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Gross Pathology of Superficial Esophageal Carcinoma with Special Reference to Depth of Tumor Invasion: An Analysis of 405 Lesions from 363 Cases, 2000-2016

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Abstract

Objectives: To clarify the gross features of superficial esophageal carcinoma that massively invaded the submucosa.

Materials and Methods: The gross features of 405 lesions（338 intramucosal carcinoma lesions, 67 submucosal invasive carcinoma lesions）from 363 cases of endoscopically or surgically resected superficial esophageal carcinomas were investigated. Macroscopic tumor type, depth of tumor invasion and histologic type of carcinoma were evaluated according to the Japanese Classification of Esophageal Cancer. Protrusion height and depth of excavation were measured from the surface of the perilesional mucosa. Also, the shapes of the base of each protruding-type lesion were evaluated.

Results: The gross types of carcinoma were as follows: superficial protruding type, 3 lesions; surface protruding type, 25 lesions; surface flat type, 73 lesions; surface excavated type, 255 lesions; superficial excavated type, 1 lesion and mixed type, 48 lesions. Depth of tumor invasion of carcinoma included intramucosal carcinoma in 338 lesions and submucosal invasive carcinoma in 67 lesions（SM1 carcinoma, 19 lesions; SM2 or deeper carcinoma, 48 lesions）. Among the SM2 or deeper carcinomas, carcinomas massively invaded the submucosa in 28 lesions, and 24 of these lesions（85.7%）formed excavations caused by ulceration, whereas the 4 lesions without ulceration（14.3%）formed a protrusion caused by expansive growth of tumor tissue.

Conclusions: Gross findings reflecting submucosal massive invasion of carcinoma were dome-like protrusion with sloping up gently（so-called “tense elevation”）and excavation accompanied by clear ulceration.

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Introduction

Currently, when deciding a therapeutic strategy for superficial esophageal carcinoma, more accurate diagnosis of the depth of tumor invasion is required. Diagnosis of invasion depth is performed using various medical imaging devices [1]. To support the diagnostic accuracy, knowledge of the gross features of the superficial carcinoma is necessary. Based on this consideration, from the results of the analysis of gross impressions and histology of resected specimens comprising 405 lesions from 363 cases of superficial esophageal carcinomas, we tried to extract the gross features as well as the main points of difference between intramucosal carcinoma and submucosal invasive carcinoma.

Materials and Methods

Patients and study setting

From the pathology division of Fukuoka University Faculty of Medicine, 306 lesions were searched histopathologically from 273 cases (treatment protocols in detail included endoscopic mucosal resection, 47 cases; endoscopic submucosal dissection, 160 cases and surgical resection, 66 cases), and from Department of Pathology of Fukuoka University Chikushi Hospital, 99 lesions were searched histopathologically from 90 cases (treatment protocols in detail included endoscopic mucosal resection, 8 cases and endoscopic submucosal dissection, 82 cases). In total, 405 lesions from 363 cases were used as materials. Among them, 34 were cases of multiple primary carcinomas (synchronous lesions diagnosed within a period of 1 year).

This retrospective study protocol was approved by the Institutional Review Board (the Ethics Committee) of Fukuoka University Hospital (Approval Number 16-11-06) and Fukuoka University Chikushi Hospital (Approval Number R17-027).

Specimen handling

Every resected specimen was appropriately spread out, and fixed in formalin solution, then cut in parallel along the long axis at a width of 2.5 to 3.5 mm, embedded in paraffin and sliced. After that, the specimens were stained with hematoxylin-eosin (HE).

Macroscopic tumor type

The gross type of carcinoma was determined by observing the mucosal surface of the fixed specimen before iodine staining and then further determined according to the Japanese Classification of Esophageal Cancer, 11th Edition [2]. Superficial type was subclassified as follows: superficial and protruding type (0-I), slightly elevated type (0-IIa), flat type (0-IIb), superficial and depressed type (0-IIc), and superficial and excavated type (0-III). In addition, combined-type carcinoma was defined as follows: when multiple macroscopic tumor types were in one lesion, it was called a combined type. In the combined type, the widest gross type was described first, followed by the next type (eg, 0-IIa + 0-IIc).

Tumor size

The foci of the intramucosal carcinoma and submucosal invasion site were overlaid on a diagram, and the greatest dimension (mm) of each was measured. Then, in the submucosal invasive carcinoma, the greatest dimension was defined as the maximum size on its intramucosal carcinoma focus of that lesion, and in cases of completely desquamated intramucosal carcinoma, the greatest dimension of the submucosal invasive site was substituted. Also, a superficial and flat type lesion, which extended longitudinally 50 mm or more, was defined as superficial spreading type [2].

Depth of tumor invasion

Subclassification of invasion depth of superficial carcinoma was in accordance with the Japanese Classification of Esophageal Cancer, 11th Edition [2]. That is, in the surgically resected specimens, the mucosal layer was subclassified into 3 layers, i.e., EP, LPM and MM (muscularis mucosae), and the submucosa was subclassified into three equal parts, i.e., SM1, SM2 and SM3 [2]. Meanwhile, in the endoscopically removed specimens, carcinoma with a vertical invasion distance of less than 200 μm from the lower end of the muscularis mucosae to the deepest part was subclassified as SM1 and

that with a vertical invasion distance exceeding 200 μm as SM2 [2-3].

