the stricture (Fig. 4.1d).

The macroscopic findings of endoscopy are very important for understanding the location, shape, and extent of ESCC, because these parameters are usually used for

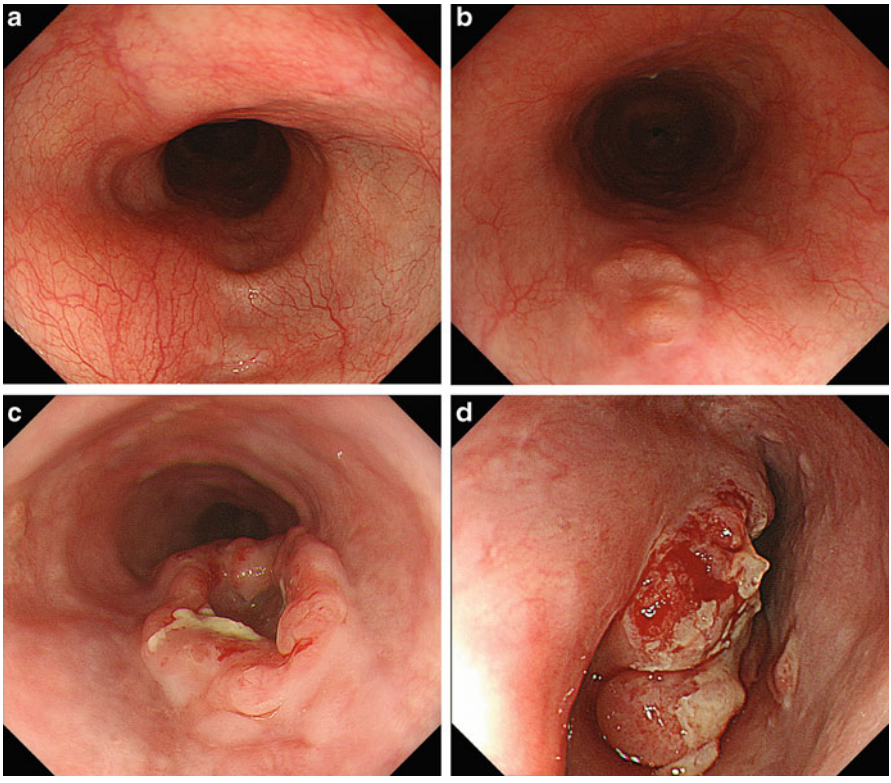

Fig. 4.1 (**a**) White light endoscopic image of normal esophageal epithelium. (**b**) Superficial squamous cell carcinoma of the esophagus (type 0–IIa). (**c**) Advanced esophageal squamous cell carcinoma (type 2). (**d**) Obstruction due to advanced esophageal cancer (type 3)

Table 4.1 Macroscopic classification of esophageal squamous cell carcinoma

Macroscopic classification	Macroscopic subclassification	Endoscopic feature	Detailed explanation
Type 0		Superficial type	
	Type 0–I	Superficial and protruding type	Definitely protruding lesion
	Type 0–IIa	Slightly elevated type	Lesion with a slight elevation up to about 1 mm in height
	Type 0–IIb	Flat type	Lesion with macroscopic elevation or depression
	Type 0–IIc	Slightly depressed type	Lesion with a slight depression. The degree of depression is equivalent to erosion
	Type 0–III	Superficial and depressed type	Lesion showing more distinct depression than the type Iic, and the bottom of the depression appears to extend beyond the muscularis mucosa
Type 1		Protruding type	Localized protruding type
Type 2		Ulcerative and localized type	The ulcerative lesion has a well-demarcated ridge
Type 3		Ulcerative and infiltrating type	The ulcerative lesion has a ill-demarcated ridge circumferentially or semi-circumferentially
Type 4		Diffusely infiltrating type	Lesion with wide intramural invasion, and generally without conspicuous ulcer and protrusion
Type 5		Unclassifiable type	The lesion with a complicated macroscopic appearance which is unclassifiable to any of macroscopic types 0–4
	Type 5a	The unclassifiable lesion without previous treatment	
	Type 5b	The lesion unclassifiable because of a changed appearance with previous treatment	

making decisions about 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 six categories (types 0–5, Table 4.1, Fig. 4.2) [2]. Tumor is defined as type 0 and recognized as superficial

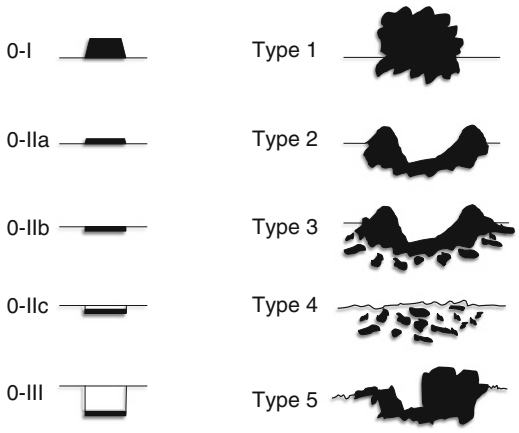

Fig. 4.2 Schematic image of each macroscopic classification of esophageal cancer in Table 4.1

when the invasion is limited to the submucosa. Superficial (type 0) ESCC is divided into three 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 four 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.

4.2 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 minimal. Therefore, an ideal strategy for the early detection of ESCC is required.

4.2.1 Conventional White Light Imaging

Conventional white light images (WLI) of superficial ESCC show disappearance of the vascular network in the mucosa (Fig. 4.3a) and/or an uneven surface with a thin white coating (Fig. 4.3b) or a reddish color change (Fig. 4.3c). The presence of these features in a suspected lesion indicates the possible presence of superficial ESCC.

4.2.2 Lugol Chromoendoscopy

Iodine solution (Lugol solution) stains nonneoplastic esophageal squamous epithelium dark brown (Fig. 4.4a). In contrast, neoplastic lesions do not stain (Fig. 4.4b) [3]. Thus, Lugol chromoendoscopy is a useful method for detecting and identifying

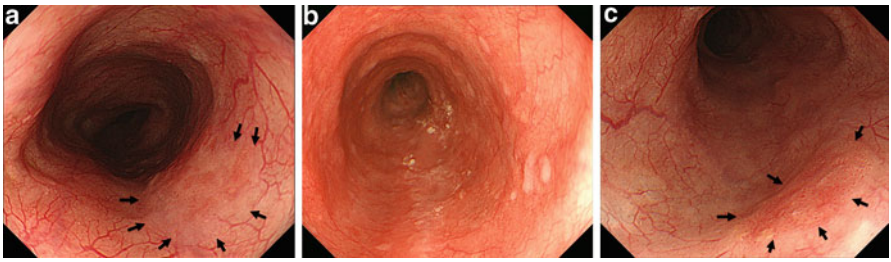

Fig. 4.3 (**a**) Superficial esophageal cancer (type 0–IIc) is clearly identified by disappearance of vascular network. (**b**) Superficial esophageal cancer (type 0–IIb) shows uneven surface with a thin white coating. (**c**) Superficial esophageal cancer (type 0–IIa) is identified as slight reddish lesion

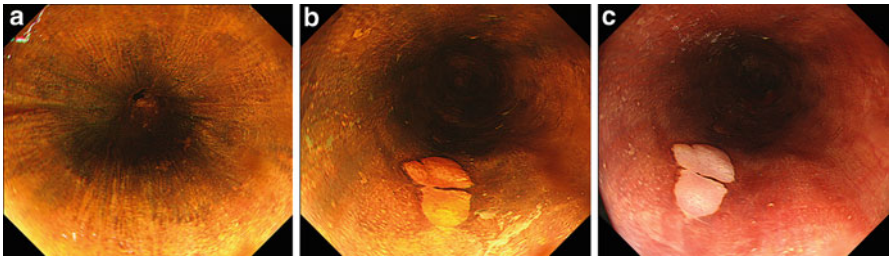

Fig. 4.4 (**a**) Normal esophageal epithelium is stained as *dark brown* by Lugol chromoendoscopy. (**b**) Cancerous lesion is clearly revealed as Lugol-voiding lesion after Lugol staining. (**c**) Definite cancerous lesion shows *pink color* change after Lugol staining

the lateral extension of ESCC. However, it causes unpleasant side effects including chest pain and discomfort in those who undergo endoscopic 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 examination is sometimes effective in preventing allergic reactions.

After staining with Lugol solution, superficial ESCC shows a pink color change (Fig. 4.4c). Shimizu et al. [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. Ishihara et al. [5] also reported that its sensitivity and specificity for 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. 4.5) [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 LVL in the background esophageal mucosa are at risk of multiple cancers in the upper aerodigestive tract.

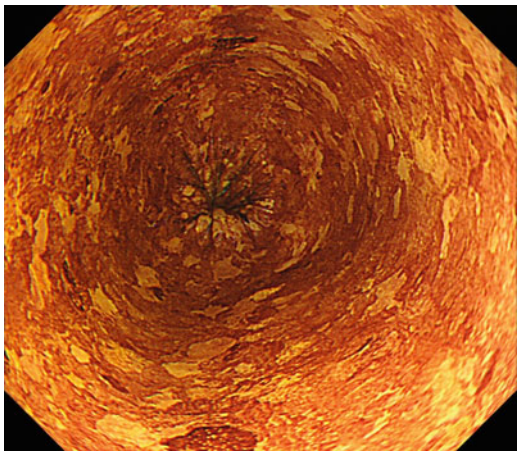

Fig. 4.5 Multiple Lugol-voiding lesions (multiple LVLs)

4.2.3 Equipment-Based Image-Enhanced Endoscopy (IEE)

Equipment-based IEE can accurately diagnose high-grade intraepithelial neoplasia and superficial ESCC with minimal invasion of the esophagus.

Among the types of equipment-based IEE, narrow-band imaging (NBI) [9, 10] has been found to provide a highly accurate diagnosis of superficial ESCC. The NBI system uses two narrow-band wavelengths of 415 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 (Fig. 4.6a, b) [11, 12]. In addition, the morphological changes of the intrapapillary capillary loop (IPCL) have been recognized as a useful parameter for ESCC diagnosis and for evaluation of depth of invasion of ESCC [13]. With magnification, irregularities in the IPCL are also more clearly identified by NBI than by conventional WLI (Fig. 4.6c, d) [11, 12].

Using the simple criteria of "brownish area" and "irregular microvascular pattern" as diagnostic findings of superficial ESCC, Muto et al. [14] reported in their 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 were 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 %, $P = 0.03$).

Takenaka et al. [15] 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 chromoendoscopy was equivalent (90.9 % vs. 100 %, not significant). Furthermore, most of the Lugol-voiding 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

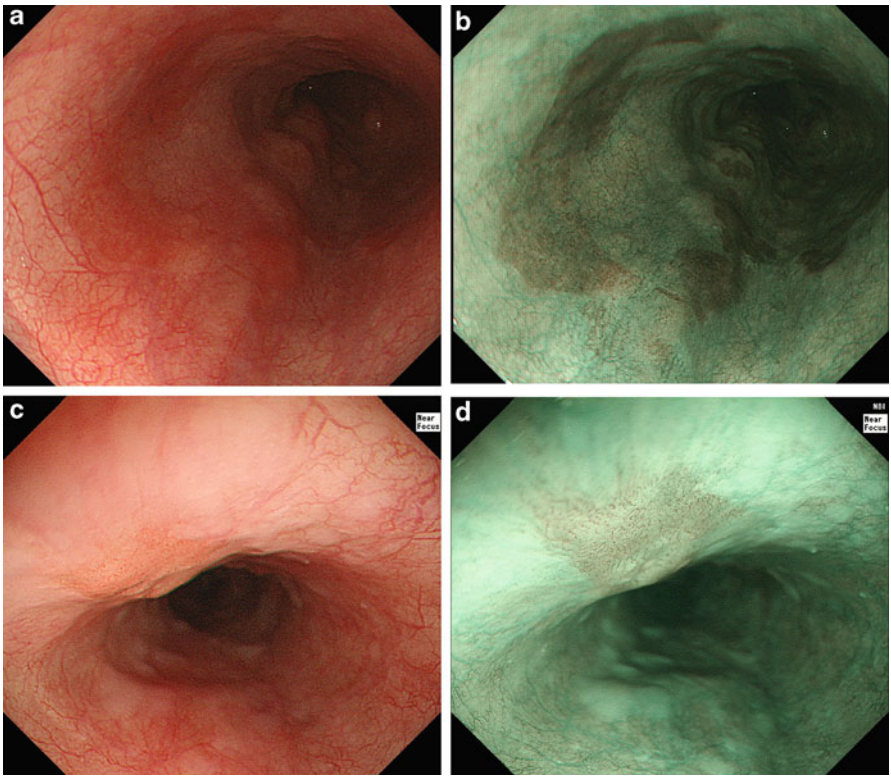

Fig. 4.6 (**a**) Slight reddish color changed is identified but its margin is unclear. (**b**) Well-demarcated *brownish* area is clearly identified. (**c**) Magnifying white light images shows irregular microvascular pattern. (**d**) Narrow-band image enhanced the irregular microvascular pattern compared to conventional white light image

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

4.3 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 [16]. The frequency of metastasis to the lymph nodes in mucosal ESCC is 3 % [16]. The risk increases to 12 % for cancer invading the muscularis mucosae and increases markedly to 26–46 % in those that invade the submucosa [16].

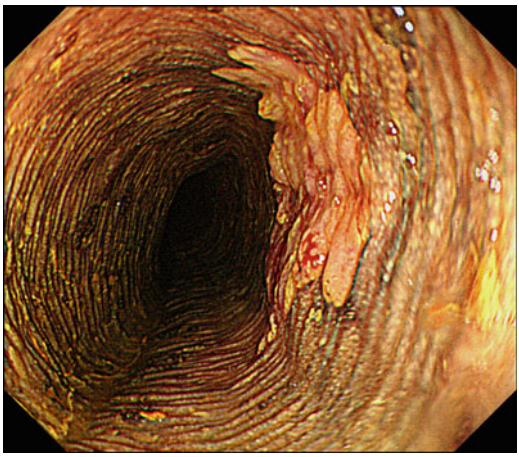

Fig. 4.7 The so-called tatami-no-me sign

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.

4.3.1 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 invasion beneath the mucosal layer. The so-called tatami-no-me sign is also a useful indicator of the depth of invasion (Fig. 4.7). Tatami is a traditional Japanese-style flooring. If the tatami-no-me sign is not seen in the cancerous lesion, the neoplasia may have invaded the deep layers of the lamina propria. If the tatami-no-me sign is seen, the lesion has not invaded the deep layers of the lamina propria.

4.3.2 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 tissue. Therefore, the 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.

4.3.3 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 invasion depth [17].

4.3.4 Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is considered the best method for the 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 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 deaerated 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 (Fig. 4.8a).

Generally, a tumor can be seen by EUS as a low-echoic mass (Fig. 4.8b). If the cancerous lesion invades the submucosal layer, EUS shows a low-echo mass in the high-echo layer corresponding submucosal layer. In protruding superficial ESC (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. Takizawa et al. [18] compared lymph node staging obtained by EUS and by 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 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 the patients with ESCC.

4.3.5 Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a high-resolution cross-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

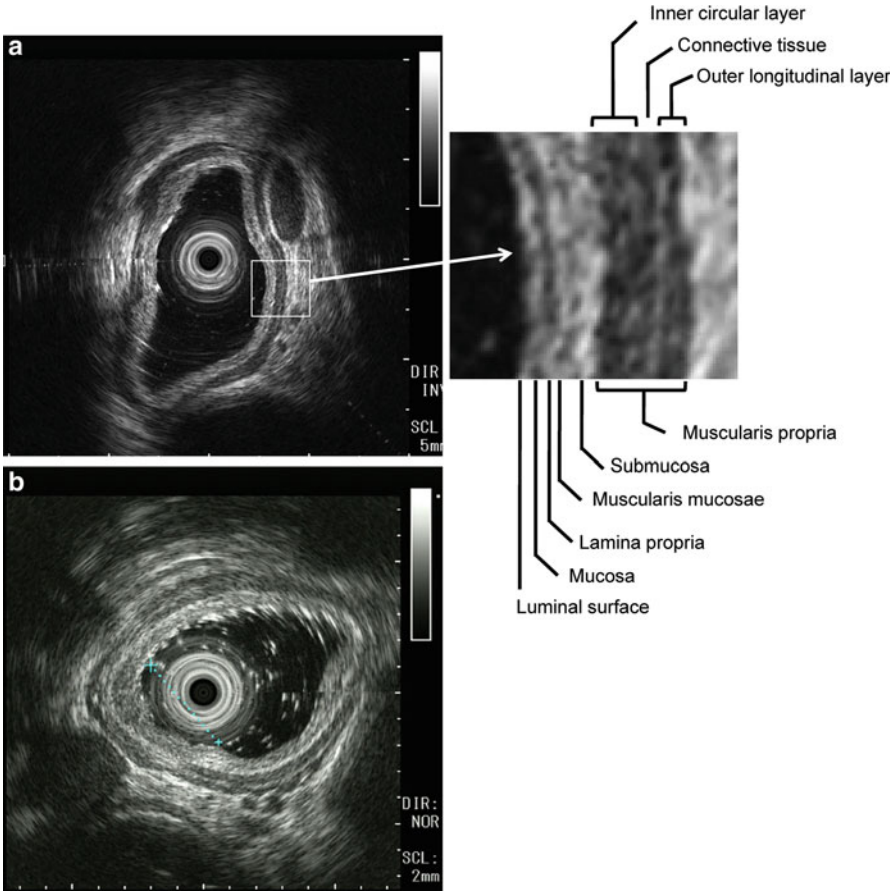

Fig. 4.8 (**a**) EUS image of the normal esophageal wall by 20 MHz miniprobe demonstrates 9-layered structures (*arrow*). The first five layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), and submucosa (high echo). Next are inner circular (low echo) and outer longitudinal layers (low echo) of muscularis propria. They are separated by a thin hyperechoic layer of the connective tissue (high echo). (**b**) EUS image demonstrates a low-echoic mass located in the sbmucosal layer

100 μm, OCT images can identify structures on a microscopic scale. Hatta et al. [19] 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 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.

4.4 Endoscopic Diagnosis of Advanced Esophageal Cancer

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 distinguish 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.

4.5 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 extend to the esophagus is sometime difficult to diagnose by endoscopy as squamous cell carcinoma or adenocarcinoma. In such case, superficial spread of IIc-like extension, which is frequently observed in the squamous cell carcinoma, could be one of the key endoscopic finding for differential diagnosis.

4.6 Histological Confirmation by Biopsy

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

4.7 Virtual Biopsy

The endocytoscopy system (ECS) enables in vivo observation of cellular nuclei in the gastrointestinal tract at up to 1,400-fold magnification (Fig. 4.9) [20–22]. This technology has been predicted to provide the possibility of "virtual biopsy,"

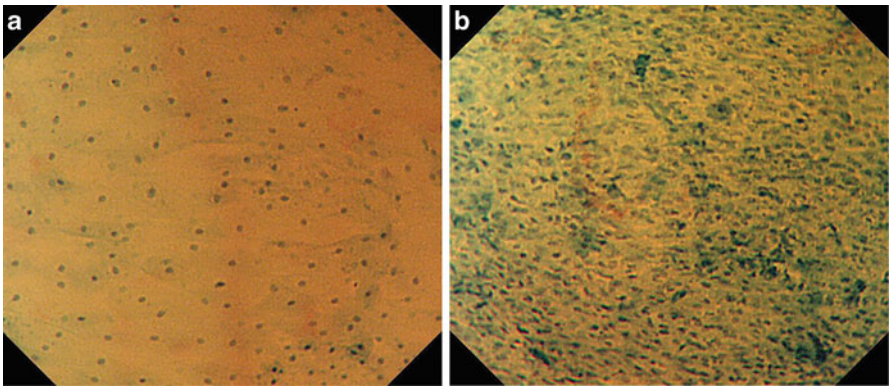

Fig. 4.9 ECS images. (**a**) Nonneoplastic epithelium. (**b**) Neoplastic lesion

especially in the esophagus and colon. Inoue et al. reported that ECS could characterize various tissues including nonneoplastic lesions, inflammatory lesions, and neoplastic lesions. Fujishiro et al. [23] 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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Stage Classifications: The UICC/AJCC Classifications and the Japanese Classification

5

Hiromasa Fujita

Abstract

The history, TNM categories, stage grouping, and related categorizations are compared between the TNM/AJCC stage classifications and the JES stage classification—Japanese Classification of Esophageal Cancer. 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 is a large difference between the UICC/AJCC Classifications and the JES Classification in the definition of the esophagogastric junction for adenocarcinoma and in the N categories. The esophagogastric junction is defined based on Siewert's Classification in the UICC/AJCC Classifications, while it is defined based on the Nishi's Classification in the Japanese Classification. The N categories are classified by the number of metastasis-positive lymph nodes in the UICC/AJCC Classification, whereas they are classified by the spread of metastasis-positive lymph nodes in the JES Classification. The UICC/AJCC consider that stage classification should be based on prognostic outcomes only, while the JES consider that stage classification should be based on clinical prognostic outcomes and additionally should play a role in the guidelines for lymphadenectomy.

Keywords

AJCC • AJCC Staging Manual • Japanese Classification of Esophageal Cancer • JES • TNM Classification • UICC

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5.1 Introduction

Several cancer staging systems are used worldwide for esophageal cancer and 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 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.

5.2 Historical Overview

5.2.1 A History of the UICC and the TNM Classification (Fig. 5.1) [1–26]

In 1933, the International Union Against Cancer—Union Internationale Contre le Cancer (UICC)—was established as a nonprofit and non-government organization.

The TNM system for the classification of malignant tumors was developed by Pierre Denoix (France) in the 1940s. 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 all sites.

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 1st edition of the TNM Classification of Malignant Tumours (Fig. 5.2) [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 latest 7th edition of TNM Classification [7] contains rules of classification and staging that correspond with prognostic factors appearing in the 7th edition of the AJCC Cancer Staging Manual (2009) [14].

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

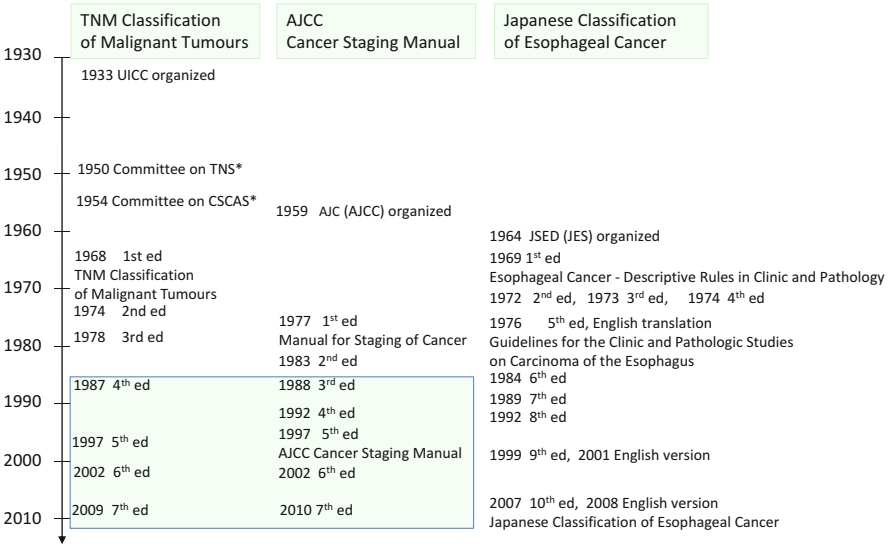
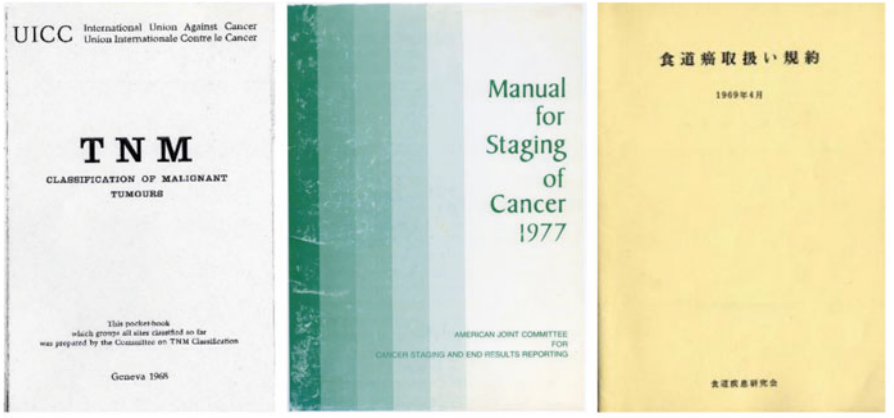


Fig. 5.1 History of TNM Classification of Malignant Tumours, *AJCC* Cancer Staging Manual and Japanese Classification of Esophageal Cancer, *TNS** Tumor Nomenclature and Statistics, *CSCAS** Clinical Stage Classification and Applied Statistics



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

1th 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. 5.2 First editions of the TNM Classification of Malignant Tumours [1], of the Manual for Staging of Cancer [8] (former name of AJCC Cancer Staging Manual), and of the Esophageal Cancer—Descriptive Rules in Clinic and Pathology [15] (former name of Japanese Classification of Esophageal Cancer)

5.2.2 A History of the AJC/AJCC and the AJCC Cancer Staging Manual (Fig. 5.1) [1–26]

The American Joint Committee for Cancer Staging and End Results Reporting (AJC) 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 1st edition of the Manual for Staging of Cancer which was published in 1977 (Fig. 5.2) [8].

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 anatomical sites. Initially in the 3rd edition of the Manual for Staging of Cancer (AJCC, 1988) [10] and the 4th edition of the TNM Classification of Malignant Tumours (UICC, 1987) [4], and since then 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 USA, and the terminology in the AJCC-TNM system is used for cancer reporting. Since the 5th edition published in 1997 [12], the new name, the AJCC Cancer Staging Manual, has been used.

5.2.3 A History of the JSED/JES and the Japanese Classification (Fig. 5.1) [1–27]

The Japanese Society for Esophageal Diseases (JSED) was founded by Komei Nakayama and colleagues in 1965. The first scientific meeting of the JSED was held in the same year, resulting in the publication in 1969 of the first edition of Esophageal Cancer—Descriptive Rules in Clinic and Pathology (Fig. 5.2) [15].

To date, there have been eight chairmen of the editorial board of the Japanese Classification. The first was Hiroshi Sato, who chaired the editorial board for 25 years from 1966 to 1991. During this period, the 1st to the 7th editions [15–21] were published. In 1976, the first English translation of the Japanese Classification was published in the Japanese Journal of Surgery [28], the official journal of the Japan Surgical Society (JSS), which was the forerunner of the journal Surgery Today. This translation was published in the 5th edition under the title of Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus [19].

During the period from 1991 to 1999, when the second, third, and fourth chairmen led the editorial board, the 8th and 9th editions of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus were published [22, 23]. 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 9th edition in 1999 [23]. The 9th edition was republished in English in 2001 [24].

During the period from 1999 to date, the fifth to eighth 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 10th edition was published in 2007 [25], and the following year its English version was published under the name of the Japanese Classification of Esophageal Cancer [26].

5.3 Anatomical Subsites: Esophagus and Esophagogastric Junction

5.3.1 The TNM Classification

The TNM classification of the esophagus and the stomach were included in the 1st edition (UICC, 1968) [1]. 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 2nd 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 3rd 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.

In the 4th edition (UICC, 1992) [4], together with the 3rd edition (AJCC, 1988) [10], the anatomical subsites of the esophagus were defined in the same fashion as in the 1st edition (JSED/JES, 1969) (Fig. 5.3) [15]. Consequently, all three stage classifications have the same definition for the esophageal subsites.

In the latest 7th edition (UICC, 2009) [7] however, the definition of the esophagogastric junction for adenocarcinoma was remarkably changed together with the latest 7th edition (AJCC, 2010) [14] according to Siewert's Classification [29].

5.3.1.1 Definition of Esophagogastric Junction (C16.0) [7, 14]

Note: An adenocarcinoma with its epicenter within 5 cm of the esophagogastric junction and which extends into the esophagus is classified and staged using the esophageal scheme. Where the epicenter in the stomach is greater than 5 cm from

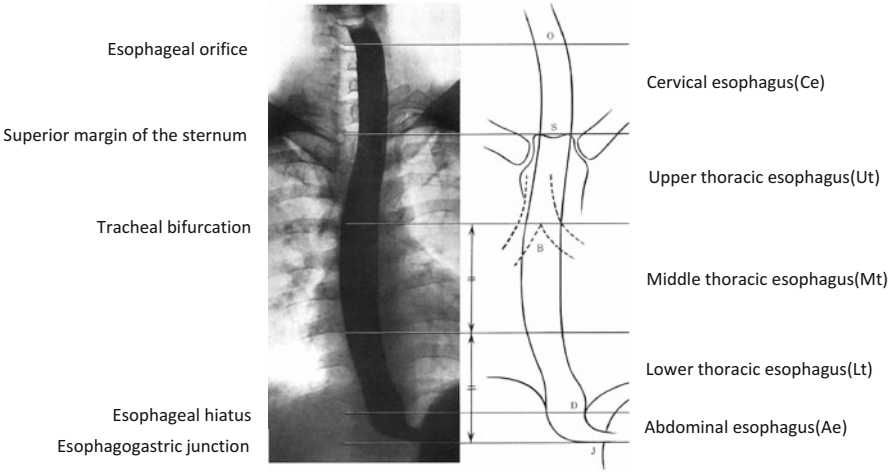


Fig. 5.3 Anatomical subsites (tumor location and anatomical esophageal nomenclature) in the 2nd edition of the Esophageal Cancer—Descriptive Rules in Clinic and Pathology (JSED, 1972) [16], unchanged in the latest 10th edition of the Japanese Classification of Esophageal Cancer (JES, 2007) [25]

the esophagogastric junction or is within 5 cm of the esophagogastric junction but without extension into the esophagus, then the adenocarcinoma is classified and staged using the gastric carcinoma scheme.

5.3.2 The AJCC Cancer Staging Manual

The anatomical subsites of the esophagus and the stomach in the 1st edition (AJC/AJCC, 1977) [8] were classified in the same fashion as the 3rd edition (UICC, 1978) [3]. Anatomical regions of the esophagus were defined by the distance from the upper incisor teeth.

In the 3rd edition (AJCC, 1988) [10], the anatomical subsites of the esophagus were labeled according to the ICD-O and defined in the same fashion as in the 1st edition (JSED/JES, 1969) (Fig. 5.3) [15].

In the 5th edition (AJCC, 1997) [12], the lower thoracic portion of the intrathoracic esophagus (C15.5) includes the intra-abdominal portion of the esophagus and the esophagogastric junction.

In the latest 7th edition (AJCC, 2010) [14], the definition of the anatomical subsites of the esophagus and the esophagogastric junction is the same as that in the 7th edition (UICC, 2009) [7] as mentioned above.

5.3.3 The Japanese Classification

The anatomical subsites of the esophagus—tumor location and anatomical esophageal nomenclature—were defined in the 1st edition (JSED/JES, 1969) (Fig. 5.3) [15]. In the 2nd edition (JSED/JES, 1972) [16], 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 latest 10th edition (JES, 2008) [25, 26], several criteria for clinical diagnosis of the esophagogastric junction are presented, and the zone of the esophagogastric junction is newly defined according to Nishi's Classification [30].

5.3.3.1 Definition of the Esophagogastric Junction (EGJ) [25, 26]

The esophagogastric junction is on the border of the esophageal muscle and gastric muscle, and the location is clinically and pathologically diagnosed as

1. The lower margin of the palisading small vessels in the lower esophagus by endoscopic findings
2. Horizontally at the same level as the angle of His in an upper gastrointestinal series (UGI)
3. Oral margin of the longitudinal fold of the great curvature of the stomach on endoscopic findings and UGI
4. Obvious macroscopic caliber change in the resected esophagus and stomach
5. The squamocolumnar junction (SCJ) is not always consistent with EGJ

5.3.3.2 Definition of the Zone of the Esophagogastric Junction [25, 26]

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

In the 1st 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) [31], and in the 1st English edition of the Japanese Classification of Gastric Carcinoma (JRSGC, 1995) [32], it is described that when a tumor was located in the upper third (C) and extended into the esophagus (E), then the case should be described as CE, and that this tumor in the esophagogastric junction should be described as CE or EC. Lymph node groups for dissection of regional lymph nodes—N categories—are added, when the tumor invades the esophagus.

In the latest 14th edition of the Japanese Classification of Gastric Carcinoma (Japanese Gastric Cancer Association, JGCA, 2010) [33], the zone of the esophagogastric junction and cancer in the esophagogastric cancer are defined in the same fashion as in the 10th edition (JES, 2008) [25, 26].

5.4 T Category—Primary Tumor

5.4.1 The TNM Classification

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

In the 3rd edition (UICC, 1978) [3], the TNM pretreatment clinical classification and the pTNM postsurgical histopathological classification were introduced. The latter was classified by the depth of tumor invasion in the same fashion as in the 2nd edition (JSED/JES, 1972) [16].

In the 4th 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. 5.4.

In the latest 7th edition (UICC, 2009) [7], the T category is modified. T1 is divided into Tis, T1a (T1a-LPM and T1a-MM), and T1b and becomes the same as in the 9th edition (JSED/JES, 1999) [23, 24]. High-grade dysplasia is added into

T –Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of rimary 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 accordong 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	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Fig. 5.4 TNM categories and stage grouping in the 4th edition of the TNM Classification of Malignant Tumours (UICC, 1987) [4], which were unified in the 3rd edition of the Manual for Staging of Cancer (AJCC, 1988) [10]

T – Primary Tumour

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

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

T2 Tumour invades muscular is propria
T3 Tumour invades adventitia
T4 Tumour invades adjacent structures
- T4a Tmour 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

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage 1B	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Fig. 5.5 TNM categories and stage grouping in the seventh edition of the TNM Classification of Malignant Tumours (UICC, 2009) [7]

the same group as Tis. T4 is divided into two categories: T4a, where the tumor invades resectable organs, and T4b, where the tumor invades unresectable organs (Fig. 5.5).

5.4.2 The AJCC Cancer Staging Manual

In the 1st edition (AJC/AJCC, 1977) [8], the same T category was adopted as that in the 2nd edition (UICC, 1974) [2]. In the 3rd edition (AJCC, 1988) [10], the T category was classified by the depth of tumor invasion in a similar way as in the 4th edition (UICC, 1987) (Fig. 5.4) [4]. After this unification, the T category of the AJCC Cancer Staging Manual becomes the same as that of the TNM Classification to date.

5.4.3 The Japanese Classification

In the 1st edition (JSED/JES, 1969) [15], the T category was classified by the extent of invasion to the adventitia: A0, no invasion to adventitia; A1, possible invasion to adventitia; A2, definite invasion to adventitia; and A3, invasion to neighboring structures. In the 2nd edition (JSED/JES, 1972) [16], clinical and histological T categories were introduced. The histological T category was classified by the depth of tumor invasion.

5.4.3.1 Histological T Categories [16]

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 9th edition (JSED/JES, 1999) [23, 24], both clinical and histological T categories were unified and were classified only by the depth of tumor invasion.

In the latest 10th edition (JES, 2007) [25, 26], the subclassification for superficial cancer is newly described, where T1a and T1b are each divided into three layers (Figs. 5.6 and 5.7).

Depth of Tumor Invasion (T)
TX Depth of tumor invasion cannot be assessed
T0 No evidence of primary tumor
T1a Invasion to the mucosa
T1a-EP Carcinoma in situ
T1a-LPM Invasion to the lamina propria mucosae (LPM)
T1a-MM Invasion up to, but not beyond, the muscularis mucosae (MM)
T1b Invasion to but not beyond the submucosa (SM)
SM1 Invasion to the submucosa but not beyond the upper one third of the submucosa
SM2 Invasion to the submucosa but not beyond the middle one third of the submucosa
SM3 Invasion to the lower one third of the submucosa
T2 Invasion to but not beyond the muscularis propria (MP)
T3 Invasion to the esophageal adventitia (AD)
T4 Invasion to adjacent organs (AI)

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	I	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
T4	III	IVa	IVa	IVa	IVa	IVb

Fig. 5.6 TNM categories and stage grouping in the English version of the 10th edition of the Japanese Classification of Esophageal Cancer (Japan Esophageal Society, 2008) [26]

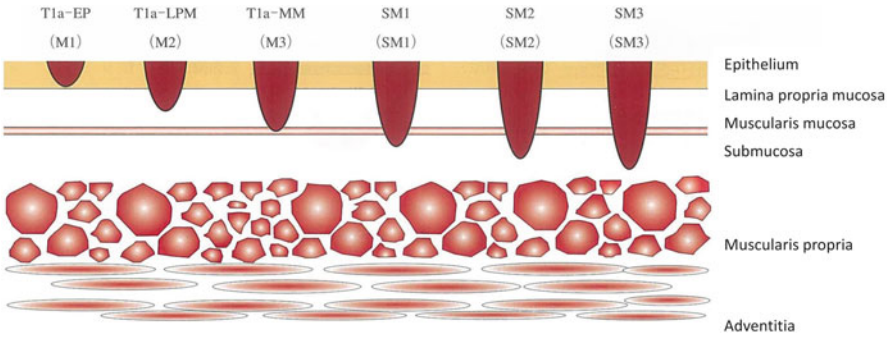


Fig. 5.7 Subclassification of superficial esophageal cancer in the 10th edition of the Japanese Classification of Esophageal Cancer (JES, 2007) [25]

5.5 N Category: Lymph Node Metastasis

5.5.1 TNM Classification

In the 1st edition (UICC, 1968) [1], the regional lymph nodes for a cancer in the cervical esophagus are defined to be the cervical nodes. Those for a 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 3rd edition (IUCC, 1978) [3], the regional lymph nodes of the intrathoracic esophagus were classified into two grades: N0, no evidence of involvement of regional lymph nodes, and N1, evidence of involvement of those on surgical exploration or mediastinoscopy.

