Early Diagnosis of Esophageal Cancer

Analysis of 11 Cases of Esophageal Mucosal Cancer

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We reviewed 11 patients with esophageal mucosal carcinoma in various aspects to improve the early diagnosis of the disease. Eighteen lesions measuring 0.5 to 5.0 cm were confirmed histologically in the 11 cases. Histologically 10 of the 18 lesions were carcinomas *in situ* (ep cancer), and the other 8 lesions were carcinomas confined to the mucosa other than ep cancer (mm cancer); all 18 lesions were squamous cell carcinomas. Six (85.7%) of the seven mm cancers showed abnormal radiographic findings regardless of the size. Similarly these findings were noted on four of five (80%) ep carcinomas 2 cm or larger in size. All 15 lesions diagnosed before operation showed abnormal findings on conventional endoscopy regardless of the size and depth of transmural invasion. Morphologic change was observed in 9 lesions (53.3%), while 13 (86.7%) showed color change; most of the lesions (80%) were manifested as redness. Dyeing of the resected specimen with Lugol solution (Katayama Chemical Industries, Osaka, Japan) showed all 18 cancerous lesions as unstained areas. Among the 18 lesions, two lesions were unstained areas, which agreed with the areas determined histologically. An additional lesion was visible with dye endoscopy as an unstained area but it was not visible with radiography or conventional endoscopy. Dye endoscopy using Lugol solution is very important because it allows detection and evaluation of the extent of esophageal mucosal cancer.

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RECENTLY THERE APPEARED several reports[1-4] describing early stages of cancer in the esophagus, with marked advances in radiologic and endoscopic diagnosis in the diseases of the alimentary tract. The Japanese Society for Esophageal Diseases[5] defines superficial esophageal cancer as tumors whose transmural invasion is confined to the submucosa. This society also defines early esophageal cancer as superficial cancers free of lymphatic metastasis. Furthermore lesions confined to the esophageal mucosa are called mucosal cancers. Among these are those confined to the epithelial layer, the ep cancer, and those whose transmural invasion is the lamina propria mucosae or the muscularis mucosae, the mm cancer.[5] Unlike early gastric cancer, superficial esophageal cancers associated with lymphatic metastasis and those whose transmural invasion is up to the submucosa show much worse prognosis than ep and mm cancers. Based on this fact, in recent trends, esophageal mucosal cancers are treated as early ones. In detecting superficial esophgeal cancer, dye endoscopy by Lugol solution (Wisconsin Pharmacal Co., Jackson, WI) plays an important role because of the minimal morphologic change of the cancer.[6]

In this study, we reviewed 11 patients with esophageal mucosal carcinoma who were recently operated on to elucidate key points in the early diagnosis.

Patients and Methods

The 11 patients included in this study were operated on at Kumamoto University Medical School, Kumamoto Regional Medical Center, Kumamoto Municipal Hospital, or Kumamoto Red Cross Hospital. There were ten men and one woman and their ages ranged from 46 through 77 years, with an average age of 64.2 ± 8.7 years (Table 1). Multiple cancers were detected in four patients (patients 2, 4, 5, and 6). Patient 2 had 4 lesions; patient 4, 3 lesions; and patients 5 and 6, 2 lesions each (11 lesions in all). Histologically 10 of the 18 lesions were carcinomas *in situ*, and the other 8 lesions were mucosal carcinoma; all 18 lesions were squamous-cell carcinomas.

All the patients received radiography, conventional endoscopy, and biopsy. Dye endoscopy[7] by Lugol solution

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TABLE 1. *Clinical Data and Pathohistology of the Lesion in 11 Patients with Esophageal Mucosal Cancer*

Patient	Lesion	Sex	Age (yrs)	Symptoms	Coexistent Digestive Disease	Opportunity of Detection	Location	Gross Type	Depth of Cancer	Histologic Type
1	1	M	67	none	none	medical check-up	lower	flat	ep	mod SCC
2	2A	F	58	smart	none	symptoms	upper	flat	ep	mod SCC
	2B						upper	flat	ep	mod SCC
	2C						upper	flat	ep	mod SCC
	2D						middle	flat	mm	mod SCC
3	3	M	68	SGC	GC	other disease	middle	flat	ep	mod SCC
4	4A	M	67	none	GC	other disease	upper	flat	ep	mod SCC
	4B						middle	depr	mm	mod SCC
	4C						middle	flat	ep	mod SCC
5	5A	M	62	none	CC	other disease	lower	depr	ep	mod SCC
	5B						middle	depr	mm	mod SCC
6	6A	M	62	none	none	other disease	middle	depr	ep	mod SCC
	6B						middle	flat	mm	mod SCC
7	7	M	70	none	Ileus	other disease	lower	depr	ep	mod SCC
8	8	M	46	pain	none	symptoms	middle	elev	mm	mod SCC
9	9	M	72	SGC	GC	other disease	middle	depr	mm	mod SCC
10	10	M	77	smart	none	symptoms	middle	flat	mm	mod SCC
11	11	M	60	fullness	LC	symptoms	upper	elev	mm	por SCC