Histologic typing and tumor infiltration pattern

Histologic typing and the infiltration pattern of the tumor were determined according to the Japanese Classification of Esophageal Cancer, 11th Edition [2]. Specifically, tumor infiltration pattern was classified into 3 types, i.e., expansive type (solid nests with a clear tumor margin), infiltrative type (small nests or dissociated cells with an unclear tumor margin) and intermediated type (infiltration pattern between expansive and infiltrative). Additionally, among squamous cell carcinomas, those with remarkable keratinization were defined as keratinized type, and those with unremarkable keratinization as non-keratinized type.

Height and depth of the lesion

Heights or depths of each lesion were measured with its basal mucosal surface as the starting point in protruded lesions, and in each excavated lesion (including lesion with cancerous ulcer), with its periclinal mucosal surface as the starting point. Measurement was done using Loupe (PEAK, TOKAI Industry Co., Ltd., Tokyo, Japan) with its minimal scale pitch at 100 μm, while a HE-stained specimen was placed on a Light Box (Light Viewer 7000PRO, HAKUBA Photo Industry Co., Ltd., Tokyo, Japan). Furthermore, the shapes of the base of each protruded lesion were also evaluated, and protrusion was subclassified into slightly elevated lesion with a gentle rise (0-IIa), sharply-marginated sessile protrusion (0-I) without constriction at the base, sharply-marginated sessile protrusion (0-I) with distinct constriction at the base and pedunculated protrusion (Figure 1).

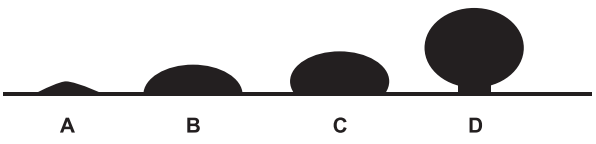

Figure 1. Schematic representation of the major variants of esophageal protruded lesions.
A: 0-IIa shows a slightly elevated lesion. The height of the lesion is low. B: 0-I shows a sharply-marginated sessile protrusion without constriction at the base. The base and the top of the lesion are about the same diameter. C: 0-I shows a sharply-marginated sessile protrusion with distinct constriction at the base. The base of the lesion is narrow. D: Pedunculated protrusion. The height of the lesion is more conspicuous than the horizontal spread of the base. The black line indicates mucosal surface.

Cancerous erosion

Ulcer was defined as a tissue defect caused by the proliferation and invasion of cancer tissue. Furthermore, subtle tissue defects were excluded as a subject for evaluation.

Histopathological evaluation

All of the histopathological evaluation was performed by three pathologists (SN, HT, and AI) independently of each other, and any discrepancies were resolved by consensus at a meeting after further histopathological review.

Results

Age, sex, and tumor location

Details of sex and age included 330 male cases and 33 female cases ranging in age from 43 to 89 years with a mean age of 66.8 years. Details according to the location of carcinoma were as follows: in all cases, carcinoma occurred in the thoracic esophagus, and among them, 5 lesions were located in the upper region, 389 were in the middle region and 11 were in the lower region.

Macroscopic tumor type and depth of carcinoma invasion (Table 1)

Details of the macroscopic tumor type of all 405 lesions were as follows: superficial and protruding (0-I) type, 3 lesions; slightly elevated (0-IIa) type, 25 lesions; surface flat (0-IIb) type, 73 lesions; slightly depressed (0-IIc) type, 255 lesions; superficial and excavated (0-III) type, 1 lesion and combined type, 48 lesions (Figure 2). When 48 of the combined type lesions were divided by the main gross types in accordance with the definition above, the details were as follows: 0-I type, 10 lesions; 0-IIa type, 29 lesions; 0-IIc type, 8 lesions and 0-III type, 1 lesion. There were no pedunculated protrusions.

The details of depth of tumor invasion of the 338 lesions of intramucosal carcinoma were as follows: pT1a-EP, 162 lesions; pT1a-LPM, 130 lesions and pT1a-MM, 46 lesions. Meanwhile, the details for the 67 lesions of submucosal invasive carcinoma were as follows: pT1b-SM1, 19 lesions; pT1b-SM2, 37 lesions and pT1b-SM3, 11 lesions.

Frequency of submucosal invasion (Table 2)

Based on the macroscopic tumor type, the rates of intramucosal localization of carcinoma were as follows: 0-IIb, 100%, followed by 0-IIc, 90.5%; 0-IIa, 48.1 % ; 0-I, 7.7 % and 0-III, 0 % . In contrast, the rates for submucosal

Table 1. Macroscopic tumor type of superficial esophageal carcinomas and their depth of tumor invasion

Macroscopic tumor type	pT1a-EP	pT1a-LPM	pT1a-MM	pT1b-SM1	pT1b-SM2	pT1b-SM3	Total No. of lesions
0-I	0	0	0	0	2	1	3
0-IIa	4	3	8	5	5	0	25
0-IIb	59	13	1	0	0	0	73
0-IIc	95	108	30	10	10	2	255
0-III	0	0	0	0	0	1	1
Combined type*	4	6	7	4	20	7	48
Total No. of lesions	162	130	46	19	37	11	405

pT1a-EP indicates carcinoma *in situ*, pT1a-LPM, carcinoma invading lamina propria mucosae; pT1a-MM, carcinoma invading muscularis mucosae; pT1b-SM1, carcinoma invading the upper third of the submucosa; pT1b-SM2, carcinoma invading the middle third of the submucosa; pT1b-SM3, carcinoma invading the lower third of the submucosa; 0-I, superficial and protruding type; 0-IIa, slightly elevated type; 0-IIb, flat type; 0-IIc, slightly depressed type; and 0-III, superficial and excavated type. *: When multiple macroscopic tumor types are mixed in one lesion, it is called a combined type.