In the 4th 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 evidence (N1) of involvement by regional lymph node metastasis (Fig. 5.4).

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

In the latest 7th edition (UICC, 2009) [7], the coeliac axis nodes and paraesophageal nodes in the neck are defined as the regional lymph nodes, irrespective of the site of the primary tumor. The N category was classified into four groups N0 to N3 by the number of metastasis-positive nodes among the regional lymph nodes according to the 7th edition (AJCC, 2010) [14] (Fig. 5.5).

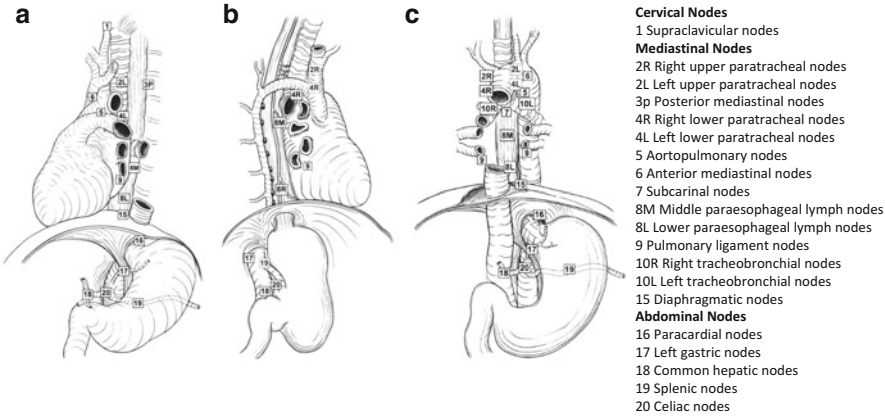


Fig. 5.8 Lymph node maps for esophageal cancer and regional lymph node stations for staging esophageal cancer, from *left side* (**a**), *right side* (**b**), and *front* (**c**) placed in the AJCC Cancer Staging Manual (AJCC, 2010) [14]

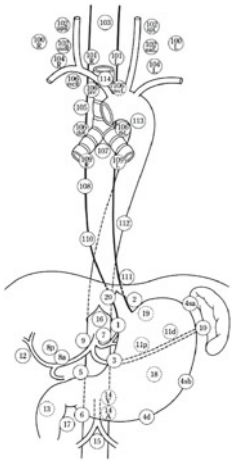
5.5.2 The AJCC Cancer Staging Manual

In the 1st edition (AJC/AJCC, 1977) [8], the regional lymph nodes are 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 in the same fashion as in the 3rd edition (UICC, 1978) [3]. The regional lymph nodes for the thoracic esophagus were considered not to be assessable (NX). After surgical evaluation, the N category can be assessed as N0, no positive nodes, or as N1, positive nodes.

In the 3rd edition (AJCC, 1988) [10], the lymph node stations belonging to specific regional lymph nodes were defined in 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. 5.4). In the 4th edition (AJCC,1992) [11], the left gastric nodes and cardiac nodes were added to the specific regional lymph nodes for the upper and middle intrathoracic esophagus in a similar way as in lower intrathoracic esophagus.

In the 6th edition (AJCC, 2002) [13], esophageal lymph node maps indicating the regional lymph node stations were presented. Specific regional lymph nodes for the gastroesophageal junction were added.

In the 7th edition (AJCC, 2010) [14], more detailed lymph node maps for esophageal cancer were presented (Fig. 5.8). The N category is classified into four groups N0 to N3 by the number of metastasis-positive lymph nodes according to evidence-based staging developed through statistical analysis of a worldwide database (UICC, 2009) (Fig. 5.5) [34, 35].



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

Thoracic lymph nodes
105 Upper thoracic paraesophageal nodes
106 Thoracic paratracheal nodes
106rec Recurrent nerve nodes
106pre Pretracheal nodes
106tb Tracheobronchial nodes
107 Subcarinal nodes
108 Middle thoracic paraesophageal nodes
109 Main bronchus nodes
110 Lower thoracic paraesophageal nodes
111 Supradiaphragmatic nodes
112 Posterior mediastinal nodes
112ao Thoracic paraaortic nodes
112pul Pulmonary ligament nodes
113 Ligament arteriosum nodes
114 Anterior mediastinal nodes

Abdominal lymph nodes
1 Right cardiac nodes
2 Left cardiac nodes
3 Lesser curvature nodes
4 Greater curvature nodes
5 Suprapyloric nodes
6 Infrapyloric nodes
7 Left gastric artery nodes
8 Common hepatic artery nodes
9 Coeliac artery nodes
10 Splenic hilum nodes
11 Splenic artery nodes
12 Hepatoduodenal ligament nodes
13 LNs on the posterior surface of the pancreatic head
14 Superior mesenteric vessels nodes
15 Middle colic artery nodes
16 Abdominal aortic nodes
17 LNs on the anterio rsurface of the pancreatic head
18 LNs along the inferior margin of the pancreas
19 Infrafdiaphragmatic nodes
20 LNs in the esophageal hiastus of the diaphragm

Fig. 5.9 Station numbers and names of regional lymph nodes in the 10th edition of the Japanese Classification of Esophageal Cancer (JES, 2007) [25]

5.5.3 The Japanese Classification

In the 1st edition (JSED/JES, 1969) [15], an esophageal lymph node map indicating the regional lymph node stations was presented, and its modified map was included in the latest 10th edition (JES, 2007) (Fig. 5.9), and the regional lymph nodes were classified into three categories, N1, N2, and N3, in each tumor location: the cervical, thoracic, and abdominal esophagus. In the 2nd edition (JSED/JES, 1972) [16], 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) (Fig. 5.6). In this edition, the N category was defined also for a tumor in the esophagogastric junction. In the 6th edition (JSED/JES, 1984) [20], the regional lymph node maps were illustrated using different colors for each N category.

In the 9th edition (JSED/JES, 1999) [23, 24], 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 (Fig. 5.10). Among members of the editorial board, there was a little controversy over whether the N category was classified by the spread or by the number of the lymph nodes with metastasis. Consequently in the 9th edition [23, 24], 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 latest 10th edition (JES, 2007) [25, 26], 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—are modified for a cancer in the cervical esophagus and for a cancer in the esophagogastric junction (Fig. 5.11).

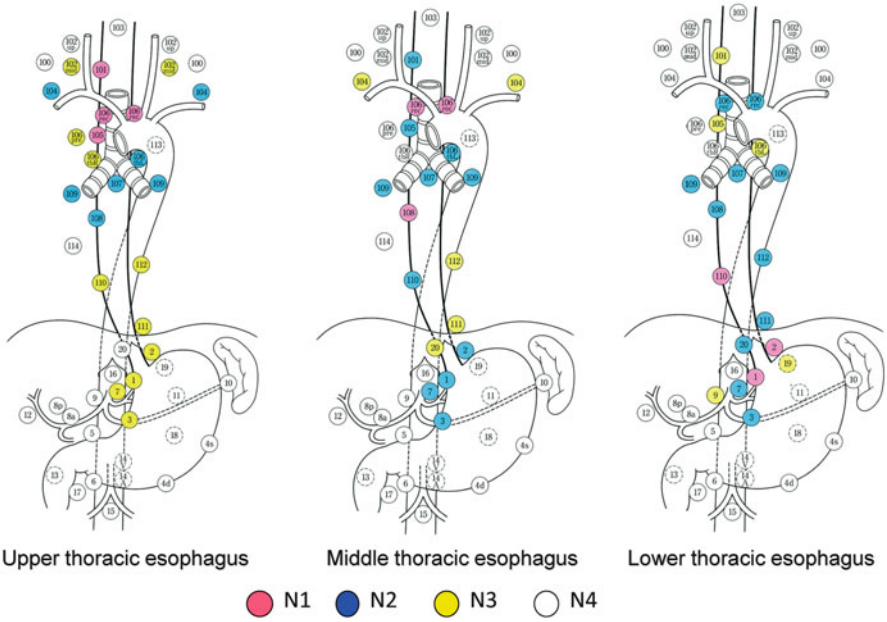


Fig. 5.10 Lymph node maps illustrating the lymph node groups—N category—for cancers in the thoracic esophagus in the 9th edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (JSED/JES, 1999) [23]

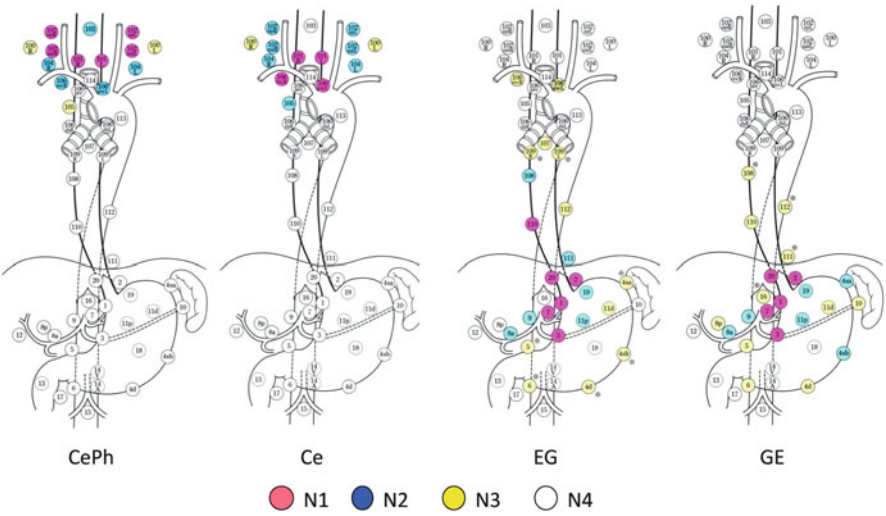


Fig. 5.11 Lymph node maps illustrating the lymph node groups—N category—for cancers in the cervical esophagus and for cancers in the esophagogastric junction in the 10th edition of the Japanese Classification of Esophageal Cancer (JES, 2007) [25]

5.6 M Category: Distant Metastasis

5.6.1 The TNM Classification

In the 1st edition (UICC, 1968) [1], distant metastasis was indicated by M. In the 2nd 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 3rd edition [3], the category M1 was subdivided according to sites and was for example described as M1-LYM (Fig. 5.4).

In the 5th 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 metastases and non-regional lymph nodes were classified into M1b.

In the latest 7th edition (UICC, 2009) [7] and (AJCC, 2010) [14], 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. 5.5).

5.6.2 The AJCC Cancer Staging Manual

In the 1st and 2nd editions (AJC/AJCC, 1977 and AJCC, 1983) [8, 9], the M category was classified according to the 3rd edition (UICC, 1978) [3]. In the 3rd edition (AJCC, 1988) [10], specific regional lymph nodes were listed in each subsite of the esophagus similarly to the Japanese Classification. Involvement of more distant nodes was defined as distant metastasis (M1-LYM) (Fig. 5.4).

In the 5th edition (AJCC, 1997) [12], distant lymph nodes metastasis was classified into two groups, M1a and M1b, in a similar way as in the 5th edition (UICC, 1997) [5].

In the 7th edition (AJCC, 2010) [14], distant metastatic sites were defined as those which are not in direct continuity with the esophagus and included the non-regional lymph nodes (M1). The M1a and M1b subclassification was deleted similarly to the TNM Classification (Fig. 5.5).

5.6.3 The Japanese Classification

In the 1st edition (JSED/JES, 1969) [15], the M category was defined as distant organ metastasis, and metastasis to lymph nodes was not included in M1. In the 2nd edition (JSED/JES, 1972) [16], pleural dissemination was classified as Pl category and was excluded from the M category—organ metastasis. In the 9th edition (JSED/JES, 1999) [23, 24], pleural and peritoneal dissemination were included into M1—distant organ metastasis.

In the latest 10th edition (JES, 2007) [25, 26], 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. 5.6). In particular, metastasis to the supraclavicular lymph node was categorized as being in N2 for a cancer in the upper thoracic esophagus, as N3 for those in the middle thoracic esophagus, and as N4 for those in the lower thoracic esophagus (Fig. 5.10).

5.7 Stage Groups

5.7.1 The TNM Classification

In the 1st edition (UICC, 1968) [1], only the breast and cervix are staged, and the stage grouping for the esophagus was not described. In the 2nd edition (UICC, 1974) [2], 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 3rd edition (UICC, 1978) [3], stage grouping was divided into four groups, stage I, II, III, and IV (any T, any N, and M1), and different stage grouping was adopted for the cervical and intrathoracic esophagus.

In the 4th edition (UICC, 1987) [4], 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. 5.4). In the 5th edition (UICC, 1997) [5], Stage IV was divided into Stage IVA (anyTanyNM1a) and Stage IVB (anyTanyNM1b).

In the latest 7th 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 (Fig. 5.5). Besides stage grouping, prognostic grouping for squamous cell carcinoma and that for adenocarcinoma were added. In the prognostic grouping for squamous cell carcinoma, a D grade and the location were added to the prognostic factors as well as the TNM categories, while in that for adenocarcinoma, a D grade was added to the prognostic factors as well as to the TNM categories (Fig. 5.12).

5.7.2 The AJCC Cancer Staging Manual

In the 1st edition (AJC/AJCC, 1977) [8], 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 2nd edition (AJCC, 1983) [9], two stage groupings, clinical-diagnostic classification for cervical

Squamous Cell Carcinoma

	T	N	M	Grade	Location*
Group 0	Tis	0	0	1	Any
Group IA	1	0	0	1, X	Any
Group IB	1	0	0	2, 3	Any
	2, 3	0	0	1, X	Lower, X
Group IIA	2, 3	0	0	1, X	Upper, middle
	2, 3	0	0	2, 3	Lower, X
Group IIB	2, 3	0	0	2, 3	Upper, middle
	1, 2	1	0	Any	Any
Group IIIA	1, 2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
Group IIIB	3	2	0	Any	Any
Group IIIC	4a	1, 2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
Group IV	Any	Any	1	Any	Any

Adenocarcinoma

	T	N	M	Grade
Group 0	Tis	0	0	1
Group IA	1	0	0	1, 2, X
Group IB	1	0	0	3
	2	0	0	1, 2, X
Group IIA	2	0	0	3
Group IIB	3	0	0	Any
	1, 2	1	0	A ny
Group IIIA	1, 2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
Group IIIB	3	2	0	Any
Group IIIC	4a	1, 2	0	Any
	4b	Any	0	Any
	Any	3	0	Any
Group IV	Any	Any	1	Any

Fig. 5.12 Prognostic staging in the seventh edition of the TNM Classification of Malignant Tumours (UICC, 2009) [7] and the AJCC Cancer Staging Manual (AJCC, 2010) [14]

esophagus (Stage 0 to IV) and postsurgical resection-pathological classification of all segments (Stage I to IV), were described.

In the 3rd edition (AJCC, 1988) [10], the stage grouping was classified into Stage 0, I, IIA, IIB, III, and IV in the same way as in the 4th edition (UICC, 1987) (Fig. 5.4) [4]. In the 5th edition (AJCC, 1997) [12], Stage IV was divided into Stage IVA and Stage IVB in the same way as in the 5th edition (UICC, 1997) [5].

In the latest 7th edition (AJCC, 2010) [14], two prognostic groups were described (Fig. 5.12), for squamous cell carcinoma and for adenocarcinoma. Here, the anatomic grouping is not placed.

5.7.3 The Japanese Classification

In the 1st edition (JSED/JES, 1969) [15], the macroscopic stage based on surgical findings and the histologic stage 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 2nd edition (JSED/JES, 1972) [16], the macroscopic stage was classified based on the A, N, M, and Pl categories, while the histologic stage 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 pl category (pl0 and pl1).

In the 9th edition (JSED/JES, 1999) [23, 24], the macroscopic stage and histologic stage were unified, and the new stage 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 latest 10th edition (JES, 2007) [25, 26], the Tis, carcinoma in situ, and T0, no evidence of primary tumor, were included into T1a, in

order to adopt for nonsurgical patients. The stage groups were classified in a block style because there were many T categories (T1a, T1b, T2, T3, T4) and N categories (N0, N1, N2, N3, N4) (Fig. 5.6).

5.8 Other Classifications

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

5.8.1 The TNM Classification/AJCC Cancer Staging Manual

5.8.1.1 G: Histopathological Grading [7, 14]

The G grading is adopted as a prognostic factor for both squamous cell carcinoma and adenocarcinoma of esophageal cancer in the 7th edition [7, 14]:

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

5.8.1.2 Residual Tumor (R) Classification [7, 14]

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. In the 10th edition (JES, 2007) [25, 26], the same R classification is included:

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

5.8.1.3 y Symbol: Post-Therapy Classification [7, 14]

y: Prefix to utilize with "c" or "p" for denoting the extent of cancer after neoadjuvant or primary systemic and/or radiation therapy
yc: Clinical information used after primary systemic or radiation therapy, or after neoadjuvant therapy before surgery
yp: Pathological information used after neoadjuvant systemic or radiation therapy followed by surgical resection

5.8.2 The Japanese Classification

5.8.2.1 Macroscopic Tumor Type [25, 26]

The tumor type classification is based on the macroscopic findings. Radiological and endoscopic classifications are based on the macroscopic classification (Fig. 5.13).

5.8.2.2 Extent of Lymph Node Dissection (D) [25, 26]

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 [7, 14]. The JES recommends that the extent of lymphadenectomy should be wider than the grading of the lymph node metastasis (D>N) [25, 26].

Extent of Lymph Node Dissection (D)
DX: Extent of lymph node dissection cannot be assessed.
D0: No or incomplete dissection of Group N1 lymph nodes
D1: Complete dissection of Group N1 lymph nodes but no or incomplete dissection of Group N2 lymph nodes
D2: Complete dissection of Group N1 and Group N2 lymph nodes, but no or incomplete dissection of Group N3 lymph nodes
D3: Complete dissection of Group N1, Group N2, and Group N3 lymph nodes

5.8.2.3 Curativity (Cur) [25, 26]

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):

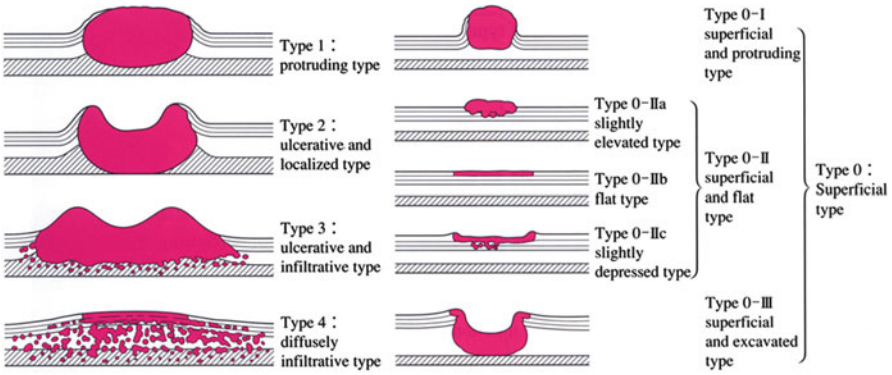


Fig. 5.13 Macroscopic type classification illustrated in the 10th edition of the Japanese Classification (JES, 2007) [25]

Cur A: Complete removal of the tumor is strongly believed.
Stage 0 ~ III, and R0, and D>N are satisfied.
Cur B: Neither Cur A nor Cur C
R1 resection, or
Stage IV (T4, M1) or D≦N, but R0 was achieved with resection of a T4 tumor or complete removal of metastatic tumor (M1) or lymph nodes.
Cur C: R2 resection, namely evident residual tumor in distant organ(s) (M1), lymph nodes, or surgical margin(s)

5.8.2.4 Revision of the Evaluation of Lymph Node Metastasis Based on the Number of Pathologically Recognized Metastasis-Positive Lymph Nodes [23–26]

1–3 metastasis-positive lymph nodes: no revision of pN category
4–7 metastasis-positive lymph nodes: correction of pN category upward by an increment of 1, but not above pN4
8 or more positive-metastatic lymph nodes: correction of pN category upward by an increment of 2, but not above pN4

5.9 Discussions

5.9.1 N Category

The most significant difference between the TNM/AJCC Classifications and the JES Classification is in the N category. In the TNM/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 TNM/AJCC Classifications is easy to use in practice. In particular, pathologists can easily define the number of metastasis-positive lymph nodes in the resected specimen which is strongly prognostic. On the other hand, the N category of the JES Classification is clinically complex to use. It is difficult for pathologists to define 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 always strongly prognostic compared to the number of metastasis-positive lymph nodes. This is the main reason why the JES Classification has not been adopted outside of Japan. However, the JES Classification has played not only a role for predicting of 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 possibly stays within the definition of being 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 1st to 6th editions (UICC/AJCC) [1–6, 8–13], 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 the concepts for lymph node metastasis seems to make the N categories different in each classification.

5.9.2 Anatomical Staging and Prognostic Staging

In the 7th editions (UICC, 2009/AJCC, 2010) [7, 14], prognostic staging is adopted as well as anatomical staging. The UICC/AJCC 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. The JES has no such consideration at present.

5.9.3 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 7th edition (UICC, 2009/AJCC, 2010) [7, 14], while they are defined as regional nodes in the 10th edition (JES, 2007) [25]. These nodes are categorized as N2 for cancer in the cervical esophagus or in the upper thoracic esophagus, as N3 for cancer in the middle thoracic esophagus, and as N4 for cancer in the lower thoracic esophagus. On the other hand, Celiac lymph nodes (No.9) are defined as regional nodes in the 7th edition (UICC, 2009/AJCC, 2010) [7, 14], while they are categoried as N2 for cancer at the esophagogastric junction, as N3 for cancer in the lower thoracic esophagus, and as N4 for cancer in the upper or middle thoracic esophagus in the 10th edition (JES) [25]. Concerning lymph nodes around the abdominal aorta (No.16), there is still some controversy in Japan over whether they are regional nodes or distant 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.

5.9.4 Collaboration Between the UICC/AJCC and the JES

The 8th edition of the UICC/AJCC Classification will be published in 2015. They are collecting worldwide data to prepare this next iteration. The JES is preparing to offer the Japan nationwide registration data to the Worldwide Esophageal Cancer Collaboration, and to publish the 11th edition of the Japanese Classification also in 2015. The JES hopes for close collaboration with the UICC/AJCC to achieve more consistency between the UICC/AJCC Classification and the Japanese Classification.

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Comprehensive Registry in Japan

6

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 Act. 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 2001–2006. A total of 28,487 cases were registered from a total of 1,352 institutions in Japan. Histological diagnoses of biopsy specimens showed that squamous cell carcinoma and adenocarcinoma accounted for 88.7–92.9 % and 2.4–3.9 % of all the cases, respectively. The 5-year survival rates of patients treated using endoscopic mucosal resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, or esophagectomy were 80.0–87.7 %, 19.3–26.4 %, 15.1–30.0 %, 1.7–8.6 %, and 42.6–50.9 %, respectively. Concerning the approach used to perform an esophagectomy, 9.9–15.9 % of the cases were performed thoracoscopically. We hope that this *Comprehensive Registry of Esophageal Cancer in Japan* helps to improve all aspects of the diagnosis and treatment of esophageal cancer.

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Keywords
Act on the Protection of Personal Information • Anonymity in an unlinkable fashion • Comprehensive registry • Hash function

6.1 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.

6.2 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 *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 were difficult to handle appropriately [5].

6.3 Attempts to Resume the Registration Project

6.3.1 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 Act.

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.

6.3.2 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.

To put it simply, a "hash function" is an encryption tool for creating pseudorandom numbers. The original data cannot be reproduced from the hash value, and the same hash value cannot be created from different data. For example, a "hash function" generated the hash value "c50ec7685bcd91d2ae65503cb6a587ec67338166" from the patient name "Shokudou Tarou." When the patient name was changed to "Shokutou Tarou," a change of just one character, the hash value was completely changed to "e0889bf3e4af2991d804b18439dcd22b3f9712f9" (Fig. 6.1). Therefore, the "hash function" encryption method was adopted to meet the "anonymity in an unlinkable fashion" requirements for personal information.

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 were 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 outcome to be followed.

Fig. 6.1 Encryption with a hash function


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

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.

6.3.3 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 comprised of 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. 6.2).

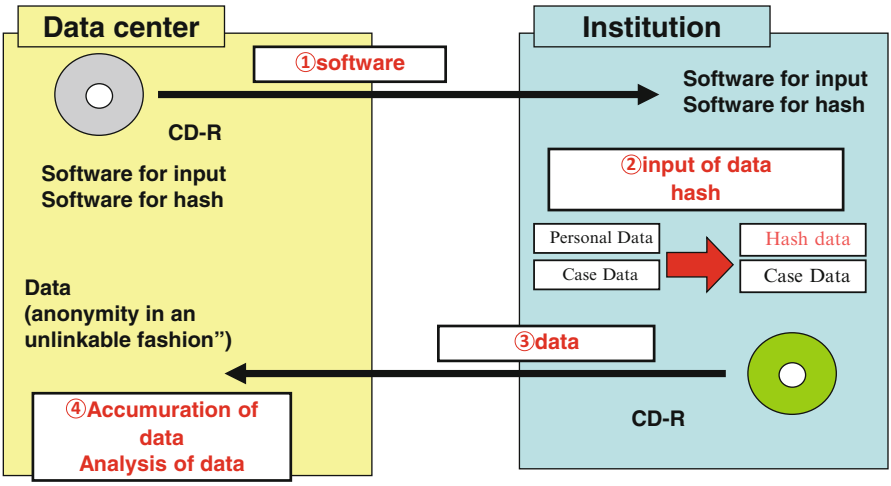

Fig. 6.3 Outline of data collection

6.3.4 Preparation of Registration Sheets

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

6.3.5 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. 6.3). 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. 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.

6.4 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 19, 2008, a total of 3,940 cases from 241 institutes (52.9 %) were registered.

6.5 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 on March 12, 2009, was sent to the approved institutions (Fig. 6.4). The Comprehensive Registry included 76 tables and 16 figures and showed the 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. 6.5).

6.6 Next Year Registration

After problems with the registration system used for the cases registered in 2001 were improved, a registration project for cases treated in 2002 was started on March 26, 2009. As of August 31, 2009, a total of 4281 cases from 222 institutes (48.7 %) 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 on March 1, 2010 [11], and sent to the approved institutions.

6.7 Problems Arising During the First 2 Years

Although the new registration system required "anonymity in an unlinkable fashion," some institutes very nearly returned data packages containing non-encrypted personal data and disease data to the data center. Although the "anonymity in an unlinkable fashion" step may seem laborious, members must understand that this step is indispensable for the continuation of the registration project.

The number of institutes that submitted CD-Rs to the data center was about 50 % of the total number of approved registration institutes. To grasp the real status of esophageal cancer treatment in Japan, more institutes 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 old registration form used for cases in 2000, to lighten the workload of the doctors in charge of registration.

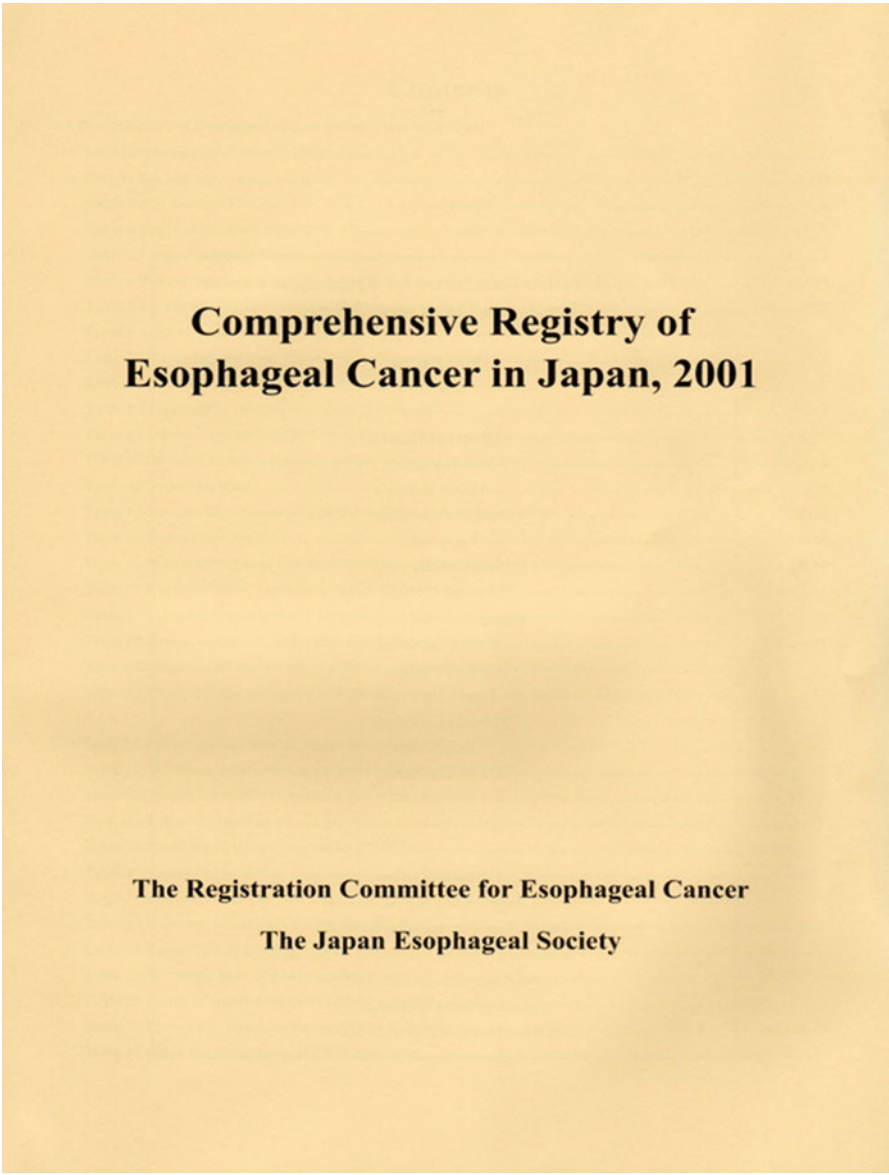

Fig. 6.4 Front cover of the *Comprehensive Registry of Esophageal Cancer in Japan*, 2001

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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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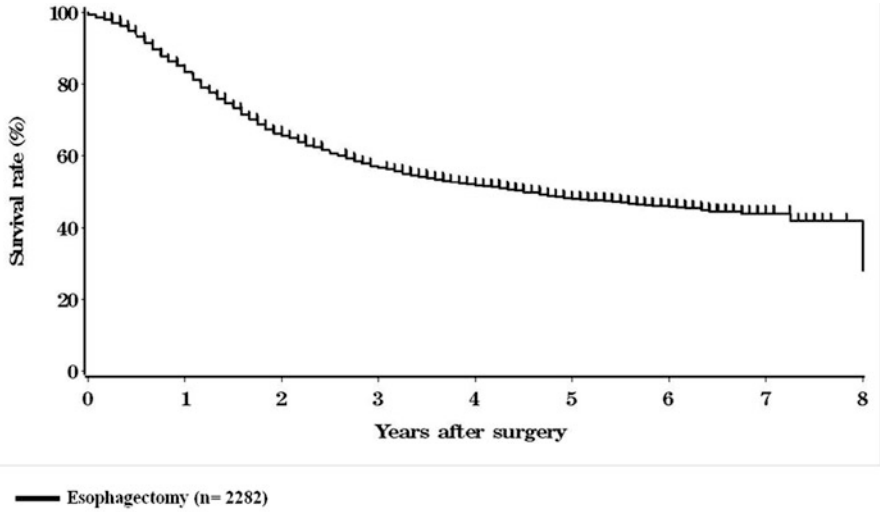
Fig. 6.5 Excerpted version of the *Comprehensive Registry of Esophageal Cancer in Japan*, 2001, published in *Esophagus* (Vol. 6, pages 95–110)



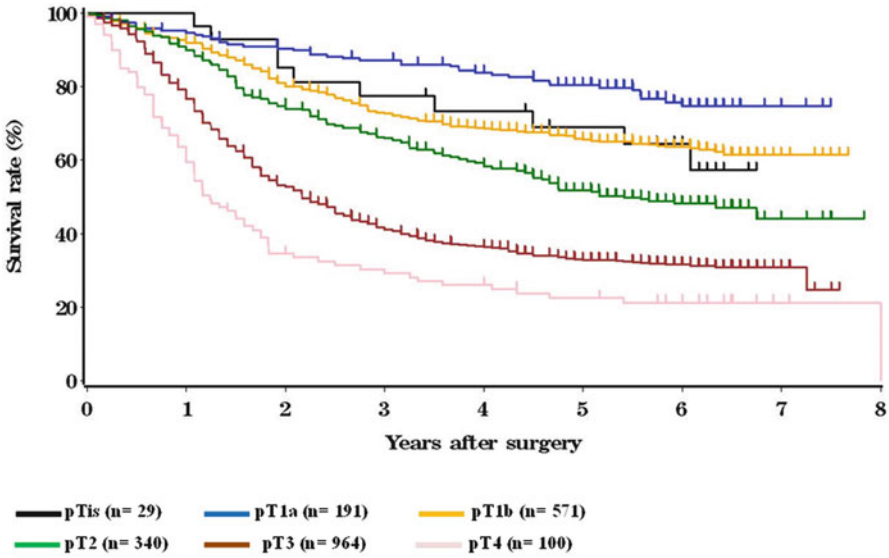
	Years after surgery							
	1	2	3	4	5	6	7	8
Esophagectomy	83.3%	66.1%	57.2%	52.2%	48.0%	45.9%	44.0%	41.9%

Fig. 6.6 Survival of patients treated by esophagectomy in 2006

6.8 Summary of the *Comprehensive Registry of Esophageal Cancer in Japan*, 2001–2006

We summarized the *Comprehensive Registry of Esophageal Cancer in Japan*, 2001–2006 [2, 11–15]. A total of 28,487 cases were registered from a total of 1,352 institutions in Japan. As for the histologic type of cancer according to biopsy specimens, squamous cell carcinoma and adenocarcinoma accounted for 88.7–92.9 % and 2.4–3.9 %, respectively. Regarding the clinical results, the 5-year survival rates of patients treated using endoscopic mucosal resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, and esophagectomy were 80.0–87.7 %, 19.3–26.4 %, 15.1–30.0 %, 1.7–8.6 %, and 42.6–50.9 %, respectively.

Survival curves of patients treated by esophagectomy in 2006 according to the *Japanese Classification of Esophageal Cancer* 9th edition [8, 9] and *UICC TNM Classification of Malignant Tumours* 6th edition [16] are shown in Figs. 6.6, 6.7, 6.8, 6.9, and 6.10. Concerning the approach used to perform an esophagectomy, 9.9–15.9 % of the cases were performed thoracoscopically.



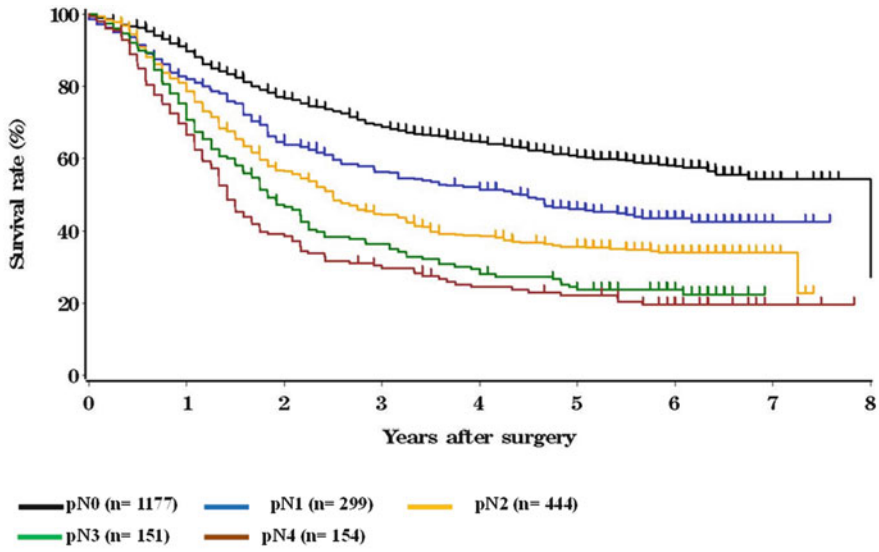
	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	100.0%	85.1%	77.4%	73.3%	69.0%	64.4%	-	-
pT1a	94.7%	90.4%	87.1%	83.8%	80.4%	74.7%	74.7%	-
pT1b	92.0%	80.8%	72.9%	68.7%	65.6%	63.6%	61.4%	61.4%
pT2	89.9%	74.6%	66.3%	59.3%	51.7%	48.2%	44.0%	44.0%
pT3	76.6%	53.1%	41.7%	36.6%	32.8%	31.5%	30.8%	-
pT4	59.5%	34.6%	30.3%	26.0%	22.5%	21.2%	21.2%	21.2%

Fig. 6.7 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion in 2006 (JSED-pTNM 9th)

6.9 Future Concepts

We have a policy of not changing the 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 [17, 18], and some changes to the registration forms to comply with the revised guidelines were necessary.

