

# Distinctive Clinicopathological Characteristics in Esophageal Squamous Cell Carcinoma

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**Esophageal cancer is an aggressive disease with a generally poor prognosis. Frequently, patients present late with obstructive symptoms indicating advanced tumors. Therefore, serial histopathological investigations of esophageal cancer are now being performed more extensively, and several distinctive clinicopathological features have been demonstrated. In this review, we present some of the distinctive features of esophageal cancer and discuss their clinicopathological significance. These characteristics include: (1) the frequent presence of lymph node metastasis, (2) the morphological features and depth of tumor invasion, (3) the synchronous and metachronous occurrence of carcinoma of other organs, (4) the frequent coexistence of squamous epithelial dysplasia, (5) the frequent coexistence of intraepithelial spread, blood vessel, and lymphatic permeation, (6) the occasional existence of intramural metastasis, (7) the frequent coexistence of multiple primary carcinomas, and (8) the occasional coexistence of glandular differentiation with squamous cell carcinoma. (Ann Thorac Cardiovasc Surg 2003; 9: 6–13)**

**Key words:** esophageal squamous cell carcinoma, pathology, clinical characteristics, dysplasia

## Introduction

The prognosis for patients with esophageal carcinoma is poor, despite attempts at aggressive multimodality treatment.<sup>1-3</sup> Recently, advances in surgical techniques and adjuvant therapy have improved the 5-year survival rate to about 40%.<sup>1,2</sup> To improve operative methods and multimodality treatment, it is important that we have a thorough knowledge of esophageal carcinoma. As the most common histological type of esophageal cancer is squamous cell carcinoma (SCC), and most cases consist of either advanced cases or preoperatively irradiated cases, among the resected cases with esophageal cancer less histopathological attention has been paid to esophageal cancer than to other gastrointestinal tract cancers, such as gastric and colon cancers. However, owing to the re-

markable development of esophago-endoscopy, esophageal carcinoma can now frequently be diagnosed at an early stage, and, as a result, the number of patients with early esophageal carcinoma has increased significantly.<sup>4</sup> Consequently, serial histopathological investigations of esophageal cancer as well as squamous epithelial dysplasia, are now being performed more extensively, and several peculiar histological features have been demonstrated. In this article, we present some of the distinctive features of esophageal cancer, and discuss the clinicopathological significance of these characteristics.

## Clinical Characteristics

### General features

Esophageal SCC is the commonest malignant tumor of the esophagus in Japan. It affects more males than females, the rates are 5.9:1 in our 378 cases, and 6.5:1 in the Japanese Society for Esophageal Diseases (JSED) data.<sup>5</sup> The condition primarily occurs in people over 50 years of age, the mean is 63.6 years for our cases and 64.1 years in the JSED data. It is relatively common in China, other Asian countries and South Africa. Smoking and alcohol are two important and well-known risk

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factors.<sup>6)</sup> Among our 378 cases, 294 (77.8%) of the patients were smokers and 291 (76.9%) consumed alcohol. The other risk factors are reported to be dietary deficiency, infectious agents (especially the papilloma virus and fungi) and chronic irritation (thermal and/or mechanical injury, achalasia, diverticulum, chronic lye stricture, radiation therapy, injection sclerotherapy and gastric resection).<sup>7-13)</sup> In China, esophageal cancer is associated with diets that are contaminated with mycotoxins and low in micronutrients and antioxidants, whereas in the United States tobacco and alcohol consumption are major risk factors for esophageal SCC.<sup>14)</sup> Genetic factors, such as a polymorphism in the aldehyde dehydrogenase-2 (*ALDH2*) gene, along with alcohol consumption, have been associated with an increased risk of esophageal SCC in Japan.<sup>15)</sup>

Patients with esophageal cancer had about a 30% family history of the condition. This frequency may be due to heredity and/or environmental and/or lifestyle factors. Recently, mutation of the *p53* gene has been the most common molecular change in various human cancers.<sup>16)</sup> Mutation, abnormal accumulation of p53, or both, have been found in a high proportion of esophageal carcinomas and have led to the hypothesis that p53 abnormalities are common genetic events in the pathogenesis of this tumor.<sup>17-19)</sup>