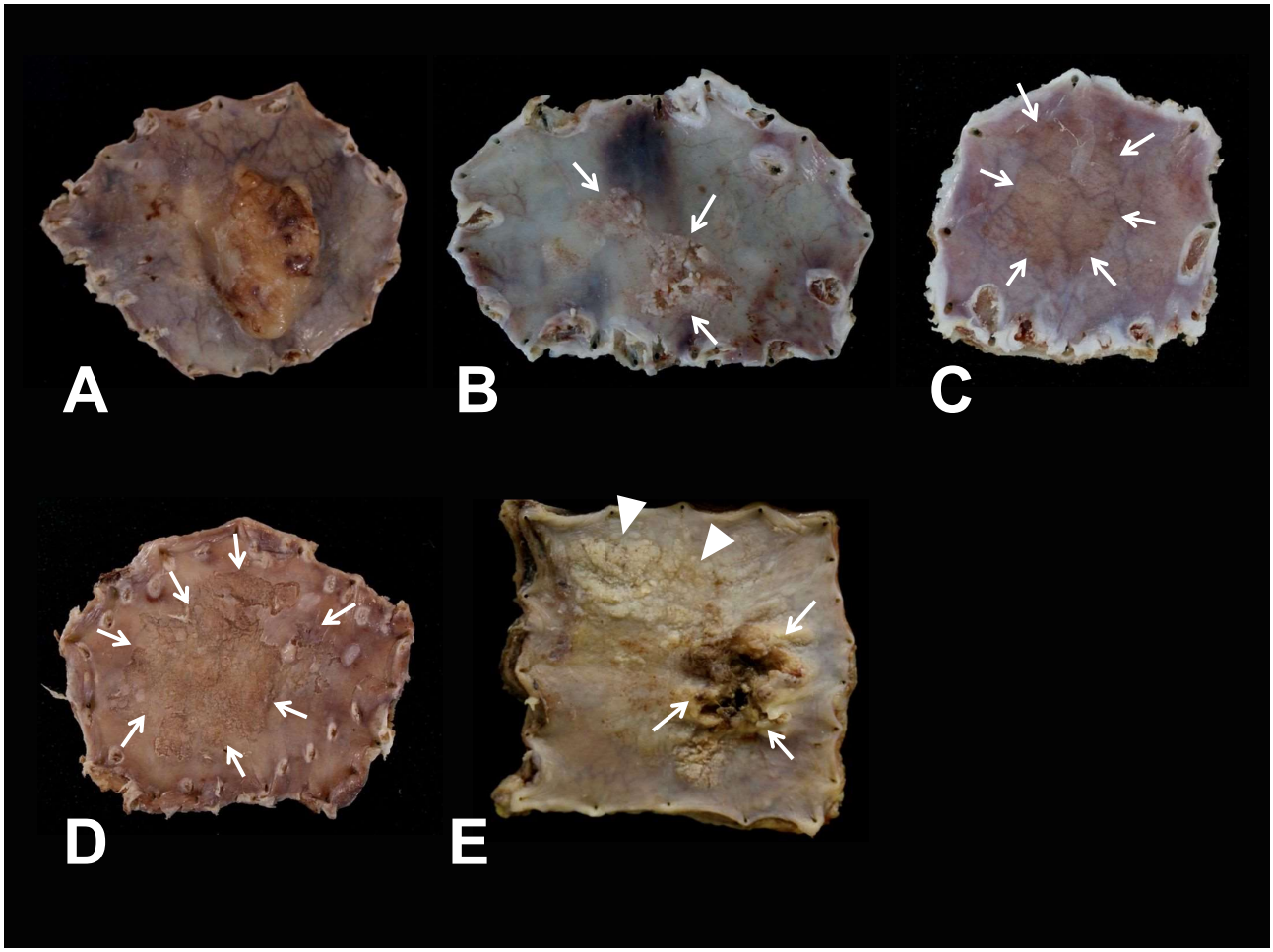

Figure 2. Macroscopic features of superficial esophageal carcinoma.
A: Superficial and protruding type corresponding to macroscopic tumor type 0-I. The well-demarcated protruding tumor has a nodular surface. B: Slightly elevated (0-IIa) type. The well-demarcated lesion has a whitish-colored irregular surface (arrows). C: Flat (0-IIb) type. The flat lesion has a translucent smooth surface (arrows). D: Slightly depressed (0-IIc) type. The well-demarcated lesion has a finely granular surface (arrows). E: Superficial and excavated (0-III + 0-IIa, combined) type. Both the much deeper excavation (cancerous ulcer, arrows) and slightly elevated area with whitish-colored irregular surface (arrowheads) are also seen.

Table 2. Frequency of submucosal invasion by macroscopic tumor type in superficial esophageal carcinomas

Macroscopic tumor type*	Total No. of lesions	Frequency of submucosal invasion	Depth of tumor invasion		
			pT1a	pT1b-SM1	pT1b-SM2 or SM3
0-I	13	12 (92.3)	1 (7.7)	0	12 (92.3)
0-IIa	54	28 (51.9)	26 (48.1)	8 (14.8)	20 (37.0)
0-IIb	73	0	73 (100)	0	0
0-IIc	263	25 (9.5)	238 (90.5)	11 (4.2)	14 (5.3)
0-III	2	2 (100)	0	0	2 (100)
Total No. of lesions	405	67 (16.5)	338 (83.5)	19 (4.7)	48 (11.9)

Parentheses indicate percentage. pT1a indicates intramucosal carcinoma including pT1a-EP, pT1a-LPM, and pT1a-MM.
*: When 48 of the combined type lesions shown in Table 1 were divided by the main gross types, the details were as follows: 0-I type, 10 lesions; 0-IIa type, 29 lesions; 0-IIc type, 8 lesions and 0-III type, 1 lesion.