The 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



	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	89.8%	77.1%	69.4%	64.9%	60.4%	57.9%	54.3%	54.3%
pN1	82.1%	64.5%	56.4%	52.1%	46.1%	43.4%	42.5%	42.5%
pN2	78.7%	56.5%	44.7%	38.7%	35.7%	34.0%	34.0%	22.7%
pN3	70.7%	47.2%	36.3%	29.4%	23.7%	23.7%	22.4%	-
pN4	66.5%	39.1%	30.3%	24.4%	22.1%	19.5%	19.5%	19.5%

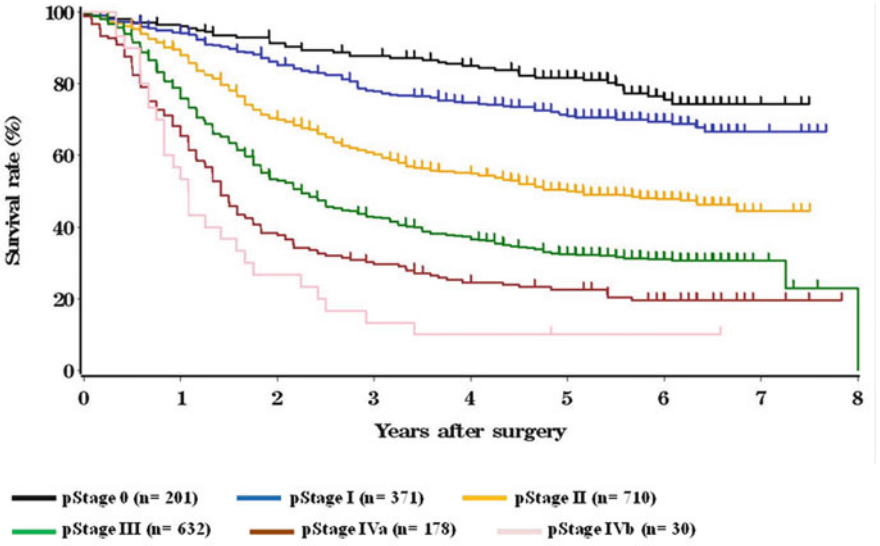
Fig. 6.8 Survival of patients treated by esophagectomy in relation to lymph node metastasis in 2006 (JSED-pTNM 9th)

effective for reporting the latest information to the world. Fortunately, the *Comprehensive Registry of Esophageal Cancer in Japan*, 2005 and 2006, was published in 2013 [14, 15]. 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 Japanese Association for Thoracic Surgery and the registration project of the National Clinical Database for more efficient registration.

6.10 Significance of the Registration Project

Three books are essential for the treatment of esophageal cancer patients in Japan: the *Japanese Classification of Esophageal Cancer* [17, 18], the *Guidelines for the Management of Esophageal Cancer* [19, 20], and the *Comprehensive Registry of*



	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	96.0%	91.3%	87.7%	85.0%	81.6%	75.5%	74.3%	74.3%
pStage I	94.0%	85.8%	78.1%	74.6%	71.0%	69.5%	66.5%	66.5%
pStage II	88.0%	70.3%	60.8%	55.2%	50.0%	47.8%	44.4%	44.4%
pStage III	75.8%	53.2%	42.9%	37.3%	32.4%	31.1%	30.7%	23.0%
pStage IVa	65.4%	38.3%	30.2%	24.6%	22.5%	19.6%	19.6%	19.6%
pStage IVb	53.3%	26.7%	17.1%	13.3%	10.0%	10.0%	10.0%	-

Fig. 6.9 Survival of patients treated by esophagectomy in relation to pathological stage in 2006 (JSED-pTNM 9th)

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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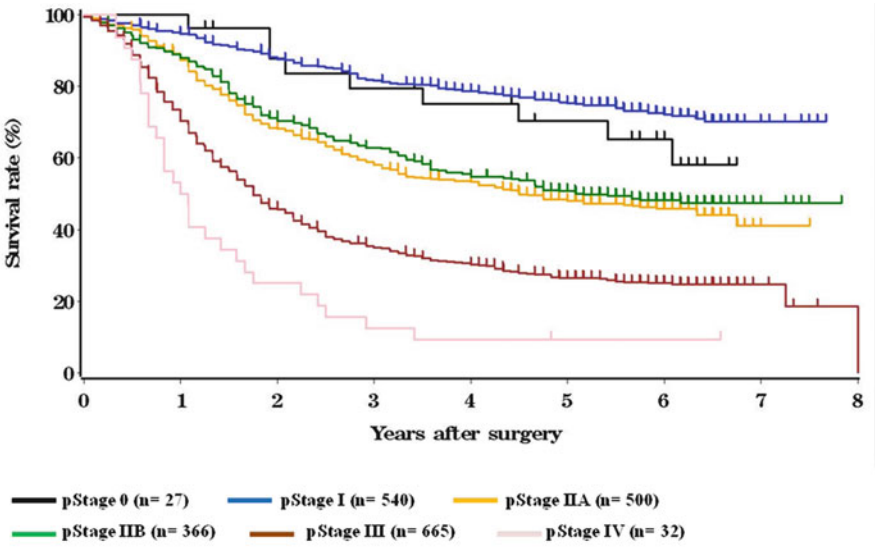

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	96.2%	87.8%	79.4%	75.0%	70.3%	65.3%	58.1%	-
pStage I	94.7%	88.0%	81.8%	78.6%	75.3%	72.2%	70.1%	70.1%
pStage IIA	87.3%	68.5%	58.9%	53.5%	47.9%	45.9%	41.1%	41.1%
pStage IIB	87.8%	71.2%	62.9%	55.6%	50.7%	48.2%	47.5%	47.5%
pStage III	70.3%	45.7%	35.3%	30.6%	26.5%	25.0%	24.7%	18.5%
pStage IV	50.0%	25.0%	12.5%	9.4%	9.4%	9.4%	-	-

Fig. 6.10 Survival of patients treated by esophagectomy in relation to pathological stage in 2006 (UICC-pTNM 6th)

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

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Guidelines for Diagnosis and Treatment in Japan

7

Yuko Kitagawa and Hiroyuki Kuwano

Abstract

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

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

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

Keywords

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

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

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

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

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

7.2 Principles and Structure of the Guidelines

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

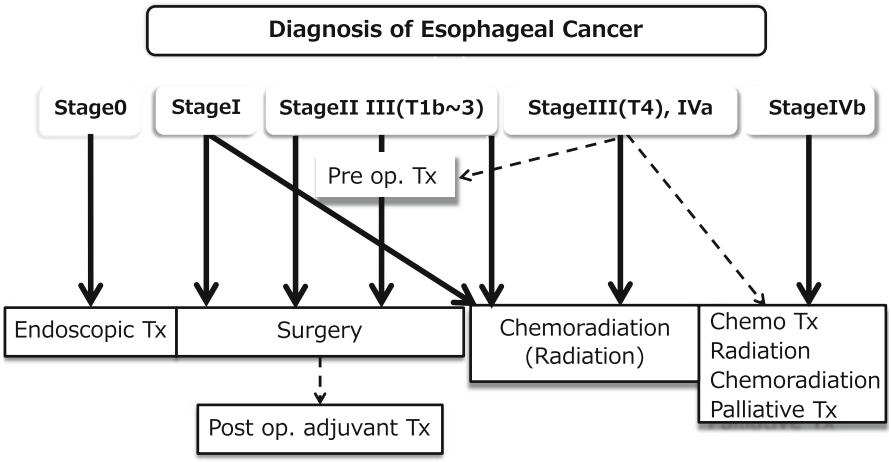

Fig. 7.1 The algorithm for treatment strategies of esophageal carcinoma

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

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

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

7.3 Epidemiology and Current Status of Esophageal Carcinoma in Japan

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

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

Alcohol drinking and smoking are important risk factors for squamous cell carcinoma, serving as risk factors in more than 90 % of all cases of esophageal carcinoma in Japan. As for the risk factors for adenocarcinoma, Barrett's epithelium derived from persistent inflammation of the lower esophagus due to gastroesophageal reflux disease (GERD) has been reported in western countries.

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

7.4 Diagnosis of Esophageal Carcinoma

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

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

7.5 Endoscopic Treatment

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

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

Among lesions that do not exceed the mucosal layer (T1a), those remaining within the mucosal epithelium (EP) or the lamina propria mucosae (LPM) are extremely rarely associated with lymph node metastasis; therefore, endoscopic resection is considered as a sufficiently curative treatment for these lesions [7].

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

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

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

7.6 Surgical Treatment

Although there are various options for therapeutic strategy for esophageal cancer according to the location of the tumor, stage, and general condition of the patient, surgical treatment remains the mainstay of treatment. There are also various options depending on the institution as to the width of the resection margin, extent of lymph node dissection, the organ and route used for reconstruction, multimodal treatment including adjuvant therapy, and salvage surgery following definitive chemoradiation.

7.6.1 Surgery for Cervical Esophageal Carcinoma

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

7.6.2 Surgery for Thoracic Esophageal Carcinoma

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

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

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

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

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

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

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

The 10th edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus* defines the esophagogastric junction region as the region within 2 cm above and below the esophagogastric junction and esophagogastric junction carcinoma as carcinoma with its center located within this region [13]. In cases of esophagogastric junction carcinoma extending more to the esophageal side than to the gastric side (E, EG), right thoracotomy with dissection including the upper mediastinal lymph nodes and reconstruction using a gastric tube are performed in the same manner as for cases of thoracic esophageal carcinoma. In some cases, lower esophagectomy with proximal gastrectomy or lower esophagectomy with total gastrectomy via left thoracolaparotomy or serial left thoracoabdominal incisions may be carried out, considering that cervical or upper mediastinal lymph node dissection is of lesser significance. A transhiatal approach to the lower mediastinum without thoracotomy is also reported. In cases of esophagogastric junction carcinoma extending more to the gastric side than to the esophageal side (G, GE), metastasis to the mediastinal

lymph nodes is less frequent; thus dissection of these lymph nodes is of lesser consequence. Therefore, these lymph nodes are classified as group 3 in the 10th edition of the *Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus*.

7.6.4 Transhiatal Esophagectomy

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

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

7.6.5 Perioperative Management and Clinical Path

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

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

7.6.6 Salvage Surgery

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

recurrent cancer after definitive (chemo)radiotherapy with 50 Gy or more as total irradiation dose [13]. The incidence of complications is higher in cases of salvage surgery than in patients treated by surgery alone or surgery combined with preoperative chemoradiotherapy (radiation dose less than 50 Gy). The reported in-hospital mortality after salvage surgery is 7–22 %, indicating that this type of surgery is associated with a higher surgical risk than usual surgery [17]. The high incidence of complications and high in-hospital mortality should be taken into account when considering the indications for salvage surgery.

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

7.7 Neoadjuvant Therapy

This is the most significantly updated part in the 2012 edition of guidelines. A number of randomized controlled trials have been conducted in western countries addressing the possible beneficial effects of neoadjuvant chemotherapy on the survival rates of patients with esophageal carcinoma. According to the results of a meta-analysis of these randomized controlled trials, the effects of neoadjuvant chemotherapy on the survival of the patients varied and had been unclear [18]. Therefore, the 2007 edition of guidelines recommended the implementation of adjuvant chemotherapy particularly in patients with positive lymph node metastasis, on the basis of the results of the JCOG (Japan Clinical Oncology Group) 9204 study (1992–1997: postoperative adjuvant chemotherapy with cisplatin + 5-FU vs. surgery alone) [19]. The randomized controlled trial (JCOG9907 study) that compared neoadjuvant chemotherapy and postoperative chemotherapy with cisplatin + 5-FU in patients with resectable stage II or III thoracic esophageal carcinoma (2002 UICC classification) revealed a significant improvement in the overall survival in neoadjuvant group [20]. Based on this finding, neoadjuvant chemotherapy + radical surgery for resectable stage II or III thoracic esophageal carcinoma is recognized as a standard treatment in Japan.

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

In meta-analyses carried out so far in the West, the patient population (histologic type, stage, etc.) and chemoradiotherapy protocols have not been consistent. The quality of surgery has been suggested to greatly influence the outcome.

No randomized controlled trials of neoadjuvant chemoradiotherapy have been carried out to date in Japan, and thus at present, there is no satisfactory rationale for recommending this therapy as effective neoadjuvant treatment.

7.8 Postoperative Adjuvant Therapy

7.8.1 Postoperative Chemotherapy

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

7.8.2 Postoperative Radiotherapy

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

7.9 Chemotherapy

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

7.9.1 Proven Effective Monotherapy Drugs

While 15–44 % of patients have been estimated to respond to monotherapy, cases of complete response (CR) are rare, and no monotherapy has been shown to have survival benefit [22]. At present, the most commonly used drugs are 5-FU and cisplatin. Basic studies have demonstrated that these two drugs are effective when used as monotherapy and exert a synergistic effect when combined with some other drugs and a sensitizing effect when combined with radiotherapy. A few reports of these drugs yielding good results when used in combination in the clinical setting have also been published. These are the reasons for the wide use of these two drugs.

7.9.2 Combination Therapy

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

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

7.10 Radiotherapy

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

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

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

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

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

7.11 Chemoradiotherapy

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

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

7.11.1 An Optimal Dose of Irradiation and Regimen of Chemotherapy

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

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

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

7.11.2 Adverse Events after Chemoradiotherapy

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

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

7.11.3 Follow-up and Salvage Treatments after Chemoradiotherapy

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

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

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

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

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

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

7.14 Follow-Up Observation After Treatment of Esophageal Carcinoma

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

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

7.15 Treatment of Recurrent Esophageal Carcinoma

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

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

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

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

7.16 Palliative Care

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

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

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

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

7.17 Therapeutic Outcomes and Recommended Guidelines in the West

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

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

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

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

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

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

(continued)

Table 7.1 (continued)

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

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

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

7.18 Future Perspective

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

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

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

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Surgery Transthoracic Esophagectomy

8

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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. Despite substantial advances in preoperative risk evaluation, improved operative techniques, and perioperative management, the risk of morbidity and mortality for esophagectomy remains high. To improve the rate of cure and the quality of life after surgery, more attention should be paid to the individualization of treatment. 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.

Keywords

Esophageal carcinoma • Extended lymphadenectomy • Transthoracic esophagectomy

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8.1 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]. ADC behaves biologically differently and these tumors should be separately considered from SCC of the esophagus. The prognosis of esophageal carcinoma is determined by the extent of the primary tumor and the lymphatic spread of the disease. 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. 8.1 [7]. The cervical and the upper mediastinal nodes are more commonly involved in patients with carcinoma of the upper thoracic esophagus,

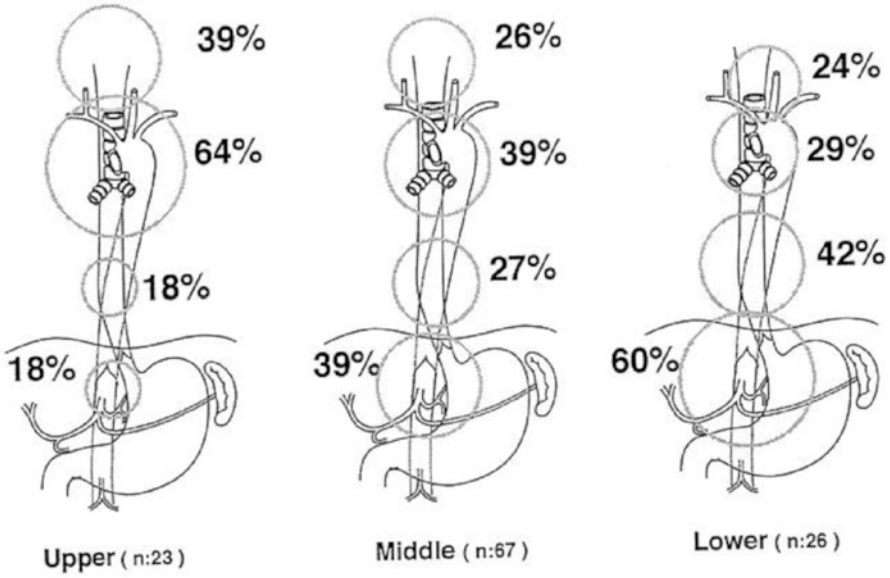


Fig. 8.1 The status of lymph node metastases according to the location of the primary tumor as reported by Ando et al. [7]

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 for thoracic esophagus SCC is introduced in this chapter.

8.2 Surgery for SCC of Thoracic Esophagus

8.2.1 Esophagectomy

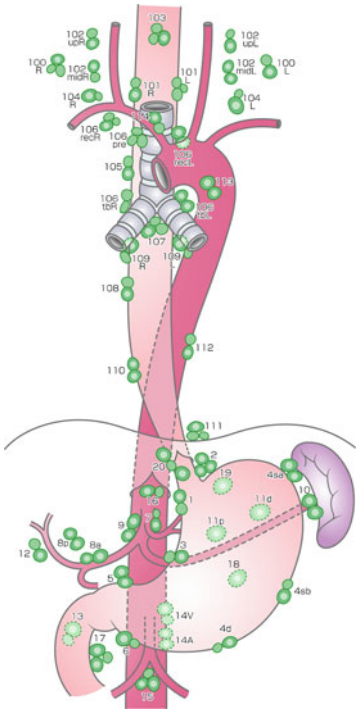
Curative resection of the primary lesion includes the removal of the gross lesion itself as well as possible concomitant spread of esophageal carcinoma. Because sufficient dissection of mediastinal lymph node is necessary, right thoracotomy and lymph node dissection plus total extirpation of the thoracoabdominal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

8.2.2 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 numbers of lymph nodes defined according to the location of lymph nodes [15] are shown in Fig. 8.2.

8.2.2.1 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



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

mediastinal or abdominal lymph nodes is less frequent, dissection usually covers all three regions.

8.2.2.2 Middle Thoracic Esophageal Carcinoma

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

8.2.2.3 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.

8.3 Surgical Procedure

8.3.1 Surgical Approach

The open approaches used for esophageal resection include transhiatal approach, right transthoracic approach, left transthoracic approach, and 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.

8.3.2 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. 8.3). 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 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

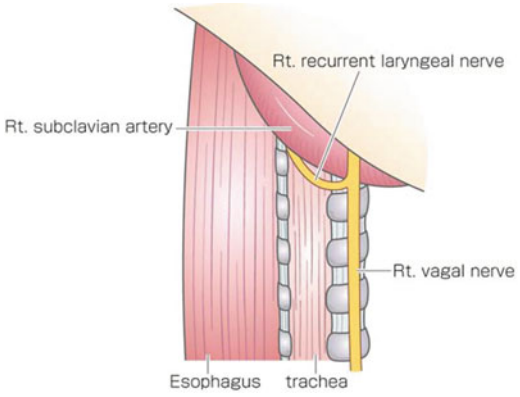


Fig. 8.3 The right recurrent laryngeal nerve was identified at the caudal end of the right subclavian artery, and lymph nodes around the right recurrent laryngeal nerve were dissected

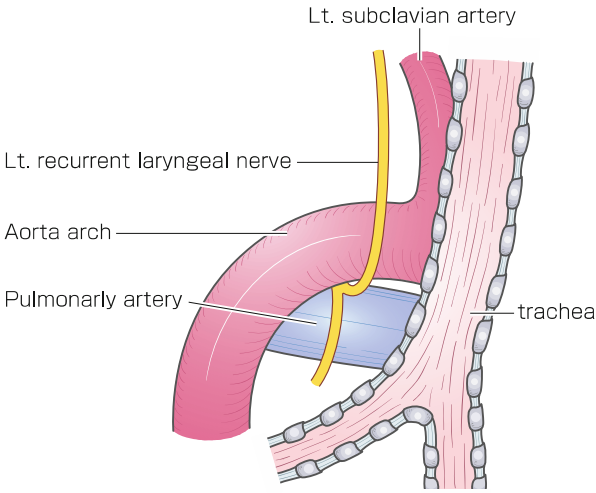


Fig. 8.4 The left subclavian artery was exposed to dissect the left recurrent laryngeal lymph nodes. The trunk of the left pulmonary artery between the aortic arch and the left main bronchus was exposed to dissect the left tracheobronchial lymph nodes

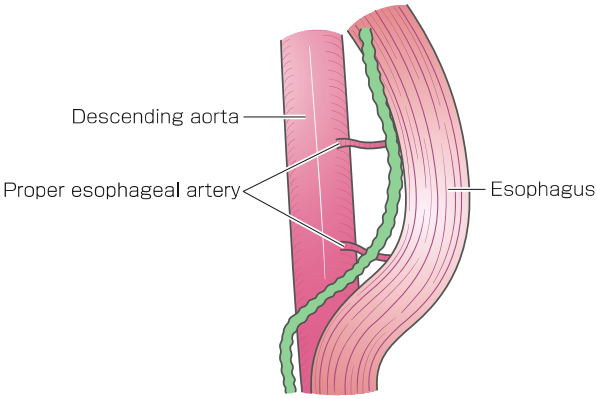


Fig. 8.5 The posterior side of the middle to lower esophagus was dissected to expose the descending aorta. The thoracic duct was ligated and divided behind the lower esophagus and resected together with the esophagus

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. 8.4).

8.3.3 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. 8.5). 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

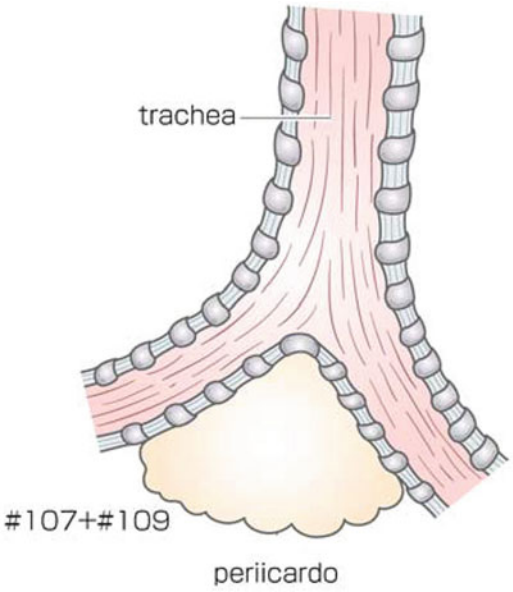


Fig. 8.6 The subcarinal nodes were separately dissected

surrounding tissue were dissected up to the hiatus. The subcarinal nodes were separately resected (Fig. 8.6). Esophageal mobilization and mediastinal lymphadenectomy were thus completed.

8.3.4 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 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.

8.4 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.

8.4.1 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 [16]. 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 3,243 esophagectomies [17]. 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 [18–20] 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 [21].

8.4.2 Morbidity

8.4.2.1 Pulmonary Complications

Pulmonary complications are the most frequent complication after esophagectomy and have been implicated in nearly two-thirds of postoperative mortalities [22]. The incidence of pneumonia has been directly linked to technical complications associated with the surgical procedure [23]. The incidence of pneumonia is reported to be higher in transthoracic esophagectomy compared with THE [24] and minimally invasive esophagectomy [25].

8.4.2.2 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 [22]. 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 [26]. 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 [22, 27, 28].

8.4.2.3 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 % [29]. The occurrence of a recurrent laryngeal nerve palsy or injury increased the incidence of perioperative pulmonary complications [30, 31]. 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 [32].

8.4.2.4 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 h 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.

8.5 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 [33]. 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 the individualization of treatment [34]. The concepts of the SLN intraoperative lymphatic mapping and sentinel lymphadenectomy appear attractive [35–38]. 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 [39, 40]. 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. Takeuchi reported the results of a radio-guided SLN navigation validation study of esophageal cancer [41]; 75 consecutive patients who were diagnosed before surgery with T1N0M0 or T2N0M0 primary esophageal cancer were enrolled. SLNs were identified in 71 (95 %) of 75 patients, and 29 (88 %) of the 33 patients with LN metastasis revealed positive SLNs. The diagnostic accuracy based on the SLN status was 94 %. We believe 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

9

Hiroya Takeuchi

Abstract

Technical advancements and development of endoscopic equipment in thoracoscopic surgery have resulted in increase in the popularity of minimally invasive esophagectomy (MIE). To date, a number of single-institution studies and several meta-analyses have demonstrated acceptable short-term outcomes of thoracoscopic esophagectomy for esophageal cancer, and the outcomes are comparable to those of conventional open esophagectomy (OE). Extended mediastinal lymphadenectomy including the upper mediastinal nodes along the bilateral recurrent laryngeal nerves (RLNs) is considered as a standard surgery for thoracic esophageal squamous cell carcinoma in Japan. Nowadays, precise upper mediastinal lymphadenectomy along the bilateral RLNs is also feasible, even with thoracoscopic approaches. However, there have been a limited number of prospective multicenter trials to verify the feasibility and benefits of MIE to date. Comparison of the left lateral decubitus position with the prone position also should be assessed as appropriate positioning for MIE, with regard to precise upper mediastinal lymphadenectomy along the bilateral RLNs for esophageal squamous cell carcinoma. Furthermore, the oncological benefit to patients undergoing MIE has not been scientifically proven because there have been no randomized controlled trials to verify the equivalency in long-term survival of patients undergoing MIE compared with that of patients undergoing OE. If future prospective studies indicate oncological benefits, MIE could truly become the standard care for patients with esophageal cancer.

Although several studies have emphasized that robot-assisted thoracoscopic esophagectomy is safe and feasible, the superiority of robot-assisted thoracoscopic esophagectomy compared with conventional thoracoscopic

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esophagectomy should be carefully evaluated because robot-assisted thoracoscopic esophagectomy is not comparable with conventional MIE in terms of the cost of a surgery.

Keywords
Decubitus • Esophageal cancer • Laparoscopy • Prone • Robotic surgery • Squamous cell carcinoma • Thoracoscopy

9.1 Introduction

Esophagectomy remains the mainstay of potentially curative treatment for patients with localized esophageal cancer including squamous cell carcinoma. It has been reported that esophagectomy with radical lymphadenectomy may improve disease control and survival outcome [1–4].

However, esophagectomy with radical lymphadenectomy is one of the most invasive gastrointestinal surgeries. Therefore, esophagectomy via a thoracoscopic and/or laparoscopic approach seems to be very attractive as a less invasive surgery [5]. Since 1992, when Cuschieri et al. first reported on thoracoscopic esophagectomy as minimally invasive esophagectomy (MIE) [6], many groups have described various methods for MIE [7–11]. Among 5,354 patients who underwent esophagectomy in 713 hospitals in Japan in 2011, a total of 1,751 (32.7 %) patients underwent total (thoracoscopic and laparoscopic approaches) or hybrid (thoracoscopic or laparoscopic approach) MIE. Of these patients with MIE, 1,436 (82.0 %) underwent surgery using the thoracoscopic approach [12]. The increase in the popularity of this procedure is a result of technical advancements and development of endoscopic equipment in thoracoscopic and laparoscopic surgeries, including newly developed dissectors, laparoscopic coagulating shears, and vessel-sealing systems, which are available for resection of the esophagus as well as extended mediastinal lymphadenectomy. However, the advantages with regard to short-term outcome and the oncological feasibility of MIE have not been established. If similar surgeries as conventional open esophagectomy (OE) are performed thoracoscopically and/or laparoscopically through smaller incisions, MIE would lead to less morbidity and equal long-term survival compared with OE. Moreover, laparoscopic gastric mobilization for reconstruction using a gastric conduit is widely accepted even in combination with OE [11].

In this chapter, we review previous reports on MIE, particularly focusing on thoracoscopic esophagectomy in the literature, and assess short-term and long-term outcomes of MIE compared with those of conventional OE.

9.2 Overview of MIE

9.2.1 Terminology of MIE

To date, several thoracoscopic or laparoscopic approaches for resection of thoracic esophageal cancer have been defined as MIE [5, 13]. Although total thoracoscopic and laparoscopic esophagectomy is representative as (total) MIE in a narrow sense, video-assisted thoracoscopic surgery (VATS) esophagectomy with minithoracotomy (up to an approximately 5-cm incision) and a laparoscopic approach is also included in MIE in a wider sense [14]. Hybrid MIE is defined as esophagectomy using either the thoracoscopic or laparoscopic approach. Laparoscopic transhiatal and mediastinoscope-assisted blunt esophagectomies were mainly developed for resection of superficial esophageal squamous cell carcinoma or esophageal adenocarcinoma which arises from Barrett's esophagus [15]. For esophagogastric anastomosis after VATS esophagectomy, cervical anastomosis or intrathoracic anastomosis with the Ivor Lewis procedure has been applied in clinical practice [16]. More recently, robot-assisted thoracoscopic and/or laparoscopic esophagectomy using the Da Vinci system seems an appealing option [17, 18].

9.2.2 VATS Esophagectomy

9.2.2.1 History

Cuschieri et al. first reported on five patients who underwent VATS of right transthoracic esophagectomy in 1992 [6], and VATS of Ivor Lewis esophagectomy with intrathoracic anastomosis was developed in 1995 [19]. In Japan, Akaishi et al. first reported on thoracoscopic total esophagectomy with en bloc mediastinal lymphadenectomy in 1996 [10]. Kawahara et al. demonstrated the details of VATS esophagectomy with extended lymphadenectomy in 1999 [7], and Osugi et al. described the long-term survival of 77 patients with esophageal squamous cell carcinoma who underwent VATS esophagectomy [14].

9.2.2.2 Indication

The indication for VATS esophagectomy is relatively wider than that for laparoscopic surgery for gastric and colorectal cancer, and VATS esophagectomy is currently applied to locally advanced esophageal cancer (even after neoadjuvant chemoradiotherapy in some reports). Only some conditions such as T4 tumor, severe intrathoracic adhesion, and 1-lung ventilation failure are considered to be excluded from the indication for VATS esophagectomy [11, 13].

9.2.2.3 Positioning

Until date, two types of patient positions have been used for thoracoscopic esophagectomy. Most thoracic surgeons prefer performing right transthoracic VATS esophagectomy in the left lateral decubitus position, similar to right

transthoracic OE. However, since Cuschieri et al. [6] first described thoracoscopic mobilization of the esophagus in the prone position, a number of single-institution reports of VATS esophagectomy in the prone position have been published [20–23].

The differences between the two positions in VATS esophagectomy have been discussed in the literatures [5, 24]. The best advantage of the prone position is that a good surgical field and view of the mid to lower posterior mediastinum, including the esophagus, can be obtained without any retraction of the right lung using a retractor or sutures, because the right lung naturally falls away under gravity in the prone position and because of additional carbon dioxide insufflation of the thoracic cavity. On the other hand, skillful retraction of the right lung by assistants is necessary to obtain the appropriate surgical field in the left lateral decubitus position.

Several studies have demonstrated that VATS esophagectomy in the prone position might result in shorter operative time and lower incidence of postoperative respiratory complications compared with that in the left lateral decubitus position [20, 25]. However, the prone position is still considered to be problematic in terms of safety of the procedure because, in this position, it is technically difficult to perform urgent conversion to right thoracotomy in an emergency situation such as sudden massive bleeding. To resolve the issue, we previously described the utility of the left semiprone position [26, 27]. It was possible to perform thoracoscopic esophagectomy with safe and precise extended lymphadenectomy in the optimal position (e.g., left lateral decubitus position, prone position) by rotating the operating table [26, 27].

9.2.2.4 VATS Esophagectomy for Thoracic Squamous Cell Carcinoma

The specific characteristics of thoracic esophageal squamous cell carcinoma, which is much more common than esophageal adenocarcinoma in Japan, include the widespread and random patterns of lymph node metastasis from cervical to abdominal areas and relatively higher risk of metastasizing to the upper mediastinal lymph nodes along the bilateral recurrent laryngeal nerves (RLNs) [2, 28]. On the basis of these clinical observations, extended radical lymphadenectomy, including the upper mediastinal nodes along the bilateral RLNs, is considered as a standard surgery in Japan [2]. In particular, three-field lymph node dissection, including dissection of cervical, mediastinal, and abdominal lymph nodes, is the standard procedure for surgically curable esophageal squamous cell carcinoma located in the middle or upper thoracic esophagus. Nowadays, precise upper mediastinal lymphadenectomy along the bilateral RLNs is also feasible, even with thoracoscopic approaches [29]. Noshiro et al. reported that a better surgical field and view around the left RLN could be obtained by thoracoscopic esophagectomy in the prone position [29].

The other specific characteristic of thoracic esophageal squamous cell carcinoma is the location of primary tumor. Thoracic esophageal squamous cell carcinoma is mainly located at the middle third of the esophagus, while adenocarcinoma is usually located at the lower third of the esophagus or esophagogastric junction.

Therefore, the esophagus is generally transected at the level of the proximal esophagus during esophagectomy in case with thoracic esophageal squamous cell carcinoma. Moreover, esophagogastrostomy should be performed in the neck or in the upper posterior mediastinum.

9.2.3 Laparoscopy/Mediastinoscopy-Assisted Esophagectomy

Sadanaga et al. reported the first laparoscopic transhiatal esophagectomy in 1994 [15], and mediastinoscope-assisted blunt dissection of the esophagus was reported in 1993 [30]. To date, several institutions have reported on laparoscopic and/or mediastinoscopy-assisted transhiatal esophagectomy with esophagogastric anastomosis in the cervical portion [15, 31]. Blunt dissection of the thoracic esophagus by a blind maneuver could be avoided by use of laparoscopy or mediastinoscopy. Safety and lower invasiveness of laparoscopy- and/or mediastinoscopy-assisted transhiatal esophagectomy have been reported by several institutions [13]. Several authors have reported that laparoscopic transhiatal esophagectomy is more beneficial than conventional open transhiatal esophagectomy in terms of shorter operative time, lesser blood loss, and shorter hospital stay [31, 32]. Tangoku et al. also reported on 42 patients with superficial esophageal cancer (41 squamous cell carcinoma and 1 adenocarcinoma) and medical risk who safely underwent mediastinoscopy-assisted transhiatal esophagectomy, with low incidence of morbidity and no mortality [33].

9.2.4 Reconstruction Procedures

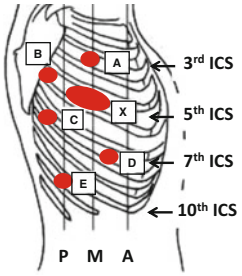
A gastric conduit is generally used for reconstruction after MIE, similar to OE. Reconstruction after esophagectomy must be technically safe and easy to perform. In general, an intrathoracic esophagogastric anastomosis is thought to be superior to a cervical esophagogastric anastomosis in terms of lower incidence of anastomotic leak and better cosmetic effect in patients who undergo OE with 2-field lymphadenectomy [34]. However, in reconstruction after VATS esophagectomy, an esophagogastric anastomosis in the cervical portion has been preferred because intrathoracic esophagogastric anastomoses are technically difficult with the thoracoscopic procedure. Several groups, including ours, have developed an easy and secure thoracoscopic intrathoracic esophagogastric anastomosis procedure that uses a circular stapler with transoral placement of the anvil or linear stapler [19, 26]. These anastomosis procedures can be applied to thoracoscopic Ivor Lewis esophagectomy.

9.2.5 Surgical Procedures (MIE in Keio University Hospital)

As previously described, patients are placed in the left semiprone 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 [26, 27].

A 4–5-cm minithoracotomy and 5 trocars in total are placed on the thoracic wall (Fig. 9.1) [26, 27]. 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. 9.2). 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. 9.3 and 9.4). 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.

Subsequently, the operating table is rotated so that the patient is in the prone position, and a 7-mmHg CO_2 pneumothorax is induced using a minithoracotomy lid. 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



A Trocar (12mm)
B Trocar (5mm)
C Trocar (5mm)
D Trocar (12mm)
E Trocar (12mm)
X Mini-thoracotomy (40-50mm)

Fig. 9.1 Placement of thoracic ports. Five ports with a small thoracotomy (4–5 cm) were introduced onto the thoracic wall. *ICS* intercostal space, *A* anterior axillary line, *M* middle axillary line, *P* posterior axillary line

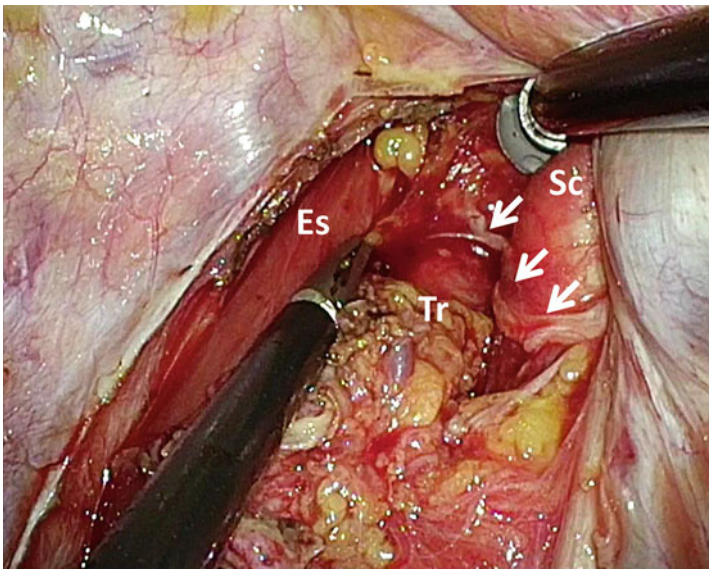


Fig. 9.2 Thoracoscopic lymphadenectomy along the right recurrent laryngeal nerve. *Arrows*, the right recurrent laryngeal nerve; *Es* esophagus, *Tr* trachea, *Sc* right subclavian artery

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 performed through a transverse minilaparotomy (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 or thorax [26, 27]. In patients with cervical anastomoses, the gastric conduit is pulled up to the neck through the posterior mediastinal route. The cervical esophagus and gastric conduit are then anastomosed using a circular stapler. If the gastric conduit is not of sufficient length for mechanical anastomosis, the anastomosis is hand sewn. In patients with intrathoracic anastomoses, esophagogastrostomy is performed using a circular stapler at the level of the thorax in the upper posterior mediastinum through a minithoracotomy [26].