M, male; F, female; SGC, symptoms caused by gastric cancer; GC, gastric cancer; CC, colon cancer; LC, liver cirrhosis; depr, depressed; elev, elevated; mod SCC, moderately differentiated squamous-cell carcinoma; por SCC, poorly differentiated squamous-cell carcinoma.

was also performed on all the patients, except for patient 11. The resected specimen was dyed with Lugol solution immediately after resection. Thereafter the specimen was stretched appropriately on a board with pins and fixed with 10% formalin. Several days later the specimen was again dyed with Lugol solution and photographed. Subsequently the specimen was serially sectioned into blocks 5 mm wide and 4 cm long. One slide from each block was stained with hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) for histologic examination. We conducted a comparative study on radiography, conventional endoscopy, dye endoscopy, biopsy, and postoperative histology by H&E and PAS.

Results

Table 2 shows diagnostic process of the 11 patients, arranged in order of the depth and size of the cancer. Only six patients (54.5%) showed symptoms that might be related to the upper alimentary tract, and the remaining five patients were asymptomatic. Of the six symptomatic patients, two had coexisting advanced gastric carcinoma, and their symptoms seemed to be caused by this carcinoma. Consequently only four patients (36.3%) showed the esophageal symptoms (2 patients had smart feeling, 1 patient had epigastric pain, and 1 patient had a sense of fullness). These four patients were associated with mucosal cancer of 2 cm or larger. Including the two patients showing symptoms caused by gastric cancer, the seven other patients (63.6%) free of esophageal symptoms were diagnosed by chance; one patient was diagnosed by a thorough medical examination, and the remaining six were diagnosed when they underwent an examination for another digestive disease. Among the 18 lesions, the sites of two lesions (2C and 2D) were not exposed on radiography or endoscopy.

Figure 1 shows the relationship between pathology (size and depth of transmural invasion) and radiographic findings in 16 lesions. Six (85.7%) of seven mm cancers showed any of the following radiographic findings, regardless of size: rigidity of the wall, irregularity of the margin, and thin barium fleck. Among the six lesions, the smallest measured 7 mm × 4 mm. No abnormal findings were recognized on radiography in three ep cancers less than 2 cm in size. On the contrary abnormal radiographic findings were shown on four of five (80%) ep cancers of 2 cm or more in size, suggesting that even in ep cancers those with a considerable size often yield some radiographic findings.

Figure 2 shows the relationship between pathology and endoscopic findings of the 16 lesions. All 15 lesions showed abnormal endoscopic findings, regardless of the size and depth of transmural invasion, except for one lesion (Table 2, lesion 4C) that was detected only by post-

TABLE 2. *Pathohistology and Findings in Radiography, Conventional Endoscopy, and Dye Endoscopy in 18 Mucosal Esophageal Cancers*

Lesion	Gross Type	Depth of Cancer	Size (cm)	Radiographic Findings	Endoscopic Findings: Morphologic Change	Endoscopic Findings: Color Change	Findings of Dye Endoscopy
4C	flat	ep	0.5 × 0.3	np	no findings		unstained
1	flat	ep	1.0 × 0.4	np		redness, PB	unstained
2A	flat	ep	1.0 × 0.7	np	elevation	redness	unstained
2B	flat	ep	1.3 × 1.0	np		redness	unstained
3	flat	ep	2.0 × 1.0	BF, RW, DL	TA		unstained
4A	flat	ep	2.5 × 1.0	np		redness	unstained
5A	depr	ep	3.0 × 2.0	RW	depression	redness	unstained
6A	depr	ep	3.0 × 2.5	RW	depression	redness	unstained
2C	flat	ep	3.5 × 1.8	not exposed	not exposed		unstained
7	depr	ep	3.5 × 2.5	BF	irregularity		unstained
4B	depr	mm	0.7 × 0.4	RW	depression		unstained
6B	flat	mm	1.5 × 1.5	RW		redness	unstained
2D	flat	mm	2.0 × 1.0	not exposed	not exposed		unstained
8	elev	mm	2.0 × 1.2	RW		redness	unstained
5B	depr	mm	2.2 × 1.6	RW	depression	redness	unstained
9	depr	mm	2.5 × 1.5	np	depression	redness	unstained
10	flat	mm	4.0 × 2.2	RW, IM		redness	unstained
11	elev	mm	5.0 × 4.0	RW	elevation	discoloration	not done

depr, depressed; elev, elevated; BF, barium fleck; RW, rigidity of the wall; DL, doubled line; np, nothing particular; IM, irregularity of the margin; PB, punctate bleeding; TA, transformation of the arc.

operative pathohistology of the specimen. Of the 15 lesions detected before operation, only 9 (60%) showed morphologic changes, while 13 (86.7%) showed color changes. Of the 9 lesions associated with morphologic change, 5 were observed as slight depression, 1 as roughness (irregularity) of the mucosal surface, 1 as slight elevation, and 1 as transformation of the arc (Fig. 3A) of the esophagus. Color change (redness) (Fig. 3A) was seen in 12 lesions (80%); discoloration appeared in 1 lesion; and punctate bleeding was visible in 1 lesion.