Table 3. Depth of tumor invasion by tumor size in superficial esophageal carcinomas

Maximum diameter of the lesion	pT1a-EP	pT1a-LPM	pT1a-MM	pT1b-SM1	pT1b-SM2	pT1b-SM3	Total No. of lesions
<10 mm	74	22	8	2	0	0	106
10-19 mm	58	34	14	4	11	3	124
20-29 mm	16	36	8	4	6	2	72
30-39 mm	6	16	9	4	6	3	44
40-49 mm	4	15	2	2	8	0	31
≥50 mm	4	7	5	3	6	3	28
Total No. of lesions	162	130	46	19	37	11	405

invasion were as follows: 0-III, 100 % ; followed by 0-I, 92.3 % ; 0-IIa, 37.0 % ; 0-IIc, 5.3 % and 0-IIb, 0 % . In other words, submucosal invasive carcinoma was extremely common in types 0-I and 0-III, and intramucosal carcinoma was extremely common in types 0-IIb and 0-IIc. For type 0-IIa, the rates of intramucosal carcinoma and submucosal invasive carcinoma were almost equal.

Tumor size and depth of tumor invasion (Table 3)

The tumor sizes of the intramucosal carcinomas were generally small, of which about 80% were less than 30 mm, whereas the tumor sizes of the submucosal invasive carcinomas varied markedly, but only 2 lesions were less than 10 mm. Next, among the superficial spreading lesions (28 lesions), the rates of intramucosal carcinoma and submucosal invasive carcinoma were 57.1% and 42.9%, respectively.

Histologic typing and tumor infiltrative pattern

Of the 405 lesions, 400 lesions were of squamous cell carcinoma and the remaining 5 lesions were of basaloid-squamous cell carcinoma. Of the squamous cell carcinomas, 6 lesions were of the keratinizing type and 394 lesions of non-keratinizing type. From the viewpoint of tumor infiltration pattern, there were no instances of infiltration by individual or trabecular cells corresponding to infiltrative type, and among the 113 lesions of pT1a-MM or deeper carcinomas, 83 lesions were of the expansive type, and 30 lesions were of the intermediate type.

Height of protrusion and shape of the base (Table 4)

When the heights of the protruded lesions (0-I: 13 lesions and IIa: 54 lesions) were measured, the minimum value was 0.1 mm and the maximum value was 3.0 mm in intramucosal carcinoma, but in 23 (85.2 %) of 27 lesions, the height was 0.5 mm or less. Meanwhile, in submucosal invasive carcinoma, the minimum value was 0.4 mm and the maximum value was 20.0 mm, but it was 2.0 mm or less in 29 (72.5%) of 40 lesions. Also, when the shape of base of the protruded lesions was evaluated, among a total of 67 lesions, 54 lesions showed slightly elevated lesion with a gentle rise (0-IIa), 10 lesions showed sessile protrusion (0-I) without constriction at the base and 8 lesions showed sessile protrusion (0-I) with constriction at the base. In addition, there were no pedunculated protrusions. The 0-IIa lesions of 0.5 mm or less in height were all intramucosal carcinomas except for 3 lesions (pT1b-SM1: 1 lesion and pT1b-SM2 or deeper: 2 lesions). Three 0-IIa lesions that

Table 4. Height of protrusion in superficial esophageal carcinomas

Macroscopic feature	pT1a-EP	pT1a-LPM	pT1a-MM	pT1b-SM1	pT1b-SM2	pT1b-SM3
0-IIa, *n*=54	0.1	0.2	0.4, 0.4	0.5	0.4, 1.0	0.5
	0.2	0.4	0.4, 0.5	1.0	1.0, 1.0	1.0
	0.2	0.4	0.5, 0.5	1.0	1.0, 1.1	1.5*
	0.2	0.5	0.5, 0.5	1.0	1.1, 1.1	
	0.3	0.5	0.5, 0.5	1.0	1.2, 1.2	
	0.4	0.5	0.8, 0.8	1.0	1.2, 1.2	
	0.4		1.0	1.0	1.3, 1.3	
				2.0	1.3, 1.3*	
					1.5	
0-I without constriction, *n*=5					2.0*	
					2.2	
					2.5	
					2.5	
					4.0	
0-I with distinct constriction, *n*=8			3.0		5.0	4.0
					5.0	5.0
					6.0*	20.0*
					8.0	

All values are expressed as the greatest height of the lesion measured from surface of the surrounding mucosa in millimeter. *: The histologic type is basaloid-squamous carcinoma. *n* indicates total number of lesions.

invaded the submucosa were all accompanied by slight ulcer (Figures 3A, B). Further, except for 3 lesions, the 0-IIa lesions with a height of 1.0 mm or more were all submucosal invasive carcinomas (pT1b-SM1: 7 lesions and pT1b-SM2 or deeper: 18 lesions). Next, the 0-I lesions with a height of 2.0 mm or more without constriction were all submucosal invasive carcinomas (pT1b-SM2: 5 lesions) (Figures 3C, D). Further, all 0-I lesions with distinct constriction had 3.0mm or more in height, and except for one lesion with an invasion depth of MM, 7 lesions (87.5%) had invaded to SM 2 or deeper (Figures 3E-G).