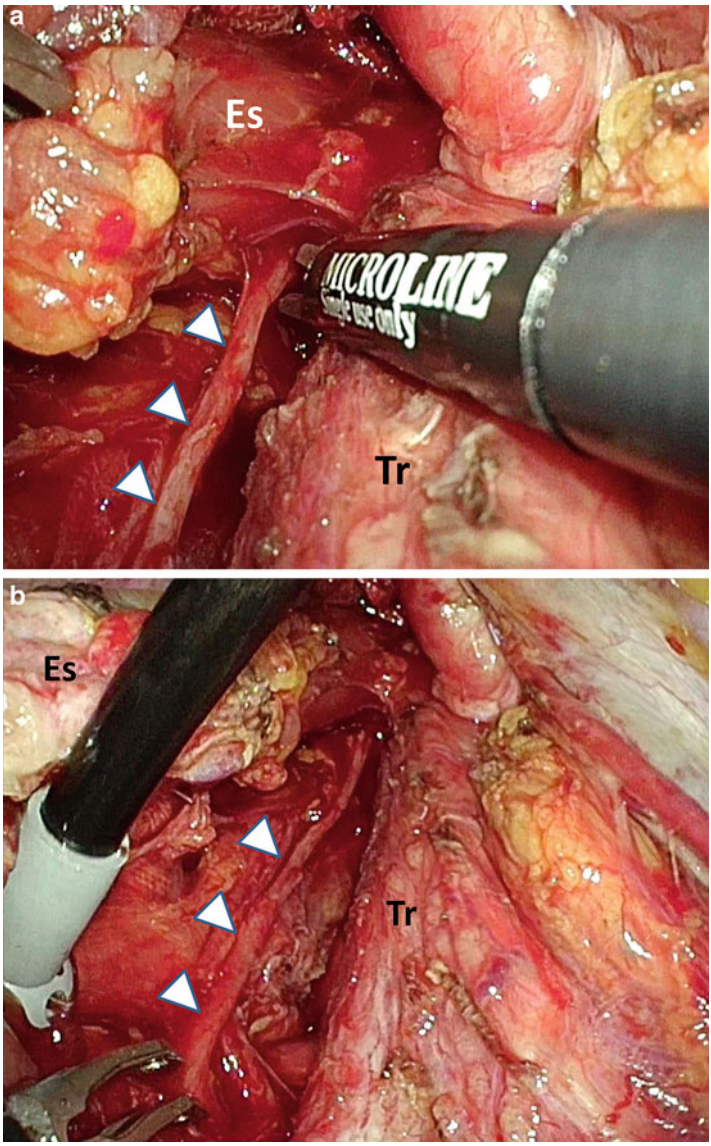


Fig. 9.3 Thoracoscopic lymphadenectomy along the left recurrent laryngeal nerve. (**a**) Magnified view. (**b**) Overview. *Arrowheads*, the left recurrent laryngeal nerve; *Es* esophagus, *Tr* trachea

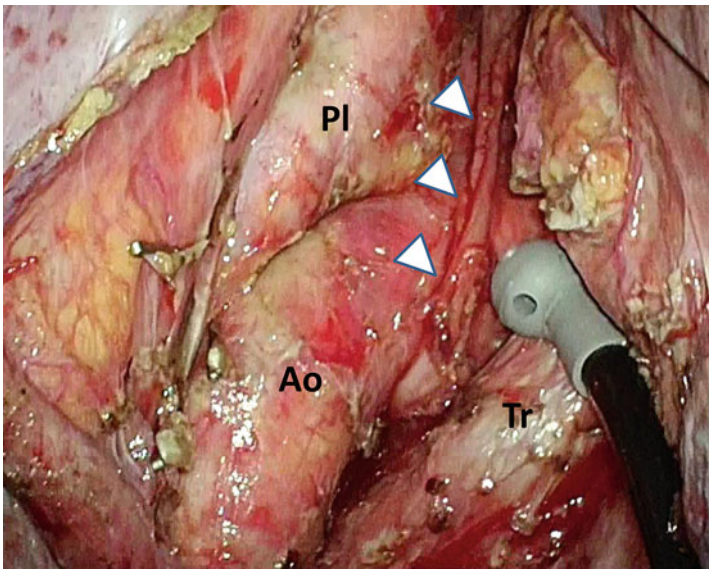


Fig. 9.4 Left upper mediastinal area after precise lymphadenectomy. *Arrowheads*, the left recurrent laryngeal nerve; *Ao* aortic arch, *Tr* trachea, *Pl* left mediastinal pleura

9.3 Short- and Long-Term Outcomes of MIE

9.3.1 Short-Term Outcomes of VATS Esophagectomy

To date, a number of single-institution studies have demonstrated acceptable short-term outcomes of VATS esophagectomy for thoracic esophageal cancer in terms of operating time, blood loss, and postoperative complications; these outcomes are comparable with those of conventional OE [13, 22]. Many studies have reported that the operating time of VATS esophagectomy was relatively longer than that of OE, but blood loss was markedly lesser than that of OE. Conversion of VATS esophagectomy to OE because of several reasons, such as adhesion and bulky tumor, was reported in 0–20 % of cases in single-institution studies [13]. Of note, massive active bleeding and bronchial injury were also reported as major intraoperative complications of VATS esophagectomy [13].

With regard to the number of retrieved mediastinal and/or total lymph nodes, most studies have demonstrated that VATS esophagectomy is almost equivalent to OE (Table 9.1) [38]. In terms of postoperative complications, the effect of VATS esophagectomy in reducing respiratory complications such as pneumonia remains controversial, but several studies demonstrated that the incidence of respiratory complications was significantly lower with VATS esophagectomy than with OE (Table 9.1). On the other hand, the incidence of anastomotic leak and RLN palsy with VATS esophagectomy is almost equivalent to that with OE [5]. Mamidanna

Table 9.1 Representative results of comparison between minimally invasive esophagectomy and conventional open esophagectomy for esophageal squamous cell carcinoma

Ref. #	Author (year)	# cases	SCC (%)	Operative time (min)	*p* value	Blood loss (ml)	*p* value	# Retrieved lymph nodes	*p* value	Respiratory complications (%)	*p* value	Anastomotic leak (%)	*p* value	In-hospital mortality (%)	*p* value	Hospital stay (day)	*p* value	Survival	*p* value
[14]	Osugi (2003)	VATS 77	77 (100)	227	0.031	284	NS	34	NS	15.6	NS	1.3	NS	0.0	NS	NA		55 % (5yOS)	NS
		OE 72	72 (100)	186		310		33		19.4		2.8		0.0				57 % (5yOS)	
[35]	Shiraishi (2006)	tMIE 78	144/153	426	0.01	670	NS	NA		20.5	NS	11.5	0.005	2.6	0.003	NA		NA	
		VATS 38	(94)	461		640				23.7		10.5		10.5					
		OE 37		487		883				32.4		24.3		13.5					
[36]	Gao (2011)	MIE 96	90 (94)	330	<0.01	347	<0.01	18	NS	13.5	NS	7.3	NS	30-day mortality (%) 2.1	NS	13	<0.01	NA	
		OE 78	72 (92)	284		519		18		14.1		7.7		3.8		18			
[37]	Kinjo (2012)	tMIE 72	71 (99)	308	<0.001	320	<0.001	28	0.002	13	0.001	4	NA	30-day mortality (%) 0.0	NS	23	<0.001	72 % (2yDFS)	NS
		hMIE 34	31 (91)	264		536		24		38		24		0.0		32		58 % (2yDFS)	
		OE 79	71 (90)	268		680		18		39		17		0.0		53		58 % (2yDFS)	
[11]	TIME trial (2012) (Randomized controlled trial)	MIE 59	24 (41)	329	0.002	200	<0.001	20	NS	8.5	0.005	11.9	NS	3.3	NS	11	0.044	NA	
		OE 56	19 (34)	299		475		21		28.6		7.1		1.8		14			

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, *SCC* squamous cell carcinoma, *OS* overall survival, *DFS* disease-free survival

et al. reported on the largest series ($n = 7{,}502$) that compared MIE with OE, using a nationwide database from 2005 to 2010 in the United Kingdom [39]. As results, there were no reports of marked differences in the overall medical morbidity (38.0 vs 39.2 %) and 30-day mortality (4.3 vs 4.0 %) between the OE and MIE groups, respectively. Furthermore, there were no marked differences in respiratory complications between the OE and MIE groups (31.4 vs 30.0 %). Of note, the reintervention rate as a result of surgical complications was significantly higher in the MIE group than in the OE group (21.0 vs 17.6 %). They concluded that the study confirmed the safety of MIE but MIE was associated with higher reintervention rates because of surgical complications, and there were no marked benefits demonstrated in the overall morbidity and mortality.

Until now, there have been three large meta-analyses that compare short-term outcomes between MIE and OE [40–42]. There were essentially no marked differences in postoperative major morbidity and mortality between the two groups in these meta-analyses. Nagpal et al. compared 672 patients for total MIE and hybrid MIE and 612 for OE from 12 studies [42]. There were no marked differences in the operating time, number of retrieved lymph nodes, incidence of anastomotic leak, and 30-day mortality between the MIE and OE groups, but MIE had significantly lower blood loss, reduced total morbidity and respiratory complications, and shorter intensive care unit and hospital stay compared with OE [42]. However, to date, MIE has been investigated in case–control studies, and various biases may have been introduced by not only the study design but also learning curves, volume outcome, and publication bias [42].

A study group in Europe has recently reported the results of the first multicenter RCT (TIME trial) that compared MIE and OE (Table 9.1) [11]. The primary outcome of this RCT was the incidence of pulmonary infection within the first 2 weeks after surgery and during the entire hospital stay. They randomly assigned 56 patients (19 patients with squamous cell carcinoma) to the OE group and 59 (24 with squamous cell carcinoma) to the MIE group. MIE was performed through right thoracoscopy in the prone position with single-lumen tracheal intubation, upper abdominal laparoscopy, and cervical incision. To maintain partial collapse of the right lung during thoracoscopy, the thoracic cavity was insufflated with carbon dioxide at 8 mmHg. The MIE and OE procedures included 2-field esophagectomy with gastric conduit formation followed by cervical or intrathoracic anastomosis. The incidence of pulmonary infection was considerably lower in the MIE group than in the OE group, both within the first 2 weeks after surgery and during the entire hospital stay. MIE was also beneficial in terms of lesser operative blood loss, better postoperative quality of life, and shorter hospital stay, but 30-day and in-hospital mortality did not differ significantly between the groups. Pathological parameters such as number of lymph nodes retrieved did not differ markedly between the two treatment groups. These findings provided evidence for the short-term benefits of MIE for patients with esophageal cancer.

9.3.2 Long-Term Outcomes of VATS Esophagectomy

To date, a limited number of case–control studies have demonstrated the long-term survival of patients who underwent MIE. In particular, there are a small number of studies reporting stage-specific survival following MIE. Smithers et al. reported 5-year stage-specific survival rates after MIE as follows: 85 % in stage I, 33 % in stage IIA, 37 % in stage IIB, and 16 % in stage III (TNM classification, sixth edition) [43]. Osugi et al. compared long-term survival of patients with esophageal squamous cell carcinoma undergoing VATS esophagectomy with those undergoing OE as historical controls, as stratified by the oncological background [14]. As results, there were no marked differences in 3- and 5-year survival between the two groups [14]. Other studies also showed statistical equivalency in long-term survival between MIE and OE (Table 9.1). Sgourakis et al. and Dantoc et al. revealed that there were no significant differences in 3-year survival between the two groups in their meta-analyses [38, 41]. However, the oncological benefits to patients undergoing MIE have not been scientifically proven because there have been no RCTs to verify the equivalency in long-term survival of patients undergoing MIE compared with that in patients undergoing OE.

9.4 Discussion and Perspective

The popularity of MIE such as thoracoscopic esophagectomy is increasing worldwide. To date, a number of single-institution studies have demonstrated acceptable outcomes of MIE, including the short-term outcome of thoracoscopic esophagectomy for esophageal cancer; these outcomes are comparable with those of conventional OE [38, 40–42].

MIE is known to have several advantages over OE, such as better cosmesis, lesser tissue trauma, lesser pain, reduced postoperative inflammatory response, and lesser morbidity [40–42]. In particular, both the meta-analysis and an RCT demonstrated that postoperative respiratory complications after MIE were markedly decreased as compared with those after OE [11, 42]. Osugi et al. showed that pulmonary complications were less common in the VATS esophagectomy group than in the OE group [14]. Moreover, vital capacity was significantly greater in the VATS esophagectomy group several months after surgery than in the OE group [14]. MIE might be beneficial compared with OE in terms of preventing postoperative pneumonia and retaining pulmonary function after esophagectomy.

The decrease in respiratory complications in the MIE group may result from the less invasive nature of the operation, which allows encouraging patients to leave bed immediately after MIE, thereby facilitating early recovery after surgery and preventing development of atelectasis due to the collapsed lung. As another possible factor for the decreased rate of postoperative respiratory complications, Biere et al. emphasized that the mediastinum lies in its usual midposition and the chest and abdomen are free of compression in prone position of MIE [11]. In addition,

their results of the RCT suggested that absence of one lung ventilation in the prone position might reduce arteriovenous shunt with better preserved oxygenation [11].

Thoracoscopic approaches are technically difficult compared with OE; however, with regard to the learning curve with MIE, a number of authors have reported that a shorter operating time and reduced blood loss could be obtained with increasing experience [14]. Moreover, the number of retrieved lymph nodes of MIE is not inferior to that of OE in most previous reports and more in MIE in several studies [38]. Magnification of the view of the surgical field by thoracoscopy might facilitate safer and more precise esophagectomy and regional lymphadenectomy based on the mediastinal microanatomy and hasten learning curves because of educational benefits such as sharing of the image on the monitor.

However, the safety and benefits of MIE still remain unclear and must be evaluated in additional prospective multicenter trials and well-designed RCTs in patients with squamous cell carcinoma. First, "minimally invasive" surgery must be particularly verified for high-risk surgical patients with various comorbidities. Theoretically, MIE should be proposed for those high-risk patients on the basis that the degree of surgical trauma with MIE is lesser than that with an open procedure. Future prospective trials would allow appropriate selection of patients for MIE.

In general, MIE after chemoradiotherapy, especially for patients with advanced bulky tumors before treatment, is technically difficult because of radiation fibrosis. Although MIE was feasible even after chemoradiotherapy in the TIME trial [11], additional feasibility studies must be conducted to evaluate the safety of MIE after chemoradiotherapy for patients with locally advanced esophageal squamous cell carcinoma.

Comparison of the left lateral decubitus position with the prone position should also be assessed by RCTs as appropriate positioning for MIE [24]. In fact, the clinical benefits in terms of respiratory complications might be because of the difference between the prone position in MIE and the left lateral decubitus position in OE in the TIME trial [11]. In addition, the superiority of the prone position over the left lateral decubitus position in MIE in terms of precise upper mediastinal lymphadenectomy along the bilateral RLNs for squamous cell carcinoma has been controversial. Additional comparison studies would be needed to confirm the superiority of the prone position compared to the left lateral decubitus position in MIE.

Surgical robots with impressive dexterity and precise dissection skills have been developed to help surgeons perform operations [17, 18]. Although several studies have emphasized that robot-assisted thoracoscopic esophagectomy is safe and feasible, the superiority of robot-assisted thoracoscopic esophagectomy compared with conventional thoracoscopic esophagectomy without robot assistance should be carefully evaluated for squamous cell carcinoma because robot-assisted thoracoscopic esophagectomy is not comparable with conventional MIE in terms of the cost of a surgery.

Although a large sample size would be necessary, because of the lack of RCTs to date, we must also conduct multicenter RCTs as soon as possible to verify the

equivalency in long-term survival of patients with MIE compared with that of patients with OE especially for squamous cell carcinoma which has different characteristics from adenocarcinoma. If those prospective studies would indicate the oncological benefits of MIE, MIE could truly become the standard care for patients with esophageal squamous cell carcinoma.

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Surgery: Esophageal Reconstruction

10

Michio Sato

Abstract

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.

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 82, 4, and 4 %, 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, a vascular pedicled colon or jejunum is selected as an esophageal substitute. The middle colic artery or ascending branch of the left colic artery is pedicled in use of the right or left colon, respectively. In case of a long segment of the jejunal flap that reaches the cervical region vascular anastomosis for supercharge 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 and anterior mediastinal routes preferably selected in Japan at rates of 36.2 and 33.0 %, respectively.

Keywords

Colon replacement • Esophageal reconstruction • Free jejunal transfer • Gastric tube • Supercharged jejunal flap

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10.1 Introduction

Esophagectomy and reconstruction using thoracoscopy or laparoscopy are increasingly performed [1], but this endoscopic surgery still accounted for only 20 and 33 % of all esophageal surgeries in Japan in 2006 and 2011, respectively [2, 3]. In this chapter, we describe the open procedure of esophageal reconstruction for esophageal squamous carcinoma. There is little evidence related to esophageal reconstruction based on randomized clinical trials, and thus we are limited to description of our own experience of this approach. Reconstruction for cervical esophageal carcinoma is described in Sect. 10.2 and that for thoracic esophageal cancer is discussed in Sect. 10.3.

Tumor locations of esophageal carcinoma (all defined by histology) are shown in Table 10.1 [2]. A middle thoracic location is the most common (50 %) and incidence of superior mediastinal lymph node metastasis from thoracic esophageal cancer is quite high [4]. Thus, superior mediastinal node dissection is normally performed for thoracic squamous cell carcinoma in Japan, with subtotal esophagectomy and esophageal reconstruction with cervical or high intrathoracic anastomosis between the remnant esophagus and esophageal substitute.

10.2 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 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. If the stomach or colon does not reach the cervical esophagus or the inferior pharynx, a free jejunal graft is additionally transferred between the proximal organ and the distal conduit.

Table 10.1 Tumor location

Location of tumor	Total	%
Cervical	198	4.2
Upper thoracic	631	13.4
Middle thoracic	2,290	48.7
Lower thoracic	1,224	26.0
Abdominal	247	5.3
EG	31	0.7
EG junction (E = G)	26	0.6
Cardia	6	0.1
Unknown	46	1.0
Total	4,699	
Missing	5	

10.2.1 Free Jejunal Transfer

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

10.2.1.1 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 vessel anastomosis.

A segment of the jejunum of 30–40 cm in 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 with isoperistalsis. The best order of performance of vessel anastomosis and intestinal anastomosis is unclear. Initial anastomosis of the 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 the operation. Vessel anastomoses are performed microscopically. Regions with arterial plaque are removed and both 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 pull on the anastomoses.

The jejunal graft is placed as straightly as possible without tension against the vessel anastomoses. The length of the jejunum for use as the graft is 12–15 cm and unneeded portions of the jejunum on the proximal and distal sides 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. 10.1).

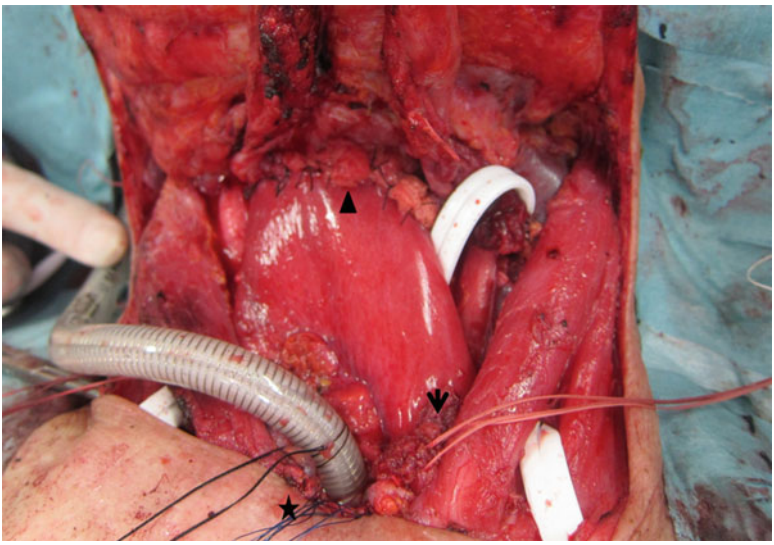

Fig. 10.1 Operative photograph of free jejunal transfer, showing anastomosis between the inferior pharynx and jejunum (*arrowhead*) and between the jejunum and esophagus (*arrow*). The tracheostoma is indicated by a *star*

10.3 Thoracic Esophageal Cancer

The stomach, colon, and jejunum are the main organs used for esophageal reconstruction in thoracic esophageal cancer. The stomach is used most frequently because fewer anastomoses are required, the operative procedure is relatively simple, and there is less surgical stress. In Japan, the stomach is used for reconstruction in 82 % of cases (Table 10.2) [2]. If the stomach cannot be used because of previous gastrectomy or synchronous gastric cancer, the vascular pedicled colon or jejunum is selected as an esophageal substitute.

10.3.1 Stomach

The use of the stomach as an esophageal substitute can involve three types of conduit with different widths: the whole stomach, a subtotal gastric tube, and a narrow gastric tube. This choice is made by the surgeon based on a consideration of 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 stomach 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 necrotize.

Table 10.2 Organs used for reconstruction in Japan (2006)

Organs used for reconstruction	Cases	%
None	46	1.8
Whole stomach	109	4.3
Gastric tube	1,989	77.6
Jejunum	103	4.0
Free jejunum	46	1.8
Colon	112	4.4
Free colon	14	0.5
Skin graft	1	0.0
Others	140	5.5
Unknown	3	0.1
Total lesions	2,563	
Total cases	2,541	
Missing	4	

10.3.1.1 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 operative 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 [5]) 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 is pulled out of the esophageal hiatus and the stomach is mobilized with the thoracic esophagus. The esophageal hiatus is sutured and closed in a case in which the anterior mediastinal or subcutaneous route is used.

The surgeon picks up the fundus to find the highest point of the stomach [6] and decides on the position of the cut line in the lesser curvature (Fig. 10.2). 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 where the left gastric peripheral arteries enter the gastric wall; and for a narrow stomach tube, the cut line is 3–4 cm from the greater curvature (Fig. 10.3). 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. The 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 useful.

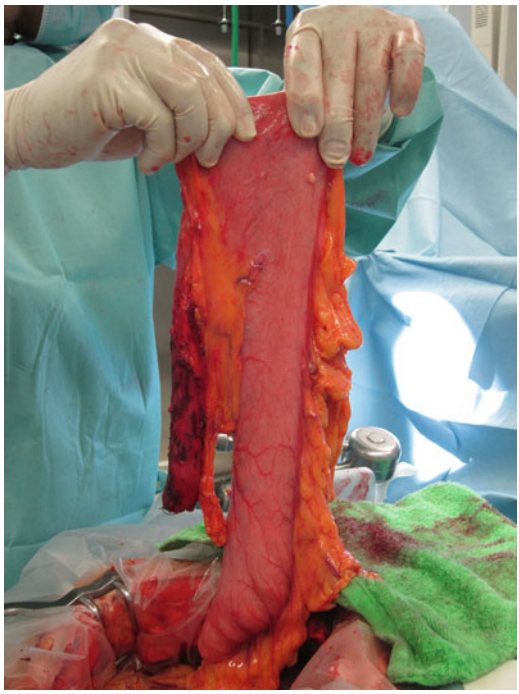

Fig. 10.2 The surgeon picks up the fundus and finds the highest point of the stomach

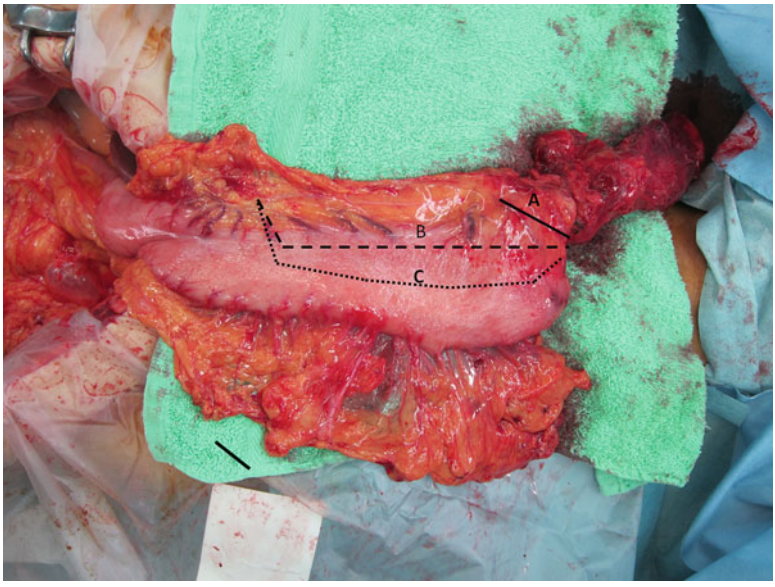

Fig. 10.3 Cut lines of the lesser curvature. For a whole stomach conduit, the cut line is made on an esophageal gastric junction (**a**, *continuous line*). For a subtotal stomach tube, the cut line is a line connecting the points where the left gastric peripheral arteries enter the gastric wall (**b**, *dashed line*). For a narrow stomach tube, the cut line is 3–4 cm from the greater curvature (**c**, *dotted line*)

Fig. 10.4 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. (**c**) First stapling by a linear stapler in an end-to-end fashion (triangulating stapling technique)

10.3.1.2 Esophagogastric Anastomosis

There are many kinds of anastomotic procedures, but these can largely be classified into hand sewn, circular stapler, and linear stapler techniques. In the hand sewn technique, an interrupted or running single-layer suture is generally performed using 4–0 absorbable sutures through all layers in an end-to-end fashion. However, hand sewing may result in more frequent leakage or stricture than other stapler methods [7–10].

In the circular stapler technique, a circular stapler with a diameter of 25 mm is used. First, an anvil head is inserted and secured in the remnant esophagus. The staple line in the tip of the gastric tube is removed 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. 10.4a). The hole where the stapler was inserted is closed using a linear stapler.

The linear stapler technique can be used for side-to-side or end-to-end anastomosis. In the side-to-side technique, 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. The posterior wall of the esophagus and the anterior wall of the gastric tube are then stapled (Fig. 10.4b). 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 [7, 8]. In the end-to-end linear stapling 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. 10.4c). A linear stapler is then applied to the anterior wall twice in an everted fashion to complete 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 [9–11].

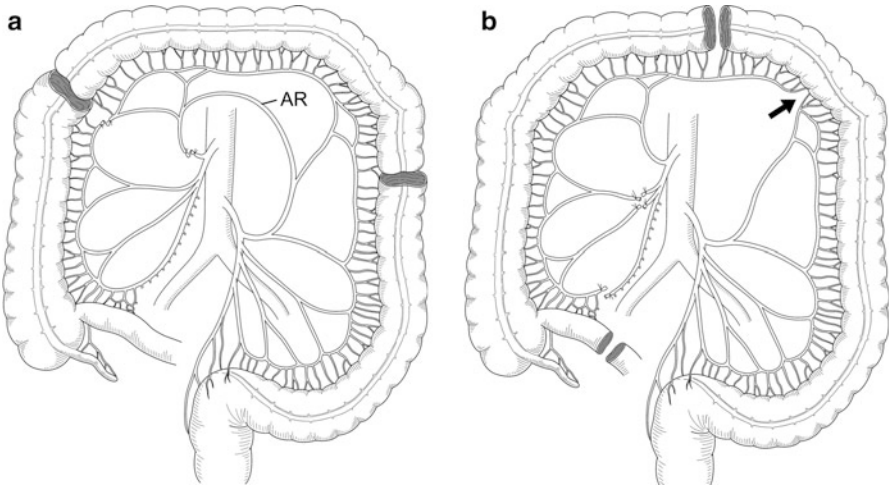

Fig. 10.5 Schema of colon replacement. (**a**) Isoperistaltic left colon replacement with arterial supply on the left colic artery. *AR* arc of Riolan. (**b**) Isoperistaltic right colon replacement with arterial supply on the middle colic artery. Discontinuity of marginal artery is appeared at Griffith's point (*arrow*)

10.3.2 Colon

Reconstruction using a pedicled colon as an esophageal substitute can be achieved with the right colon and middle colic artery or the left colon and left colic artery as a vascular pedicle with isoperistalsis (Fig. 10.5). 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 more common than in the left colon. The final decision on which 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.

10.3.2.1 Operative Technique

The ascending colon with the terminal ileum and the descending colon are dissected from retroperitoneal tissues. The mesenterium of the colon is transilluminated and the colon vessels are 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 10 min and the color of the colon graft is checked to ensure that it does not worsen. 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. 10.5a). 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. 10.5b).

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 in an end-to-side fashion.

10.3.3 Jejunal Roux-en-Y Reconstruction with Vascular Anastomoses for Supercharge

10.3.3.1 Operative Technique

The superior mesentery 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 jejunum is divided approximately 15 cm distal to the ligament of Treitz. The jejunal mesentery is divided between the second and third and the third and fourth jejunal branches to lengthen the jejunal flap. If the jejunum does not reach the cervical esophagus preserving the marginal vessels, these vessels have to be cut. A jejunal flap without marginal arterial blood flow requires additional microvascular blood flow augmentation.

A 4-cm long section of the left 3rd costal cartilage is resected 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 [12, 13].

The anastomosis between the cervical esophagus and the pulled 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 thorax, the redundant portion of the jejunum is resected and anastomosed to straighten the conduit (Fig. 10.6). Roux-en-Y jejunal anastomosis is performed in the abdomen.

10.3.4 Reconstruction Route

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

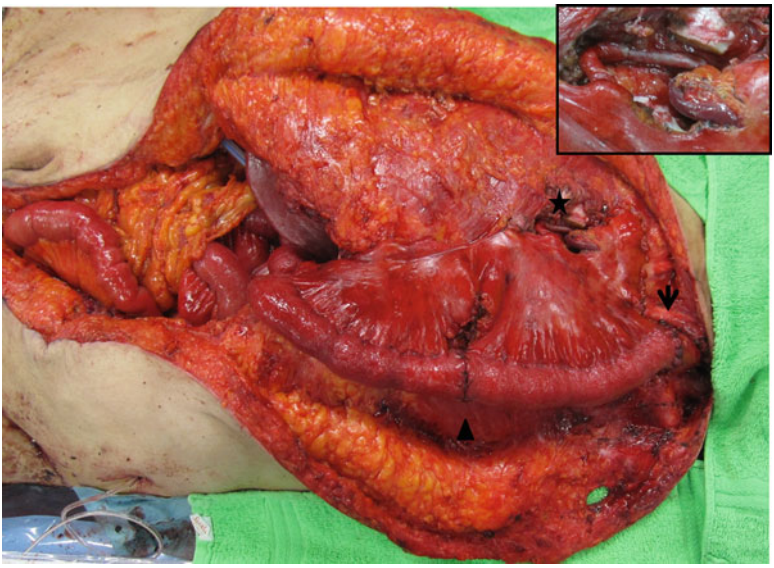

Fig. 10.6 *Large picture*: a vascular pedicled jejunal flap brought up through an opened subcutaneous route, with anastomosis between the cervical esophagus and the pulled up jejunum (*arrow*); anastomosis of the jejunum after resection of the redundant jejunum (*arrowhead*); and microvascular anastomosis (*star*). *Small picture*: anastomosis of the internal thoracic vessels below the right third costal cartilage to the second jejunal artery and vein

Table 10.3 Reconstruction routes used in Japan (2006)

Reconstruction route	Cases	%
None	37	1.5
Subcutaneous	314	12.5
Anterior mediastinal	833	33.0
Intrathoracic	365	14.5
Posterior mediastinal	913	36.2
Cervical	33	1.3
Others	22	0.9
Unknown	4	0.2
Total	2,521	
Missing	24	

is selected by the surgeon based on the patient's physical condition and other factors. In Japan, posterior mediastinal and anterior mediastinal routes are preferably selected at similar rates of 36.2 % and 33.0 %, respectively (Table 10.3) [2]. The advantages and disadvantages of the four routes are shown in Table 10.4.

Table 10.4 Advantages and disadvantages of reconstruction routes

Reconstruction route	Advantages	Disadvantages
Subcutaneous	1. Easy to anastomose	1. Longest distance among all reconstructive routes
	2. Easy and safe to manage anastomotic leakage	2. Higher risk of anastomotic leakage
	3. Easiest to treat secondary cancer of the reconstructive organ	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	1. The reconstructive organ presses against the heart
	2. Easy and safe to manage anastomotic leakage compared with a posterior or intrathoracic route	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 short distance	1. Serious postoperative morbidity in a case with anastomotic leakage (intrathoracic)
	2. Lower frequency of anastomotic leakage	2. Inability to divide high position of the cervical esophagus (intrathoracic)
	3. Less surgical stress	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

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Neoadjuvant and Adjuvant Therapy

11

Nobutoshi Ando

Abstract

Most clinicians today are conscious of the necessity of a multimodality approach 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. The most recent 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. Next, the clinical question of which is better, preoperative aggressive chemotherapy or preoperative chemoradiotherapy, still requires resolution. The JEOG has launched a three-arm randomized controlled trial 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 incorporating molecular-targeted therapeutics into multimodality treatment for esophageal cancer will be initiated in the near future.

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Keywords
Esophageal squamous cell carcinoma • Multimodality treatment • Neoadjuvant chemoradiotherapy • Neoadjuvant chemotherapy

11.1 Introduction

Surgery has improved 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, with many reports on this subject appearing during the past three decades.

The results of currently available 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 [3], for example, dissimilar distribution of 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 AC, to Asian practice.

The Japan Esophageal Oncology Group (JEOG), a subgroup of the Japan Clinical Oncology Group (JCOG) [4], 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 [5] and have been adopted as new evidence in the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus [6]. Therefore, this chapter begins with the results of these JCOG studies specifically in ESCC and then reviews and discusses results of studies on esophageal cancer outside of Japan.

11.2 Adjuvant and Neoadjuvant Therapy for ESCC in Japan

11.2.1 Historical Changes in Surgical Adjuvant Therapy of ESCC in Japan

11.2.1.1 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 [7]. 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 [8].

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 [9]. 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 [10] (Fig. 11.1). 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.

11.2.1.2 Postoperative Chemotherapy

Postoperative Radiotherapy vs. 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 $\times$ 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 was not yet popular. Although this study showed no significant difference in the 5-year overall survival rate between the two groups [11] (Fig. 11.2), 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

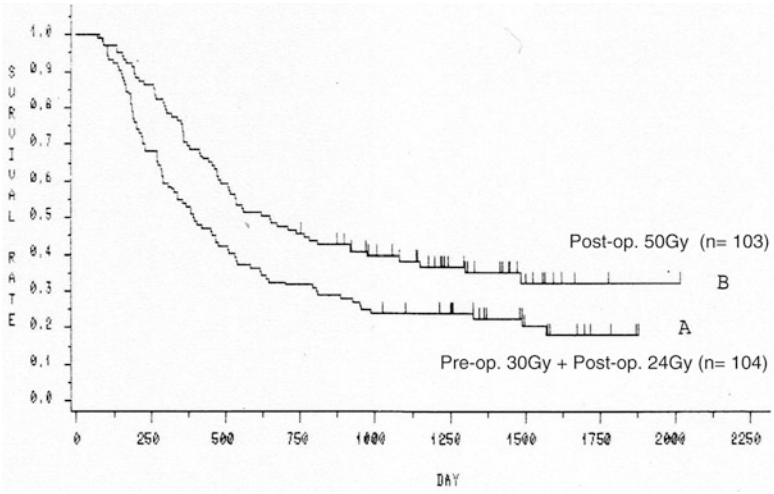

Fig. 11.1 Preoperative vs. postoperative radiotherapy. Survival rate in the postoperative radiotherapy-alone group (**B**) was significantly better than that in the pre- plus postoperative radiotherapy group (**A**)

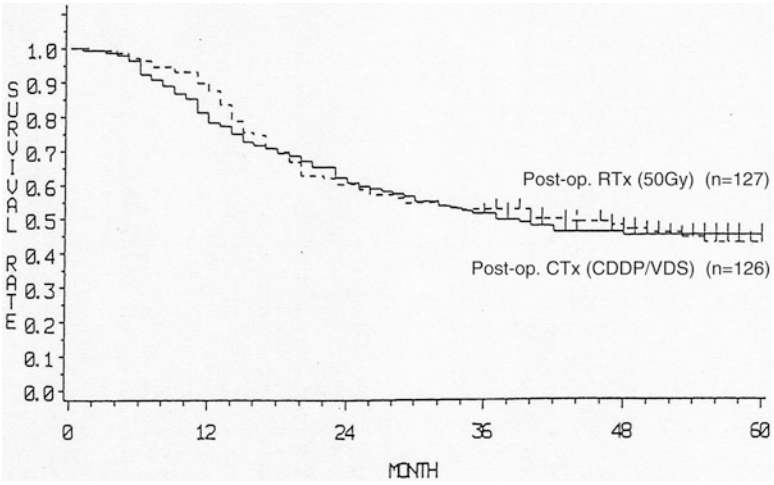

Fig. 11.2 Postoperative radiotherapy vs. postoperative chemotherapy. The 5-year survival rate was 44 % in the postoperative radiotherapy group and 42 % in the postoperative chemotherapy group, showing no significant difference between the two groups

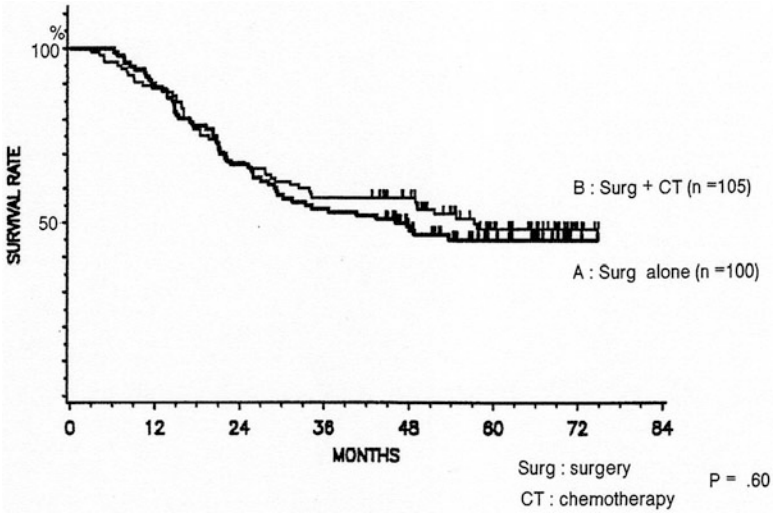

Fig. 11.3 Surgery alone vs. postoperative chemotherapy (cisplatin + vindesine). The 5-year survival rate was 45 % in the surgery-alone group and 48 % in the postoperative chemotherapy group, showing no significant difference between the two groups

result, postoperative chemotherapy gained common acceptance as adjuvant therapy for ESCC in Japan.