### Early cancer and superficial carcinoma

So-called “early cancer” of the esophagus is a clinical concept which, in terms of pathology, corresponds to invasive carcinoma strictly confined to the mucosa or submucosa, with or without lymph node spread. In the most recent edition of the “Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus”,<sup>20)</sup> the definition of early carcinoma has been changed. Early carcinoma is now defined as an intramucosal carcinoma without nodal or distant metastasis. Superficial carcinoma is defined as carcinoma *in situ*, or carcinoma involving mucosa or submucosa, regardless of the presence of lymph node metastasis. It is a distinctive feature of esophageal cancer that lymph node metastasis is often found in superficial cancers, while it is relatively less frequent in gastric or colon cancer.<sup>21,22)</sup>

### Lymph node metastasis

Because there is abundant lymphatic plexus in the esophageal tissue, lymph node metastasis is commonly found in carcinoma of the esophagus, even if the tumor invades only the submucosa. It is reported that lymph node metastasis of esophageal carcinoma occurs widely in the

periesophageal area, below the diaphragm and upward into the cervical nodes.<sup>23,24)</sup> Our data on the relationship between depth of invasion of esophageal carcinoma and the presence of metastasis in nodes dissected at surgery revealed the following: lymph node metastasis was not found in the single case of carcinoma *in situ*; was found in 1 (7.1%) of 14 mucosal carcinomas other than carcinomas *in situ*; 16 (44.4%) of 36 carcinomas which had invaded the submucosa; 13 (61.9%) of 21 carcinomas which had reached the muscularis propria; 35 (72.9%) of the 48 carcinomas which had extended to the adventitia, but showed no direct invasion; and, 6 (85.7%) of the 7 carcinomas which had invaded other organs directly. Recently, in Japan, mucosal carcinomas which did not invade the muscularis mucosae have been found to be curable by endoscopic mucosal resection.<sup>25)</sup>

### Morphological features and local spread

Squamous cell carcinoma can occur in any portion of the esophagus but most commonly in the middle and lower esophagus (Table 1). Morphological types were classified according to the “Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus”<sup>20)</sup> (Table 1). In summary, superficial type carcinomas (tumor with invasion limited to the mucosa or submucosa, including carcinoma *in situ*) were classified macroscopically into three types: 0-I, superficial and protruding type; 0-II, superficial and flat type; 0-III, superficial and distinctly depressed type. Advanced carcinomas were classified into five types the same as Borrmann’s classification of gastric carcinoma: Type 1, protruding type; Type 2, ulcerative and localized type; Type 3, ulcerative and infiltrating type; Type 4, diffusely infiltrating type; and Type 5, miscellaneous type. In our data and the JSED data,<sup>5)</sup> the superficial and flat types are most common in superficial type carcinomas (Table 1). The two most frequent types of advanced carcinoma are Types 2 and 3. The macroscopic classification and the histologic types of malignant esophageal tumors are closely related. Polypoid types of protruding superficial and advanced malignant tumors are usually found to be carcinosarcomas, squamous cell carcinomas or malignant melanomas. Plateau types of protruding tumors are usually basaloid squamous cell carcinomas, adenoid cystic carcinomas, poorly differentiated squamous cell carcinomas or adenocarcinomas. Predominantly, subepithelial types of protruding tumors are small cell type undifferentiated carcinomas, basaloid squamous cell carcinomas or adenoid cystic carcinomas.