Depth of excavation (Table 5)

When depths of the excavated lesions of types 0-IIc or 0-III were measured, the minimum value in intramucosal carcinoma was 100 μm and the maximum value was 400 μm, indicating that the depth was less than 500 μm in all lesions. Next, in submucosal invasive carcinoma, the difference between the minimum value of 200 μm and the maximum value of 3700 μm was large. From the results of this study, those lesions with a depth of 500 μm or more were all submucosal invasive carcinomas, and those with a depth exceeding 1000 μm were all SM2 or deeper (Figure 4). There was no case of intramucosal carcinoma with a depth of 500 μm or more, but within the excavated lesions with a depth of less than 500 μm (248 lesions in total), 10 lesions (pT1b-SM1: 6 lesions, pT1b-SM2: 3 lesions and pT1b-SM3: 1 lesion) of submucosal invasive carcinoma were included. Among these 10 lesions, except for one lesion of pT1b-SM3 associated with ulcer directly at the site of submucosal invasion, the amount of invasion in the remaining 9 lesions was quite small, and no gross findings were obtained that suggested submucosal invasion.

Surface condition of the carcinoma focus, particularly the presence or absence of ulcer (Table 6)

The surface condition of the top portion of the protruding lesions and the base of the depressed lesions were observed, and the presence or absence of ulceration was evaluated. As a result, of the 405 lesions, 35 lesions (8.6%) were accompanied by ulcer. The details were as follows: protruded lesions, 20; excavated lesions, 15 and flat-surface lesions, 0. Next, according to the depth of tumor invasion, 4 lesions were intramucosal carcinomas and 31 lesions were submucosal invasive carcinomas. Then, based on the incidence of ulcer for every invasion depth, as shown in Table 6, EP was 0.6 %, LPM 0.8 %, MM 4.3 %, SM1 10.5 %, SM2 54.1 % and SM3 81.8 %. As the invasion became deeper, the incidence of ulcer gradually increased. Most of the SM1 lesions (89.5%) were not accompanied by