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 postoperative adjuvant chemotherapy conferred a survival benefit on patients undergoing radical esophageal cancer surgery. This study (JCOG8806, 1988–1991) compared surgery alone with surgery plus postoperative chemotherapy (70 mg/m^2 cisplatin plus 3 mg/m^2 vindesine $\times$ 2 courses). This study showed no significant difference in the 5-year overall survival (OS) rate between the two groups [12] (Fig. 11.3). Based on this result, surgery alone became the standard of care for ESCC at that time.

The efficacy of combination of cisplatin and 5-fluorouracil (5-FU) in patients with advanced esophageal cancer was superior to that of cisplatin and vindesine, based on our experience of two phase II studies. The fifth JEOG RCT was, therefore, initiated to determine whether postoperative adjuvant chemotherapy using cisplatin and 5-FU 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 postoperative chemotherapy (80 mg/m^2 cisplatin on day 1 plus

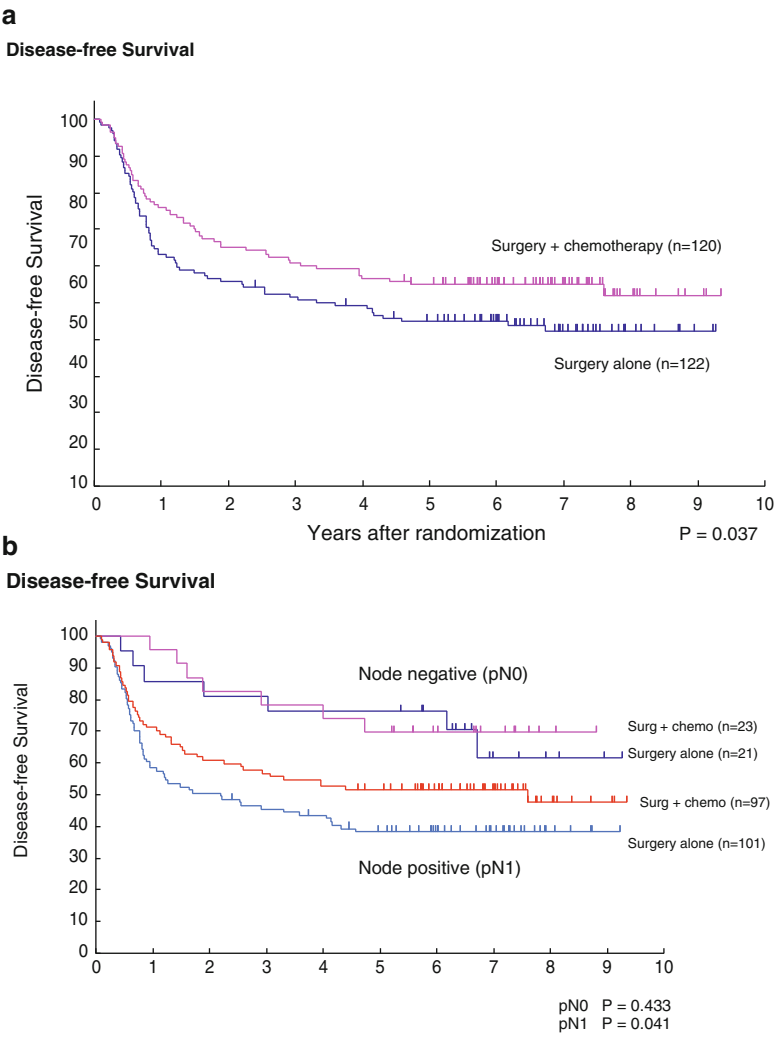

Fig. 11.4 (**a**) Surgery alone vs. postoperative chemotherapy (cisplatin + 5-FU). Disease-free survival curves of all registered patients. The 5-year disease-free survival was 45 % in patients with surgery alone and 55 % in patients with surgery plus chemotherapy ($p = 0.037$). (**b**) Surgery alone 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 ($p = 0.041$)

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 group (122 patients) and 55 % in the postoperative chemotherapy group (120 patients) ($p = 0.04$), while the 5-year overall survival rates (OS) were 52 and 61 %, respectively, ($p = 0.13$). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis [13] (Fig. 11.4a, b). On the basis of these data, postoperative

adjuvant chemotherapy using cisplatin and 5-FU came to be considered the standard of care for patients with ESCC in the early 2000s.

11.2.1.3 Preoperative Chemotherapy (Neoadjuvant Chemotherapy)

Even though postoperative adjuvant chemotherapy 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 [14]. 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; $p = 0.04$) [15] (Fig. 11.5a, b). Though renal dysfunction after surgery in the Pre group was slightly higher than that in the Post group, preoperative chemotherapy did not increase the risk of complications or hospital mortality after surgery [16]. There are three possible reasons for the better preoperative chemotherapy results. First, downstaging was achieved in some patients by preoperative chemotherapy. While the proportion of the patients with clinical stage II disease was similar in the two groups, the proportion with pathologic 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, preoperative chemotherapy with cisplatin plus 5-FU came to be regarded as the standard of care for patients with stage II/III SCC, and this treatment modality was described as the new standard of care in the latest revision of the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus. Thus, the optimal perioperative timing of surgical adjuvant therapy once again became before surgery.

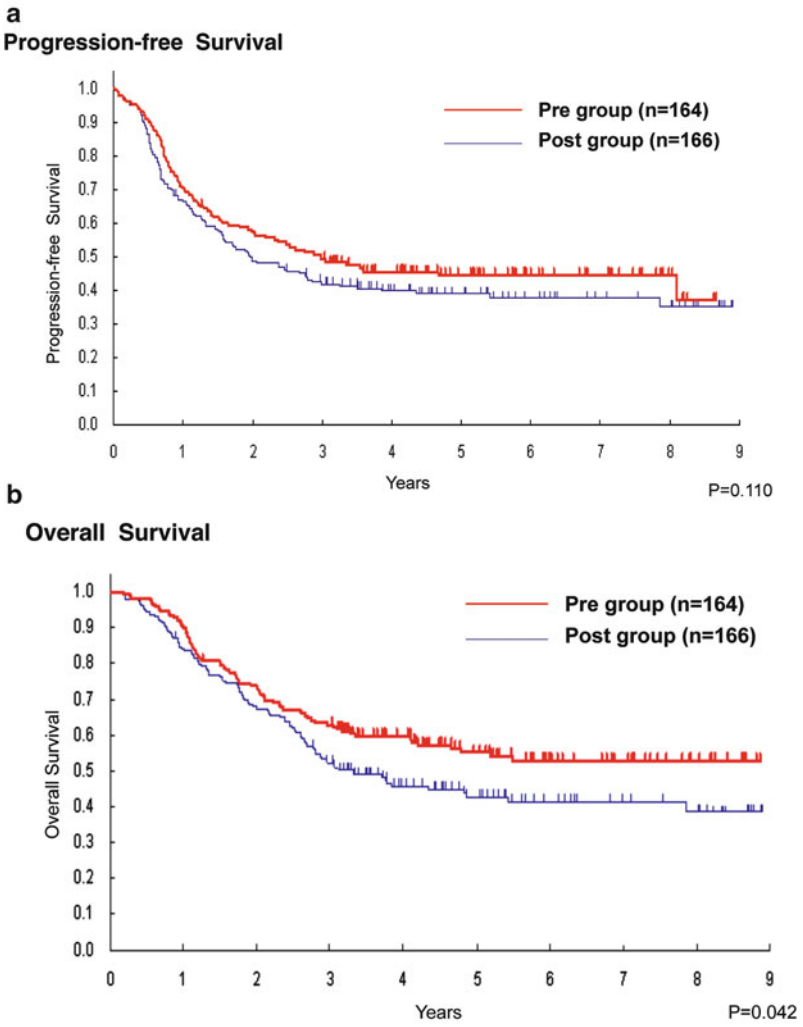

Fig. 11.5 (**a**) Preoperative vs. postoperative chemotherapy. Progression-free survival. Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy. No significant difference was observed in progression-free survival between the two groups. (**b**) Preoperative vs. postoperative chemotherapy. Overall survival. Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy. The 5-year OS was 43 % in the Post group and 55 % in the Pre group ($p = 0.04$)

11.2.2 Future Candidates for Surgical Adjuvant Therapy for ESCC in Japan

The results of subgroup analyses in JCOG9907 showed that preoperative chemotherapy 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 isolated loco-regional recurrence of 31 % among tumor recurrence cases in the postoperative chemotherapy group and of 25 % in the preoperative chemotherapy group may result from our meticulous surgical procedure. The results of our study suggest that preoperative chemotherapy using cisplatin and 5-FU is a good treatment strategy, if sufficient local tumor control is achieved by aggressive surgical procedures, while if local tumor control is insufficient, more aggressive adjuvant therapy such as preoperative chemoradiotherapy with an aim of local tumor control or more intensive preoperative chemotherapy with an aim of systemic disease control may be a preferable treatment modality. Docetaxel is one of the most promising drugs for esophageal cancer and the recently reported 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 [17]. The clinical question of which is better, preoperative chemotherapy or preoperative chemoradiotherapy, still needs to be clarified.

Based on these background features, the JEOG has launched a three-arm randomized controlled trial JCOG1109 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 [18]. 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 1,000 mg/m^2 5-FU, c.i. on days 1–4) repeated every 4 weeks (Fig. 11.6).

11.3 Adjuvant and Neoadjuvant Therapy for ESCC Out of Japan

Table 11.1 presents a comprehensive overview of the literature-based evidence on adjuvant and neoadjuvant therapies for ESCC out of Japan and from Japan.

11.3.1 Adjuvant Therapy Specified to ESCC

Very few studies are reported on literature-based reviews of adjuvant chemotherapy for ESCC. The French Association for Surgical Research performed a randomized controlled trial comparing surgery alone with postoperative adjuvant chemotherapy using cisplatin and 5-FU for patients with ESSC [19]. 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$^2 \times 5$ days) and 5-fluorouracil (1,000 mg/m$^2 \times 5$ days) within 1.5 months after surgery. Overall survival was similar in the

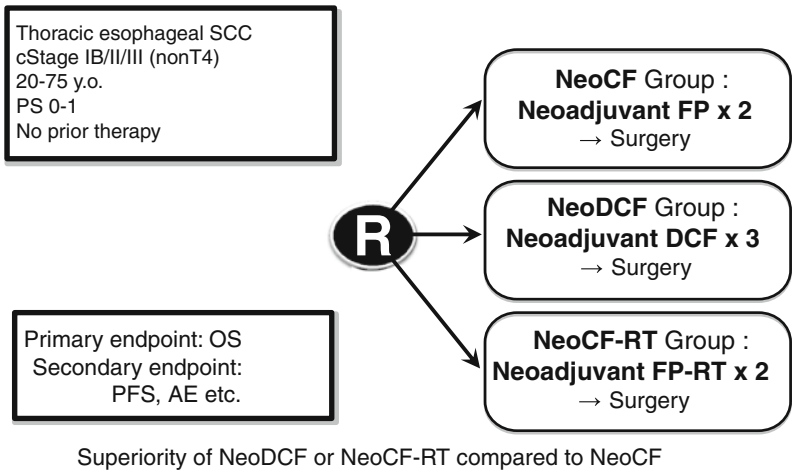

Fig. 11.6 Three-arm phase III trial comparing cisplatin plus 5-FU (CF) vs. docetaxel, cisplatin plus 5-FU (DCF) vs. radiation therapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT Study)

two groups, with almost identical medians of 13 months in the adjuvant chemotherapy group (52 patients) and 14 months in the surgery-alone group (68 patients). The survival curves with or without chemotherapy were similar in the stratum of curative resection, with an identical median of 20 months, and also in the palliative resection stratum, with identical medians of 9 months. On the basis of these data, it was concluded that cisplatin and 5-fluorouracil preceded by surgery are not useful for patients with ESCC.

Korean oncologists carried out a prospective study of postoperative chemotherapy (60 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–4 × 3 courses with a 3-week interval) 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 [20]. 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 postoperative chemotherapy 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.

11.3.2 Neoadjuvant Therapy Specified to ESCC

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

Table 11.1 Literature-based evidence on adjuvant and neoadjuvant therapies for ESCC

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients		Survival		*p* value
						+ CT, CRT	Surg. alone	+ CT, CRT	Surg. alone	
Adjuvant CT vs. surgery alone										
Pouliquen X [19] (FASR)	1987–1992	Excluding T4, N0	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 6–8 cycles		TTE	68	52	MST: 12 months	MST: 12 months	NS
Ando [13] (JCOG)	1992–1997	IIA, IIB, III, IVa	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	120	122	5-year DFS: 55 %	5-year DFS: 45 %	0.037
Lee [20]	1989–1995	IIb, III, IVa	Cisplatin (60 mg/m^2) 5-FU (1,000 mg/m^2) × 3 cycles		TTE	40	52 (historical control)	3-year DFS: 47.6 %	3-year DFS: 35.6 %	0.049
Neoadjuvant CT vs. surgery alone										
Law [21]	1989–1995	Excluding T4 and stage IV	Cisplatin (100 mg/m) 5-FU (500 mg/m^2) × 2cycles		TTE	74	73	MST: 16.8 months	MST: 13 months	0.17
Ancona [22]	1992–1997	IIA, IIB, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 2cycles		TTE	48	48	5-year OS: 34 %	5-year OS: 22 %	0.55

(continued)

Table 11.1 (continued)

First author	Accrual period	Stages enrolled	Chemotherapy	Radiotherapy	Surgery	No. of patients		Survival		*p* value
						+ CT, CRT	Surg. alone	+ CT, CRT	Surg. alone	
Kelsen [23, 24] (RTOG)[a]	1990–1995	I, II, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 3cycles		TTE and THE	213 (54 %; ADC)	227 (53 %; ADC)	MST: 14.9 months	MST: 16.1 months	0.53 SCC/ADC NC/NC
MRC [25, 26][a]	1992–1998	Resectable tumor	Cisplatin (80 mg/m^2) 5-FU (1,000 mg/m^2) × 2 cycles		TTE and THE	400 (66 %; ADC)	402 (67 %; ADC)	MST: 16.8 months	MST: 13.3 months	0.004 HR: SCC/ADC 0.78/0.78
Neoadjuvant CT vs. adjuvant CT										
Ando [15] (JCOG)	2000–2006	IIA, IIB, III	Cisplatin (80 mg/m^2) 5-FU (800 mg/m^2) × 2 cycles		TTE	Pre-op 164	Post-op 166	Pre-op 5-year OS: 55 %	Post-op 5-year OS: 43 %	0.04
Neoadjuvant CRT vs. surgery alone										
Nygaad [31]	1983–1988	I, II, III	Cisplatin (20 mg/m^2)×5 Bleomycin10mg/m^2 × 5 × 2 cycles	35 Gy	TTE	26	15	MST: not stated	MST: not stated	0.3
Le Prise [32]	1988–1991	I, II	Cisplatin (100 mg/m) 5-FU (600 mg/m^2) × 2cycles	20 Gy	Not stated	41	45	1-year OS: 46.6 %	1-year OS: 46.7 %	0.56

Apinop [33]	1986–1992	IIB, III	Cisplatin (100 mg/m) 5-FU (1,000 mg/m^2) × 2cycles	40 Gy	TTE	35	34	MST: 9.7 months	MST: 7.4 months	0.4
Bosset [34]	1986–1992	I, II	Cisplatin (80 mg/m^2) × 2 cycles	37 Gy	TTE	143	139	MST: 18.6 months	MST: 18.6 months	0.78
Lee [3]	1999–2002	IIA, IIB, III	Cisplatin (60 mg/m^2) 5-FU (1,000 mg/m^2) × 2 cycles	45.6 Gy	TTE	51	50	MST: 28.2 months	MST: 27.3 months	0.69 study stopped

[a]Pivotal study including ADC

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

11.3.2.1 Neoadjuvant Chemotherapy Specified to ESCC

In a study from Hong Kong, Law and colleagues compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 500 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses with a 3-week interval) plus surgery for resectable ESCC [21]. 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 preoperative chemotherapy group (74 patients) ($p = 0.17$). They concluded that survival provided by preoperative chemotherapy was not better than that in the surgery-alone group, but they suggested a trend for survival advantage for patients who underwent preoperative chemotherapy. They emphasized the necessity of reliable predictors, with chemo-responders being faring better than nonresponders.

In Italy, Ancona and colleagues compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–5 × 2 courses with a 3-week interval) plus surgery for stage II/III ESCC [22]. The surgical procedure adopted in this study was transthoracic esophagectomy plus two-field lymphadenectomy. The 5-year overall survival (primary endpoint) was 22 % in the surgery-alone group (48 patients) and 34 % in the preoperative chemotherapy group (48 patients) ($p = 0.55$). They concluded that improved long-term survival was obtained in patients with clinically resectable ESCC who underwent preoperative chemotherapy and obtained a pathologic complete response. They also emphasized the necessity of major efforts to identify patients who are likely to respond to preoperative chemotherapy.

Two pivotal RCTs in terms of neoadjuvant chemotherapy are known worldwide, the RTOG (Radiation Treatment Oncology Group) trial (USA intergroup study) and the MRC (Medical Research Council) trial (UK and the Netherlands), although both SCC and ADC histologic types were included. Kelsen and four study group investigators compared surgery alone with preoperative chemotherapy (100 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–5 × 3 courses with 4-week intervals) plus surgery followed by two cycles of postoperative chemotherapy in operable esophageal cancer cases [23]. 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 preoperative chemotherapy group (213 patients) ($p = 0.53$). There were no differences in survival between patients with SCC and those with ADC. They concluded that preoperative chemotherapy with a combination of cisplatin and 5-FU did not improve overall survival 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 preoperative chemotherapy vs. 1.3 years for those undergoing surgery alone [24]. They described similar outcomes as other researchers, with objective response to preoperative chemotherapy being associated with better survival.

Investigators in the Medical Research Council Oesophageal Cancer Working Party compared surgery alone with preoperative chemotherapy (80 mg/m^2 cisplatin on day 1 plus 1,000 mg/m^2 5-FU, c.i. over days 1–4 × 2 courses with a 3-week interval) plus surgery for resectable esophageal cancer [25]. Two thirds of patients (67 % in the surgery-alone group and 66 % in the preoperative chemotherapy 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 preoperative chemotherapy 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 preoperative chemotherapy improved survival in the treatment of patients with resectable esophageal cancer. In a long-term update result of this trial, they reported that the 5-year survival was 17.1 % in the surgery-alone group and 23.0 % in the preoperative chemotherapy group, with consistent treatment effect achieved in both histologic types [26]. They emphasized that preoperative chemotherapy is an essential standard of care for patients with resectable esophageal cancer.

Because these two pivotal studies demonstrated completely different conclusions, the benefit of preoperative chemotherapy, 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 USA where ADC constitutes the majority of patients with esophageal cancer [27, 28], compared with the UK where preoperative chemotherapy is the standard of care based on the result of the MRC study [29]. However, preoperative chemoradiotherapy is regarded as the standard of care in the French guidelines for treatment [30]. Even within Europe they have no consensus as to the optimal neoadjuvant approach.

11.3.2.2 Neoadjuvant Chemoradiotherapy Specified to ESCC

More than ten RCTs comparing neoadjuvant chemoradiation followed by surgery with surgery alone have been reported during the past two decades. Among them, four trials in the 1990s were limited to ESCC and showed no survival benefit ascribable to preoperative chemoradiotherapy [31–34]. In the 2000s, a Korean group compared surgery alone with preoperative chemoradiotherapy (60 mg/m^2 cisplatin on days 1 and 21 plus 1,000 mg/m^2 5-FU, c.i. over days 2–5 plus radiotherapy delivered twice a day up to a dose of 45.6 Gy in 38 fractions) followed by surgery for stage II/III ESCC. 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 preoperative chemoradiotherapy 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 dropout rate for esophagectomy and resultant excessive loco-regional failure rate in the preoperative chemoradiotherapy group. Therefore they

concluded that preoperative chemoradiotherapy provided no survival benefit for resectable ESCC [35].

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 preoperative chemoradiotherapy did not show a significant survival benefit in patients with resectable esophageal cancer [36]. 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. [37] included 12 RCTs comparing preoperative chemoradiotherapy vs. surgery alone, with a total of 1,854 patients. A significant survival benefit was evident for preoperative chemoradiotherapy 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 [38]. This analysis also compared preoperative chemotherapy vs. preoperative chemoradiotherapy and demonstrated a non-statistically significant survival benefit for preoperative chemoradiotherapy (HR 0.88, 0.76–1.01; $p = 0.07$).

11.4 Future Perspective of Adjuvant and Neoadjuvant Therapeutic Modality

The important role of individualized treatment of esophageal cancer has long been emphasized [39]. 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 [40]. In the field of multimodal treatments, identification of chemo- and radio-responders is an urgent subject based on the evidence that histologic complete response is predictive of long disease-free and overall survival outcomes as described in previous chapters. If it were possible to predict outcomes 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 [41]. 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 USA evaluating pretreatment expression of EGFR, increased levels of EGFR were associated with worse overall survival but not with histologic response [42]. Clinical trials incorporating molecular-targeted therapeutics into multimodality treatment for esophageal cancer are being initiated. EGFR inhibitors, e.g., cetuximab and gefitinib, are now incorporated into preoperative chemoradiotherapy [43], and inhibitors of vascular endothelial growth factor receptor (VEGF) are being applied to combination chemotherapy [44].

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Chemotherapy and Chemoradiotherapy

12

Ken Kato

Abstract

There are various roles of chemotherapy for the treatment of esophageal squamous cell carcinoma. The standard treatment for metastatic esophageal cancer has been 5-FU and cisplatin for decades. Recently, taxanes and targeted therapies are on the way of development. Definitive chemoradiotherapy is a standard treatment for patients with esophageal squamous cell carcinoma who refuse surgery or are ineligible for surgery. Since the 1990s, 5-fluorouracil and cisplatin (CF) plus radiation (RT) at a dose of 60 or 50.4 Gy has been the standard treatment. Replacement of cisplatin with oxaliplatin was evaluated in the PRODIGE 5 trial. From the results of the SCOPE1 and RTOG0436 trials, addition of cetuximab for definitive chemoradiotherapy seemed to have a negative effect on survival. Therefore, more effective drugs or strategies are needed.

Keywords

Chemoradiotherapy • Chemotherapy • Second-line • Targeted therapy

12.1 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 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

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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 and 4. There is no obvious evidence for the adequate follow-up duration, with evaluation frequencies of every 2 or 3 months for metastatic cancer and evaluations at every course for preoperative chemotherapy or CRT. Recently, it was reported that early changes in the standardized uptake value on fluorodeoxyglucose positron emission tomography might predict the response to chemotherapy [1].

12.2 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 12.1).

12.2.1 Bleomycin

Bleomycin has been used for ESCC since the 1970s and 1980s. Bleomycin as a single agent for ESCC has been reported to have a response rate of 15–20 % [2–4]. 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.

12.2.2 Antimetabolites

5-FU, in combination with other drugs and/or radiation therapy, is the most commonly used chemotherapeutic drug for ESCC. When 5-FU was used as a single agent, a 15 % response rate was observed in previously treated patients administered intermittent bolus of 5-FU in an Eastern Cooperative Oncology Group trial [5]. 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 25 % [6].

Table 12.1 Single-agent chemotherapy for advanced esophageal cancer

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	References
Bleomycin	SCC 29	First	NA	14	NA	NA	[2]
Bleomycin	SCC + AC 20	First	NA	20	NA	NA	[3]
Bleomycin	SCC 14	First	NA	0	NA	NA	[4]
5-FU	SCC 26	First	5-FU 500 mg/m^2 × 5 days/q5wks	15	3.4	NA	[5]
S-1	SCC 20	Second or third	S-1 40–60 mg × twice daily day 1–28/q6wks	25	3.3	10.8	[6]
Cisplatin	SCC 44	First	Cisplatin 100 mg/m^2/q3wks	19	4.1	6.4	[7]
Carboplatin	SCC 11	First	NA	9	NA	NA	[8]
Carboplatin	SCC 18	First	Carboplatin 130 mg/m^2/day days 1, 3, 5	0	NA	NA	[9]
Nedaplatin	SCC 29	First or second	Nedaplatin 100 mg/m^2/q4wks	51.7	NA	NA	[10]
Paclitaxel	SCC 18	First	Paclitaxel 250 mg/m^2/q3wks	SCC 28	3.9	13.2	[11]
	AC 32			AC 34			
Paclitaxel	SCC 20	First, second	Paclitaxel 80 mg/m^2 Day 1,8,15,22/q4wks	12	3.1	9.0	[12]
	AC 66						
Paclitaxel	SCC 52	Second	Paclitaxel 100 mg/m^2 Day 1,8,15,22,29,35/q7wks	44.2	3.9	10.4	[13]
Docetaxel	AC 41	First	Docetaxel 100 mg/m^2/q3wks	17	NA	NA	[14]
Docetaxel	AC 22	First or second	Docetaxel 75 mg/m^2/q3wks	First 18	NA	3.4	[15]
				Second 0			
Docetaxel	SCC 35	First or second	Docetaxel 70 mg/m^2/q3wks	First 36	4.7	8.1	[16]
	AC 3			Second 16			
Vindesine	SCC 26	First	Vindesine 3.0 mg/m^2 weekly	17.3	NA	NA	[17]
Vindesine	SCC 9	First or second	Vindesine 4.0 mg/m^2/q2wks	22.2	NA	NA	[18]

(continued)

Table 12.1 (continued)

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	References
Vindesine	SCC 52	First	Vindesine 3 mg/m^2 weekly	27	NA	NA	[19]
Vinorelbine	SCC 46	First or second	Vinorelbine 25 mg/m^2 weekly	First 20	NA	6.0	[20]
				Second 6			
Etoposide	SCC 26	First	Etoposide 200 mg/m^2 day 1, 2, 3/q3wks	19	4.0	NA	[21]
Irinotecan	SCC 10	First or second	Irinotecan 125 mg/m^2 Day 1, 8, 15, 22/q6wks	15	3.8	6.1	[22]
	AC 3						
Methotrexate	SCC 26	First	Methotrexate 40 mg/m^2 weekly	12	NA	3.2	[5]
Ifosfamide	SCC 32	First or second	Ifosfamide 1.5 g/m^2 × 5 days	7	NA	NA	[23]
Gemcitabine	SCC 6	First	Gemcitabine 1,250 mg/m^2 Day 1, 8, 15/q4wks	0	2	5	[24]
	AC 14						
Doxorubicin	SCC 20	First	Doxorubicin 60 mg/m^2/q3wks	5	NA	1.8	[5]

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

12.2.3 Platinum Agents

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, 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]. 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]. Oxaliplatin, a platinum derivative with less emetogenic, nephrotoxic, and ototoxic effects compared to CDDP, has been evaluated mainly in combination regimens for esophageal cancer. Nedaplatin, a second-generation platinum derivative, is ten 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, five partial responses (55.6 %) were observed in nine patients with ESCC who had received prior chemotherapy, including two partial responses in four patients previously treated with CDDP [10].

12.2.4 Taxanes

Taxanes have shown activity against not only adenocarcinoma but also squamous cell carcinoma of the esophagus. Paclitaxel promotes the stabilization of microtubules, and it is a cell cycle-specific agent affecting cells in the G2/M phase [28]. Paclitaxel as monotherapy has been evaluated as first-line chemotherapy at a dose of 250 mg/m^2 administered via 24-h intravenous infusion every 3 weeks. Of 52 patients who enrolled to this study, 18 patients had ESCC. Five (25 %) partial responses and five (28 %) minor responses were observed among the patients with squamous cell carcinoma. On the other hand, complete and partial responses were observed in 34 % of the adenocarcinoma group [11]. The efficacy of a weekly schedule of paclitaxel was also evaluated in 86 patients with esophageal cancer, including 32 cases of squamous cell carcinoma, at a dose of 80 mg/m^2 weekly over a 1-h infusion. Of 15 squamous cell cancer patients who did not receive prior chemotherapy, 2 (13 %) achieved a partial response, and there were no responses among patients who received prior chemotherapy [12]. A weekly schedule at a dose of 100 mg/m^2 administered via 1-h intravenous infusion on days 1, 8, 15, 22, 29, and 36 every 7 weeks was also evaluated for previously treated patients with esophageal cancer in a phase II trial. The overall response rate of patients with squamous cell cancer was 43.1 %, with four 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]. 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.

12.2.5 Vinca Alkaloids

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]. 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].

12.2.6 Topoisomerase Inhibitors

There have been reports on the use of topoisomerase inhibitors for the treatment of ESCC. 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]. Irinotecan, a type I topoisomerase inhibitor, has shown modest activity in ten previously treated patients with ESCC, with a 10 % response rate [22].

12.2.7 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 [5], ifosfamide [23], gemcitabine [24], mitomycin-C [26], and doxorubicin [5].

12.3 Combination Chemotherapy

Because of the limited activity of single-agent chemotherapy, most of the drugs described above have also been tested in combination regimens. Two randomized trials compared best supportive care to combination chemotherapy. 5-FU and CDDP combination therapy failed to show an advantage in overall survival (both 12 months) compared to best supportive care in patients with ESCC, with or without prior surgery [31]. 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 12.2).

12.3.1 Combination with Platinum Agents

CDDP-based combinations appear to be the most studied 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 showed poorer outcomes with combination therapy with 5-FU and CDDP than with CDDP monotherapy, CDDP (100 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2/day continuous infusion for 96–120 h) repeated every 3–4 weeks have been the standard regimen for the treatment of patients with ESCC for two decades. 5-FU and CDDP showed a higher response rate (35 vs. 19 %) and longer survival (28 and 33 weeks), but these findings were not statistically significant [7]. 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]. The combination of CDDP with vinorelbine was evaluated in 71 untreated patients with ESCC. A confirmed partial response was achieved in 33.8 % of patients, and the median survival time was 6.8 months [36]. CDDP (50 mg/m^2; days 1 and 8) followed by gemcitabine (800 mg/m^2; days 2, 9, and 16) repeated every 4 weeks was administered to 36 untreated patients with esophageal adenocarcinoma (67 %) and squamous cell carcinoma (33 %). The response rates for all patients and patients with squamous cell cancer were 41 and 42 %, respectively. The median survival time for all patients was 9.8 months [37]. A phase II study evaluated capecitabine, an oral fluoropyrimidine agent, in combination with CDDP for metastatic ESCC. Patients received 60 mg/m^2 CDDP intravenously on day 1 and 1,250 mg/m^2 capecitabine orally twice daily on days 1–14. Treatment cycles were repeated every 3 weeks. The overall response rate was 57.8 %, and the median survival time was 11.2 months. Common grade 3 or 4 non-hematological adverse events were anorexia (18/191, 9.4 %), fatigue (9/191, 4.7 %), constipation (6/191, 3.1 %), hand-foot syndrome (6/191, 3.1 %), and diarrhea (4/191, 2.1 %) [38].

Other platinum agents were also tested in clinical trials. Carboplatin failed to substitute for CDDP. A phase II trial of carboplatin and vinblastine reported no

Table 12.2 Combination chemotherapy for esophageal squamous cancer

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	References
5-FU + cisplatin	SCC 44	First	Cisplatin 100 mg/m^2 day 1 5-FU 1,000 mg/m^2/day day1–5/ q3wks	35	6.2	7.6	[7]
5-FU + cisplatin	SCC 72	First	Cisplatin 20 mg/m^2 day 1–5 5-FU 1,000 mg/m^2/day day1–5/ q4wks	NA	NA	12	[31]
5-FU + cisplatin	SCC 39	First	Cisplatin 70 mg/m^2 day 1 5-FU 700 mg/m^2/day day1–5/q3wks	35.9	Responders 3.5	Responders 9.5	[32]
5-FU + cisplatin	SCC 36	First	Cisplatin 20 mg/m^2 day 1–5 5-FU 800 mg/m^2/day day1–5/q4wks	33.3	NA	7.5	[33]
5-FU + cisplatin + leucovorin	SCC 5 AC 5	First	Cisplatin 50 mg/m^2 day 1 5-FU 2,000–2,600 mg/m^2/day day1,8 Leucovorin 500 mg/m^2/day day1,8/ q2wks	40	NA	10.6	[34]
5-FU + cisplatin	SCC 30	First	Cisplatin 100 mg/m^2 day 1 5-FU 1,000 mg/m^2/day day1–5/ q4wks	13	3.6	5.5	[35]
Vinorelbine + cisplatin	SCC 71	First	Vinorelbine 25 mg/m^2/day day1, 8 Cisplatin 80 mg/m^2/day day1/q3wks	33.8	3.6	6.8	[36]
Gemcitabine + cisplatin	SCC 12 AC 24	First	Gemcitabine 800 mg/m^2/day day2,9,16 Cisplatin 50 mg/m^2/day day1,8/ q4wks	SCC 42 AC 41	NA	9.8	[37]

Capecitabine + cisplatin	SCC 45	First	Capecitabine 1,250 mg/m^2 twice day1–14 Cisplatin 60 mg/m^2/day day1/q3wks	57.8	4.7	11.2	[38]
Vinblastine + carboplatin	SCC 16	First	Vinblastine 5 mg/m^2 day1, 15, 29 Carboplatin 450 mg/m^2 day1, 29, 57/q6wks	0	NA	NA	[39]
FOLFOX	SCC 56	First	Oxaliplatin 100 mg/m^2 day1 Leucovorin 400 mg/m^2 day1 5-FU 400 mg/m^2 day1 iv 5-FU 2,400 mg/m^2 day1–2 46 h div	23.2	4.4	7.7	[40]
XELOX	SCC 64	First or second	Capecitabine 1,000 mg/m^2 twice daily day1–14 Oxaliplatin 120 mg/m^2 day1/q3wks	43.8	4	10	[41]
5-FU + nedaplatin	SCC 42	First	5-FU 800 mg/m^2/day day1–5 Nedaplatin 90 mg/m^2 day1/q4wks	39.5	2.5	8.8	[42]
Paclitaxel + carboplatin	SCC 13 AC 22	First	Paclitaxel 200 mg/m^2/day day1 Carboplatin AUC5mg/h/ml/q3wks	SCC 31 AC 50	3.4	8.8	[43]
Paclitaxel + cisplatin	SCC 30 AC 33	First	Paclitaxel 100–200 mg/m^2/day day1 Cisplatin 60 mg/m^2 day1/q2wks	SCC 48 AC 59	NA	NA	[44]
Paclitaxel + cisplatin	SCC 14 AC 6		Paclitaxel 90 mg/m^2/day day1 Cisplatin 50 mg/m^2 day1/q2wks	SCC 50 AC 17	NA	7	[45]
Paclitaxel + cisplatin	SCC 39	First	Paclitaxel 175 mg/m^2/day day1 Cisplatin 75 mg/m^2 day1/q3wks	48.5	7	13	[46]
Nab-paclitaxel + cisplatin	SCC 33	First	Nab-paclitaxel 250 mg/m^2/day day1 Cisplatin 75 mg/m^2 day1/q3wks	60.6	6.2	15.5	[47]
Paclitaxel + nedaplatin	SCC 36 AC 3	First	Paclitaxel 175 mg/m^2/day day1 Nedaplatin 80 mg/m^2 day1/q3wks	SCC 44.5 AC 33.3	6.1	10.3	[48]

(continued)

Table 12.2 (continued)

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	References
Paclitaxel + nedaplatin	SCC 46	First	Paclitaxel 175 mg/m^2/day day1	41.7	6.1	11.5	[49]
	AC 2		Nedaplatin 80 mg/m^2 day1/q3wks				
Paclitaxel + nedaplatin	SCC 39	First	Paclitaxel 175 mg/m^2/day day1	46.1	7.1	12.4	[50]
			Nedaplatin 80 mg/m^2 day1/q3wks				
Capecitabine + paclitaxel	SCC 32	First or second	Capecitabine 900 mg/m^2 twice daily day1–14	56.3	5.2	11.7	[51]
			Paclitaxel 80 mg/m^2/day day1, 8/q3wks				
Docetaxel + cisplatin	SCC 38	Second	Docetaxel 70 mg/m^2/day day1	34.2	4.5	7.4	[52]
			Cisplatin 75 mg/m^2 day1/q3wks				
Docetaxel + nedaplatin	SCC 12	Second	Docetaxel 30–40 mg/m^2/day day1, 15	25	NA	NA	[53]
			Nedaplatin 70–90 mg/m^2 day1/q4wks				
Docetaxel + nedaplatin	SCC 48	Second	Docetaxel 30 mg/m^2/day day1	27.1	3.1	5.9	[54]
			Nedaplatin 50 mg/m^2 day1/q2wks				
Docetaxel + nedaplatin	SCC 12	Second	Docetaxel 50 mg/m^2/day day1, 8	0	2	7.8	[55]
			Nedaplatin 50 mg/m^2 day8/q3wks				
Docetaxel + nedaplatin	SCC 9	Second	Docetaxel 50–60 mg/m^2/day day1	22	2.1	9.5	[56]
			Nedaplatin 70 mg/m^2 day1/q4wks				
Paclitaxel + 5-FU + cisplatin	SCC 31	First	Paclitaxel 175 mg/m^2/day day1	SCC 50	5.7	10.8	[57]
	AC 30		5-FU 750-1,000 mg/m^2 daily	AC 46			
			Cisplatin 20 mg/m^2 weekly/q5wks				

Docetaxel + 5-FU + cisplatin	SCC 39	First	Docetaxel 50 mg/m^2/day day1 5-FU 700 mg/m^2/day day1–5 Cisplatin 70 mg/m^2 day1/q3wks	66.6	7	13	[58]
Docetaxel + 5-FU + cisplatin	SCC 18	First	Docetaxel 30–40 mg/m^2/day day1 5-FU 400 mg/m^2/day day1–5 Cisplatin 40 mg/m^2 day1/q2wks	88.9	NA	NA	[59]
Docetaxel + 5-FU + cisplatin	SCC 30	First	Docetaxel 60 mg/m^2/day day1 5-FU 800 mg/m^2/day day1–5 Cisplatin 60 mg/m^2 day1/q3–4wks	72	NA	8.9	[60]
Docetaxel + 5-FU + cisplatin	SCC 40	First	Docetaxel 70 mg/m^2/day day1 5-FU 700 mg/m^2/day day1–5 Cisplatin 70 mg/m^2 day1/q3wks	72.5	14	1-year 74.6	[61]
Docetaxel + 5-FU + cisplatin	SCC 29	First	Docetaxel 50 mg/m^2/day day1 5-FU 700 mg/m^2/day day1–5 Cisplatin 70 mg/m^2 day1/q3wks	34.5	2.8	10.4	[62]
Docetaxel + 5-FU + nedaplatin	SCC 43	First	Docetaxel 75 mg/m^2/day day1 5-FU 375 mg/m^2/day day1 5-FU 2,600 mg/m^2/day1–2 46 h div Nedaplatin 100 mg/m^2 day1/q3wks	62.8	6.6	10.2	[63]
Doxorubicin + 5-FU + cisplatin	SCC 41	First	Doxorubicin 30 mg/m^2/day day1 5-FU 700 mg/m^2/day day1–5 Cisplatin 14 mg/m^2/day day1–5/ q4wks	43.9	5	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

response in 16 patients [39]. 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 of 56 patients with squamous cell carcinoma [40]. Another trial with a high proportion of patients with adenocarcinoma (82 %) reported a higher response rate (40 %) and similar median survival time (7.1 months), but no response was observed among the patients with squamous cell carcinoma [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 1,000 mg/m^2 capecitabine administered orally twice daily on days 1–14 in a 21-day treatment cycle. Among 64 patients with ESCC, the overall response rate was 43.8 % and the median survival time was 10 months [41]. 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 [42].

