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Polypoid Carcinoma of the Esophagus

Masaki Mori,[1] Koshi Mimori, Noriaki Sadanaga, Masayuki Watanabe, Hiroyuki Kuwano and Keizo Sugimachi

Second Department of Surgery, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812

Polypoid carcinoma of the esophagus is rare and little is known about its clinical and histopathologic features. We reviewed 500 surgical cases of esophageal carcinoma and analyzed 12 polypoid carcinomas. Clinical records were reviewed. Histologic examination was done on an average of 68 sections in each tumor. Immunohistochemical examination for proliferating cell nuclear antigen (PCNA) was done in selected sections. No special findings were seen with respect to age, sex, symptoms, or tumor location. The tumors, however, had several interesting features: 1) the main histologic type was squamous cell carcinoma, but other histologic features such as so-called carcinosarcoma, adenoid cystic carcinoma, and verrucous carcinoma were occasionally seen, 2) bidirectional differentiation to squamous and adenocarcinomatous components was recognized, 3) intraepithelial spreading of the carcinoma was often present, 4) depth of invasion in the wall was often shallow, and 5) the prognosis was relatively good. The PCNA labeling index was well correlated with lymphatic or blood vessel permeation.

Key words: Esophageal carcinoma — Polypoid carcinoma — Adenocarcinoma — Squamous cell carcinoma — Carcinosarcoma

Most carcinomas of the esophagus show variable admixtures of the gross types and do not fit exclusively in any one category. Pure intraluminal polypoid type carcinomas of the esophagus are rare and most of them are reported to be histologically so-called carcinosarcomas.[1–3] Some of these tumors, however, exhibit other histologic types such as squamous cell carcinoma.[4]

There is little information on clinical and histopathologic features of intraluminal polypoid carcinoma of the esophagus. We analyzed 12 such cases and the findings are described here.

MATERIALS AND METHODS

From 1965 to 1991, 500 patients with esophageal carcinoma underwent subtotal or total esophagectomy in the Second Department of Surgery, Kyushu University Hospital. Twelve of the 500 tumors were grossly intraluminal polypoid lesions. Only large, intraluminal, polypoid tumors were considered. Plaque-like fungating masses and tumors with multiple facets of expression were excluded. A representative tumor is shown in Fig. 1.

We reviewed the clinical records of the 12 patients. Macroscopic and microscopic evaluations were made according to rules established by the Japanese Research Society for Esophageal Cancer.[5] The new TNM classification was used to determine the stage of the disease.[6] The resected esophagus containing the primary tumor was cut into multiple slices of approximately 4 mm thickness, and all the slices were further cut into 35 to 109 blocks (average 68). Each block was cut into 5-μm-thick sections, which were stained with hematoxylin and eosin for histologic examination. Selected sections were also stained with periodic acid-Schiff and Alcian blue (PAS-AB) for mucin and with Grimelius for cytoplasmic argyrophilia.

To assess the proliferating activity in each tumor the avidin-biotin-peroxidase complex (ABC) method[7] was used to immunostain for proliferating cell nuclear antigen (PCNA). The primary antibody, PC10, which is a monoclonal mouse antibody for rat PCNA, was purchased from Dako Corp. (Carpinteria, CA). The procedure is described elsewhere.[8] For statistical analysis of the PCNA data, the chi-square test was used.

Survival curves were drawn using the Kaplan-Meier procedure, and the data were analyzed using the generalized Wilcoxon test.

RESULTS

Clinical data are summarized in Table I. All patients were Japanese. The youngest was a 36-year-old man and the oldest a 77-year-old man, the mean age at presentation being 66 years. Ten tumors occurred in men and two in women. The presenting symptom was dysphagia in ten. The other two had complained of epigastric pain and

[1] To whom correspondence should be addressed, at the Department of Surgery, Medical Institute of Bioregulation, Kyushu University, 4546 Tsurumibaru, Beppu 874.