Dye endoscopy before operation and dyeing of the resected specimen visualized all 18 lesions as unstained areas—those showing neither morphologic nor color change, as well as those showing both or either of them in conventional endoscopy.

Case Reports

Case 1

This case (Table 2, lesion 3) was the smallest lesion that was detected by radiographic examination. The lesion diameter measured 2 cm and was ep cancer located in the middle esophagus. In radiography (Fig. 4) bending appearance (indicated by a forked arrow) due to rigidity of the wall was seen. In addition thin barium flecks (indicated by the other arrow in Fig. 4) were seen near this bending. Conventional endoscopy (Fig. 4A) revealed ill-circumscribed redness accompanied by mild transformation of the arc. Dye endoscopy (Fig. 3B) by Lugol solution demonstrated this lesion as a well-circumscribed unstained area.

Case 2

This case (Table 2, lesion 1) was a flat lesion measuring 1 cm in diameter and was ep cancer located in the lower esophagus. No abnormal

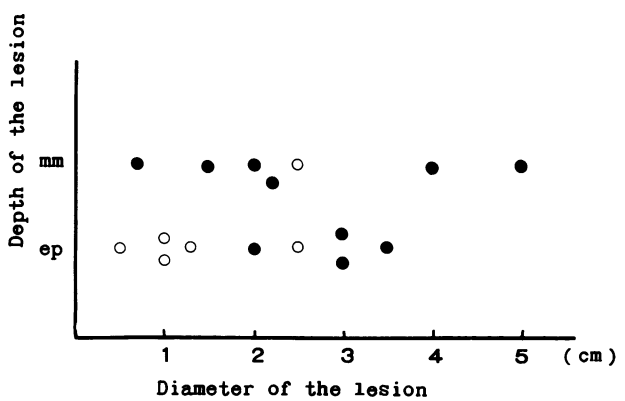


FIG. 1. Relationship between pathology (size and depth of transmural invasion) and radiographic findings in 16 lesions. ·, a lesion showing findings; ○, a lesion without findings.

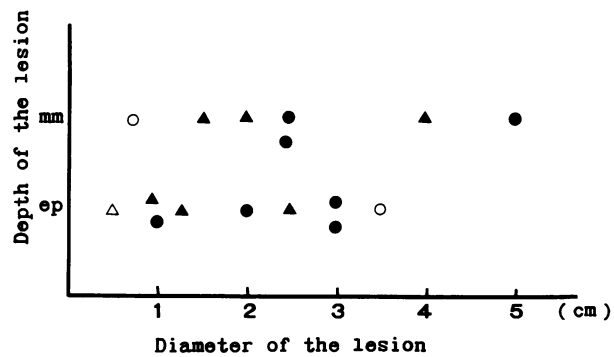
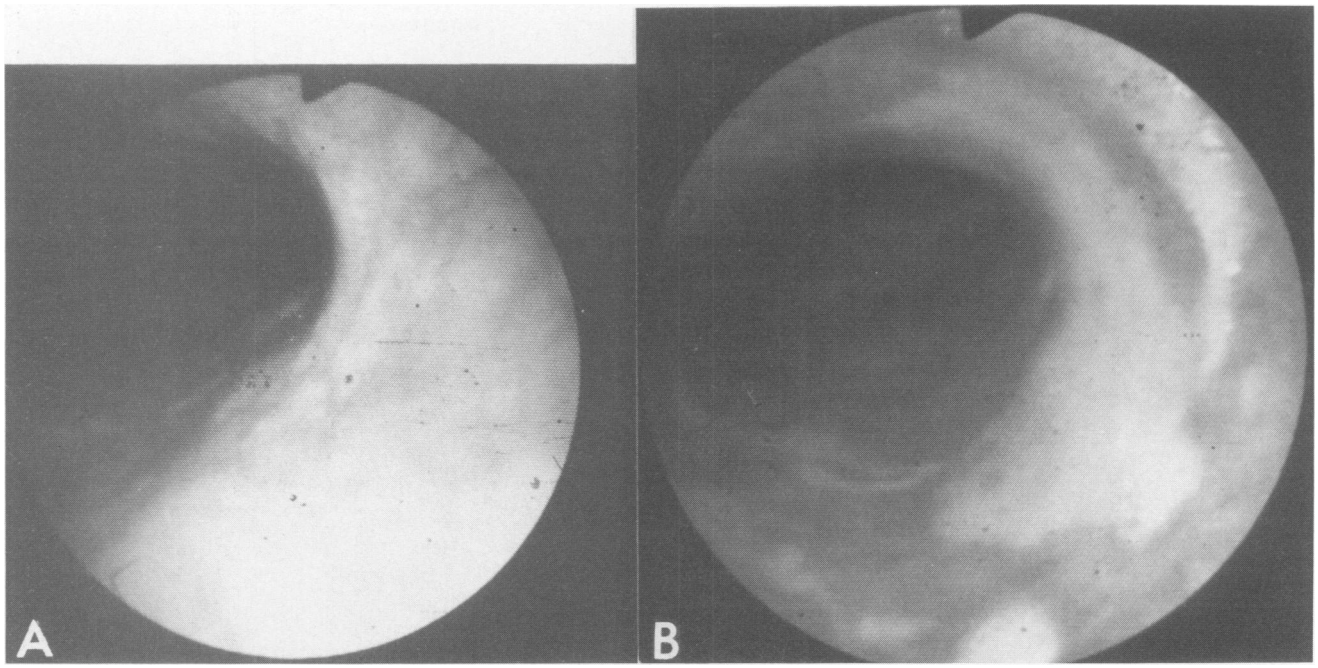