12.3.2 Combination with Taxanes

As a single agent, paclitaxel is among the most active compounds against esophageal cancer. Combination regimens have also been evaluated in many trials. Paclitaxel (200 mg/m^2; day 1 every 3 weeks) and carboplatin (area under the curve 5; day 1 every 3 weeks) have been used for many cancers such as lung, ovary, and unknown primary cancers, and this combination has 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 [43]. A phase I trial, which included equal numbers of patients with squamous cell carcinoma and adenocarcinoma, evaluated the combination of paclitaxel and CDDP and showed a 52 % response rate [44]. Another phase II study with 30 % patients with adenocarcinoma reported that, among the patients with squamous cell carcinoma, the response rate was 50 %, and the median survival time of all eligible patients was 7.0 months [45]. A phase II trial of paclitaxel (175 mg/m^2; day 1 every 3 weeks) and CDDP (75 mg/m^2; day 1 every 3 weeks) in 45 patients with squamous cell cancer reported a response rate of 57.8 % and a median survival time of 13.0 months [46]. 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) was reported with the combination of nab-paclitaxel and CDDP [47]. 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 [48–50]. The combination of paclitaxel and capecitabine, an oral fluoropyrimidine, was evaluated in 32 patients with ESCC. Of the 12 patients who received this therapy as first-line treatment, 9 (75 %) achieved

an objective response, and the median survival time was 14.5 months. Of the 20 patients who received this therapy as second-line treatment, 9 (45 %) patients achieved an objective response, and the median survival time was 8.5 months [51]. Docetaxel combinations have been evaluated as second-line treatment after failure of 5-FU and platinum regimens. 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 and 7.4 months, respectively [52]. 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 and 7 months, respectively [53–56, 66].

12.3.3 Triplet Combinations

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 [57]. The combination of 5-FU, CDDP, and docetaxel, the most evaluated triplet combination for ESCC, has shown response rates of 44.3–88.9 % and median survival times of 8.9–14 months [58–62]. The most common serious adverse events with this regimen are neutropenia and febrile neutropenia. Nedaplatin may sometimes be used instead of 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]. 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].

12.4 Chemoradiotherapy

The role of 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 [67]. 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 12.3).

12.4.1 Definitive Chemoradiotherapy for Resectable Esophageal Cancer

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 [76]. 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 were observed, but curative resection was achieved in most of these cases via endoscopy or surgery. Based on these results, the randomized control trial JCOG0502 compared surgery to CRT in patients with 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 % [71]. In JCOG9906, chemotherapy consisted of two courses of protracted infusion of 5-FU (400 mg/m^2 daily) on days 1–5 and 8–12 and a 2-h infusion of CDDP (40 mg/m^2) on days 1 and 8; this was repeated every 5 weeks. Radiotherapy was delivered using megavoltage ($\geq$6 MV) X-rays; a total dose of 60 Gy was administered in 30 fractions with 40 Gy of elective lymph node irradiation. A 2-week break was given after 30-Gy irradiation, and radiotherapy was resumed on day 36, with the second course of chemotherapy. 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 underwent "salvage" surgery for residual or recurrent disease after completion of CRT [77–79]. 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 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) [69]. One of the reasons for this was the low tolerability of the high dose because of toxicities. A lower dose of radiotherapy might reduce the incidence of late, potentially fatal toxicities, operative complications, and mortality in the "salvage" setting. A phase II study of CRT for patients with stage II/III ESCC included two courses of 5-FU infusion (1,000 mg/m2) on days 1–4 and a 2-h infusion of CDDP (75 mg/m2) on day 1, with concurrent radiotherapy at a dose of 50.4 Gy. In this study, 3-dimensional treatment planning was required, and the clinical target volume included the

Table 12.3 Chemoradiotherapy for esophageal squamous cell cancer

Trial name	Stage histology	Regimen	Radiation dose (Gy)	CRR (%)	Survival (%)	References
RTOG84-01	Stage I/II/III	Radiation alone	64	NA	5-year (0)	[68]
	SCC, AC	5-FU 1,000 mg/m^2 day1–4, 29–32	50.4	NA	5-year (26)	
		Cisplatin 75 mg/m^2 day1, 29				
RTOG95-04	Stage I/II/III	5-FU1,000 mg/m^2 day1–4, 29–32	50.4	NA	2-year (31)	[69]
		Cisplatin 75 mg/m^2 day1, 29				
	SCC, AC	5-FU1,000 mg/m^2 day1–4, 29–32	64.8	NA	2-year (40)	
		Cisplatin 75 mg/m^2 day1, 29				
JCOG9708	Stage Ib	5-FU 700 mg/m^2 day1–4, 29–32	60	87.5	5-year (75.5)	[70]
	SCC	Cisplatin 70 mg/m^2 day1, 29				
JCOG9906	Stage II/III	5-FU 400 mg/m^2 day1–5, 8–12, 36–40, 43–47	60	62.2	3-year (44.7)	[71]
	SCC	Cisplatin 40 mg/m^2 day1, 8, 36, 43				
mRTOG	Stage II/III	5-FU 1000 mg/m^2 day1–4, 29–32	50.4	70.6	3-year (63.8)	[72]
	SCC	Cisplatin 75 mg/m^2 day1, 29				
PRODIGE5	Stage I–IVA	5-FU 1000 mg/m^2 day1–4, 29–32	50	41.3	3-year (26.9)	[73]
		Cisplatin 75 mg/m^2 day1, 29				
	SCC, AC	Oxaliplatin 85 mg/m^2 day1, 15, 29	50	41	3-year (19.9)	
		Leucovorin 200 mg/m^2 day1, 15, 29				
		Bolus 5-FU 400 mg/m^2 day1, 15, 29				
		Infusional 5-FU 1,600 mg/m^2 day1–3, 15–17, 29–31				
JCOG9516	Unresectable	5-FU 700 mg/m^2 day1–4, 29–32	60	15	2-year (31.5)	[74]
	Local	Cisplatin 70 mg/m^2 day1, 29				
	SCC					
KDOG0501	Unresectable	5-FU 400 mg/m^2 day1–5, 15–19, 29–33	61.2	42.1	1-year (63.2)	[75]
	Local	Cisplatin 40 mg/m^2 day1,15, 29				
	SCC	Docetaxel 20–40 mg/m^2 day 1, 15, 29				

SCC squamous cell carcinoma, *AC* adenocarcinoma, *NA* not available, *wks* weeks, *5-FU* 5-fluorouracil, *CRR* complete response rate

primary tumor with a 2-cm craniocaudal margin, metastatic lymph nodes, and regional lymph nodes [72]. Although the radiation dose was reduced, the incidence of grade 3–4 acute toxicities such as esophagitis and anorexia was approximately 30–40 %. This may be caused by the increased dosage of 5-FU. The complete response and 3-year survival rates were 70.6 and 63.8 %, respectively. After a 5-year follow-up period, late toxicities greater than grade 3 were pneumonitis (5.9 %) and pericarditis (2.9 %).

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 [80, 81]. Although there is no robust evidence, this regimen has shown non-inferior antitumor activity and reduced non-hematologic toxicity. The combination regimen of 5-FU and oxaliplatin (FOLFOX) was evaluated in PRODIGE5, a phase III study that included 85 % 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 [73]. Despite the increased incidence of peripheral neuropathy, the FOLFOX radiation regimen is considered a standard regimen for ESCC because of its convenience.

12.4.2 Chemoradiotherapy for Unresectable Locally Advanced Esophageal Cancer

For patients with local but unresectable lesions, CRT is the only treatment with a potentially curative intent. In a single institution phase II trial, 18 of 54 (33 %) patients with clinical T4 and/or M1 only in cervical lymph node who received CDDP/5-FU with concurrent 60-Gy irradiation achieved a complete response, and the median survival time and 3-year survival rate was 9 months and 23 %, respectively [82]. JCOG9516, a multicenter phase II trial, showed a 15 % complete response rate and a 2-year survival rate of 31.5 % [74]. The triplet combination of 5-FU, CDDP, and docetaxel with concurrent irradiation for T4 ESCC was evaluated in a phase I study [75]. Chemotherapy 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. Radiotherapy doses of 61.2 Gy/34 fractions were administered without a planned split. Dose-limiting toxicities included febrile neutropenia and grade 4 leukopenia lasting 3 days. Dose-limiting toxicities occurred in two of six patients at every level of 20, 30, 35, and 40 mg/m^2. The main grade 3–4 toxicities were neutropenia (68.4 %), febrile neutropenia (31.6 %), and esophagitis (31.6 %). 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 control of severe adverse events is critical for practical use.

12.5 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 12.4).

12.5.1 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 [88–90]. Overexpression of EGFR may correlate to invasion and poor prognosis [91]. Rare mutations in *EGFR* and *KRAS* have also been reported [92, 93]. 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, was administered to 36 platinum- and 5-FU-refractory patients with esophageal cancer, including 27 patients with squamous cell carcinoma and 9 patients with adenocarcinoma. One patient (2.8 %) achieved a partial response, and ten (27.8 %) had stable disease. Progression-free and overall survival times were 2 and 5.5 months, respectively. In a subgroup analysis, the outcome was significantly better in female patients, those with high EGFR expression, and those with squamous cell histology [83]. Erlotinib, another oral EGFR TKI, was also evaluated in 30 patients, including 13 patients with squamous cell carcinoma and 17 with adenocarcinoma, who had previously received a platinum-containing regimen. There was no response observed in patients with adenocarcinoma, whereas 15 and 13.3 % of patients with ESCC achieved a complete/partial response and stable disease, respectively. The median time to progression in patients with ESCC was 3.3 months and that in patients with adenocarcinoma was 1.6 months [84]. 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. A total of 450 patients (75 % with adenocarcinoma and 25 % with squamous carcinoma) were assigned to each arm, and the primary endpoint was overall survival. Progression-free survival times in the gefitinib arm and placebo arm were 1.60 and 1.17 months, respectively. Overall survival times in the gefitinib and placebo arm were 3.73 and 3.60 months, respectively (hazard ratio = 0.90; $p = 0.285$). Although the subgroup of patients with ESCC showed a trend of improved progression-free survival, this was not statistically significant [85]. The overall efficacy of EGFR

Table 12.4 Targeted agents for esophageal squamous cell cancer

Agent	Histology and number of pts	Treatment line	Regimen	Response (%)	PFS (m)	MST (m)	References
Gefitinib	SCC 27	Second	Gefitinib 500 mg/day	2.8	2	5.5	[83]
	AC 9						
Erlotinib	SCC 13	Second	Erlotinib 150 mg/day	SCC 15	SCC 3.3	SCC 8.2	[84]
	AC 17			AC 0	AC 1.6	AC 11.2	
Gefitinib	SCC 107	Second	Placebo	0.4	1.17	3.6	[85]
	AC 340		Gefitinib 500 mg/day	3.1	1.6	3.73	
Cetuximab	SCC 30	First	5-FU 1,000 mg/m^2 day1–5	30 %	3.9	5.5	[35]
			Cisplatin 100 mg/m^2 day1/q4wks				
	SCC 32		5-FU 1,000 mg/m^2 day1–5	34 %	5.9	9.5	
			Cisplatin 100 mg/m^2 day1/q4wks				
			Cetuximab 250 mg/m^2 weekly (after a loading dose of 400 mg/m^2)				
Cetuximab SCOPE1	SCC 96	cT1-4N0-1M0 First	Capecitabine 625 mg/m^2 twice daily day 1–84	NA	21.6	25.4	[86]
	AC 32		Cisplatin 60 mg/m^2 day1, 22, 43, 64				
			Radiation 50Gy				
	SCC 92		Capecitabine 625 mg/m^2 twice daily day 1–84	NA	15.9	22.1	
	AC 33		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)				

Cetuximab RTOG0436	SCC 59 AC 79	cT1N1M0 cT2-4NanyM0 cTanyNanyM1a First	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 %	[87]
	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

TKIs is modest and limited to ESCC. Detection of predictive biomarkers for EGFR TKI development is needed for further application.

Cetuximab, an anti-EGFR monoclonal chimeric antibody, was evaluated for the treatment of metastatic ESCC in combination with CDDP and 5-FU as first-line treatment. A randomized phase II trial compared daily 5-FU (1,000 mg/m^2, continuous infusion 5 days) and CDDP (100 mg/m^2 day 1) with or without 250 mg/m^2 cetuximab administered weekly (after a loading dose of 400 mg/m^2) for metastatic ESCC as first-line treatment [35]. Although a trend towards longer progression-free survival (5.9 vs. 3.9 months) and overall survival (9.5 vs. 5.5 months) was observed in the cetuximab arm, these differences were not statistically significant. Regarding toxicity, grade 3 or 4 toxicities of skin rash and diarrhea were seen more in the cetuximab arm. Cetuximab was also evaluated in combination with CRT. The SCOPE1 trial was a phase II/III trial that compared capecitabine and CDDP with radiotherapy, with or without cetuximab. In the SCOPE1 trial, the patient population included over 70 % of patients with ESCC. After the interim analysis, the independent data monitoring committee recommended stopping recruitment because the predetermined criteria for the futility of this trial were met. Overall survival was significantly worse in the CRT plus cetuximab group than in the CRT only group (hazard ratio = 1.53; $p = 0.035$) [86]. While two courses of neoadjuvant capecitabine and CDDP were administered before two cycles of CRT in this trial, significantly more patients did not receive radiotherapy in the cetuximab group (19 %) than in the non-cetuximab group (8 %). The dose intensity of capecitabine was also low in the cetuximab group. Moreover, non-hematological toxicities such as skin rash and cardiac disorders were seen more often in the cetuximab group. This indicated that lower treatment intensity because of toxicities in the cetuximab group resulted in worse survival. In the subgroup analysis, this tendency was the same in patients with adenocarcinoma and those with squamous cell carcinoma. In the RTOG0436 phase III trial, which included 38 % patients with ESCC, weekly concurrent paclitaxel (25 mg/m^2) and CDDP (50 mg/m^2) plus radiotherapy at a dose of 50.4 Gy with or without cetuximab was compared. After a median follow-up time of 15.4 months, the 1- and 2-year survival rates were 64 and 44 % in the cetuximab group and 65 and 42 % in the non-cetuximab group, respectively. These tendencies were the same among patients with adenocarcinoma and squamous cell carcinoma. The addition of cetuximab to concurrent CRT did not improve overall survival [87].

12.5.2 Other Potential Molecular Targets

Amplification and overexpression of HER2 has been reported to be a predictive and prognostic factor, and trastuzumab, an anti-HER2 monoclonal antibody, is commonly used to treat breast and gastric cancer. Approximately 15–20 % of ESCC exhibit overexpression of HER2 on immunohistochemistry, and approximately 1–20 % of cases exhibit gene amplification on fluorescent in situ

hybridization [88, 94–97]. Some studies have shown a worse survival when HER2 is overexpressed in ESCC [88, 94, 95]. The efficacy of trastuzumab for ESCC has only been evaluated as part of a combination phase I study. A phase I study of paclitaxel and trastuzumab with interleukin 12 in HER2-overexpressing carcinomas included 4 patients with ESCC, and 2 of these patients achieved a partial response.

Anti-angiogenesis are also a potential therapeutic target. Vascular endothelial growth factor-A expression is seen in 24–93 % of ESCC cases [98]. The overexpression of vascular endothelial growth factor isoforms has been shown to correlate significantly with poor prognosis in ESCC [99, 100].

Mammalian target of rapamycin (mTOR), which plays a role in RNA translation, proliferation, and angiogenesis, is recognized as a target in some cancers. Everolimus, an mTOR inhibitor, has shown activity against renal cell, breast, and neuroendocrine cancers. mTOR expression and activity has been reported to occur in 25–70 % of ESCC cases, and patients with active mTOR have a worse overall survival than those non-active mTOR [101–103]. As mTOR may be activated by the phosphatidylinositol 3-kinase (PIK3K) pathway, PI3K inhibition may be effective for the treatment of ESCC. Mutation of exon 9 and/or 20 in the *PIK3CA* gene occurs in 11.2–20 % of ESCC cases [104–106]. Some phase II trials of PIK3CA inhibitors for ESCC are currently ongoing.

There have been some reports that overexpression or amplification of *cyclin D1* is related to poor prognosis [107, 108]. Anti-program death (PD)-1 antibody is a new target drug in melanoma and other cancers [109]. PD-L1 and PD-L2, receptors of PD-1, are expressed in 43.9 % and 56.1 % of ESCC cases, as detected by real-time quantitative polymerase chain reaction, respectively [110]. Overexpression of PD-L1 and PD-L2 has been reported to be a poor prognostic marker. These molecules may be potential new targets in ESCC therapy, but there is limited evidence from clinical trials.

12.6 Future Directions

While many aspects regarding ESCC have been reported, there is limited clinical evidence for ESCC treatment options. One of the reasons for this is that the dominant histologic type in western countries is adenocarcinoma, so there have not been many clinical trials for squamous cell carcinoma. In Asian countries, squamous cell carcinoma is the major histologic type; therefore, ESCC-specific clinical evidence is needed. Biological analysis of ESCC based on robust preclinical data 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.

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Radiation Therapy

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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 result of randomized trial that compared chemoradiotherapy with radiotherapy alone. For locally advanced unresectable esophageal cancer, definitive chemoradiotherapy is the 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 standard treatment for locally advanced esophageal cancer in Western countries; however it is investigational in Japan. Combination chemotherapy of new agents and new radiotherapy technique 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

Brachytherapy • Chemoradiotherapy • Esophageal cancer • Radiotherapy • Treatment planning

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13.1 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]. And radiotherapy alone is a treatment option since many patients with esophageal cancer are elderly, of poor PS, or have metastases at the time of presentation. Radiotherapy is also useful to palliate dysphagia or pain.

13.2 Radiation Therapy Techniques

13.2.1 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- to 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.

13.2.2 Treatment Planning

13.2.2.1 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 esophageal cancer and intraepithelial spread of the advanced esophageal cancer. In the treatment of the superficial esophageal cancer, endoscopic clips are inserted in the esophageal wall near the proximal and distal end of the primary tumor as fiducial markers before

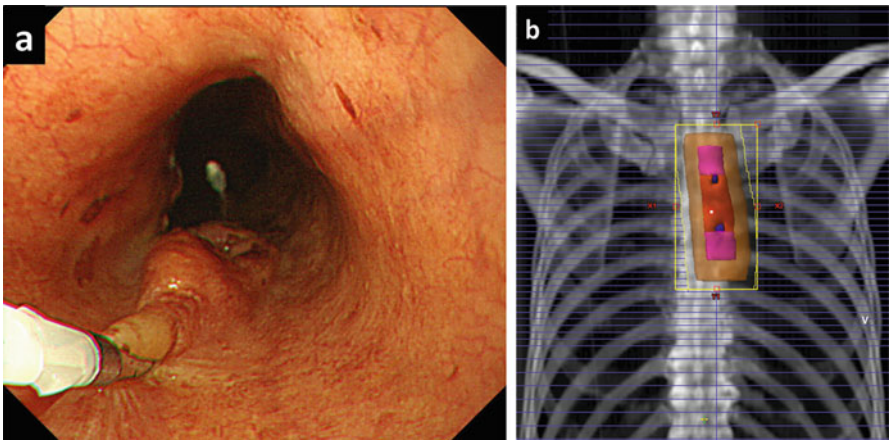


Fig. 13.1 Example 3D treatment planning for a cT1bN0 middle thoracic esophagus tumor. (**a**) Endoscopic insertion of clips in the esophageal wall near the proximal and distal end of the primary tumor. (**b**) Target volume of local radiotherapy planning. Clips (*blue*), GTV of primary tumor (*red*), CTV of primary tumor (*pink*), GTV plus 2 cm margin proximally and distally along the length of the esophagus, PTV (*orange*)

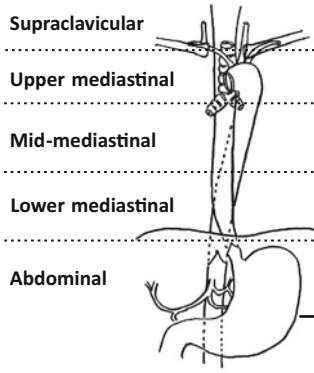
radiotherapy treatment planning (Fig. 13.1a). Diagnostic PET/CT has more recently been integrated into radiation treatment planning of esophageal cancer and definition of GTV [9]. The metastatic lymph nodes are defined as GTVn mainly based on the CT scan and palpitation. Similarly, EUS may detect enlarged 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 [10].

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 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 [11].

CTVn is defined as the GTVn with 0–0.5 cm margin in all directions.

The regional lymph nodes are defined as CTV subclinical (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 was 47–70 % and patterns of involved nodal spread were different from each primary site [12–14] (Fig. 13.2). Retrospective analysis from Japan showed that elective nodal irradiation was effective for regional lymph node



	Primary site		
	Upper thoracic tumor	Middle thoracic tumor	Lower thoracic tumor
Supraclavicular	16.7%	4.0%	1.5%
Upper mediastinal	38.9%	3.8%	3.0%
Mid-mediastinal	11.1%	32.9%	22.7%
Lower mediastinal	5.6%	7.1%	37.0%
Abdominal	5.6%	17.1%	33.2%

Fig. 13.2 Location and frequency of nodal involvement (%) by ESCC according to the primary site (From Huang et al. [14])

Table 13.1 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	a. Supraclavicular lymph nodes, superior mediastinal lymph nodes, subcarinal lymph nodes, middle mediastinal lymph nodes, lower mediastinal lymph nodes, perigastric lymph nodes
	b. Superior mediastinal lymph nodes, subcarinal 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

failure [15]. Guidelines 2012 for the treatment of esophageal cancer in Japan shows the inclusion of regional lymph nodes in CTVs for each primary site (Table 13.1) (Fig. 13.3a–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. 13.4a). 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

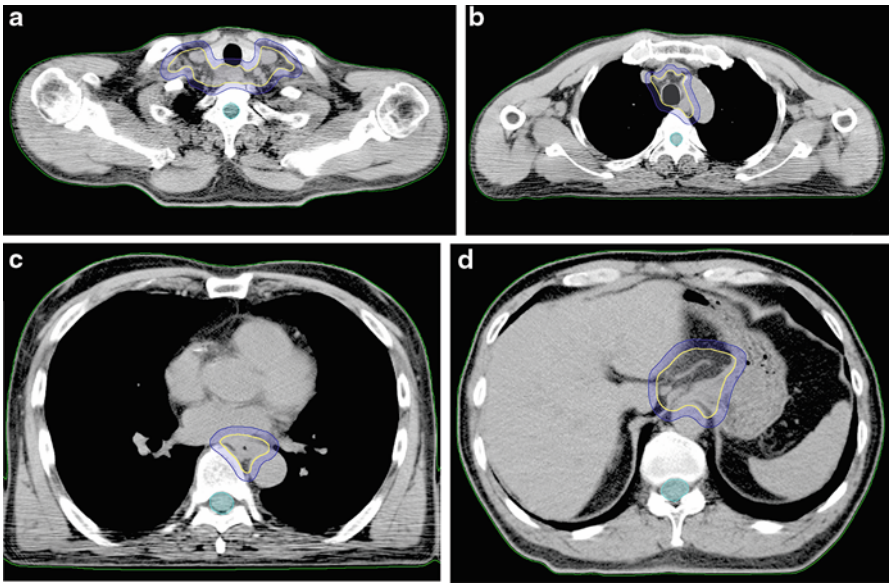


Fig. 13.3 Example of target volume delineation of CTV of elective nodal region. CTVs (*yellow*), PTVs (*blue*)

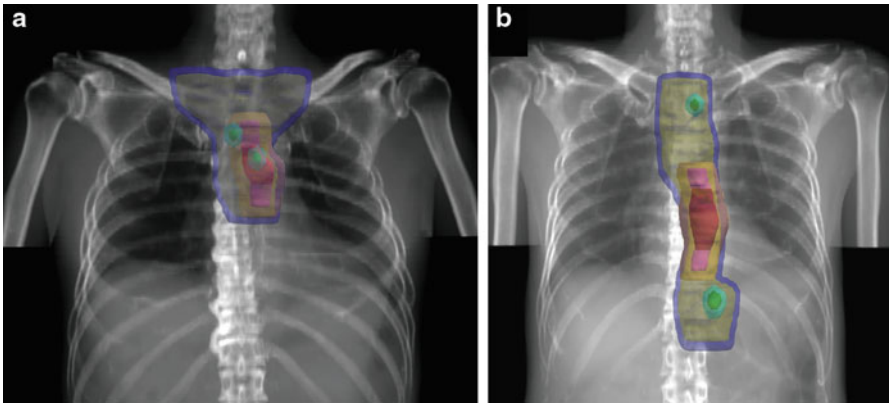


Fig. 13.4 Examples of target volume with elective nodal region in the 3D treatment planning for cT3N1 thoracic esophagus tumor. (**a**) For cancer of the upper thoracic esophagus. (**b**) For cancer of the middle or lower thoracic esophagus. GTV of primary tumor (*red*), GTV of metastatic lymph nodes (*green*), CTV of primary tumor (*pink*), CTV of elective nodal region (*yellow*), initial PTV (*blue*), boost PTV (*orange* and *cyan*)

middle or lower thoracic esophagus (Fig. 13.4b). Celiac axis lymph nodes are also included for carcinoma of the lower thoracic esophagus. There is no consensus about inclusion of regional lymph nodes in CTVs for carcinoma of the middle thoracic esophagus.

Planning Target Volume (PTV)

PTV is defined as 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 axial margin of ± 1.8 cm would provide tumor motion coverage for 95 % of the cases [16].

13.2.2.2 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. 13.1b). By contrast in the treatment including the elective nodal irradiation, anteroposterior (AP)/posteroanterior (PA) fields are 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 are usually used as off-cord boost fields. For upper, middle, and lower esophageal tumor, RAO and left posterior oblique (LPO) are 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. 13.5). However, it is necessary to minimize the volume of irradiated lung (beam weight; AP/PA $\gg$ obliques) as to the lung toxicity. In the case of existence of hot spot such as >110 % of the prescribed radiation dose, field-in-field technique is considered to improve the conformity of the dose distribution. More recently, intensity-modulated

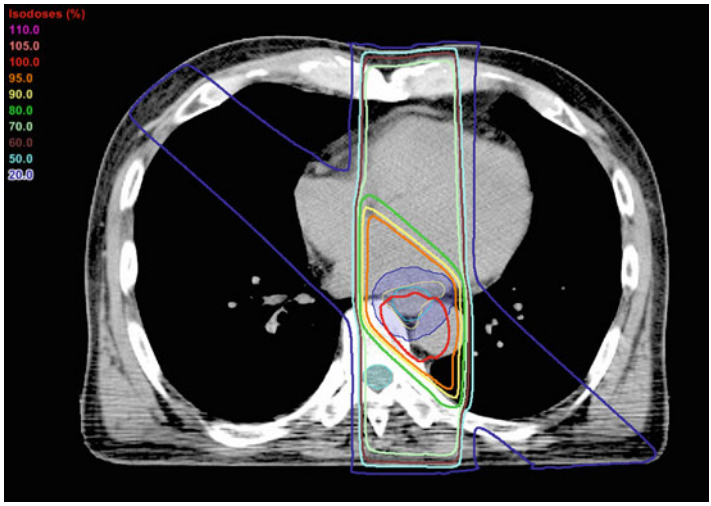


Fig. 13.5 Example of dose distribution treated with a four-field technique for a middle thoracic esophagus tumor (beam weights arrangement of 180 cGy per fraction; anterior 60 cGy, posterior 70 cGy, obliques 25 cGy). Daily heart dose: <80 % of the prescribed dose, Daily lung dose: <30 % of the prescribed dose

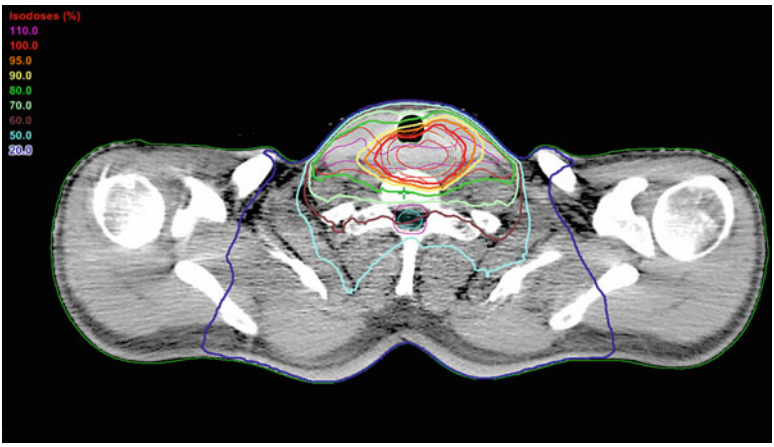


Fig. 13.6 Dose distribution of IMRT plan for a cervical esophagus tumor

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. 13.6). 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 [17]. A potential disadvantage of IMRT is the possibility of delivering 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.

13.2.2.3 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 [18], standard dose of radiotherapy for esophageal cancer is usually 50–50.4 Gy at 1.8–2 Gy per fraction in the definitive setting. In addition pattern care of study reported that median total dose of external radiotherapy was 60 Gy for definitive chemoradiotherapy patients in Japan [19]. In the neoadjuvant setting, 40–50.4 Gy at 1.8–2 Gy per fraction is the standard radiation dose.

13.2.2.4 Dose Constraints

In radiotherapy treatment planning of esophageal cancer, normal-tissue tolerance should always be considered. Accurate delineation of adjacent organs, including the lungs, spinal cord, heart, kidneys, and liver, is important. And it is necessary to

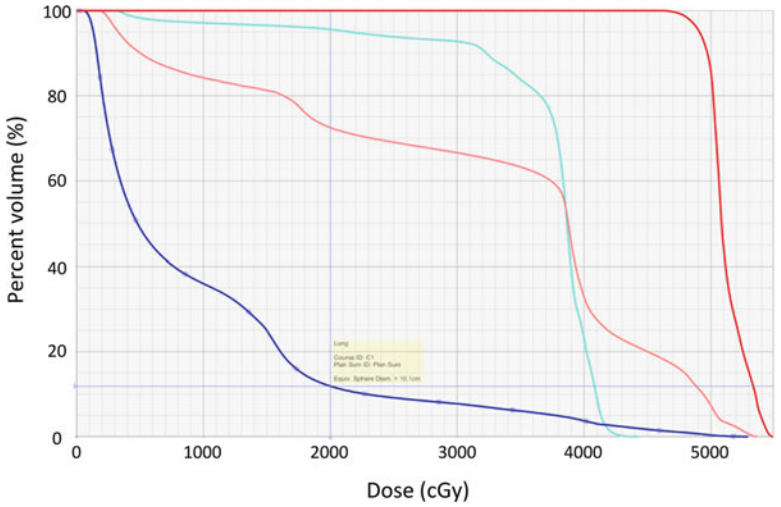


Fig. 13.7 DVH analysis of a four-field technique for a middle thoracic esophagus tumor (50.4 Gy in 28 fraction with elective nodal irradiation of 41.4 Gy). Boost PTV (*red*), total lung (*blue*), heart (*pink*), spinal cord (*cyan*)

evaluate the dose-volume histogram (DVH) analyses for each organ (Fig. 13.7). 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 [20–26]. In the treatment of esophageal cancer using 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]) [20]. Investigators from United States reported that the volume of the lung spared from doses of 5 Gy or higher (VS5) was the factor most strongly associated with postoperative pulmonary complications (pneumonia and ARDS) for esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery [21]. 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 (grade 2) was 30.5 % [22]. 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 % [23]. Wei and colleagues performed an analysis of pericardial effusion risk from DVH parameters among patients treated with definitive chemoradiotherapy [24]. Their data showed that the risk of pericardial effusion increased significantly with a mean pericardial dose of 26.1 Gy ($p = 0.002$) and pericardium V30 greater than 46 % ($p = 0.001$). 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 [25]. 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 [27].

13.2.2.5 Brachytherapy

Brachytherapy 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 %) [28–34]; on the other hand, it is used to relieve symptom such as dysphagia for palliative intent in the treatment of advanced esophageal cancer in Western countries [35, 36]. Brachytherapy involves intraluminal placement of a radioactive source into the esophagus with an intraorally or intranasally inserted applicator. Brachytherapy can be administered by two general methods: low-dose rate (LDR) brachytherapy and 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 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 2–4 fractions (3–4 Gy per fraction) HDR brachytherapy is generally used. It was reported that higher dose per fraction is 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 [32]. 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 [37]. Figure 13.8 illustrates the dose distribution and 3D view in the treatment planning of HDR brachytherapy.

13.3 Results

13.3.1 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 8,400 patients treated with radiation therapy alone, overall survival rates at 1, 2, and 5 years were 18, 8, and 6 %, respectively [38].

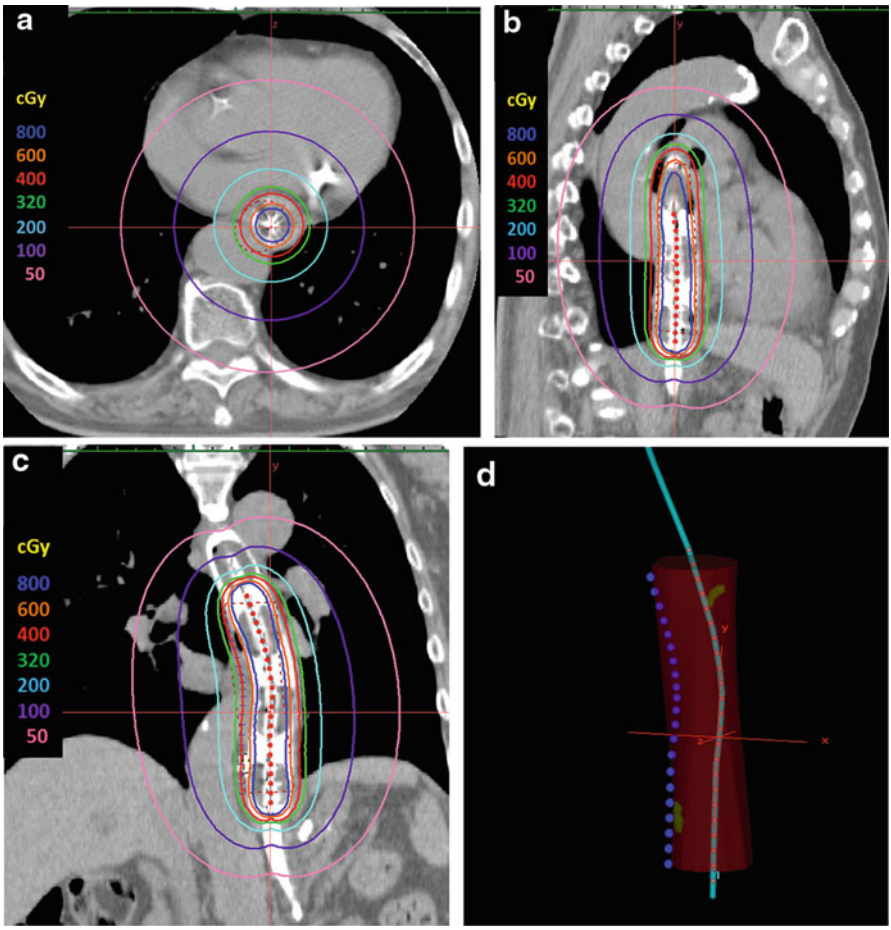


Fig. 13.8 Dose distribution of intraluminal brachytherapy for a cT1bN0 middle thoracic esophagus tumor. Prescription dose: 400 cGy at a depth of 5 mm of the esophageal submucosa as the reference dose point. (**a**) axial view. (**b**) sagittal view. (**c**) coronal view, (**d**) 3D-view. Clips (*green*), high-risk CTV (*red*): GTV plus 2 cm margin proximally and distally along the length of the esophagus, reference dose point (*blue*), catheter (*cyan*), dwell points (*red*)

Hancock and Glatstein reviewed 9,511 patients and found that only 5.8 % were alive at 5 years [39]. Okawa and colleagues reported 5-year survival rates by stage [40]. For patients with stage I disease, the 5-year survival rate was 20 %; stage II, 10 %; stage III, 3 %; and stage IV, 0 %. Overall, the 5-year survival rate 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-T3N0M0 squamous cell carcinoma of the thoracic esophagus, median survival time and 3-year overall survival rate were 30 months and 39 %, respectively [41].