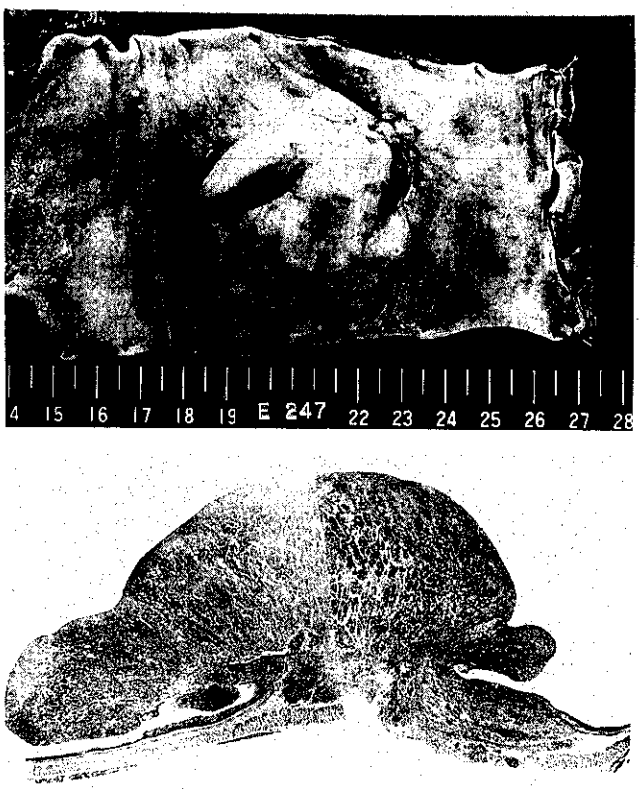

Fig. 1. A case of polypoid carcinoma of the esophagus (Case 3). The upper panel shows the surgically resected specimen. The polypoid lesion is pedunculate. The lower panel shows the cut section of the pedunculated polypoid carcinoma. The main location of the tumor is the mucosa and the submucosa. Invasion is seen beyond the proper muscular layer.

retrosternal pain, respectively. Seven tumors were in the middle third of the thoracic esophagus, one in the upper third, one in the lower third, and one in the cervical esophagus. The remaining two were located in both the middle and the lower thoracic esophagus. All patients underwent surgical resection, with or without combined treatment. Four died of recurrent or metastatic disease, and two died of other diseases. The other six were well with no evidence of metastases. The 5-year survival rate of these 12 patients was 44% and better than that of the other 488 patients (24%, $P<0.01$).

The pathologic data are summarized in Table II. The tumor length ranged from 1.5 cm to 8.5 cm, the mean being 4.3 cm. Histologically, three tumors were moderately differentiated squamous cell carcinomas, and four were poorly differentiated squamous cell carcinomas. The other five exhibited rare histologic types in part or in whole; one well differentiated squamous cell carcinoma partly accompanied with verrucous carcinoma (Fig. 2), two squamous cell carcinomas with basaloid and adenoid cystic carcinomatous areas (Fig. 3), and two so-called carcinosarcomas. The verrucous area in Case 10 showed a papillary tumor composed of well-differentiated squamous epithelium with hyperkeratosis, marked acanthosis, swollen rete-pegs and pushing margins. The squamous cell carcinomas of Cases 3 and 7 were intermingled with both basaloid patterns and cystic or cribriform patterns. The cystic spaces showed positive staining with AB and negative staining with PAS (Fig. 3). The so-called carcinosarcoma consisted mainly of anaplastic spindle cells arranged in broad fascicles that randomly intersected with each other. Islands of squamous cell carcinoma were present within the sarcomatous components.

Table I. Clinical Data on 12 Patients with Polypoid-type Carcinoma of the Esophagus

Case	Age/Sex	Symptoms	Tumor site	Treatment	Follow up (months)
1	62/M	Dysphagia	Middle 1/3	SE	Died of other disease (98)
2	75/M	Dysphagia	Middle 1/3	SE	DOD (2)
3	71/F	Dysphagia	Middle 1/3	SE+chemoradiotherapy	DOD (34)
4	72/F	Dysphagia	Middle 1/3	SE	Died of other disease (30)
5	73/M	Dysphagia	Lower 1/3	SE	DOD (25)
6	43/M	Dysphagia	Cervical	TE+radiotherapy	Alive and well (38)
7	57/M	Dysphagia	Upper 1/3	SE	Alive and well (34)
8	36/M	Epigastralgia	Middle 1/3	SE	Alive and well (34)
9	77/M	Retrosternal pain	Middle and lower	SE	DOD (3)
10	75/M	Dysphagia	Middle and lower	SE	Alive and well (25)
11	73/M	Dysphagia	Middle 1/3	SE	Alive and well (22)
12	66/M	Dysphagia	Middle 1/3	SE	Alive and well (4)

SE: subtotal esophagectomy with regional lymph nodes dissection. TE: total esophagectomy with regional lymph nodes dissection. DOD: died of disease. The number in parenthesis is the number of months after operation. Cases 3 and 5 showed widespread metastases especially to the lung and liver through the hematogenous route. Cases 2 and 9 showed lymphatic recurrence.