**Table 1. Pathological findings of resected specimens (location histology morphological types)**

			Our cases (1983-2001)		JSED (1997)	
Location	Ce	Cervical esophagus	1	(0.8%)	89	(4.6%)
	Ut	The upper thoracic portion	15	(11.8%)	208	(10.7%)
	Mt	The mid-thoracic portion	81	(63.8%)	1,003	(51.5%)
	Lt	The lower thoracic portion	30	(23.6%)	629	(32.3%)
		Others			19	(1.0%)
Morphological type	0-I	Superficial and protruding type	12	(9.4%)	143	(7.3%)
	0-II	Superficial and flat type	34	(26.8%)	426	(21.9%)
	0-III	Superficial and distinctly type	5	(3.9%)	17	(0.9%)
	1	Protruding type	13	(10.2%)	141	(7.2%)
	2	Ulcerative and localized type	16	(12.6%)	544	(27.9%)
	3	Ulcerative and infiltrating type	44	(34.6%)	472	(24.2%)
	4	Diffusely infiltrating type	2	(1.6%)	44	(2.3%)
	5	Miscellaneous type	1	(0.8%)	74	(3.8%)
		Others			87	(4.5%)
	Histopathological classification		Squamous cell carcinoma	116	(91.3%)	1,777
		Adenocarcinoma	5	(3.9%)	37	(1.9%)
		Adenosquamous carcinoma	2	(1.6%)	18	(0.9%)
		Basaloid carcinoma	2	(1.6%)	20	(1.0%)
		Undifferentiated carcinoma	1	(0.8%)	9	(0.5%)
		True carcinosarcoma	1	(0.8%)	3	(0.2%)
		So-called carcinosarcoma	0	(0.0%)	13	(0.7%)
		Adenoid cystic carcinoma	0	(0.0%)	3	(0.2%)
		Others			66	(3.4%)
		Not examined			2	(0.1%)
Total			127		1,948	

### Synchronous and metachronous occurrence of carcinoma of other organs

The presence of other cancers synchronously or metachronously associated with esophageal carcinoma is also relatively common. According to the JSED data, 20.2% of patients with esophageal carcinoma had synchronous or metachronous carcinoma at another site (Table 2). In our data, 64 of 387 cases (16.5%) had carcinomas of other organs. Synchronous carcinomas were found in 19 cases (29.7% of the carcinomas in other organs), the previous occurrence of carcinoma in other organs was 13 (20.3%) cases, and the number of later cases was 8 (12.5%). Occasional occurrence of dual primary carcinomas of the head and neck (H&N) and esophagus have been known, but in Japan the occurrence of dual primary carcinomas of the stomach and esophagus are also well known. There are reports that gastric carcinoma is the most frequent carcinoma at another site.<sup>26)</sup> Our data show that gastric carcinomas were 33 cases (51.6% of

the occurrence of carcinoma in other organs) and H&N cancers were 10 (15.6%). Therefore, both preoperative screening and postoperative follow-up studies of the stomach and H&N regions are essential. In cases of esophageal cancer associated with concurrent gastric and H&N cancers, the intraesophageal multiplicity of the esophageal carcinoma is more frequent than in other types of esophageal cancer.<sup>11)</sup> In addition, cancer of the colon/rectum is relatively frequent. Preoperative screening is essential because the colon is often used for reconstruction after esophagectomy if the stomach is not available.

### Histopathological Characteristics

#### Squamous epithelial dysplasia

Dysplasia is a disordered growth of epithelium that can be regarded as precancerous, and includes intraepithelial lesions that are not sufficiently atypical to designate as carcinoma *in situ*. Dysplasia and carcinoma *in situ* of the

**Table 2. Double primary cancer-organs (in cases of esophagectomy)**

Organs	Our cases (1971-2000)			JSED (1997)		
	Synchronous	Metachronous		Synchronous	Metachronous	
		Before E-Ca	After E-Ca		Before E-Ca	After E-Ca
Stomach	20 (71.4%)	10 (37.0%)	3 (20.0%)	85 (50.0%)	33 (28.4%)	5 (21.7%)
Head and neck cancer	3 (10.7%)	3 (11.1%)	4 (2.67%)	42 (24.7%)	23 (19.8%)	9 (39.1%)
Lung/trachea/bronchus	1 (3.6%)	2 (7.4%)	3 (20.0%)	4 (2.4%)	10 (8.6%)	4 (17.4%)
Breast		3 (11.1%)			7 (6.0%)	
Colon/rectum	3 (10.7%)	1 (3.7%)	2 (13.3%)	20 (11.8%)	14 (12.1%)	2 (8.7%)
Liver	1 (3.6%)		1 (6.7%)	2 (1.2%)	1 (0.9%)	
Skin		1 (3.7%)		2 (1.2%)	2 (1.7%)	
Uterus/ovaruum		1 (3.7%)			4 (3.4%)	
Prostate/urinary bladder		2 (7.4%)	2 (13.3%)	1 (0.6%)	4 (3.4%)	1 (4.3%)
Others				14 (8.2%)	15 (12.9%)	2 (8.7%)
Unknown		4 (14.8%)			3 (2.6%)	
Lesions	28 (100.0%)	27 (100.0%)	15 (100.0%)	170 (100.0%)	116 (100.0%)	23 (100.0%)