13.3.2 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) [1]. 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 [2, 3].

13.3.2.1 Chemoradiotherapy for Unresectable Locally Advanced Esophageal Cancer

For the locally advanced unresectable esophageal cancer, chemoradiotherapy is the standard treatment with potentially curative intent. Results of clinical trials of definitive chemoradiotherapy for esophageal cancer including T4 are shown in Table 13.2 [6–8, 18, 42–49]. 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 [18]. This study was closed after 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. Eleven treatment-related deaths occurred in the high-dose arm compared with 2 in the standard-dose arm, with 7 of the 11 high-dose arm deaths occurring in patients who received 50.4 Gy or less. 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 were 9 months and 23 %, respectively [6]. 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 [7, 8, 42–44]. Other combination regimen using new drugs (paclitaxel, docetaxel, oxaliplatin, S-1, and cetuximab) with concurrent radiotherapy have been evaluated [46–49].

Table 13.2 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 [18] (USA)	T1-4N0-1 (T4: 8 %)	86	109	FP + 50.4 Gy	NR	2 years: 31 %
			109	FP + 64.8 Gy	NR	2 years: 40 %
Ohtsu [6] (Japan)	T4/M1Lym (T4: 67 %)	100	54	FP + 60 Gy	33 %	1 years: 41 %
						3 years: 23 %
JCOG9516 [7] (Japan)	T4/M1lym (T4: 100 %)	100	60	FP + 60 Gy	15 %	2 years: 31.5 %
Nishimura [8] (Japan)	T4/M1Lym (T4: 100 %)	100	28	FP + 60 Gy	32 %	StageIII;2 years: 27 %
						StageIV;1 years: 23 %
JCOG0303 [42] (Japan)	T4/M1lym (T4: 75 %)	100	71	FP + 60 Gy	0 %[a]	3 years: 30 %
			71	Low dose FP + 60 Gy	1.4 %[a]	3 years: 26 %
KROSG0101/ JROSG021 [43, 44] (Japan)	Stage II–IVA (T4: 44 %)	100	46	FP + 60 Gy	NR	2 years: 46 %, 5 years: 35 %
			45	Low dose FP + 60 Gy	NR	2 years: 44 %, 5 years: 22 %
Shahl [45] (Germany)	T3-4N0-1 (T4: 17 %)	100	86	FLEP → EP + 60 Gy	NR	3 years: 55 %
			86	FLEP → EP + 40 Gy + S	NR	3 years: 58 %
PRODIGE5/ ACCORD17 [46] (France)	Stage I–IVA (T4: NR)	86	133	FP + 50 Gy	43 %	3 years: 26.9 %
			134	FOLFOX + 50 Gy	43 %	3 years: 19.9 %
SCOPE1 [47] (UK)	Stage I–III (T4: NR)	73	129	CP + 50 Gy		2 years: 56.0 %
			129	CP + Cetuximab + 50 Gy		2 years: 41.3 %

(continued)

Table 13.2 (continued)

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate	Survival
RTOG0436 [48] (USA)	T1N1/T2-4N0-1/M1a (T3-4: 80 %)	38	169	Cisplatin + PTX + 50.4 Gy	59 %	1 year: 65 %, 2 years: 42 %
			159	Cisplatin + PTX + Cetuximab + 50.4 Gy	56 %	1 year: 64 %, 2 years: 44 %
KDOG0501 [49] (Japan)	T4/M1lym (T4: 69 %)	100	42	DCF + 50.4 Gy, 61.2 Gy	52.4 %	1 years: 66 %, 3 years: 44 %

[a]Only one point assessment of tumor 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

13.3.2.2 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 are shown in Table 13.3 [1–5, 50–52]. 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. 13.1b). CR rate was 87.5 % and 5-year overall survival rate was 75.5 % [4]. 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 [53–56]. 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 %) related to late toxicities. Moreover, 8–15 % of high mortality rate was seen in patients who underwent salvage surgery to residual or recurrent disease after chemoradiotherapy [55, 56]. 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

Table 13.3 Results of clinical trials of definitive CRT for resectable (non T_4) ESCC

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate	Survival
RTOG8501 [1–3] (USA)	T1-3N0-1	88	62	64 Gy	NR	2 years: 10 %, 5 years: 0 %
			134	FP + 50 Gy	NR	2 years: 38 %, 5 years: 26 %
Bedenne [50] (France)	T3N0-1	89	130	FP + 30 Gy or 46 Gy → FP + 15Gy or 20 Gy	NR	3 years: 34 %
			129	FP + 30 Gy or 46 Gy → S	NR	3 years: 29 %
JCOG9708 [4] (Japan)	Stage I	100	72	FP + 60 Gy	87.5 %	4 years: 80.5 %
JCOG9906 [5] (Japan)	Stage II/III	100	76	FP + 60 Gy	62.2 %	3 years: 44.7 %
						5 years: 36.8 %
Kato [51] (Japan)	Stage II/III	98	51	FP + 50.4 Gy	70.6 %	1 years: 88.2 %
						3 years: 63.8 %
JCOG0604 [52] (Japan)	Stage II/III	100	44	S-1 + cisplatin + 50.4 Gy	59.5 %	3 years: 61.9 %

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, *NR* not reported

conducted [51]. 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 %.

13.3.2.3 Neoadjuvant Chemoradiotherapy

Several randomized trials comparing surgery alone to neoadjuvant chemoradiotherapy were conducted and the results were conflicting (Table 13.4) [57–63]. Bosset and colleagues reported a European Organisation for Research and Treatment of 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 [57]. 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

Table 13.4 Results of clinical trials of neoadjuvant chemoradiotherapy for ESCC

Author	Pathology: rate of SCC (%)	Regimen	No. of patients	MST (months)	*p*-Value
Bosset [57] (France)	100	S	139	18.6	N.S.
		FP + 37 Gy + S	143	18.6	
Urba [58] (USA)	25	S	50	17.6	N.S.
		FP + VBL + 40 Gy + S	50	16.9	
Lee [59] (Korea)	100	S	51	27.3	N.S.
		FP + 45.6 Gy (HF) + S	50	28.2	
Burmeister [60] (Trans-Tasman)	38	S	128	19.3	N.S.
		FP + 35 Gy + S	128	22.2	
Tepper [61] (USA)	25	S	30	21.6	0.002
		FP + 50.4 Gy + S	26	54	
Van Hagen [62] (Netherland)	23 %	S	188	24	0.003
		PTX + CBDCA + 41.4 Gy + S	178	49.4	
Kato [63] (Japan)	100	FP + 41.4 Gy + S	31	2 years OAS: 77.4 %	–

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, *N.S.* not significant

(23 % SCC) showed a significant survival benefit in patients receiving preoperative chemoradiotherapy [62]. 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 %). 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 [64]. Recently, Sjoquist and colleagues performed an updated meta-analysis of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy [65]. 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. Currently, neoadjuvant chemoradiotherapy is accepted as the standard treatment for locally advanced esophageal cancer in Western countries. However, there is no randomized trial performed that compared neoadjuvant chemoradiotherapy to surgery alone or neoadjuvant chemotherapy in Japan. Therefore neoadjuvant chemoradiotherapy for resectable esophageal cancer is investigational in Japan. Kato and colleagues conducted a first multi-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 [63]. 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 [66].

13.3.3 Palliative Therapy

Palliative radiotherapy is also useful in the purpose of relieving symptoms such as dysphagia and pain and improvement 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 [67]. 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 [68]. 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 have improved dysphagia score [69]. Intraluminal brachytherapy has also been used for palliation of dysphagia [37]. 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 [35].

13.4 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 symptom. 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 [70]. 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 two 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 [71]. 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 [72]. In JCOG9906, late toxicities included grade 3/4 esophagitis (13 %), pericardial (16 %) and pleural (9 %) effusions, and radiation pneumonitis (4 %), which caused four deaths [5]. This high incidence 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, the use of multiple field technique with reducing both the radiation dose and the volume of the heart within the radiation field is recommended while keeping the volume of irradiated lung at a lower percentage [51]. About half of the esophageal strictures are due to local persistence 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 [33, 73–75]. 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 [76].

13.4.1 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 which utilize heavy-ion beams have 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 rates were T1, 83 %; T2–4, 29 %; and survival T1, 55 % and T2–4,13 % [77]. Mizumoto and colleagues reported the results of locally advanced ESCC using protons with or without photons to a total dose of 70–98 GyE [78]. 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) [79]. 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. Akutsu and colleagues conducted a phase I/II clinical trial of preoperative carbon-ion radiotherapy for ESCC [80]. Thirty-one patients were enrolled and the radiation dose was escalated from 28.8 GyE up to 36.8GyE. 12 (38.7 %) patients achieved a pathological CR. The overall 3- and 5-year survival rates in stage I cases were 81 and 61 %, were 85 and 77 % for stage II, and 43 and 29 % for 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. These new approaches remain investigational, so further research is necessary to evaluate the efficacy and safety of new technique and technology in a prospective trial.

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Endoscopic Treatment: EMR and ESD

14

Osamu Goto and Naohisa Yahagi

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 lesion by using a snare. On the contrary, endoscopic submucosal dissection (ESD) can resect superficial lesion in an en bloc fashion irrespective of the size or presence of submucosal fibrosis, which has made the indication of endoscopic resection expanded. Although skillful hands in endoscopy and sufficient knowledge of possible complications are required, ESD is a promising technique as a minimally invasive treatment.

Keywords

Complication • Endoscopic mucosal resection • Endoscopic submucosal dissection • Indication

14.1 Introduction

Due to improvement of therapeutic endoscopy in recent years such as ESD, size limitation of a resectable extent by endoscopy has disappeared. In a so-called "pre-ESD" era, 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 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,

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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 the size or presence of submucosal fibrosis [3, 4]. Indication and methods of each technique as well as management of complications are summarized in this chapter.

14.2 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 10–15 % 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 inhere 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 feeding disorder 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 dilatation must be a burden for the patients [12, 13]. In this reason, general indication of endoscopic resection for lateral tumor extension is up to three-fourths of 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.

14.3 Endoscopic Mucosal Resection (EMR)

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. 14.1).

EMR with a ligation device (EMR-L) requires an O-ring used for esophageal varices ligation (Fig. 14.1a) [14]. In this technique, after suctioning a lesion and 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

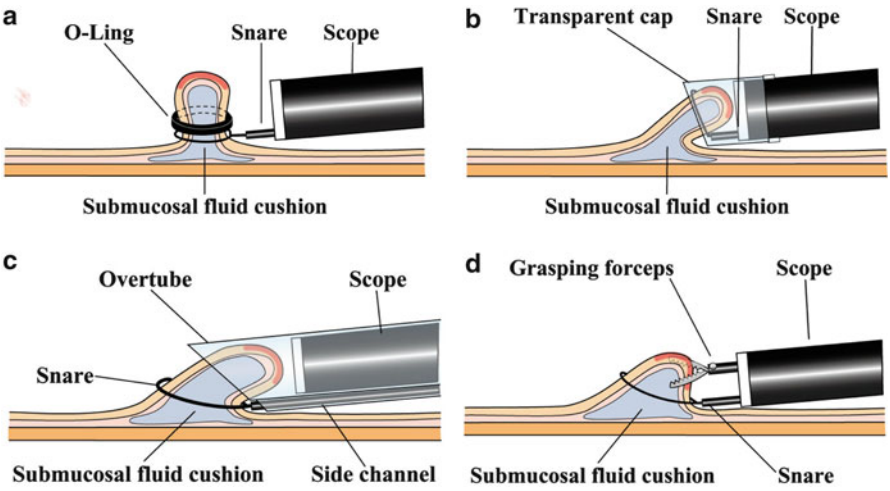

Fig. 14.1 Variety of EMRs. (**a**) EMR with a ligation device (EMR-L). A lesion is suctioned and ligated with O-ring before resection. (**b**) EMR using a cap-fitted endoscope (EMR-C). A lesion is suctioned into a transparent hood and resected by the snare. (**c**) Endoscopic esophageal mucosal resection (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

before the resection is conventionally desirable in order to avoid unexpected perforation, endoscopic resection using a ligation device without submucosal injection seems to be also acceptable 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. 14.1b) [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 this technique, setting the snare along the rim of the hood can be difficult and time-consuming that it sometimes makes the operator irritated.

In endoscopic esophageal mucosal resection (EEMR)-tube method, a long transparent silicon overtube is used (Fig. 14.1c) [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. 14.1d) [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 ligated tissue.

Because the size of snares is limited in these EMRs, 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 1 cm or less without fibrosis would be suitable for a candidate of EMR in usual clinical settings.

14.4 Endoscopic Submucosal Dissection (ESD)

This epoch-making technique is composed of four steps: marking around the lesion after chromoendoscopy, submucosal injection, circumferential mucosal incision, and dissection of the submucosal connective tissue (Fig. 14.2). 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 the size or presence of submucosal fibrosis.

14.4.1 Details of Practical Skill

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 (Fig. 14.3) [21–23].

Successful resection requires accurate endoscopic diagnosis of a tumor extent. Although promising image-enhancement endoscopy techniques have been introduced, conventional chromoendoscopy using iodine spraying would be still most useful in determining the extent of the lesion. 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 a 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 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 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 and subsequently continue the procedure from the oral side.

It is very important to conduct submucosal dissection under direct vision using transparent hood. 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.

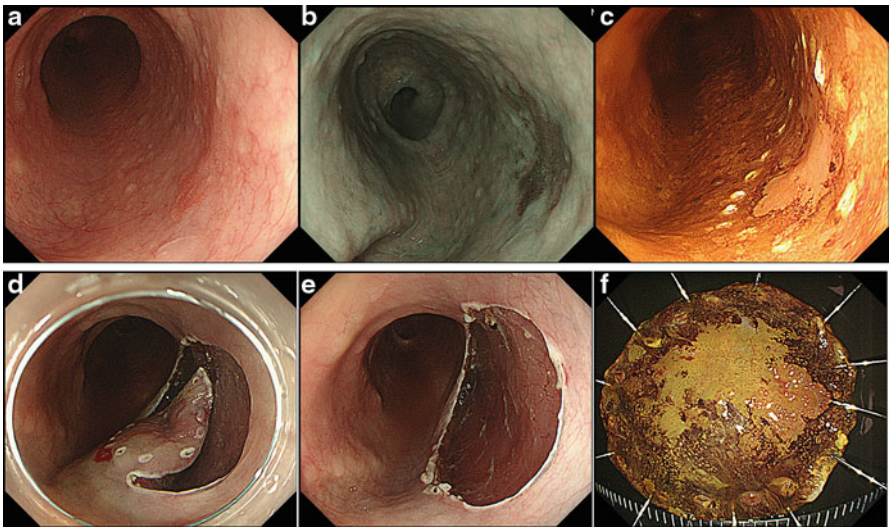

Fig. 14.2 Representative case of esophageal endoscopic submucosal dissection (ESD). (**a**) Conventional image of squamous cell carcinoma. A reddish lesion is located on the posterior wall of the esophagus. (**b**) Image-enhanced endoscopy by narrow-band imaging. The lesion can be visualized more clearly compared to the conventional image. (**c**) Markings are placed around the lesion with an appropriate margin. (**d**) Circumferential mucosal incision except for one lateral side and subsequent submucosal dissection is made from the upper side. (**e**) Resection wound after ESD. (**f**) An en bloc resection enables precise histological assessment (esophageal squamous cell carcinoma, pT1-a, 18 × 14 mm, ly0, v0, pHM0, pVM0)

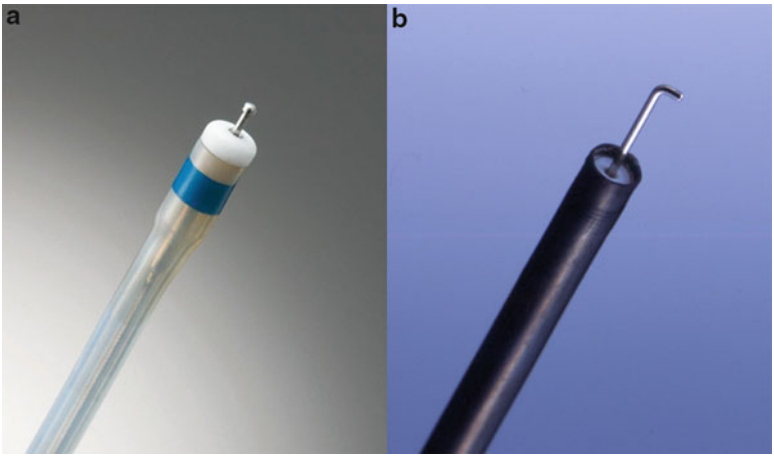

Fig. 14.3 Pointed tip-type knives. (**a**) Dual knife. (**b**) Hook knife

14.5 Management of Complications

14.5.1 Bleeding

Unlike gastric ESD, the rate of postoperative bleeding is relatively low (0–2 %) [24–27]. In case of minor bleeding, hemostasis using the retracted tip of the knife is firstly 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 carefully inspected to check for visible vessels. And every thick exposed blood vessels should be coagulated, avoiding excessive thermal damage.

14.5.2 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 [28, 29]. Indeed, pneumomediastinum was found by CT scan in a half of treated cases after esophageal ESD, although fortunately these were almost subclinical [28]. 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, patients are treated at rest with fasting and administered 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 spread of mediastinitis.

14.5.3 Postoperative Stricture

The risk of postoperative stricture is particularly higher in esophageal ESD (Fig. 14.4) [10, 11]. Because the probability of stricture mostly depends on the resected size, a lesion over three-fourths of circumference is relative indication of ESD as previously mentioned. Several attempts to prevent postoperative stricture have been tried [30–35], e.g., prophylactic endoscopic balloon dilatation and local injection or oral administration of steroids. Preclinical trials are also considered such as adipose tissue stem cell transplantation [36] or cultured cell sheet transplantation [37, 38], but there has been no decisive method so far. Further investigation would be necessary to overcome this problem.

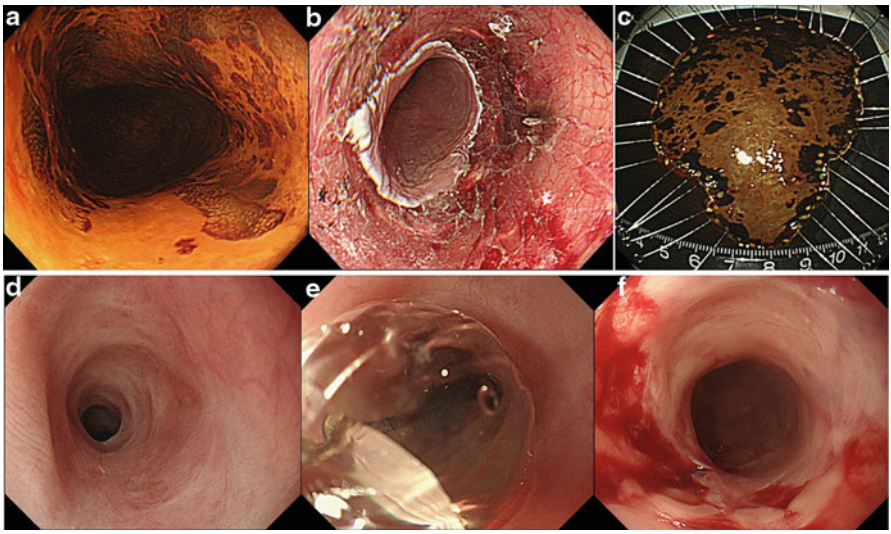

Fig. 14.4 Severe stricture after extensive resection. (**a**) Superficial cancer extending a whole of circumference. (**b**) Since resection wound become circumferential, steroid solution is injected into remaining submucosa in order to prevent severe stricture. (**c**) Complete margin-free resection is achieved. (**d**) Even after steroid injection, severe stricture has been developed a few weeks later. (**e**) Endoscopic dilatation using CRE™ balloon dilator (Boston Scientific Co., USA). (**f**) Mucosal and submucosal fissure after balloon dilatation. It took nearly half a year to have stable condition with multiple balloon dilatation

14.6 Outcomes of ESD for Esophageal Squamous Cell Carcinoma

14.6.1 Short-Term Outcomes

Favorable treatment results have been reported from high-volume centers particularly in Japan [24–27]. In short-term outcomes such 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 complication occurred, it can be managed conservatively and thus hardly becomes a life-threatening condition. Technically, ESD for the lesion near the esophagogastric junction is sometimes difficult and time-consuming because intraoperative bleeding from abundant collecting vessels occurs frequently. The lesion located in the cervical esophagus, one of natural constrictions, is also difficult to resect because of poor visualization. Furthermore, the risk of aspiration pneumonia becomes extremely high by reflux of fluids (e.g., blood, rinsing water, submucosal fluid). In that case, ESD with general anesthesia should be considered.

Considering the severity of potential postoperative complications, ESD is an apparently less invasive resection method 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].

14.6.2 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 is recommended after curative resection in cases of an 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 chemoradiotherapy) are refused after complete local resection.

14.7 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 [39]. 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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Hong Kong Experience

15

Daniel Tong and Simon Law

Abstract

Esophageal cancer is the sixth most common cancer 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 rising prevalence of obesity, gastroesophageal 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 squamous cell in origin. There has not been a convincing rise in 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. In 2010, the Cancer Registry of Hong Kong identified esophageal cancer as the eighth leading cause of cancer deaths. The overall 5-year survival rate was disappointing at around 20 % only [2].

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.

Keywords

Diagnosis • Esophageal carcinoma • Treatment experience

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15.1 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 including those who are chronic heavy smokers and alcohol drinkers, and those who have had a history of head and neck cancers, are offered screening endoscopy. Chromoendoscopy with Lugol's iodine solution is used, and in recent years, optical chromoendoscopy such as narrow band imaging with magnifying endoscopy is routinely utilized. Any suspicious lesion is biopsied and appropriate treatment is offered according to the pathology.

15.2 Investigations

Once the diagnosis is confirmed, investigations are directed to (1) accurate staging of disease and (2) assessment of comorbidities 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. 15.1.

15.2.1 Staging

Clinical staging follows the American Joint Committee on Cancer Staging (AJCC) TNM classification system. In addition to endoscopy, bronchoscopy [3], percutaneous ultrasound of the neck with or without fine-needle aspiration (FNA) cytology, endoscopic ultrasonography (EUS) with or without fine-needle aspiration [4], and 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 [5, 6]. This is especially important for tumors that are located in the middle and upper portions of the esophagus. In one study, the reported complication 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 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. In the previous AJCC staging classification (sixth edition), cervical nodal metastases were regarded as stage IV disease and our policies have been to treat these patients

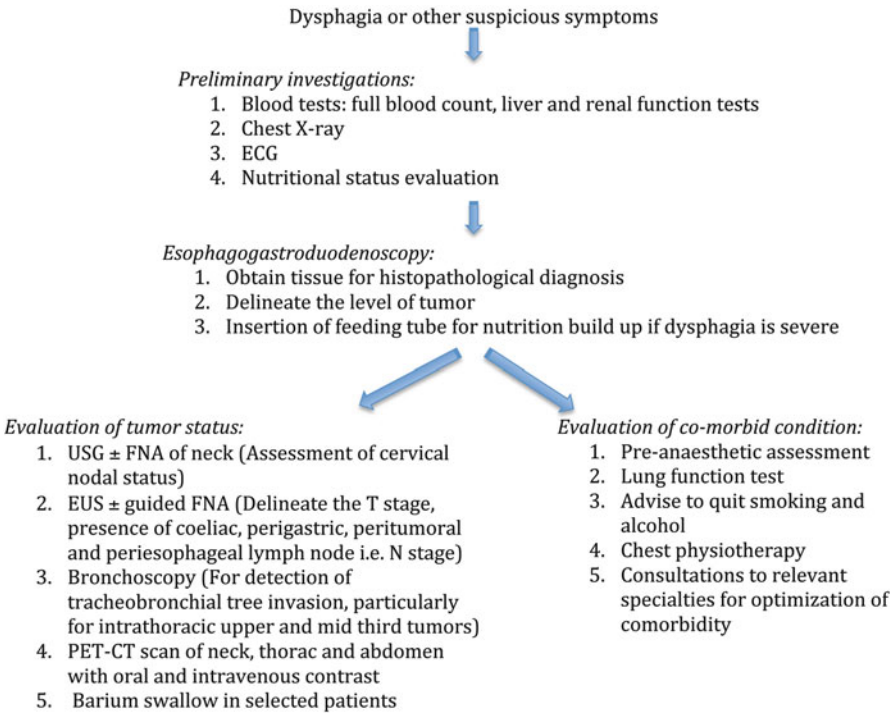

Fig. 15.1 Investigation algorithm for esophageal cancer at The University of Hong Kong

with up-front chemoradiation followed by surgery if restaging demonstrates resectable disease.

We have been using endoscopic ultrasound (EUS) for staging since the 1990s [4]. 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 % [4], results that are comparable with other reports [7–9]. 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 untraversable tumor stenosis for conventional dedicated radial endo-ultrasonic endoscope.

In Hong Kong, FDG-PET has gained popularity for esophageal cancer staging since about a decade ago; it is used in most of our patients although one limitation is that the scan is still not publicly funded so only contrast CT scans are used in the minority of patients who cannot afford a PET scan. In an early study, we found that the maximum standard uptake value (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 an R0 resection [10].

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, T2, T3, and T4 tumors were 2.74, 4.55, 12.9, and 13.6, respectively. In addition, an SUVmax of 7.3 or more predicted a T3/T4 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 [10]. For patients who undergo neoadjuvant therapy, our policy is to repeat a PET/CT at 4 weeks post therapy before a decision is made for surgical resection.

15.2.2 Patient Pretreatment Evaluation

Accurate tumor staging provides guidance for stage-directed therapy. In addition to tumor stage, careful pretreatment risk evaluation is important in selecting the appropriate patients for surgery.

The physiological reserve is an important factor to evaluate for potential surgical candidate. 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 [11, 12]. 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 [13]. 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 cardio-revascularization 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 chosen in these patients with the purposes of: first with an aim to downstage tumor, second it would allow the patient to recover from the cardiac procedure, and third, antiplatelet agents, especially clopidogrel, can then be stopped during the time of esophagectomy.

15.3 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 radiotherapy also increases the choice of therapeutic options. The management algorithm for ESCC at The University of Hong Kong is shown in Fig. 15.2.

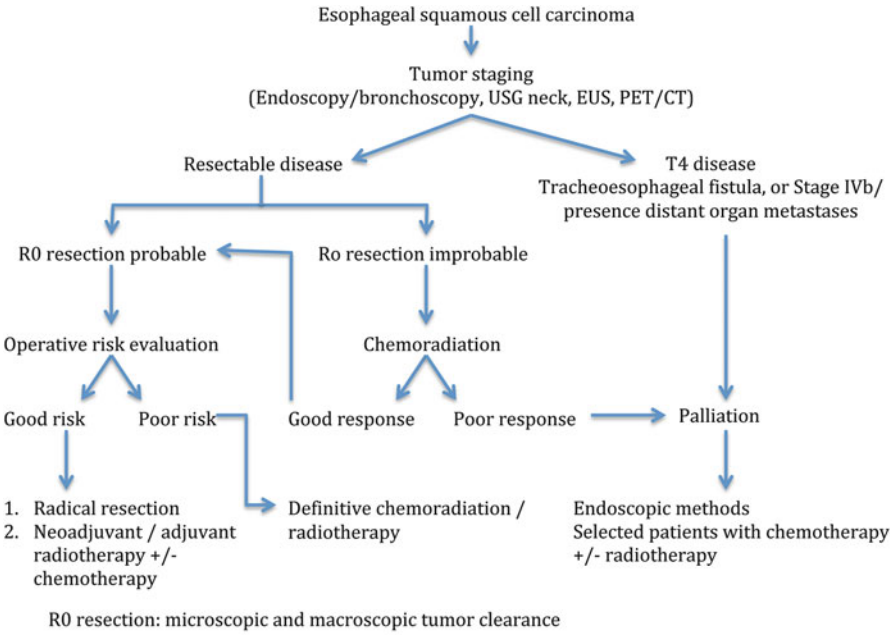

Fig. 15.2 Management protocol for esophageal squamous cell carcinoma at The University of Hong Kong

15.3.1 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 [14]. Distinguishing m1 and m2 disease (where chance of nodal metastases is negligible) from deeper lesions is often difficult, and we practice endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) to assess the lesions in detail pathologically before deciding on further treatments.

15.3.2 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 [15–17], while in the United States chemoradiation is more widely practiced [18–20]. With the recent published CROSS trial from Europe, neoadjuvant chemoradiation is another standard strategy in many centers [21].

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 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 [22]. 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 [23, 24].

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 [25]. Attempts were made to identify predictors of response, but none was found to be reliable [26].

Disappointed by the results of chemotherapy, chemoradiotherapy as neoadjuvant therapy has been investigated since the mid-1990s. For most patients, the most common chemotherapy regime is 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 % can be achieved. Pathological complete response rate in the primary tumor is 45 % and overall pathological complete response rate (including negative nodes) is 31 % [27]. In a study of 175 patients received neoadjuvant chemoradiation followed by surgery were studied; the 5-year survival rates of patients of complete pathological response versus those with residual tumor cells were 61.6 versus 30.4 %, $p < 0.01$ (Fig. 15.3). The survival of these patients based on gender and respective pathological stages was shown in Figs. 15.4 and 15.5, respectively. In more recent years, the technique of radiotherapy has improved; often intensity-modulated radiation therapy (IMRT) and 3-D conformal radiotherapy planning are used replacing the traditional AP opposing radiation field. The choice of chemotherapeutic agents has widened to include taxanes as well, in response to the positive results of the CROSS trial.

A historical cohort comparison on patients treated with surgery alone and surgery with neoadjuvant chemoradiation demonstrated that the latter had better overall survival [28]. The adoption of chemoradiation allowed better patient selection for curative surgery and resulted in more R0 resection by tumor downstaging [28].

The timing of surgery after chemoradiation is an important consideration; when the interval between chemoradiation and surgery is short, the resultant pathological

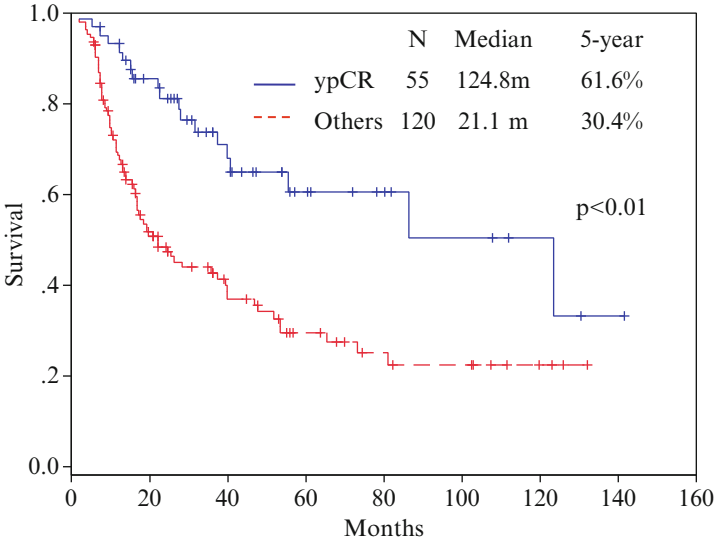

Fig. 15.3 Survival curve for patients with pathological complete response (ypCR) and other stages of disease

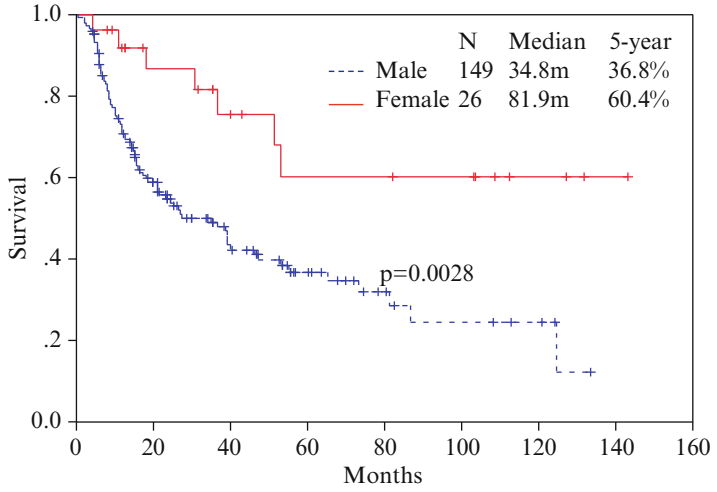

Fig. 15.4 Survival curve with gender as a predictor of survival

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 ensue which may make dissection more difficult. More importantly, tumor may have more chance to regrow and metastasize. Our policy is to

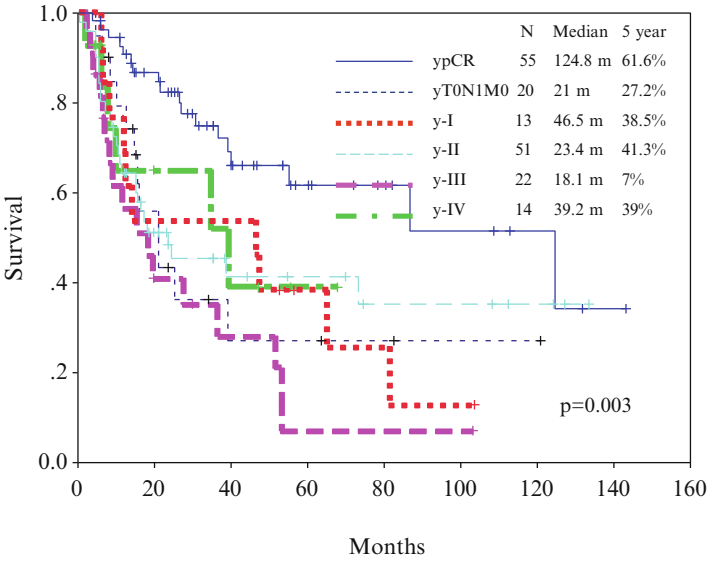

Fig. 15.5 Survival curve of ypTNM stage for patients treated with neoadjuvant chemoradiation followed by surgery

restage the patients at 4 weeks post therapy, including endoscopy and PET/CT scan. Surgery is then performed around 6–10 weeks post therapy.

In 107 ESCC patients who received neoadjuvant chemoradiation, the impact of the interval to surgery was studied. Patients were divided into two groups using 64 days from the end of therapy (median interval). When an R0 resection could be performed, the 3-year survival of the early surgery group was 71.7 % compared to 56.5 % of the delayed surgery group ($p = 0.023$). Postoperative morbidity and mortality rates were not affected by the timing of surgery [29]. Our previous data had also demonstrated the safety of neoadjuvant chemoradiation with regard to postoperative morbidity rates [13, 28]. 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 and 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 [30]. Instead the percent of residual viable cells in the primary tumor and nodal status were independent prognostic factors [27], while ypT stage was not. The cutoff 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. 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. No reliable clinical predictors exist. The use of PET scans to assess response during the early part of neoadjuvant therapy has some promise, but most reports to date studied chemotherapy-treated patients with substantial number being adenocarcinomas [31, 32]. At the authors' institute, work is being carried out to develop a blood-based assay to predict response, for example, measuring serum microRNAs release from tumor cells. Further results are awaited.

15.3.3 Surgery

Most patients seen at the authors' institute have advanced disease with comorbidities. Early cancers are uncommon and therefore most who come to surgery will have had neoadjuvant chemoradiation. These have to be taken into account when operative strategies are planned.

15.3.3.1 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 University of Hong Kong [33]. 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 video-assisted thoracoscopic surgery (VATS) became available [34, 35].

In recent years, laryngeal preservation has been the aim of treatment and definitive chemoradiation therapy is increasingly used. In addition, the availability of the technique of free jejunal graft to replace the cervical esophagus has also reduced the need for PLE. The annual average number of PLE performed in the authors' center dropped from 15 to around 6 [36]. Currently our practice is to offer patients a definitive chemoradiation for cervical ESCC. Surgery is performed in those who refuse nonoperative treatment and in those with contraindications for chemoradiation and for salvage of treatment failure or recurrent disease. Free jejunal graft for reconstruction is used for those with primary hypopharyngeal cancer or those with limited involvement of the cervical esophagus; otherwise, a PLE will be performed.

While the policy of up-front definitive chemoradiation is widely practiced, our data showed that this type of strategy was not without drawbacks. Chemoradiation-related complications included mucositis, bilateral vocal cord palsies, esophageal stricture, carotid blowout, hypothyroidism, and hypoparathyroidism. Persistent dysphagia affected 29 % of patients and 38 % eventually required surgery for salvage [36].