Table II. Histopathologic Data on 12 Polypoid-type Carcinomas of the Esophagus

Case	Tumor size (cm)	Histologic type	Adeno-differentiation	Grimelius	ly	v	n	PCNA index (%)	ep	Depth of invasion	TNM stage
1	3.5×2.5×1.2	Mod SCC	−	−	−	−	−	39	+	sm	I
2	3.5×2.0×1.1	Mod SCC	+	−	+	−	+	68	−	sm	IV
3	5.5×4.8×2.6	SCC with adenoid cystic and basaloid	+	−	+	+	−	74	+	a	IV
4	2.8×2.4×1.4	Poor SCC	−	−	−	−	−	47	+	sm	I
5	3.1×1.6×1.4	Poor SCC	−	−	−	+	−	63	+	sm	I
6	8.0×5.0×4.6	Carcinosarcoma	−	−	−	+	−	59	+	sm	I
7	1.5×0.9×1.9	SCC with adenoid cystic and basaloid	+	−	−	−	−	54	+	sm	I
8	2.0×1.0×1.1	Mod SCC	+	−	+	−	−	65	+	sm	I
9	8.5×5.2×3.2	Poor SCC	+	−	+	−	+	71	+	pm	IIIa
10	6.0×4.5×2.8	Well SCC with verrucous	−	−	−	−	−	38	−	pm	I
11	3.0×2.1×2.1	Poor SCC	+	−	−	−	−	42	−	sm	I
12	3.2×2.0×2.0	Carcinosarcoma	+	−	+	−	+	76	+	pm	IIIa

SCC: squamous cell carcinoma. Well: well differentiated. Mod: moderately differentiated. Poor: poorly differentiated. Adeno-differentiation: adenocarcinomatous differentiation. ly: lymph vessel invasion. v: blood vessel invasion. n: lymph node metastasis. PCNA index: proliferating cell nuclear antigen labeling index. ep: intraepithelial spreading. sm: submucosal layer. pm: proper muscular layer. a: adventitia. The involved lymph nodes were the middle thoracic paraesophageal and tracheal bifurcation lymph nodes in Cases 2 and 12, and the middle and lower thoracic paraesophageal lymph nodes in Case 9. The number of metastatic/total lymph nodes was 3/18 in Case 2, 3/26 in Case 9, and 5/24 in Case 12.