FIG. 2. Relationship between pathology and endoscopic findings of 16 lesions. ·, a lesion showing both morphologic and color changes; ○, a lesion showing morphologic change but not color changes; ▲, a lesion showing color change but not morphologic changes; △, a lesion showing neither morphologic nor color change.



FIGS. 3A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on Case I (lesion 3 in Table 2).

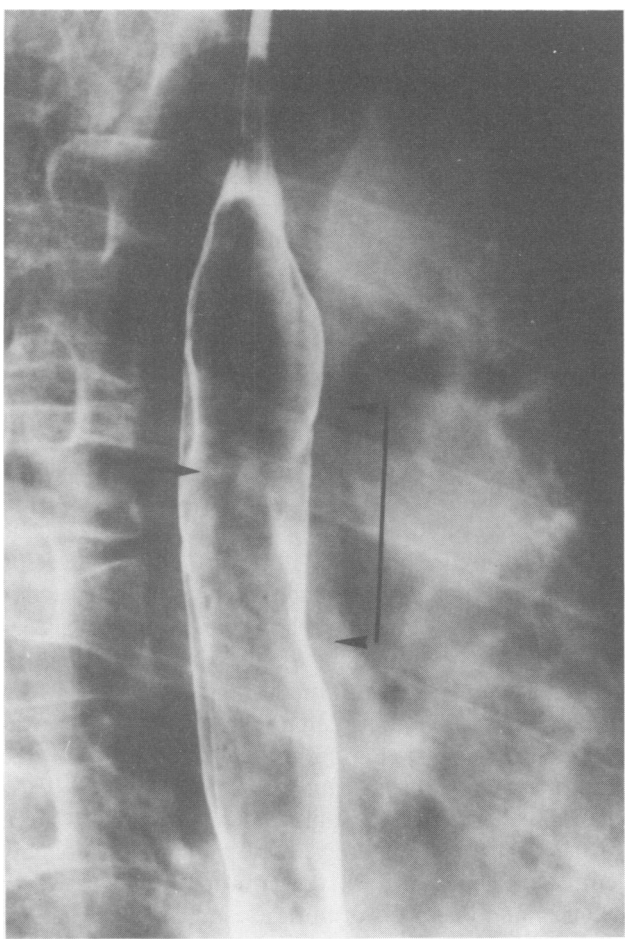


FIG. 4. Radiography of case 1 (Table 2, lesion 3). A forked arrow indicates a bending appearance, and the other arrow indicates a barium fleck.