E-Ca: esophageal cancer

esophagus are being diagnosed with increasing frequency, particularly in areas with a high incidence of invasive esophageal carcinoma.<sup>27,28)</sup> Epithelial dysplasia is characterized by cellular atypia, abnormal differentiation and disorganized architecture, all of these features being more prominent in severe or high-grade dysplasia. Dysplasia of the squamous epithelium is classified as mild, moderate or severe, according to the degree of atypia in the “Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus” proposed by the JSED.

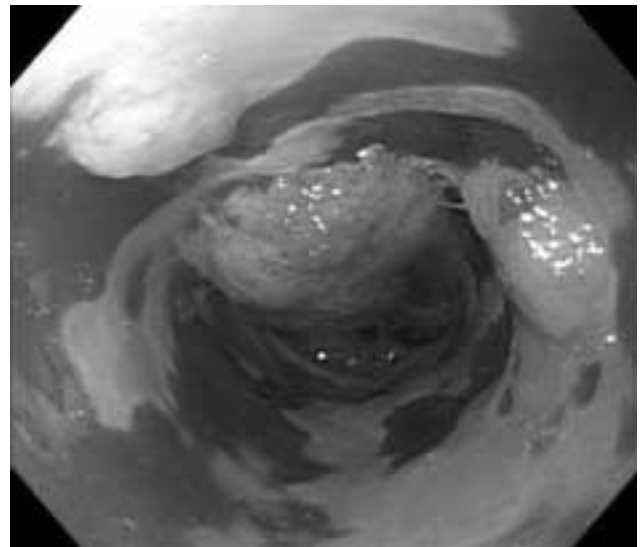
#### Coexistence of squamous epithelial dysplasia

Squamous epithelial dysplasia is frequently found in the esophagus with squamous cell carcinoma, and several studies have also suggested its significance as a precancerous lesion.<sup>29)</sup> Our study revealed dysplastic lesions in 43 (64.2%) in the 67 cases of esophageal cancer without any preoperative treatment. According to the “Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus” proposed by the JSED, there are moderate-severe dysplasia lesions in 30 of the 43 cases with dysplasia. We also showed that the less advanced the lesion, the higher the incidence of dysplasia; while in cases with dysplastic lesions, both the multiplicity of squamous cell carcinoma and the intraepithelial spread of the main lesion were more frequent, suggesting the multicentric occurrence of dysplastic lesions and carcinomas.<sup>30)</sup>

#### Coexistence of intraepithelial spread

Intraepithelial spread is infiltration by tumor cells within the mucosal surface epithelium, without extending into

the deeper wall layers (Fig. 1). The occurrence of intraepithelial carcinoma of the esophagus, associated with invasive carcinoma, has important implications for both evaluation of the extent of surgical treatment and the understanding of the pathogenesis of esophageal carcinoma.<sup>31)</sup> We investigated 127 cases of esophageal carcinoma, which included 56 (44.1%) with intraepithelial carcinoma contiguous with the main lesion (Table 3). To interpret these findings, the theory of widespread carcinomatous transformation is the most acceptable explanation for the histogenesis of the intraepithelial carcinomatous area.<sup>32)</sup>