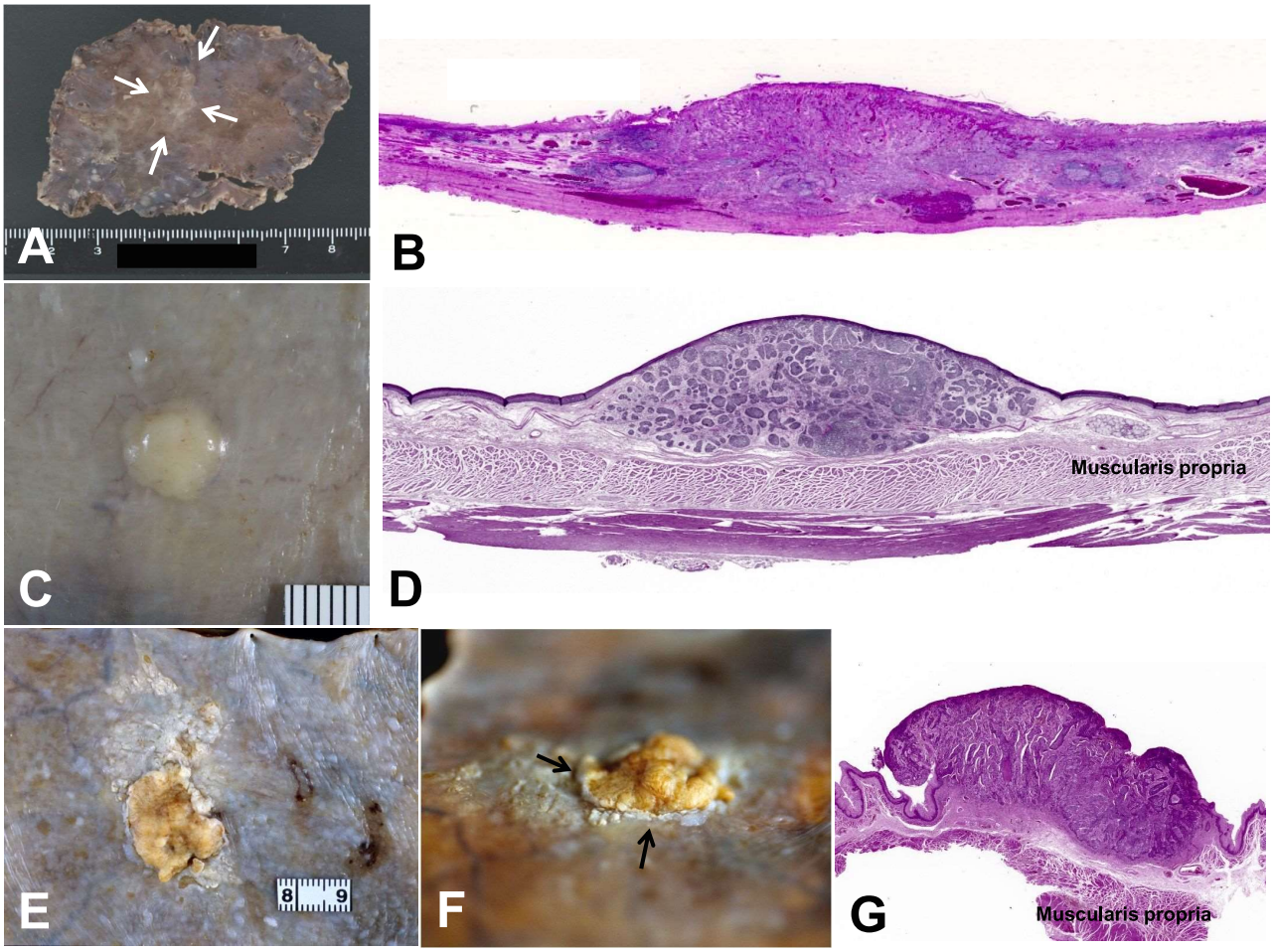

Figure 3. Pathological features of protruding type esophageal carcinoma.
A: Poorly-marginated protrusion with a gentle rise (arrows). B: Whole-mount view of the cut section of the protrusion shown in Figure 3A. The tumor tissues invade the submucosa forming nests of cancer cells. C: Sharply-marginated sessile ("dome-like") protrusion without constriction at the base ("tense elevation"). D: Whole-mount view of the cut section of the protrusion shown in Figure 3C. Histologically, the protrusion is formed by massive amounts of tumor tissue (basaloid-squamous carcinoma) pushing up epithelial layers directly above the tumor. E, F: Sharply-marginated sessile protrusion with distinct constriction at the base (arrows). G: Whole-mount view of the cut section of the protrusion shown in Figure 3E-F. Histologically, mass-forming tumor associated with submucosal invasion is also seen. The surface of the protrusion is superficially ulcerated.

Table 5. Depth of excavation in superficial esophageal carcinomas

Depth of the lesion*	pT1a-EP	pT1a-LPM	pT1a-MM	pT1b-SM1	pT1b-SM2	pT1b-SM3	Total No. of lesions
<250 μm	95	79	3	1	0	0	178
250-499 μm	1	32	28	5	3	1	70
500-749 μm	0	0	0	3	3	1	7
750-999 μm	0	0	0	6	6	3	5
1000-1249 μm	0	0	0	0	3	0	3
≥1250 μm	0	0	0	0	1	1	2
Total No. of lesions	96	111	31	11	11	5	265

*: The greatest vertical depth of the lesion measured from surface of the surrounding mucosa.

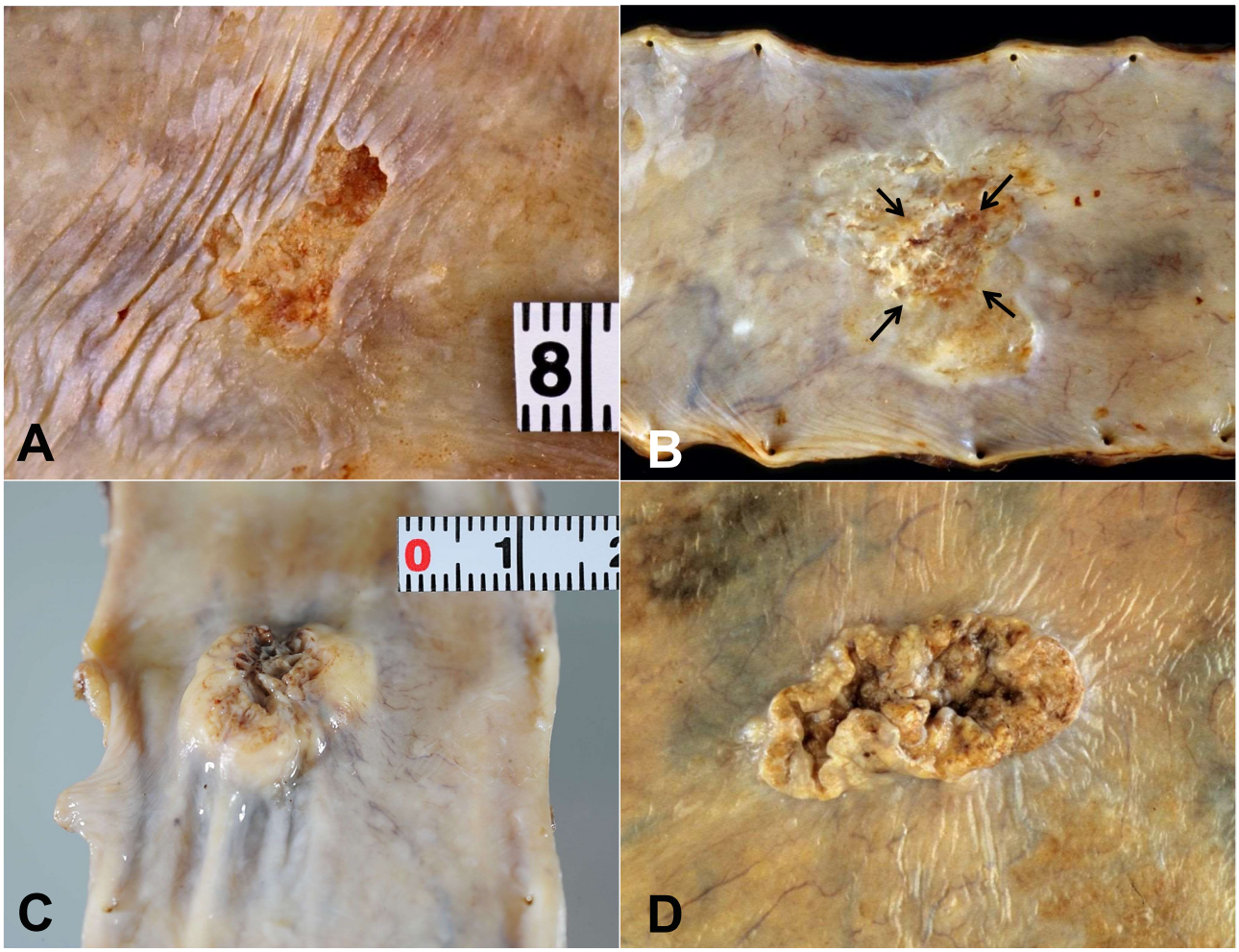

Figure 4. Macroscopic features of superficial esophageal carcinoma with excavation.
A: A sharply-marginated excavation by sloughing of the mucosal tissues directly above the invasion site. The depth of tumor invasion is pT1b-SM2. B: A much deeper excavation (arrows) within a shallow depressed area. The depth of tumor invasion is pT1b-SM3. C: An excavation within a dome-like protrusion. The depth of tumor invasion is pT1b-SM3. D: A much deeper excavation with everted margins. The depth of tumor invasion is pT1b-SM3. The surface of those ulcers is almost coarse. The greatest vertical depth of each lesion measured from surface of the surrounding mucosa is more than 800 μm.