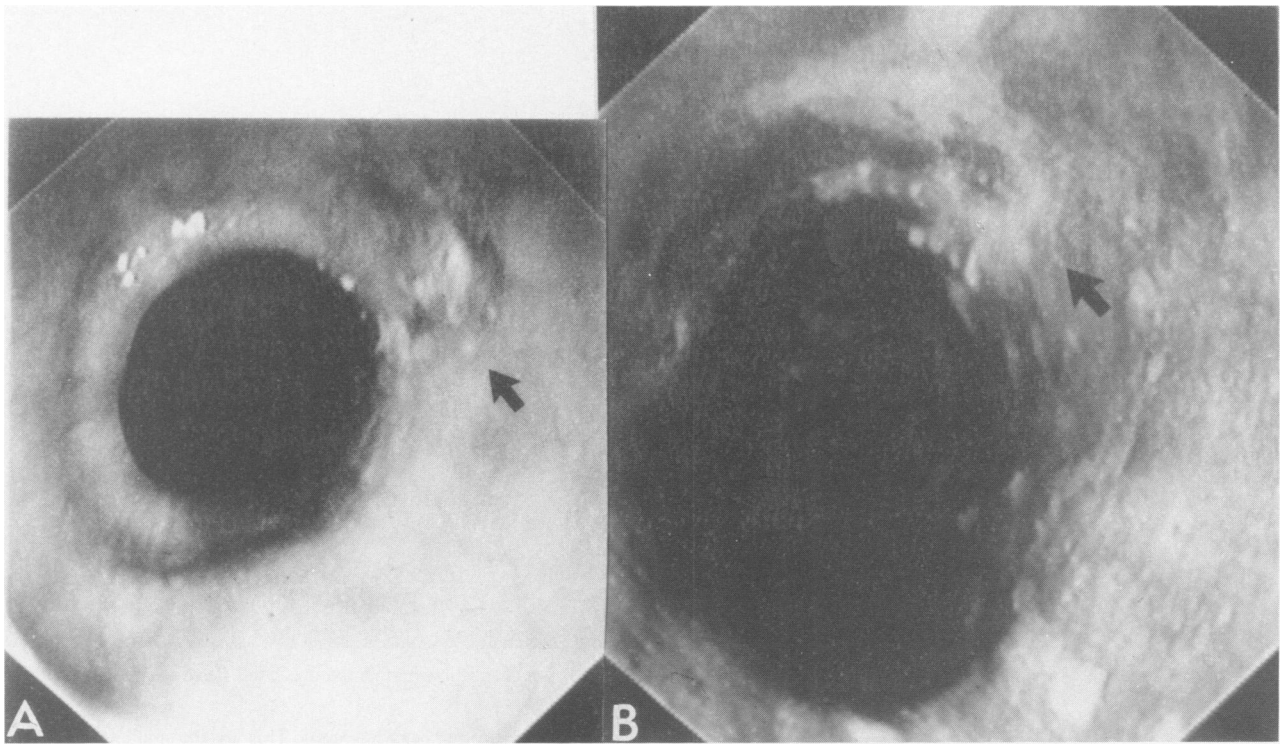
findings were found in radiography. This was the smallest ep cancer that was detected by conventional endoscopy and confirmed by dye endoscopy. A well-circumscribed reddened area associated with punctate bleeding was found in conventional endoscopy (Fig. 5A). However no morphologic change was noted in conventional endoscopy (Fig. 5A) or the resected specimen (Fig. 6A). This lesion was confirmed as a well-circumscribed unstained area by dye-endoscopy (Fig. 5B) and on the resected specimen (Fig. 6B) that was dyed with Lugol solution.

Case 3

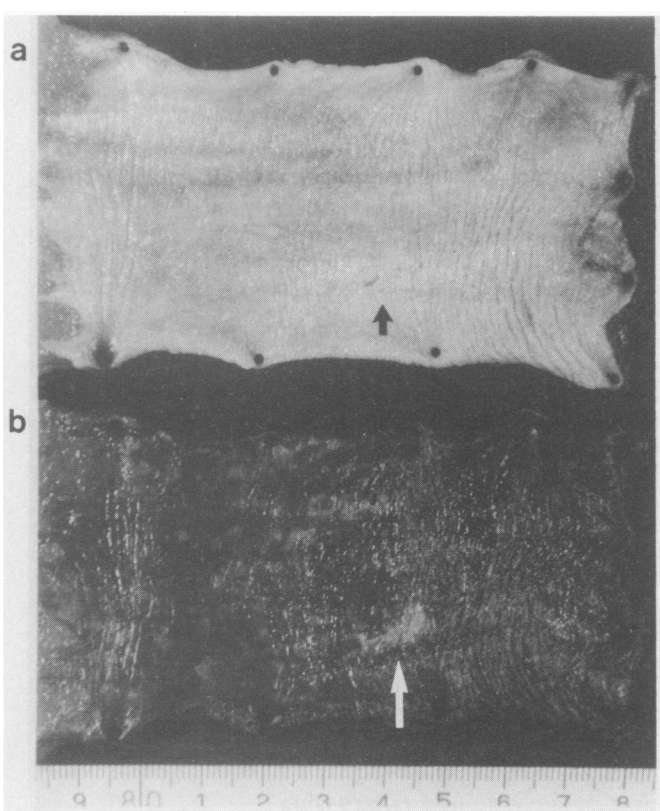
This case (Table 2, lesions 4A to 4C) included three cancerous lesions, one of which was recognized only by postoperative histology. Retrospectively we also identified it by dye endoscopy, but not by radiography or conventional endoscopy. Conventional endoscopy (Fig. 7A) demonstrated a reddened area (indicated by an arrow), lesion A, which was not identified by radiography. This lesion was confirmed by dye endoscopy to be an unstained area. Apart from lesion A, conventional endoscopy (Fig. 8A) disclosed a shallow and well-circumscribed depression (as indicated by arrow A), lesion B, which showed rigidity of the wall on radiography. Lesion B was also confirmed by dye endoscopy to be a well-circumscribed unstained area (Fig. 8B). Both unstained areas, which were almost the same as the areas determined histologically, were wider than the depressions seen in conventional endoscopy. This result indicates that dyeing with solution leads to more accurate evaluation of the range of the lesion. In addition to the two lesions, a small unstained area (indicated by arrow C) was found by dye endoscopy (Fig. 8B); this lesion showed no abnormal findings on conventional endoscopy (Fig. 8A). Lesion C, however, had been overlooked before operation and was retrospectively identified. On the resected specimen (Fig. 9), all three lesions were unstained by Lugol solution. The unstained area of lesion C measured 3 mm and histologically was minute ep cancer (Fig. 10) of the same size.