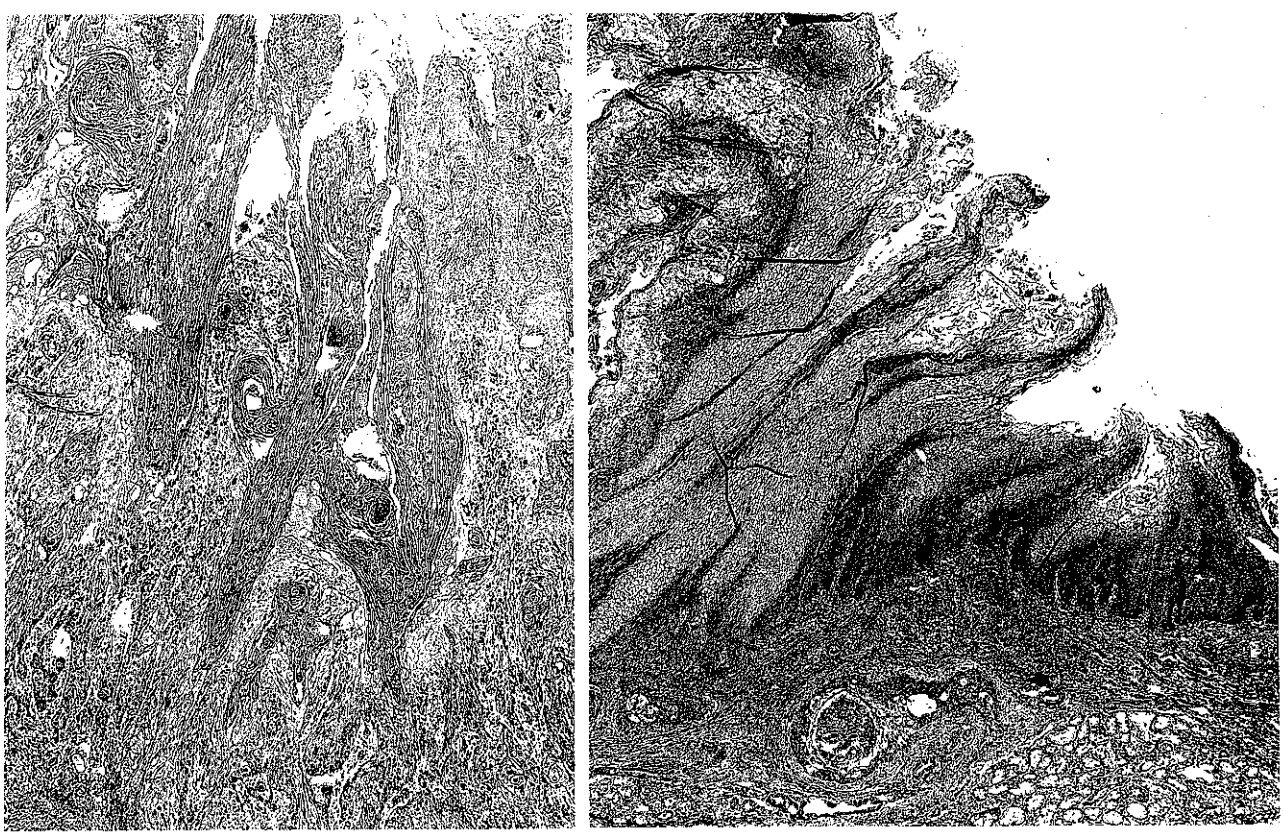

Fig. 2. A well differentiated squamous cell carcinoma accompanied with an area of verrucous carcinoma of the esophagus (Case 10, hematoxylin and eosin, ×66). A well differentiated squamous cell carcinomatous area is shown on the left, and a verrucous carcinomatous area on the right.

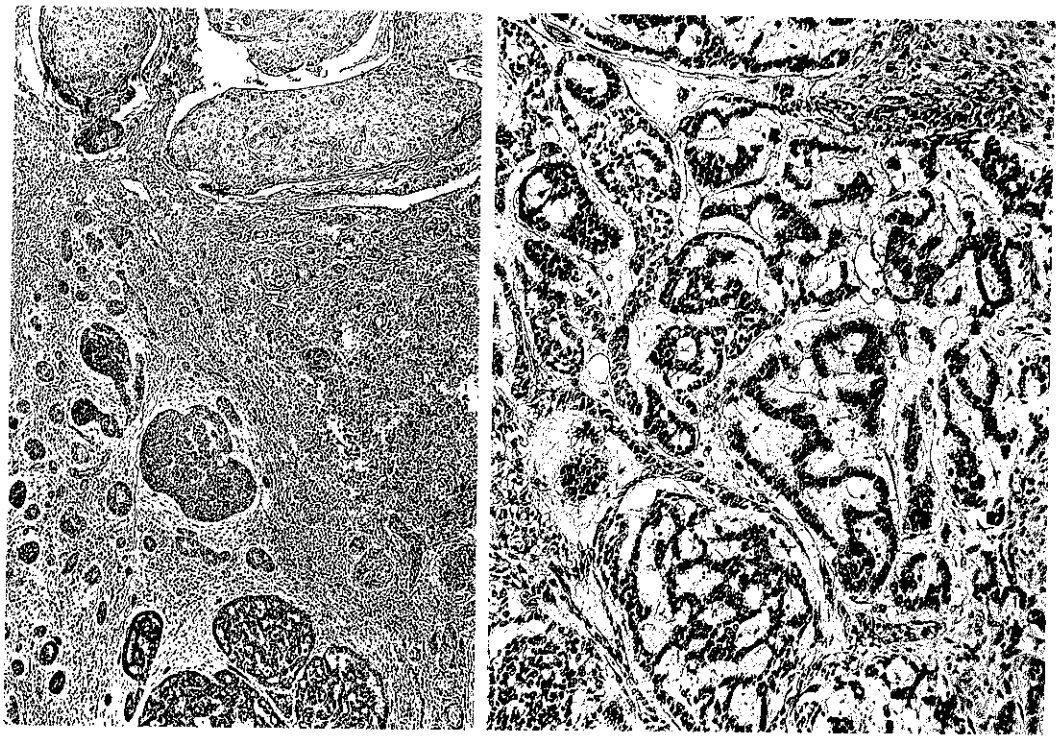

Fig. 3. A squamous cell carcinoma accompanied with areas of adenoid cystic carcinoma or basaloid carcinoma of the esophagus (Case 3, hematoxylin and eosin, ×98). Nests of squamous cell carcinoma are shown in the upper portion of the left photograph, and adenoid cystic components are shown in the left lower portion of the left photograph and on the right photograph.