Table 6. Incidence of ulceration in superficial esophageal carcinomas

Depth of the tumor invasion	Ulceration*		Total. No. of the lesions
	Present	Absent	
pT1a-EP	1 (0.6)	161 (99.4)	162
pT1a-LPM	1 (0.8)	129 (99.2)	130
pT1a-MM	2 (4.3)	44 (95.7)	46
pT1b-SM1	2 (10.5)	17 (89.5)	19
pT1b-SM2	20 (54.1)	17 (45.9)	37
pT1b-SM3	9 (81.8)	2 (18.2)	11
Total. No. of the lesions	35 (8.6)	370 (91.4)	405

Parentheses indicate percentage. *: Ulceration associated with carcinoma invasion.

ulcer, whereas more than half of the SM2 or deeper lesions (60.4%) were accompanied by ulcer.

Amount of cancer tissue and incidence of occurrence of ulceration in the submucosal invasive area

The amount of cancer tissue of SM2 or deeper (48 lesions in total) was examined, and the results showed that in 28 lesions, cancer tissues massively invaded forming large amounts of cancer nests, and in 20 lesions, cancer tissues slightly invaded narrow range. The incidence of ulcer in the former was 82.1% (23 of 28 lesions), and that of the latter was 30.0% (6 of 20 lesions). Among the 28 lesions with massive invasion, in 5 lesions without ulcer, protrusion was formed by tumor tissues that grew expansively to form large cancer cell nests. Three of these lesions were basaloid-squamous carcinomas, and the tumor tissues had grown by pushing up the epithelial layers (Figures 3C, D). They demonstrated the gross impression of predominantly subepithelial type (0-I sep) according to the Japanese Classification of Esophageal Cancer, 9th Edition [4].

Discussion

Evaluation of invasion depth is essential to determining the therapeutic strategy of esophageal cancer. To evaluate depth of tumor invasion with high accuracy before the initiation of therapy, the accumulation of gross findings with histopathological evidence is necessary, and macroscopic criteria that are widely accepted should be obtained. When compared with early gastric cancer, there is always room for examination in the macroscopic diagnosis of invasion depth for superficial esophageal carcinoma [5-12].

Accordingly, our final goal was to obtain gross findings showing the high probability that cancer massively invaded the submucosa, and we thus analyzed the gross impressions and histological appearances of 405 lesions from 363 cases of superficial esophageal carcinoma.

Generally, when amount of submucosal invasion of a primary gastrointestinal carcinoma is small, this is rarely reflected in the gross impression. However, if tumor tissues massively invade the submucosa, the formation of protrusions or ulcers often occurs. In particular, when the tumor mass is formed and the tumor growth is expansive, the findings are likely to be reflected in the gross impression [13-16].

In our study, the frequency of submucosal invasion was higher in 0-I and 0-III lesions than that in 0-IIc lesions (92.3 %, 100 %, and 9.5 %, respectively). Meanwhile, there were no submucosal invasive carcinomas in 0-IIb lesions. Further, for 0-IIa lesions, the rates of intramucosal carcinoma and submucosal invasive carcinoma were almost equal (48.1 % and 51.9 %, respectively). Among the 28 0-IIa lesions with submucosal invasion, 25 lesions were those with a height of 1.0 mm or more, and 3 lesions were accompanied by ulcer. Furthermore, the incidence of ulceration gradually increased, as the invasion became deeper (EP 0.6%, LPM 0.8%, MM 4.3%, SM1 10.5%, SM2 54.1 %, and SM3 81.8 %, respectively). However, in the 28 lesions with massively submucosal invasion, 5 protruding lesions without ulcer existed.

When the analysis results were reviewed, the gross findings indicating that the tumor had massively invaded the submucosa were as follows: one of the findings was a dome-like protrusion sloping up gently (so-called "tense elevation"). Histologically, large amounts of tumor tissue had formed protrusions by pushing up the epithelial layers. Another finding was excavation accompanied by distinct ulceration. Histologically, because large amounts of cancer tissues invaded the deep mucosal portion or the submucosa, the mucosal tissues directly above sloughed off, and a cancerous ulcer was formed in the same location. Similar results in surgical resected specimens were reported by some investigators in Japan [8].

The previously mentioned protrusions included subepithelial tumors and protrusions within excavations. Also, when considering the histological structure of the protrusions, in the gross impression of protrusions with distention, it was possible to get a sense of tension of the protrusions, which was caused by the expansion of cancer tissue growth that was restrained by an outer framework, i.e., the epithelial layer.

Furthermore, because excavations with ulceration were formed by conditions in which cancer tissue of the submucosal invasion site was exposed to the base of the excavation by sloughing of the mucosal tissues directly above the invasion site, the site could be viewed as a conspicuously coarse brown-colored area. Also, this excavation was sometimes viewed as a much deeper excavation within a shallow excavation or as an excavation within a protrusion.

The above gross findings appear along with an increase in the amount of submucosal invasion of cancer and therefore become useful criteria for the diagnosis of the invasion depth of superficial esophageal carcinoma. This is illustrated schematically in Figure 5.