Discussion

Superficial esophageal cancer causes no symptoms in 20% to 40% of patients and, when asymptomatic, it is



FIGS. 5A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on case 2 (Table 2, lesion 1).

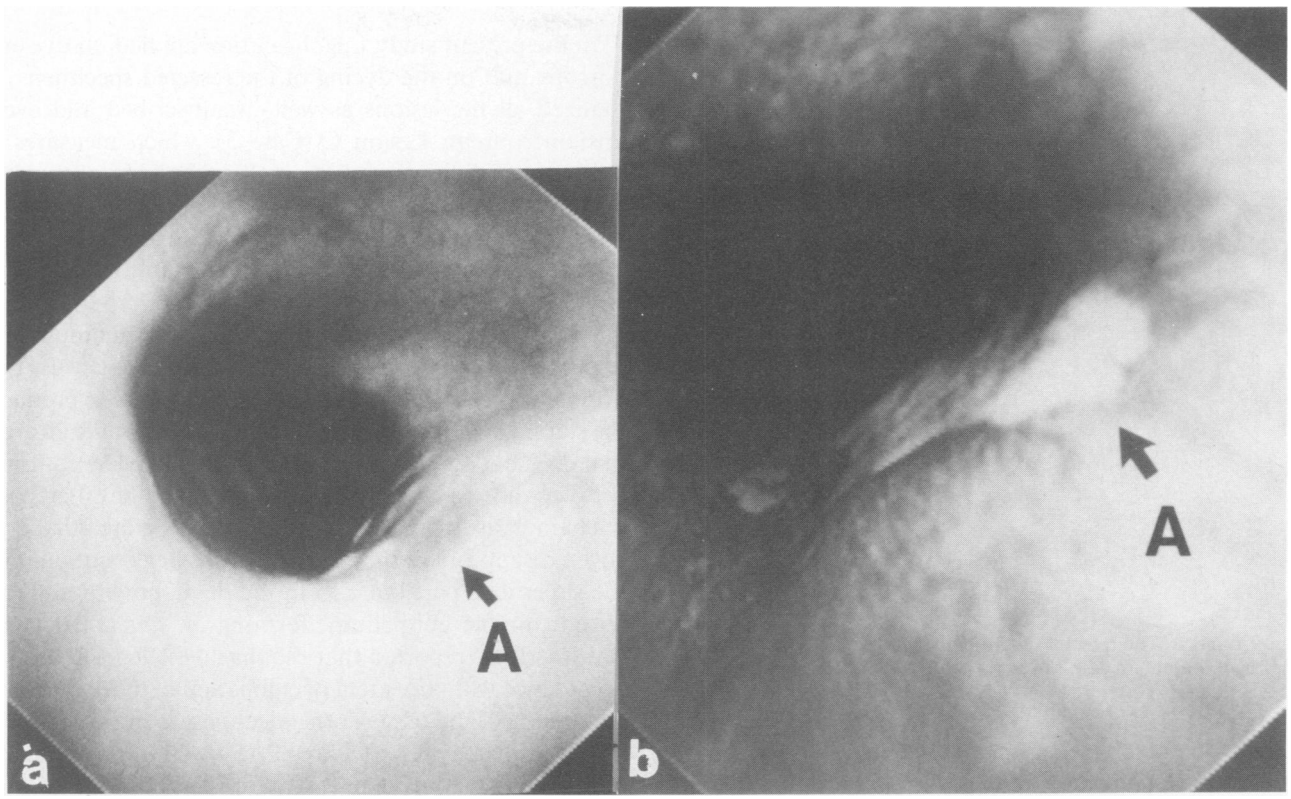


FIGS. 6A and B. The resected specimen before (A), and after (B) dyed with Lugol solution in case 2.