**Fig. 1.** Endoscopic view of a protruded mid-esophageal carcinoma with intraepithelial spread (Lugol-staining).

**Table 3. Pathological findings of resected specimens**

		Our cases (1983-2001)		JSED (1997)	
Blood vessel invasion	v (-)	69	(54.3%)	940	(48.3%)
	v (+)	58	(45.7%)	897	(46.0%)
	Unknown			111	(5.7%)
Lymphatic vessel invasion	ly (-)	46	(36.2%)	542	(27.8%)
	ly (+)	81	(63.8%)	1,300	(66.7%)
	Unknown			106	(5.4%)
Intraepithelial spread	ie (-)	71	(55.9%)	1,069	(54.9%)
	ie (+)	56	(44.1%)	693	(35.6%)
	Unknown			186	(9.5%)
Intramural metastasis in the esophageal wall (im-e)	im-e (-)	113	(89.0%)	1,680	(86.2%)
	im-e (+)	14	(11.0%)	171	(8.8%)
	Unknown			97	(5.0%)
Intramural metastasis in the stomach wall (im-st)	im-st (-)	119	(93.7%)	1,743	(89.5%)
	im-st (+)	8	(6.3%)	43	(2.2%)
	Unknown			162	(8.3%)
Multiple primary carcinoma	(-)	106	(83.5%)	1,570	(80.6%)
	(+)	21	(16.5%)	374	(19.2%)
	Unknown	0	(0%)	4	(0.2%)
Total		127		1,948	

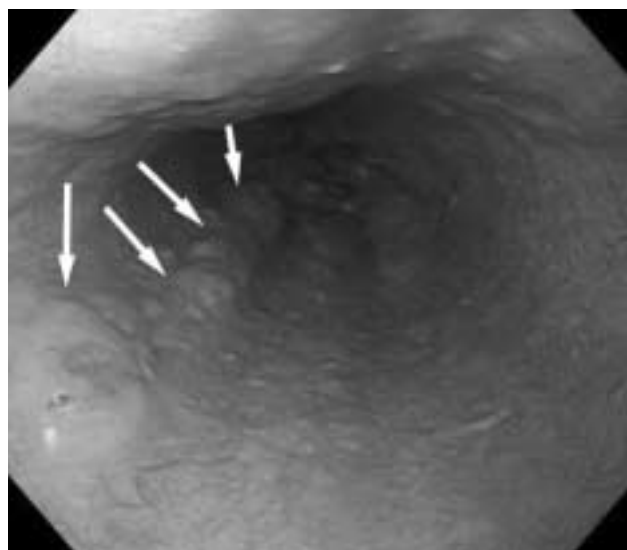
### Blood vessel and lymphatic permeation

The occurrence of blood vessel and lymphatic permeation was found in 58 (45.7%) and 81 (63.8%) of resected specimens, respectively (Table 3). In our data, blood vessel permeation was not found in 14 cases of mucosal carcinoma, while lymphatic permeation was found in one case (7.1%). However, blood vessel and lymphatic permeation were found in 44.4% and 63.9% of cases with submucosal carcinoma, respectively. It was reported that vascular permeation was found in 29% of cases with mucosal carcinoma which had invaded the lamina propria and muscularis mucosae.<sup>33)</sup> Because it was reported that lymphatic permeation was a good predictor of lymph node metastasis in patients with superficial esophageal carcinoma,<sup>34,35)</sup> the expansive indication for endoscopic membrane resection (EMR) and an additional operation, should be considered according to indications in cases of mucosal and submucosal carcinoma.

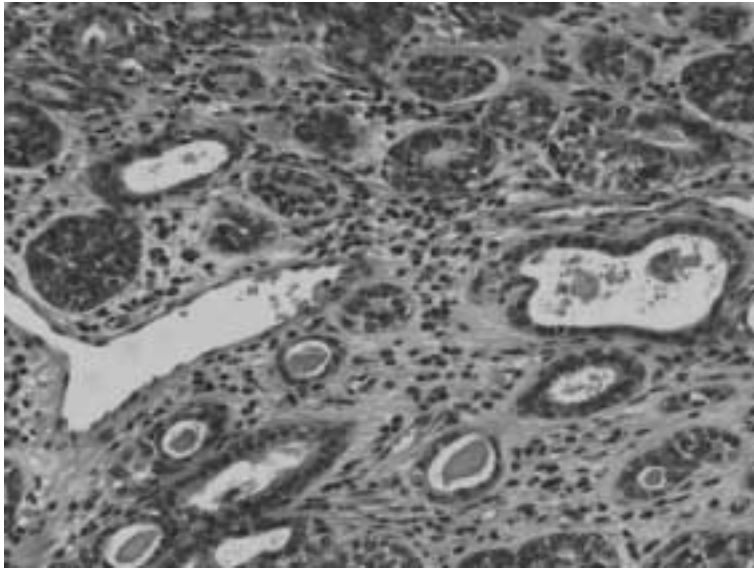
### Intramural metastasis

Metastasis from an esophageal carcinoma to the esophagus or stomach is termed intramural metastasis (Fig. 2), and this has been considered an important pathway for

tumor spread.<sup>36)</sup> Intramural metastasis from the primary lesions in the esophagus has often been found in the resected esophagus, with an incidence of 11-16%.<sup>37-39)</sup>