The polypoid carcinomas showed several interesting histologic features. The first was that they consisted of abundant carcinomatous tissue and little stroma in all but the so-called carcinosarcoma cases. The tumors oppressed the normal squamous epithelium at the edge of the tumor in seven cases. The advancing margin was well circumscribed, showing expansive growth in 10 cases. The second feature was that many tumors showed bidirectional differentiations; five squamous cell carcinomas demonstrated small areas of adenocarcinomatous differentiation evidenced by glandular appearance or mucin production (Fig. 4). Two other squamous cell carcinomas showed areas of adenoid cystic pattern (Fig. 3). No neuroendocrine differentiation, however, was recognized in any case by Grimelius staining. The third feature was the high frequency of intraepithelial spreading of squamous cell carcinoma (Fig. 5). This was seen in nine cases. The exact spreading area was hardly recognizable by naked-eye observation but was readily visible by Lugol staining. The fourth feature was that the depth of the tumor invasion was shallow; only four invaded the proper muscular layer or beyond it. The frequency of stage I cases was high (8/12) in the polypoid carcinomas.

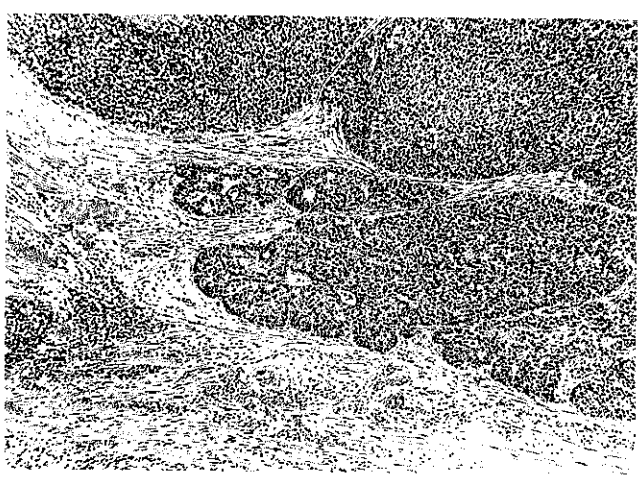

Fig. 4. A case of poorly differentiated squamous cell carcinoma with an area of adenocarcinomatous differentiation. Note small glandular components in the advancing margin (Case 9, hematoxylin and eosin, ×98).

There was a heterogeneity of PCNA labeling index in each tumor; a high index was often seen in the advancing margin of the tumor and a low index in the other areas

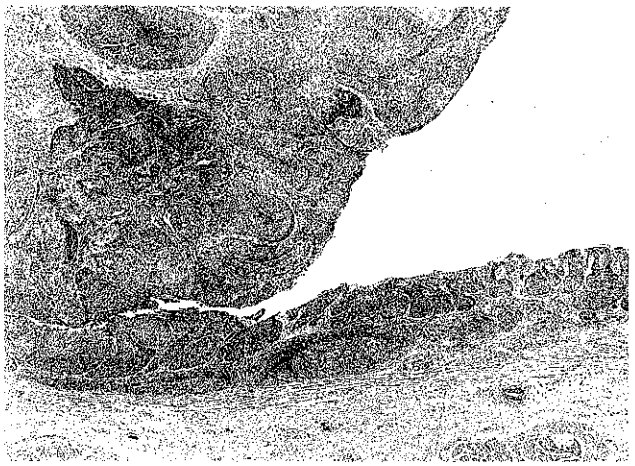

Fig. 5. Intraepithelial spreading of the squamous cell carcinoma contiguous to the main polypoid carcinoma (Case 7, hematoxylin and eosin, ×42).