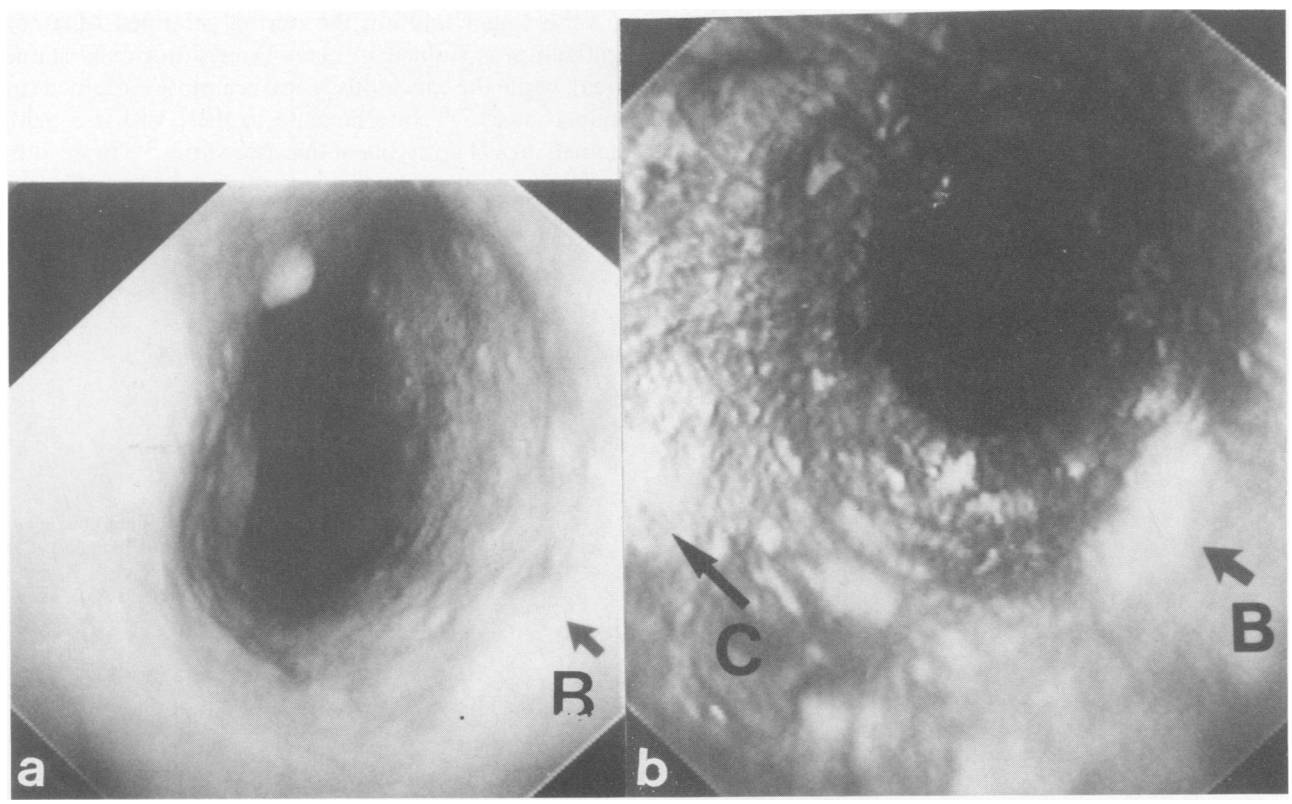
detected during examination for another disease or periodic check-up.[8-10] Statistics found by Nabeya et al.[11] on Japanese patients revealed that only 16% of early esophageal cancers elicited symptoms such as severe disturbance of swallowing and passage, and that about 40% of early esophageal cancers were discovered without symptoms. In this series only 6 (54.5%) of 11 patients complained of symptoms. Furthermore two of the six patients had concomitant advanced gastric carcinoma, and their symptoms seemed to be derived from gastric carcinoma. Consequently only four patients (36.3%) showed esophageal symptoms.

Radiography and endoscopy are the main diagnostic aids for the disease. Recently discovery of the cancer by endoscopy, particularly by panendoscope, has increased.[12] Diagnostic ability of radiography in early esophageal cancer [8,10,13,14] has been investigated for more than 20 years. Sato et al.[10] stated that minute lesions as small as 5 mm were impossible to identify. In this study 75% of mm cancers yielded radiographic findings regardless of size; the smallest esophageal mm cancer (Table 2, lesion 3 [Case 1]) that we detected radiographically measured 7 × 4 mm. Furthermore this study showed that radiography possibly identifies ep cancer if it is 2 cm or more in size. However detection and diagnosis of minute esophageal cancer are still difficult by radiography.[4]

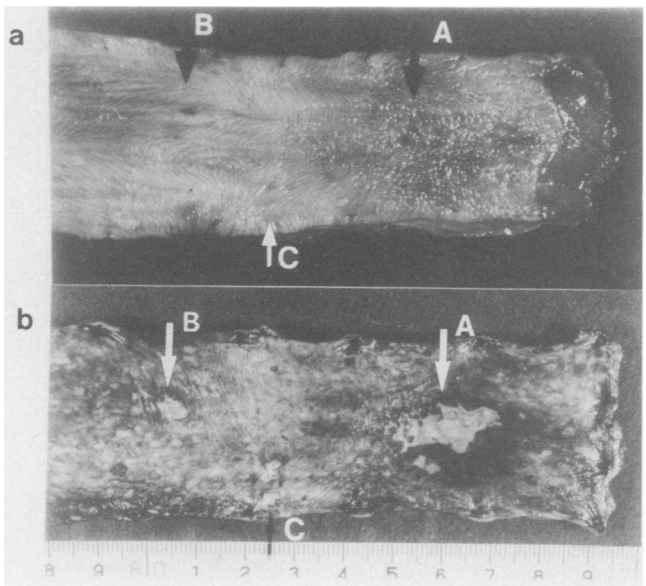
Minute esophageal cancers are identified endscopically



FIGS. 7A and B. Conventional endoscopy (A) and dye-endoscopy (B) with Lugol solution performed on case 3 (Table 2, lesion 4A). Each arrow indicates lesion A.



FIGS. 8A and B. Conventional endoscopy (A) and dye endoscopy (B) with Lugol solution performed on case 3 (Table 2, lesions 4B and 4C). Arrows B and C indicate lesions B and C.