**Fig. 2.** Endoscopic view of intramural metastasis (arrows) from an ulcerated lower esophageal carcinoma.



**Fig. 3.** Microscopic photograph of a glandular differentiation in esophageal squamous cell carcinoma (H&E,  $\times 200$ ).

According to the JSED data, 8.8% of resected esophaguses had intramural metastasis within the esophageal wall, while our data showed 14 cases (11%) (Table 3). The incidence of intramural metastasis to the gastric wall was 2.2% in the JSED data, but was 6.3% in our data. Although the prognosis for multiple carcinomas is similar to that for a single carcinoma, the prognosis for carcinoma with intramural metastasis is much poorer than that for carcinomas without intramural metastasis. This is the reason that almost all the cases of esophageal carcinoma with intramural metastasis also have lymph node metastasis at surgery, and also distant organ metastasis is significantly more frequent in patients with intramural metastasis than in those without it.<sup>40)</sup> Therefore, it is considered as one of the independent significant prognostic factors for predicting a poor prognosis in esophageal cancer.

#### **Multiple primary carcinomas**

The occurrence of the multiple independent growth of carcinomas in any organ was thought to be a rare phenomenon, with the exception of polyposis of the colon and epidermal tumors of the skin. However, our data on 127 patients in our institution with esophageal squamous cell carcinoma who underwent a subtotal esophagectomy revealed 21 cases (16.5%) and 63 lesions (mean, 3.0) with multiple primary squamous cell carcinomas (Table 3). In the JSED data, 12.1% of the resected specimens showed multiple primary carcinomas. There are other reports concerning multiple primary carcinomas.<sup>41)</sup> Based on these findings, multiple squamous cell carcinoma of the esophagus is not rare. In addition, Pesko et al. recently demon-

strated a 31% incidence of multiplicity in esophageal squamous cell carcinoma, and proposed the concept that the entire esophagus may therefore be considered as one entity in the area of carcinogenesis.<sup>42)</sup>

#### **Coexistence of glandular differentiation with squamous cell carcinoma**

The most common histologic type of esophageal cancer is squamous cell carcinoma. In contrast, primary adenocarcinoma of the esophagus occurs only rarely. Primary adenocarcinoma of the esophagus is thus considered to occur most commonly in the esophagogastric junction, including Barrett's esophagus, or in the ectopic gastric mucosa. However, they also occur in the esophageal submucosa, exhibiting a histologic pattern resembling that seen in adenoid cystic or mucoepidermoid tumors of salivary gland origin.<sup>43)</sup>

Our study of 67 patients with carcinoma of the esophagus included 13 cases (19.4%) with glandular and/or mucus-secreting components in addition to the ordinary components of squamous cell carcinoma. The histologic features of such glandular differentiation were reminiscent of those seen in salivary gland tumors, and they were frequently located in the submucosa and lamina propria mucosae, suggesting that such differentiation had arisen in either the esophageal glands or their ducts (Fig. 3). These findings suggest that this type of esophageal tumor originated not only from the covering squamous epithelium but also from the esophageal mucus gland or ductal epithelium, thus supporting the concept of the field origin of carcinogenesis in esophageal carcinoma.<sup>44)</sup>

Consequently, serial histopathological investigations revealed that the esophageal cancer was not a monotonous squamous cell carcinoma but instead it showed various clinicopathological characteristics. As a result, surgeons must be careful to do serial preoperative assessments, not only of the extension of the esophageal lesions, but also of any associated malignancies, especially in the H&N and gastric regions, while bearing in mind the occasionally peculiar histological features of esophageal cancer.