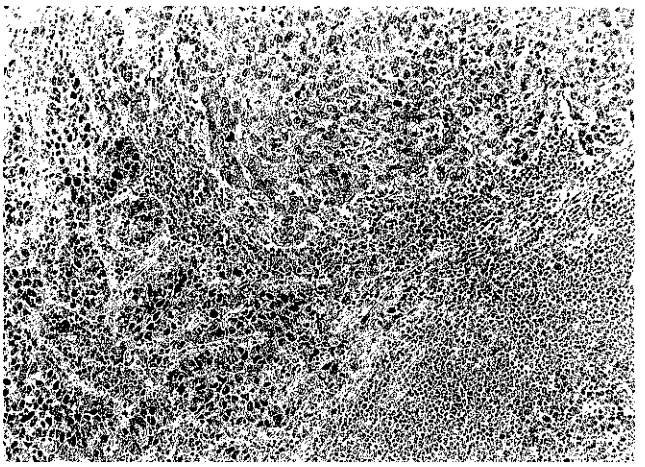

Fig. 6. Immunohistochemical stain for PCNA (Case 2, ×210). The positive staining is seen in the nucleus. The carcinoma cells in the advancing margin frequently stain positive, while those in the central area stain infrequently, showing a heterogeneity of tumor proliferation state.

(Fig. 6). The PCNA labeling index was, therefore, evaluated in the advancing margin according to our method.[8] Interestingly, the PCNA labeling index was high (67 ± 6.1) in six tumors with vessel permeation and low (44 ± 6.6) in five without vessel permeation, a significant difference ($P < 0.01$).

DISCUSSION

Pure polypoid carcinoma of the esophagus is rare. Olmsted *et al.* reported 22 bulky polypoid epithelial malignancies of the esophagus, of which 15 were squamous cell carcinomas with anaplastic spindle cells.[1] On the other hand, some of the squamous cell carcinomas of the esophagus take the gross appearance of the polypoid type: Sasajima *et al.* reported seven such cases.[4] In our series, the most common histologic type of polypoid-type carcinoma of the esophagus was squamous cell carcinoma.

Although squamous cell carcinoma was the most common histologic type in the polypoid carcinomas of the esophagus, histologic areas other than so-called carcinosarcoma were occasionally seen. One tumor showed an area of verrucous carcinoma, which is a rare variant of well-differentiated squamous cell carcinoma.[9] Another two showed areas of adenoid cystic carcinomas and basaloid carcinomas.[10, 11] We have not encountered any case of carcinoma with predominant adenoid cystic area in any other gross type of esophageal carcinoma. Only 50 cases of this type of tumor have been reported in the English literature.[10]

We have reported that 20% of esophageal squamous cell carcinomas had small areas of adenocarcinomatous differentiation somewhere in the tumor.[12] Another interesting feature of polypoid carcinoma of the esophagus was the greater tendency to show adenocarcinomatous differentiation in the squamous cell carcinomas. This was recognized in four squamous cell carcinomas and one of two so-called carcinosarcomas. These findings suggest the multipotentiality of esophageal carcinoma cells; the cells can differentiate toward squamous and adenocarcinomatous components, as we described in cases of small cell carcinoma of the esophagus.[13]

Surgeons should carefully consider the resection line of the proximal esophagus because 20% of squamous cell caricnomas had intraepithelial spreading of the carcinoma.[14, 15] Our polypoid carcinomas of the esophagus exhibited more frequent intraepithelial spreading than does ordinary squamous cell carcinoma. Lugol staining of the esophagus during operation would be useful to determine an adequate resection line of the esophagus.[15]

Sasajima *et al.* reported that 1) the survival rate of patients with the polypoid type of esophageal cancer was much better than that of patients with the other gross types and 2) the depth of tumor invasion in the wall was less compared with the other types.[4] These findings were confirmed in our study; the 5-year survival rate was 56%, better than the ordinary type, and eight of the 12 tumors were restricted to within the submucosal layer. As the polypoid-type carcinomas may easily lead to dysphagia, they may be diagnosed at an early stage, resulting in a good prognosis.

The PCNA labeling index is a good marker for tumor cell proliferation and may be a useful prognostic indi-

cator in certain tumors.[16] There are differences in proliferating activity in different areas of the same tumor (that is, a heterogeneity of tumor proliferation state).[17] We have demonstrated that PCNA-positive cells occur more frequently in the advancing margin of the cancer compared to the other areas.[8] This finding was also recognized in polypoid carcinoma of the esophagus. The labeling index was well correlated with the status of lymph or blood vessel permeations, thereby suggesting its usefulness for predicting malignant potential.

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