FIGS. 9A and B. The resected specimen before (A), and after (B) dyed with Lugol solution in case 3. Arrows A, B, and C indicate lesions A, B, and C.

by such characteristics as shallow depression, slight elevation (like a flat board), redness, or discoloration.[4] Endo et al.[15] emphasized that induction of the panendoscope affords the detection of minute lesions as small as 2 to 3 mm. In this series conventional endoscopy showed a high rate (83%) of abnormal findings. Morphologic changes accompanying mucosal cancers are usually shallow depression or slight elevation and color change (redness). Lesion 1 in Table 2 (Case 2) was the smallest ep cancer that was discovered with conventional endoscopy. This lesion was observed as well-circumscribed redness accompanied by punctate hemorrhage in the absence of morphologic change.

In the present study Lugol solution applied on dye endoscopy and on the dyeing of the resected specimen visualized all the lesions as well-circumscribed and even unstained areas. Lesion C (Case 3), which measures 3 mm, especially illustrates the high availability of the dye endoscopy.

The esophageal Lugol test originates in a color reaction between the glycogen within the tissue and iodine. The amount of glycogen within the tissue relates to the intensity of this reaction.[16] Mature nonkeratosic squamous epithelial cells contain a large amount of glycogen. In the normal mucosa this glycogen reacts with iodine to produce the staining in black-brown or green-brown, while an area that does not contain glycogen is unstained. The contrast between the two facilitates the evaluation of the differences in characteristics of the mucosa. Schiller[17] stated that glycogen disappears in the carcinomatous layer, not only in the superficial part but also in the down growth and extension in the epithelium, forming an unstained area. Brodmerkel[18] reported that esophagitis is less stained in accordance with the extent of exfoliation of the epithelium and that necrotic tissue at the ulcer base is unstained. We observed that each area where PAS reaction was weak or negative was equivalent to an unstained area in the esophageal mucosa with Lugol solution, and that an unstained area of the resected specimen dyed with Lugol solution coincided completely with a histologically determined cancerous area.[19]

With Lugol solution the normal stratified squamous epithelium is stained in black-brown (normally stained area), while the cancerous lesion is almost unstained (unstained area).[16,20] Intermediate to these two is a lightly stained area. The atypia of this area varies.[21] On the other hand glycogen acanthosis, one of so-called small leukoplakia,[18,21] and some hyperplasia[21] of considerable exten-

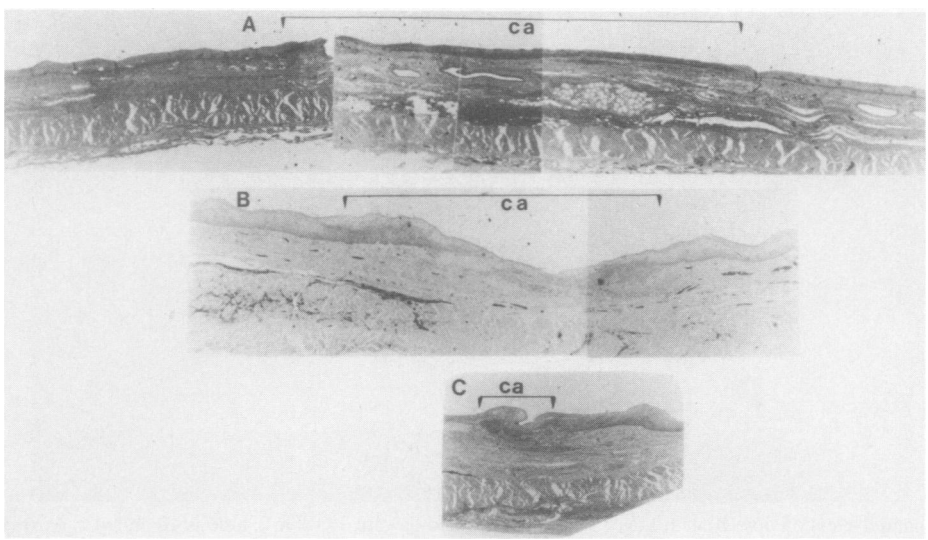


FIG. 10. Photomicrograph showing three lesions (A–C) of case 3. Arrows A, B, and C indicate lesions A, B, and C.

sion are stained more darkly than normal with Lugol solution.

In addition to cancer, unstained esophageal mucosal lesions include esophagitis, edema, mucosal atrophy, severe inflammation, dysplastic epithelium, erosion, ulcer, and ectopic mucosa.[22,23] Therefore unstained esophageal lesions are not exclusive to esophageal cancer. However if biopsy is combined for such a lesion, the diagnostic accuracy would surely increase. Furthermore, as illustrated in this study, unstained areas of cancerous lesions agreed much more than areas of cancer observed by conventional endoscopy.

In conclusion endoscopy is more helpful than radiography in the diagnosis of esophageal mucosal cancer. Particularly dye endoscopy using Lugol solution is very important because of easier detection of minute or superficial esophageal cancer and easier evaluation of the extent of the lesion.

Acknowledgments

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