## References

1. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 2000; **232**: 225–32.
2. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcome of resected esophageal cancer. *Ann Surg* 2002; **236**: 376–85.
3. Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2002; **183**: 274–9.
4. Sugimachi K, Ohno S, Matsuda H, Mori M, Kuwano H. Lugol-combined endoscopic detection of minute malignant lesions of the thoracic esophagus. *Ann Surg* 1988; **208**: 179–83.
5. The Japanese Society for Esophageal Diseases. Comprehensive Registry of Esophageal Cancer in Japan (1995, 1996, 1997), 2nd ed., The Japanese Society for Esophageal Diseases, Japan, 2001.
6. Sugimachi K, Sumiyoshi K, Nozoe T, et al. Carcinogenesis and histogenesis of esophageal carcinoma. *Cancer* 1995; **75**: 1440–5.
7. Ribeiro U Jr, Posner MC, Safatle-Ribeiro AV, Reynolds JC. Risk factors for squamous cell carcinoma of the oesophagus. *Br J Surg* 1996; **83**: 1174–85.
8. Chang F, Syrjanen S, Wang L, Syrjanen K. Infectious agents in the etiology of esophageal cancer. *Gastroenterology* 1992; **103**: 1336–48.
9. Toh Y, Kuwano H, Tanaka S, et al. Detection of human papillomavirus DNA in esophageal carcinoma in Japan by polymerase chain reaction. *Cancer* 1992; **70**: 2234–8.
10. Crespi M, Munoz N, Grassi A, Qiong S, Jing WK, Jien LJ. Precursor lesions of oesophageal cancer in a low-risk population in China: comparison with high-risk populations. *Int J Cancer* 1984; **34**: 599–602.
11. Kuwano H, Morita M, Tsutsui S, Kido Y, Morei M, Sugimachi K. Comparison of characteristics of esophageal squamous cell carcinoma associated with head and neck cancer and those with gastric cancer. *J Surg Oncol* 1991; **46**: 107–9.
12. Kuylenstierna R, Munck-Wikland E. Esophagitis and cancer of the esophagus. *Cancer* 1985; **56**: 837–9.
13. Oettle GJ, Paterson AC, Leiman G, Segal I. Esophagitis in a population at risk for esophageal carcinoma. *Cancer* 1986; **57**: 2222–9.
14. Blot WJ. Esophageal cancer trends and risk factors. *Semin Oncol* 1994; **121**: 403–10.
15. Yokoyama A, Muramatsu T, Ohmori T, Higuchi S, Hayashida M, Ishii H. Esophageal cancer and aldehyde dehydrogenase-2 genotypes in Japanese males. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 99–102.
16. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancer. *Science* 1991; **253**: 49–53.
17. Hollstein MC, Metcalf RA, Welsh JA, Montesano R, Harris CC. Frequent mutation of the p53 gene in human esophageal cancer. *Proc Natl Acad Sci U S A* 1990; **87**: 9958–61.
18. Kato H, Yoshikawa M, Miyazaki T, et al. Expression of p53 protein related to smoking and alcoholic beverage drinking habits in patients with esophageal cancers. *Cancer Lett* 2001; **153**: 121–7.
19. Sasano H, Gouton Y, Nishihara T, Nagura H. In situ hybridization and immunohistochemistry of p53 tumor suppressor gene in human esophageal carcinoma. *Am J Pathol* 1992; **141**: 545–50.
20. Japanese Society for Esophageal Diseases. Guidelines for the clinical and pathological studies on carcinoma of the esophagus, 9th ed., Tokyo: Kanehara; 1999.
21. Namieno T, Koito K, Higashi T, Sato N, Uchino J. General pattern of lymph node metastasis in early gastric carcinoma. *World J Surg* 1996; **20**: 996–1000.
22. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002; **45**: 200–6.
23. Akiyama H, Tsurumaru M, Kawamura T, Ono Y. Principles of surgical treatment for carcinoma of the esophagus. *Ann Surg* 1981; **197**: 428–46.
24. Nishimaki T, Tanaka O, Suzuki T, Aizawa K, Hatakeyama K, Muto T. Patterns of lymphatic spread in thoracic esophageal cancer. *Cancer* 1994; **74**: 4–11.
25. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery* 1998; **123**: 432–9.
26. Tanaka Y, Mafune K, Miyama K, et al. Studies of esophageal cancer with other primary malignant tumors. *J Saitama Med Soc* 1986; **21**: 381–5. (in Japanese)
27. Ackerman LV, Weinstein IB, Kaplan HS, et al. Cancer of the esophagus. In: Kaplan HS, Tsuchitani PJ, eds.; Cancer in China. New York: Alan R Liss Inc., 1978; pp 111–36.
28. Sugimachi K, Ikebe M, Kitamura K, Toh Y, Matsuda H, Kuwano H. Long-term results of esophagectomy for early esophageal carcinoma. *Hepatogastroenterology* 1993; **40**: 203–6.
29. Takubo K, Tsuchiya S, Fukushi K, Shiota A, Mitomo Y. Dysplasia and reserve cell hyperplasia-like change in human esophagus. *Acta Pathol Jpn* 1981; **31**: 999–