Meanwhile, submucosal microinvasive cancer and

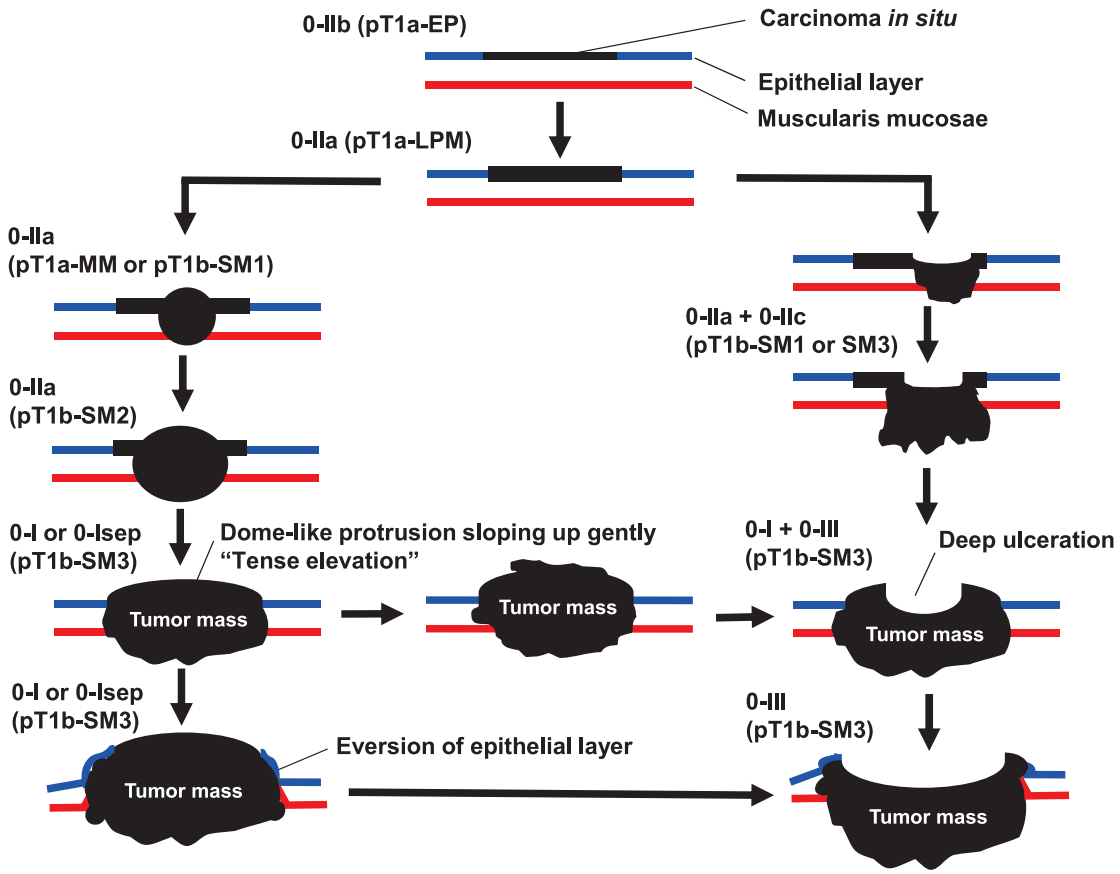

Figure 5. Chronological development model of superficial esophageal carcinoma based on our data.
In the earliest stage, the carcinoma focus arises at the basal layer of the mucosa (0-IIb, the black line). Next, tumor cells involve the whole thickness of the mucosa (0-IIa or 0-IIc, the black bold line). If tumor tissues invade the submucosa in large amounts, the formation of dome-like protrusion sloping up gently (0-I or 0-Isep) or excavation accompanied by ulceration (0-III) often occurs. Histologically, the former is a protrusion formed by massive amounts of tumor tissue (tumor mass) pushing up epithelial layers directly above the tumor, and the latter is an excavation caused by a cancerous ulcer that was formed by submucosal invasion of massive amounts of tumor tissue. The blue line indicates epithelial layer; the red line, muscularis mucosae; 0-I sep, subepithelial type; 0-IIa, slightly elevated type; 0-IIb, flat type; 0-IIc, slightly depressed type; and 0-III, superficial and excavated type.

intramucosal carcinoma with slight ulcer, which are not reflected in gross findings, also exist, and gross estimation of the invasion depths of those cancers was quite difficult. This is a limitation in the diagnosis of invasion depth [8]. Points to which further attention should be given are as follows: one is that submucosal invasive carcinoma that presents as a protrusion with a height of 0.5 mm or less or an excavation with a depth of less than 0.5 mm, is likely to be assessed more shallowly than the actual invasion depth. Another one is that intramucosal carcinoma with slight ulcer is likely to be assessed as being deeper than the actual invasion depth. This is a pitfall of the diagnosis of invasion depth.

The following conclusions have been drawn: if the height and the shape of base of the protruded lesions and the depth of excavation and the presence or absence of ulcer for excavated lesions are sufficiently taken into consideration, the gross diagnosis of the invasion depth of submucosal invasive carcinoma in large amounts is possible. However, the diagnosis of invasion depth of submucosal invasive carcinoma in small amounts is almost impossible. Thus, we need to approach the diagnosis of invasion depth using a variety of medical imaging devices based on the usefulness of gross observation and its limitations and pitfalls.

Finally, in some cases, the base of protruded lesions cannot be detected easily with overhead macroscopic photographs alone. This is a limitation in evaluation of shape of the base of protruded lesions regarding objective assessment. Therefore, we assessed shape of the base of protruded lesions by using HE stained tissue samples corresponding to cut section of the lesion.

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