On the other hand, the outcomes of PLE have significantly improved over the last few decades [37–40]. Both the anastomotic leak and mortality rates were reduced to 9 % [37]. Improvements of surgical technique including thoracoscopic esophageal mobilization and better perioperative care and patient selection all contributed to better results [34, 35]. Free jejunal graft as an esophageal substitute has a failure rate of 2 % and anastomotic leak rate of 4.6 % [41, 42]. Optimal treatment strategy for cervical esophageal cancer patients needs individual consideration.

15.3.3.2 Intrathoracic Esophageal Cancer

The Approach to Resection

Our preferred surgical approach is a transthoracic one. This is related to the fact that most of our tumors are squamous in type, located proximally in the esophagus, and advanced in nature and often neoadjuvant therapy has been given. We performed a randomized trial comparing transthoracic and transhiatal approach for lower third tumors [43]. 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 [44]. At the initial stage, thoracoscopic esophageal dissection was applied in lieu of open thoracotomy or transhiatal mobilization of the esophagus in PLE [34]. 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 esophagogastrostomy [45]. Our early hypothesis was that minimally invasive method 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 [44]. 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 over 220 patients. MIE is the approach in about 65 % of our patients; in over 40 % of these patients prior neoadjuvant therapy has been applied (and in recent years, over 60 % of patients have had neoadjuvant chemoradiation). VAT esophagectomy with laparotomy was performed in 108 patients, totally MIE in 112. The median thoracoscopy time was 135 min, blood loss 300 ml. Our conversion rate (VAT) was 18 %, reflecting our policy of unselected choice of patients. In no case was conversion urgent because of complications; most were related to extensive lung adhesions or advanced post chemoradiated tumors that were found to be unsafe to dissect. Pulmonary complications occurred in 17 % of patients, anastomotic leaks in 4.5 %, and hospital

mortality rate in 1 %. Two patients died, one from radiation pneumonitis postoperatively and another from ischemic gastric conduit which required further surgery. Although this was successfully salvaged surgically, the patients succumbed from postoperative myocardial infarction [unpublished data]. These results compare well with our open surgery results. Oncologically the number of nodes harvested was not different from open esophagectomy; both methods retrieved approximately 40 nodes per patient.

A recently published European randomized controlled trial demonstrated the benefit of minimally invasive esophagectomy in lowering pulmonary complications. Postoperative quality of life was also superior [46]. It is anticipated that the uptake of MIE will become more widespread around the globe [47].

Extent of Resection and Lymphadenectomy

A curative (R0) resection implies histological clear proximal, distal, and lateral margins. There is 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 [48]. 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 [49]. A negative margin, however, may not totally preclude anastomotic recurrence. In our experience, a positive resection margin occurred in 7.5 % of patients compared to 4.9 % in those with negative margin [48].

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 up-front 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 versus 3 months. More importantly, in those with up-front chemoradiation and then esophagectomy, a median survival of 35 months was achieved [50]. 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 absence of metastases after chemoradiation.

In patients with no evidence of cervical nodal metastases on preoperative work-up including PET/CT scan and ultrasound, routine cervical lymphadenectomy is not performed. Neck dissection can still be performed later should recurrence occur 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 4 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 [49].

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 the recurrent laryngeal nerve as well as airway injury. With these policies, the transient recurrent laryngeal nerve palsy rate is 18.1 %, but permanent palsy affects 4.5 % of patients only [50].

15.3.3.3 Reconstruction

Restoration of the gastrointestinal tract continuity after esophagectomy has 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 [51]. A pyloromyotomy was shown to be as effective [52, 53]. 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 ileocolonic interposition is our second choice for esophageal replacement. Colonic interposition reconstruction is associated with higher morbidity rates, such as more blood loss, longer operative duration, and higher anastomotic leak rate [54]. 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 in 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 [55].

Our preferred route of reconstruction when cervical anastomosis is performed is the posterior mediastinum. The retrosternal route is recommended when there is residual tumor left in the posterior mediastinum or postoperative radiotherapy is planned to the tumor bed. 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. It has been reported that retrosternal route is associated with increased cardiopulmonary morbidity [56]. However, 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 [57].

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 [58]. 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 [59]. However, in our experience, a cervical anastomosis is no more likely to leak compared to its intrathoracic 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 circular stapling device and a hand-sewn method. Similar leak rates were found: 1.8 % for hand-sewn and 5 % for circular stapler [60]. The stricture rate however was fourfold with the stapling technique of 9.1 versus 40 % [60]. 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 and the transoral placement of the OrVil anvil with a DST stapler is often used (DST Series™ EEA™ OrVil™ devices, Covidien, USA).

At the authors' institution, currently the leak rate is below 5 % and most are related to technical faults [12, 61] such as 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, general condition of the patient, and the location of the anastomosis, approaches to manage anastomotic leak vary from conservative treatment by nasogastric tube drainage and enteral nutrition only to injection of TISSEEL glue or insertion of esophageal stent and surgical exploration for drainage. In patients with frank conduit ischemia, it is important to diagnose and explore early before actual leakage occurs and sepsis ensues. Immediate reanastomosis is sometimes possible in stable patients with limited necrosis, for most takedown of the ischemic stomach is necessary and staged reconstruction later carried out. 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, making a leak-

related mortality of 9.8 %; in the 1980s and 1990s, leakage rate was 3.5 %, and 35 % of whom died, making a leak-related mortality rate of 1.2 %. This subsequently improved to 3.2 %, and there was no mortality [28, 61, 62].

15.3.3.4 Other Morbidities and Mortality

In our experience, the most common medical complications are atrial fibrillation and pulmonary morbidities (pneumonia, atelectasis, sputum retention, 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 [63]. 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 [13]. 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 supracarinal 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 [64].

The hospital mortality rate in the 1980s in the authors' institution was 11–15.5 % [12, 65]. The respective figures reduced to 3.2 % in the early 1990s and 1.1 % in the late 1990s, respectively [13, 65]. Mortality rate since 2000 has remained around 1 %. Surgical volume and experience have obvious positive impact on outcome. The number of patients managed since 1982 is approaching 3,000.

15.3.3.5 Palliation

With the availability of various treatment modalities, palliative surgery is seldom necessary nowadays. Palliative resections were not uncommonly performed, in addition to bypass procedures such as the Kirschner bypass using gastric or colonic conduits [66, 67]. Radiotherapy with or without chemotherapy is also used for palliation in selected patients. Various endoscopic methods are available for relief

of dysphagia, our preferred method being placement of self-expanding metallic stents (SEMS) [68].

15.4 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. Although progress has been made in prolonging long-term survival, there is still much room for improvement. Future progress should be made in finer individualization of treatment strategy in patients using clinical data or biomarkers and discovery of more effective systemic drugs or agents to treat this highly lethal cancer, so that survival can be prolonged and quality of life optimized.

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Squamous Cell Carcinoma of the Oesophagus: The Indian Experience

16

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Abstract

Oesophageal cancer is a relatively common cancer among both men and women and is the fourth most common cause of cancer-related deaths in India. Squamous cell carcinoma is the most common histology (80 %) although there has been a recent relative increase in the incidence of adenocarcinoma. Aetiological factors for oesophageal squamous cell carcinoma (OSCC) in India are unique and include alternative forms of tobacco consumption, alcohol, tea drinking, nutritional and dietary factors and possibly human papillomavirus (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 OSCC in India is similar to other countries though the use of PET–CT and endoscopic ultrasonography is not universal. The treatment of early stage disease (T1/T2 and N0) is primarily surgery alone, while for patients with more advanced, resectable disease (T3/T4a or N+), the treatment is usually neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. Unresectable or metastatic disease is treated with palliative radiotherapy or oesophageal stenting. Surgical technique is widely variant with both transthoracic and transhiatal oesophagectomies being performed along with minimally invasive oesophagectomy depending on the specialization and expertise of the surgeon. Research on oesophageal cancer has focused on epidemiology, aetiological 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 promote collaborative research and standardization of treatment across the country.

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Oesophageal cancer • India • Squamous

16.1 Introduction

Oesophageal cancer is a morbid disease and, globally, is a major cause of cancer-related deaths [1]. Worldwide, squamous cell carcinoma is the most common type of oesophageal 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 gastro-oesophageal junction and lower oesophagus in North America and Europe [3–5].

16.2 Epidemiology, Aetiology, Diagnosis and Staging of Squamous Oesophageal Cancer in India

16.2.1 Epidemiology of Oesophageal Cancer in India

In India, oesophageal cancer is the fourth most common cancer in males and the fifth most common cancer in females, with an estimated incidence of over 48,000 new cases in 2008 [2]. It is also the fourth most common cause of cancer-related deaths in India [2]. As in most parts of Asia, the majority of oesophageal 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 1,000 oesophageal cancer patients over a 16-year period, patients were divided into four cohorts of 4 years each. Lower oesophageal cancers outnumbered the mid-oesophageal cancers in the fourth cohort though mid-oesophageal 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 oesophageal cancer in India. Regional variations in the incidence of oesophageal squamous cancer have been observed in India with markedly higher rates seen in the Kashmir Valley [10] and northeastern India [11]. Overall, approximately 80 % of all oesophageal cancers in India are squamous cancers, with 20 % being adenocarcinomas.

16.2.2 Aetiology

The common risk factors for oesophageal squamous cell carcinoma (OSCC) in India include smoking, alcohol consumption, the combination of both, low socio-economic 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 oesophageal 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].

16.2.2.1 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 oesophageal cancer [11, 18–21]. In a case–control study of 702 cases and over 1,600 controls, Dar and colleagues found that cigarette smoking was not a major risk factor for oesophageal cancer in the Kashmir Valley [17]. However, the consumption of smokeless tobacco (nass) and hookah smoking were associated with a significantly increased risk [17]. Nass chewing had an increased risk of oesophageal squamous cancer with an OR of 2.88. Ever-hookah smoking was associated with an increased risk of OSCC (OR 1.85; 95 % CI 1.41–2.44). They also found association between the intensity, duration and cumulative amount of hookah smoking [17].

A study conducted in South India identified both smoked tobacco and chewed tobacco to be associated with an increased risk of squamous oesophageal cancer with risk ratios of 2.8 and 2.5, respectively [21]. Another study found a risk of 3.16 times associated with the consumption of betel leaf with tobacco and 1.95 times with bidi smoking [18]. In a case–control study of 343 cases and 686 controls, Nandakumar and colleagues [19] found that chewing areca preparations was associated with an increased risk of developing cancer in the middle third of the oesophagus; in contrast, chewing tobacco was associated with lesions in the lower third of the oesophagus [19]. A study from the northeastern state of Assam (which has among the highest rates of oesophageal cancer in India) found betel nut chewing to be associated with higher risks of developing oesophageal 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 case–control study conducted at the authors' institute included 442 cases of oesophageal cancer and 1,628 hospital controls [20]. 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 twofold for cigarette smokers [20].

16.2.2.2 Alcohol

Alcohol consumption is not as common in India as it is in other parts of the world both in frequency and quantity of consumption [28, 29]; however, it is one of the

known etiological factors for oesophageal cancer in India. In a case–control study conducted in South India with more than 500 oesophageal cancer patients and over 1,700 controls, alcohol consumption was shown to increase the risk by more than three times [23]. A significant dose–response relationship was observed for the duration of drinking and average daily amount of alcohol consumption with OSCC. Among all types of alcohol analysed, arrack, a locally brewed preparation, showed the highest risk—4.5 times that of the controls [23]. The intake of other types of alcohol (gin, rum, whisky and 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 [21]. In the study conducted in the authors' institute [20], alcohol 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 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 oesophageal cancer with the use of alcohol in the range of 1.8–3.5.

16.2.2.3 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 [30]. In a case–control study conducted at the All India Institute of Medical Sciences, low consumption of green leafy vegetables, low consumption of other vegetables, and consumption of alcohol were the three factors that are associated with increased risk for oesophageal 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 [18, 26]. A case–control study done in Assam found a positive association between increased risk of oesophageal cancer and the consumption of spicy food, hot foods and beverages while green leafy vegetables and fruits were protective for oesophageal cancer [11]. The risk associated with the consumption of locally prepared food items, e.g. kalakhar, was found to be eight times.

The consumption of salt tea has been associated with increased risk of oesophageal cancer in Kashmir, where 90 % of the cases had history of salt tea consumption [12]. The mechanism of carcinogenic activity of salt tea has been attributed to the presence of nitroso compounds, which get activated due to its peculiar method of brewing and the presence of salt. Hyperthermic injury to the oesophageal mucosa due to consumption at high temperatures may also be responsible [13]. The presence of higher levels of nitrosamines was found in the sun-dried vegetables and chillies, which are commonly consumed in Kashmir [31]. A study conducted in the authors' institute showed a fourfold higher risk with tea drinking [20]. They also found that the 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 oesophageal cancer [14]. 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 chilli (OR = 1.76, 95 % CI = 1.07–2.89) [14]. Pickle consumption was associated with an odds ratio of 2.5 in a study conducted in South India [21].

16.2.2.4 Low Socio-economic Status

Studies have associated oesophageal 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 oesophageal squamous carcinoma risk in the Kashmir Valley [15]. A total number of 703 histologically confirmed OSCC cases were matched with 1,664 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 oesophageal cancer risk. Compared to farmers, individuals who had government jobs or worked in the business sector were at lower risk of oesophageal squamous cancer. They also found an inverse association between poor oral hygiene and increased risk of oesophageal cancer, suggesting that oral hygiene could be used as a surrogate marker for socio-economic status [15].

16.2.2.5 Genetic Factors

A study from Kashmir [32] which analysed TP53 mutations in oesophageal SCC in 55 patients revealed the presence of mutations in 36.4 % (20/55) tumours. Another study analysed the interaction of various habit-related factors and polymorphism of GSTM1/GSTT1 genes towards inducing promoter hypermethylation of multiple tumour suppressor genes [33]. In 112 cases with 130 matched controls, significantly higher methylation frequencies were observed in tobacco chewers than non-chewers for the genes under study ($p < 0.01$) [33].

Other studies have also found a high rate of protein overexpression and alterations in p53 gene expression in subjects with oesophageal squamous cancer and correlated a higher expression with increased intake of chillies [34]. These results have been corroborated by other workers who showed that somatic chromosomal mutations, especially in exon 6 of Tp53 gene, among oesophageal 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”, that are rich in nitrosamines and familial cancer history [35].

16.2.2.6 Role of Human Papillomavirus (HPV)

The role of human papillomavirus as a causative factor for oesophageal cancer is unclear. Various studies have demonstrated the presence of HPV in oesophageal cancer specimens in the range of 15–80 % [36]. 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 OSCC tumour and adjoining mucosa in 23 patients with paired samples [37]. They found an HPV positivity rate of 87 % in oesophageal cancer patients and higher rates were seen in smokers [37]. Another study identified HPV DNA in 46 % of non-keratinizing squamous cell carcinomas of the oesophagus and in none of the keratinizing squamous cell carcinomas or adenocarcinomas postulating an aetiological association with this subtype of OSCC [38].

16.2.3 Diagnosis

Most patients in India present at advanced stages of disease [39, 40]. The available investigations for the diagnosis and staging of oesophageal 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 fibre-optic bronchoscopy. The usual workup followed in India in the diagnostic and staging process of a patient suspected to have oesophageal cancer includes 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 are available. Fibre-optic bronchoscopy is used to rule out the involvement of the tracheobronchial tree in patients with upper and middle third tumours planned for curative treatment.

16.2.3.1 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 oesophageal cancer. However, it is conventionally performed at a primary health centre level prior to an endoscopic diagnostic procedure.

16.2.3.2 Endoscopy

Flexible upper gastrointestinal endoscopy visualizing the oesophagus from the cricopharyngeal to the gastro-oesophageal 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 tumour. In the authors' institute and in several other centres, 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 oesophageal cancer on endoscopy. One study evaluated the utility of brush cytology and its correlation with biopsy in 100 patients with upper gastrointestinal symptoms [41]. 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 [41]. Two other studies compared the sensitivity and specificity of cytology and biopsy in establishing the diagnosis of oesophageal cancer [42, 43]. Both 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 [42, 43]. A small study evaluated 48 patients with carcinoma of the oesophagus to assess the optimal number of biopsy specimens required to obtain the highest yield [44]. 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 %.

16.2.3.3 Endoscopic Ultrasonography

Accurate staging of oesophageal cancer is essential to plan the treatment. EUS helps to delineate the different layers of the oesophageal 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 oesophageal cancers restricted to the mucosa without involvement of the lamina propria. Loco regional staging of the tumour 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 the evaluation of the residual oesophageal disease after neoadjuvant chemotherapy or chemoradiation, as it cannot reliably differentiate between fibrosis due to inflammation and residual/recurrent disease. However, the use of routine EUS in all patients diagnosed with oesophageal 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 centres.

16.2.3.4 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 oesophageal cancer. CECT scanning in the pre-treatment assessment of oesophageal cancer in the Indian setting was found to be highly accurate in the determination of the tumour "T" stage, invasion of surrounding structures and distant metastases but not effective in the determination of the nodal involvement [45]. 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 oesophageal cancer [46, 47].

Table 16.1 Clinical usefulness and accuracy of modalities used in staging of oesophageal cancer

Modality	Clinical utility	Overall accuracy (%)
Computed tomography (chest, abdomen)	Invasion of local structures (airways, aorta)	≥90
	Metastatic disease	≥90
Endoscopy	Local tumour (T) staging (operator dependent)	80–90
Endoscopic 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

16.2.3.5 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 oesophageal 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 oesophageal carcinoma with contrast-enhanced computed tomography followed by PET/CT after 2 weeks [48]. Nine patients were upstaged by PET/CT compared to CECT, out of which seven (25 %) were correctly upstaged and two (7.14 %) were falsely upstaged. They concluded that PET/CT improved their ability to detect distant metastases in 25 % of patients who were missed by CECT [48]. Unusual sites of metastases, such as muscular metastases, have been detected without any morphological evidence of disease [49].

The clinical utility and accuracy of various imaging modalities [50] in the diagnosis of oesophageal cancer are summarized in Table 16.1.

16.2.4 Staging

TNM staging is one of the most important and reliable prognostic variables. Standardised and accurate staging of cancer is important for uniform reporting and comparison of results from various centres. 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). The seventh edition of the AJCC TNM classification came into effect in 2009 [51].

Some of the key modifications from the sixth edition are:

1. Inclusion of gastro-oesophageal junction tumours and tumours in the proximal 5 cm of the stomach extending into the oesophagus.

2. T4 is subclassified as T4a (resectable cancer invasion) and T4b (unresectable cancer invasion).
3. N staging is subclassified based on the number of positive regional lymph nodes (N1, 1–2 nodes; N2, 3–6 nodes; and N3, $\geq$7 nodes).
4. M classification is redefined based on the presence of distant metastasis, and the term non-regional lymph node is eliminated.
5. Histological grade and tumour location are incorporated.
6. Separate stage grouping for adenocarcinoma and squamous carcinoma.

The new staging system has shown remarkable homogeneity within stage groups and excellent separation of survival curves between stages. The authors also welcome the separation of resectable (T4a) from unresectable (T4b) tumours. However, while the seventh edition is clearly superior in terms of prognostication, it is not ideal for baseline clinical staging or staging of patients who have undergone preoperative therapy. This is because the emphasis on nodal count rather than anatomic location and the introduction of histological grading make pre-resectional staging extremely difficult and highly likely to be inaccurate. Moreover, most of the data on which the stage grouping was based was drawn from western countries with a predominance of adenocarcinomas. Whether the same prognostic separation of the stage holds true for squamous oesophageal cancers remains to be seen.

16.2.5 The Tata Memorial Centre Experience

The authors' institution, the Tata Memorial Centre, is the largest tertiary level cancer centre in the country and is a high-volume centre for the treatment of oesophageal cancer. Between 1,200 and 1,300 new patients with oesophageal cancer are seen every year, most of them presenting in advanced stage of disease or in an emaciated condition, precluding potentially curative treatment. Squamous oesophageal cancers predominate in a ratio of 80:20 and the most common location of tumours is in the lower third of the oesophagus. The typical diagnostic workup of patients with a good performance status includes a detailed flexible fibre-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 fibre-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 co-morbidities undergo a thorough cardiopulmonary evaluation and are discussed in a special "high-risk multidisciplinary team" meeting by surgeons, intensivists and critical

care specialists, anaesthesiologists and pulmonary physicians to optimize them prior to surgery. The preferred therapeutic approach is discussed in a subsequent section of the chapter.

16.3 Treatment of Squamous Oesophageal Cancer in India

16.3.1 Treatment

India is a vast and populous country with significant resource constraints. The wide variation in the 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-centre variability of care are still considerable. Efforts by the authors' institute and the Indian Council of Medical Research (ICMR) have culminated in the establishment of uniform oesophageal cancer treatment guidelines tailored to the country's varied levels of expertise and availability of infrastructure. One of the core recommendations of the guidelines is the establishment of multidisciplinary teams for the management of oesophageal cancer. While some major cancer centres in India have a multidisciplinary 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 and medical or radiation oncologist.

16.3.1.1 Patient Evaluation

The initial evaluation of the patient includes the 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, 29] 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. 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 [52]. All patients considered for radical treatment undergo extensive evaluation of cardiopulmonary 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. Early institution of chest physiotherapy and tobacco and alcohol cessation are routinely advocated as soon as a diagnosis of oesophageal cancer is made.

16.3.1.2 Principles of Management

Broadly, decisions regarding the 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 considerable proportion of patients in India. Concurrent radical chemoradiation is the preferred therapeutic strategy for lesions in the upper third of the oesophagus, i.e., within 5 cm of the cricopharynx, while surgery is the preferred treatment for lesions in the middle and lower third oesophagus. 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 practised in India primarily due to the fact that very few patients present at a stage amenable to the procedure and also due to the limited availability of expertise in select centres across the country. Patients with locally advanced disease (T3/T4, N+) undergo multimodality treatment, generally with neoadjuvant chemotherapy [53, 54] or neoadjuvant chemoradiotherapy followed by surgery. Patients with metastatic disease are usually treated with palliative radiotherapy or oesophageal stenting or a combination of the two and rarely with palliative chemotherapy.

16.3.2 Surgery

Surgery is the preferred modality of treatment for middle and lower third oesophageal cancer [55–58]. 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 oesophagectomy albeit at the cost of significantly higher post-operative morbidity. In spite of the established role of surgery in the radical treatment of oesophageal cancer, there is very little consensus on what constitutes a standard oesophagectomy 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. Oesophageal resections in India are performed by surgeons from varied surgical specialties including general surgery [55, 56], gastrointestinal surgery [57], thoracic surgery [58] and surgical oncology [59].

16.3.2.1 Approach

Transthoracic oesophagectomy 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 tumours [55–59]. In a large series of 367 transhiatal oesophagectomies performed over a period of 18 years at the All India Institute of Medical Sciences, the 5-year overall survival was 38 % with a post-operative mortality rate of 12 %. Since there is no strong evidence favouring one approach over the other, both approaches are widely practised in India with a

bias towards transthoracic approach in high-volume oncology centres. In these centres, transhiatal resection is performed in limited numbers as a compromise surgery in patients with poor pulmonary function or extensive pulmonary fibrosis precluding transthoracic resection.

16.3.2.2 Lymphadenectomy

Lymphadenectomy for oesophageal cancer is a controversial topic in India, as in many other parts of the world [60]. Surgical oncologists who predominantly perform transthoracic oesophagectomies place more emphasis on extensive lymph nodal clearance. Infracarinal nodal dissection or a standard two-field dissection is considered to be the standard template for dissection by most surgeons performing a transthoracic oesophagectomy. In India, very few centres with high volumes of oesophageal 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 transhiatal resection is low and is usually limited to the perioesophageal lymph nodes. However, as mentioned in the previous section, transhiatal resections are usually performed only as a compromise surgery in high-volume centres.

16.3.2.3 Minimally Invasive Surgery

Surgeons in India were early to adopt minimally invasive oesophagectomy. A few high-volume centres have published data showing better results with a minimally invasive approach with respect to pulmonary morbidity and operative blood loss [57, 59, 61–63]. A prospective study comparing minimally invasive oesophagectomy with open oesophagectomy [63] demonstrated comparable results in terms of lymph node yield (9.5 vs 7.3), duration of surgery (312 vs 262 min), average blood loss (276 vs 313 mL) and morbidity (26.5 vs 28.6 %). A larger series [57] of 463 thoracoscopic oesophagectomies demonstrated a lower morbidity rate (16 %) and post-operative mortality rate (0.9 %). However, no long-term (survival) outcome data is available from any of these studies. Different surgical groups in India use different patient positions for thoracoscopic oesophagectomy 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 oesophagectomy through the lateral approach. Robotic surgery for oesophageal cancer has just started in India and is confined to few centres currently. A series of 32 robotic oesophagectomies [64] showed comparable results to thoracoscopic oesophagectomy. However, no distinct advantage over thoracoscopic oesophagectomy has been demonstrated.

16.3.2.4 Reconstruction

The stomach is the preferred conduit for reconstruction, and in cases where the stomach is not available, the colon, either the 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 transthoracic oesophagectomy. A small randomized study of 49 patients comparing posterior mediastinal versus retrosternal conduit placement [65] found both routes to have comparable outcomes. The anastomosis is usually performed in the neck either by a stapled or handsewn technique [66]. Both techniques are widely practised in India depending upon surgeon preference and cost constraints. Some clinical trials on anastomotic technique are described in a subsequent section of the chapter.

16.3.3 Multimodality Management

India was late to embrace multimodality management in oesophageal cancer. This may have been primarily because of the delayed establishment of multidisciplinary 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 oesophageal cancer are treated with either neoadjuvant chemotherapy [53, 54] or neoadjuvant chemoradiotherapy. The common chemotherapy regimens include doublets consisting of cisplatin with 5-fluorouracil or cisplatin with paclitaxel, while few centres 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. 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 centres are stringent in patient selection for this regimen, and the early results have been very encouraging.

Post-operative radiotherapy or chemoradiotherapy is not practised as a routine after oesophagectomy. The use of adjuvant radiotherapy is restricted to patients with positive resection margins and, occasionally, patients with significant residual metastatic lymphadenopathy after neoadjuvant chemotherapy.

16.3.4 Chemoradiotherapy

Chemoradiotherapy is the primary modality of treatment of upper third oesophageal 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 practised 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 [67]. In institutes with facilities for intraluminal brachytherapy the radiation regimen may be changed to teletherapy 50 Gy in 25# in 5 weeks followed by 2# of high-dose rate intraluminal brachytherapy of 12 Gy after 2 weeks, the chemotherapy regimen remaining the same. Several concurrent chemotherapy regimens are practised including three-weekly cisplatin and 5-fluorouracil and three-weekly paclitaxel and cisplatin along with standard doses of radiation.

16.3.5 Palliative Therapy

The emphasis of management in patients presenting with metastatic oesophageal 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 [68]. Patients with absolute dysphagia who need immediate palliation are treated with oesophageal stents, most commonly self-expanding metal stents [69]. A few centres offer intraluminal radiotherapy for metastatic and locally advanced oesophageal cancer and have been found to offer faster and sustained palliation of dysphagia [70]. Rarely patients with bulky disease obstructing the tracheobronchial tree as well as the oesophagus are treated with double stents i.e., tracheal and oesophageal stents.

16.3.6 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. The diagnostic workup and treatment guidelines are summarized in Fig. 16.1. Over 1,700 surgeries have been performed for oesophageal cancer over the last 10 years. The preferred choice of surgery is a transthoracic three-stage oesophagectomy while transhiatal oesophagectomy 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

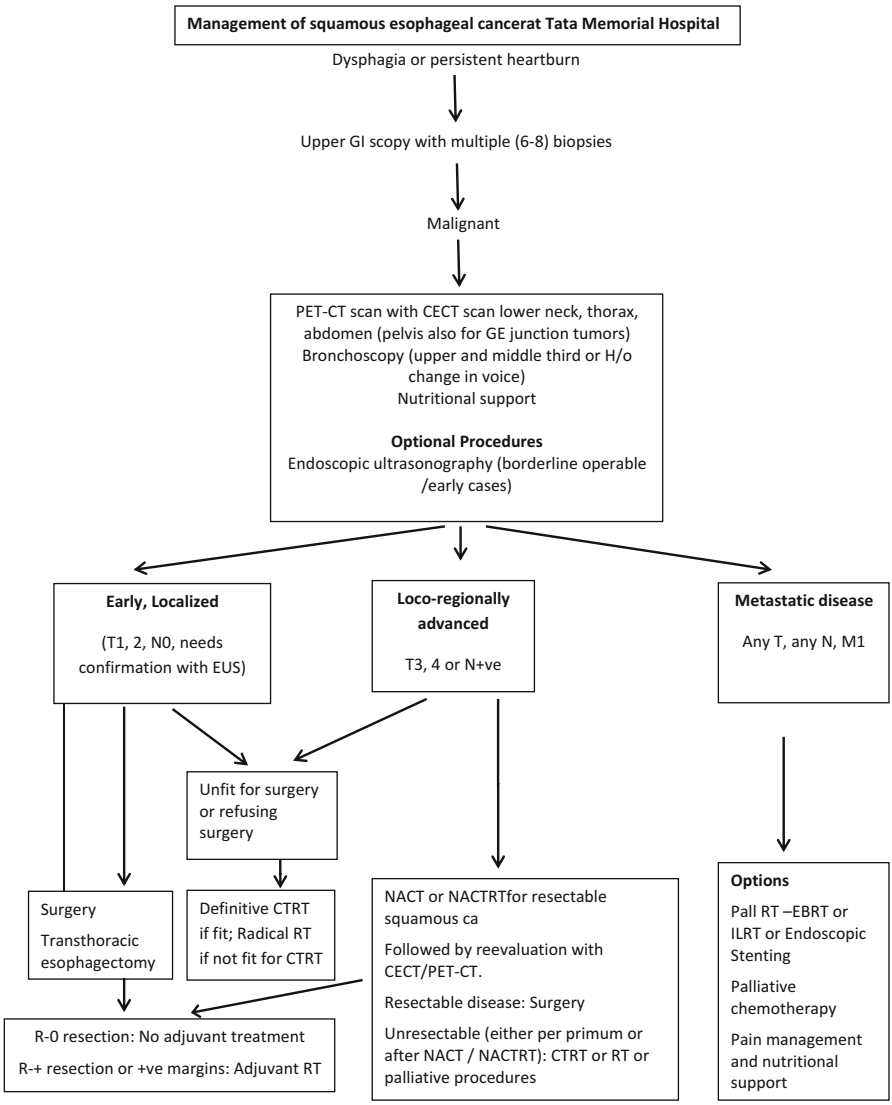

Fig. 16.1 OSCC treatment algorithm at the Tata Memorial Hospital

features are considered for randomization to a trial comparing standard two-field with elective radical three-field lymphadenectomy. Minimally invasive oesophagectomy (thoracoscopy and/or laparoscopy) is performed in approximately half of the patients undergoing transthoracic oesophagectomy. The preferred conduit is the stomach and the posterior mediastinum, the most common route of reconstruction. Oesophagogastric anastomosis is performed in the neck by a

triangulated stapled anastomosis. A nasojejunal tube is placed intraoperatively for post-operative enteral feeding.

Preoperative preparation includes chest physiotherapy, incentive spirometry and nutritional rehabilitation along with smoking cessation. Anti deep vein thrombosis (DVT) prophylaxis is started 12 h prior to surgery and continued post-operatively. Prophylactic antibiotics are given preoperatively and repeated once after 3 h intraoperatively and are not continued routinely in the post-operative period. Most patients are extubated immediately 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. Enteral (nasojejunal) feeding is started the morning after surgery and stepped up gradually to full enteral feeds by the evening of the second post-operative day. The nasogastric 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 post-operative 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 8th 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 of patients undergoing total oesophagectomy was 42 % with a median survival of 36 months (95 % confidence interval, 25.5–46.5 months).

16.4 Research in Oesophageal Cancer in India

Research on oesophageal cancer in India has a long history. The main areas of focus in oesophageal cancer research have been the possible aetiological factors and associations with squamous oesophageal cancer, the choice of primary treatment for the disease, modifications in surgical technique, the role of neoadjuvant and adjuvant treatment and palliative treatment options.

16.4.1 Epidemiology Research

Epidemiological research from the Kashmir Valley, which is a high incidence area for squamous oesophageal cancer, established that low socio-economic status was an independent risk factor [15]. A large case–control study, matched for age, sex and geographic area, showed a strong inverse association between higher education and wealth status and OSCC risk. The same study also established the probable aetiological role of “hookah” smoking and “nass chewing” on oesophageal squamous cell cancer with odds ratios of 1.85 and 2.88, respectively [17]. In a small study evaluating the prevalence of human papillomavirus (HPV) strains in OSCC,

researchers found that a high proportion (87 %) of patients with OSCC harboured high-risk HPV strains [37]. While association between HPV strains and OSCC 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 OSCC, 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 [33]. Betel quid chewing, alcohol consumption and a null GSTT1 genotype had maximum risk for OSCC without promoter hypermethylation whereas tobacco chewing, smoking and null GSTT1 variants were found to be associated with OSCC with promoter hypermethylation on logistic regression analysis [33].

16.4.2 Primary Treatment

One of the two randomized trials [71, 72] comparing surgery with radical radiotherapy for localized oesophageal 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 [72]. 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 oesophageal cancer, was superior in the surgery arm compared to the radiotherapy arm. The secondary endpoint of survival was vastly superior in the surgery arm compared to the radiotherapy arm ($p = 0.002$) [72]. To date, this is one of only two randomized trials [71, 72] performed so far to address this important question.

16.4.3 Neoadjuvant Therapy

A small randomized trial compared quality of life (QOL) outcomes after transhiatal oesophagectomy with or without neoadjuvant chemotherapy [54]. 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 [54]. Currently, there is an ongoing phase II randomized trial comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy (both followed by radical surgery) in the authors' institution.

16.4.4 Surgical Trials

A number of trials have been conducted on surgical techniques and variations therein. These include the use of pedicled omentum to reinforce oesophagogastric anastomosis [73], modifications of the anastomotic technique [74] and the route of reconstruction [65]. In addition, observational studies on minimally invasive oesophagectomy [57, 59, 61–63] and robotic oesophagectomy [64] have also been performed.

A small randomized trial [65] 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 post-operative 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 %) [65]. Long-term outcomes including stricture rate, dysphagia, aspiration, reflux and weight loss were also similar in the two groups [65]. In a small study involving patients who underwent oesophagectomy with a cervical anastomosis, patients were randomized into either no pyloric drainage or pyloroplasty with gastric emptying as the primary endpoint [75]. The study demonstrated significant delay in gastric emptying in both 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 intrathoracic stomach causes delayed gastric emptying and pyloroplasty failed to prevent its occurrence [75].

16.4.4.1 Anastomotic Technique

A randomized trial [73] was performed to evaluate whether the addition of a pedicled omental wrap on the oesophagogastric anastomosis would decrease the incidence of anastomotic leaks. Patients undergoing radical oesophagectomy (63 % Ivor Lewis and 37 % transhiatal oesophagectomy) were randomized to conventional anastomosis (manual end-to-side oesophagogastric anastomosis) 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 [73]. This difference was seen in both the Ivor Lewis and the transhiatal oesophagectomy 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 [74]. One hundred patients were randomized to the control arm (end-to-side oesophagogastric 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 [74]. Another randomized trial was done comparing a side-to-side stapled anastomosis to a handsewn technique with anastomotic leaks and strictures as the

primary and secondary endpoints, respectively [66]. 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 [66].

16.4.4.2 Perioperative Management

Two relatively large randomized trials of perioperative management were conducted in the authors' institute. The first, a randomized trial, evaluated whether it was safe to shorten the duration of nasogastric drainage after oesophagectomy [76]. One hundred and fifty patients undergoing modified McKeown three-stage or transhiatal oesophagectomy with gastric tube reconstruction were randomly allocated to either conventional (6–10 days) or shortened (2 days) nasogastric 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 [76]. The trial established that it was feasible and safe to remove the nasogastric drainage tube two days after oesophagectomy and a neck anastomosis without any adverse effects [76]. The authors performed another randomized trial to evaluate the impact of restricted intraoperative and post-operative fluid administration on major post-operative pulmonary complications [77]. 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 [77]. Another randomized trial from the authors' institution evaluating the role of perioperative erythromycin (a motilin agonist) in reducing the immediate post-operative and medium-term occurrence of delayed gastric emptying is completed and awaiting data analysis [78].

16.4.5 Palliative Treatment

A randomized trial was conducted to evaluate whether the combined treatment of oesophageal stenting and radiotherapy was superior to stenting alone in advanced inoperable oesophageal cancer [68]. 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 [68].

16.4.6 Ongoing Research

There are several ongoing trials on various aspects of oesophageal 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 aerodigestive tract (oral, hypopharyngeal and oesophageal) 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/oesophageal 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 oesophageal cancer [79]. Patients with operable oesophageal cancer are randomized intraoperatively (after confirming operability and absence of gross supracarinal lymphadenopathy) to either standard two-field or radical three-field lymphadenectomy—430 out of a target 700 patients have been accrued so far.

16.5 Future Directions

Treatment for oesophageal cancer in India has so far been carried out in institutions with a wide range of experience in managing this disease without an organizational framework. Challenges to improve overall patient outcomes in oesophageal 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 centre level, while tertiary level treatment centres 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 the management of oesophageal cancer, training adequate manpower, centralization of treatment, wider adoption of multidisciplinary treatment teams and multimodality 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 and Stomach (ISES) was recently formed to address this gap. The mandate for the ISES includes the formulation and adoption of uniform guidelines for the management of oesophageal diseases, more systematic data collection and collaborative multicentric research studies. It is expected that this society will also provide a forum for discussion among surgeons and oncologists treating oesophageal 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

oesophageal cancers among countries like Japan, China, Iran and India where they are far more common than 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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