- 1013.
30. Kuwano H, Watanabe M, Sadanaga N, Ikeda M, Mori M, Sugimachi K. Squamous epithelial dysplasia associated with squamous cell carcinoma of the esophagus. *Cancer Lett* 1993; **72**: 141–7.
  31. Soga J, Tanaka O, Sasaki K, Kawaguchi M, Muto T. Superficial spreading carcinoma of the esophagus. *Cancer* 1982; **50**: 1641–5.
  32. Kuwano H, Matsuda H, Matsuoka H, Kai H, Okudaira Y, Sugimachi K. Intra-epithelial carcinoma concomitant with esophageal squamous cell carcinoma. *Cancer* 1987; **59**: 783–7.
  33. Takubo K, Takai A, Takayama S, Sasajima K, Yamashita K, Fujita K. Intraductal spread of esophageal squamous cell carcinoma. *Cancer* 1987; **59**: 1751–7.
  34. Tajima Y, Nakanishi Y, Ochiai A, et al. Histopathological findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; **88**: 1285–93.
  35. Nakajima Y, Nagai K, Miyake S, Ohashi K, Kawano T, Iwai T. Evaluation of an indicator for lymph node metastasis of esophageal squamous cell carcinoma invading the submucosal layer. *Jpn J Cancer Res* 2002; **93**: 305–12.
  36. Watson WL. Carcinoma of the oesophagus. *Surg Gynecol Obstet* 1933; **56**: 884–97.
  37. Takubo K, Sasajima K, Yamashita K, Tanaka Y, Fujita K. Prognostic significance of intramural metastasis in patients with esophageal carcinoma. *Cancer* 1990; **65**: 1816–9.
  38. Kato H, Tachimori Y, Watanabe H, Itabashi M, Hirota T, Yamaguchi H. Intramural metastasis of thoracic esophageal carcinoma. *Int J Cancer* 1992; **50**: 49–52.
  39. Kuwano H, Watanabe M, Sadanaga N, et al. Univariate and multivariate analyses of the prognostic significance of discontinuous intramural metastasis in patients with esophageal cancer. *J Surg Oncol* 1994; **57**: 17–21.
  40. Takubo K. Epithelial dysplasia and squamous cell carcinoma: pathology of the esophagus. Tokyo: EDUCA Inc., 2000; pp 131–68.
  41. Hosokawa M, Koizumi H. Report on Questionnaire Survey of Multiple Superficial Carcinoma of the Esophagus (1992-1996) in the 38th Meeting of the Japanese Research Society for Early Esophageal Cancer and Chromoendoscopy. Sapporo: 1997.
  42. Pesko P, Rakic S, Miliceric M, Bulajic P, Gerzic Z. Prevalence and clinicopathologic features of multiple squamous cell carcinoma of the esophagus. *Cancer* 1994; **73**: 2687–90.
  43. Bell-Thompson J, Haggitt RC, Ellis FH Jr. Mucoepidermoid and adenoid cystic carcinomas of the esophagus. *J Thorac Cardiovasc Surg* 1980; **79**: 438–46.
  44. Kuwano H, Ueo H, Sugimachi K, Inokuchi K, Toyoshima S, Enjoji M. Glandular or mucus-secreting components in squamous cell carcinoma of the esophagus. *Cancer* 1985; **56**: 514–8.