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Original article

Early gastric cancer shows different associations with adipose tissue volume depending on histological type

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Abstract

Background. **Visceral obesity is known to be a risk factor for diabetes and cardiovascular disease. Cancer of the gastric cardia has been shown to have a close association with obesity in Western countries. In order to examine the possible relationship between fat volume and the development of gastric cancer (GC), we quantified visceral and subcutaneous fat areas of computed tomography (CT) images of patients with early GC.**

Methods. **A total of 210 patients who underwent endoscopic resection or surgical gastrectomy and whose disease was pathologically diagnosed as early GC were investigated for total fat area (TFA), visceral fat area (VFA), and subcutaneous fat area (SFA) with Fat Scan software, using a CT slice at the umbilical level, and the relationships of these findings with clinical and pathological data were analyzed. The same analysis was performed in 147 patients with early colorectal cancer (CRC).**

Results. **TFA, VFA, and SFA values in GC patients were not significantly different from the values in CRC patients. These values did not differ with the location of the GC. However, patients with undifferentiated-type GC had significantly smaller VFAs and SFAs than those with differentiated-type GC. Among the patients with undifferentiated GC, TFA and SFA values in the patients with submucosal cancer were significantly smaller than those in the patients with mucosal cancer.**

Conclusion. **GC has different associations with adipose tissue volume according to its histological type. As compared with differentiated GC, lower adipose tissue volume may be a preferential environment for the development and progression of undifferentiated GC.**

Key words Early gastric cancer · Visceral fat · Subcutaneous fat · Differentiated type · Undifferentiated type

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Introduction

The metabolic syndrome is one of the greatest concerns in healthcare in Japan, as well as in Western countries. Abdominal obesity has been shown to be associated with an increased risk not only for cardiovascular disease [1–7], diabetes [8], and hypertension [9] but also for malignant disease [10–14]. Since Lew and Garfinkel [15] first reported that overweight status and obesity increased the risk of mortality from cancer, many epidemiologic studies have shown a positive association between obesity and cancers in various organs, such as the endometrium [16], kidney [17], breast (in postmenopausal women) [18], colon [19], gallbladder [20], prostate [21], thyroid [22, 23], gastric cardia [24–26], and esophagus [27].

The incidence of gastric cardia cancer has been increasing in Western countries, whereas the rate of distal stomach cancer has declined [28–33]. This divergent trend in incidence suggests different etiologies of these gastric cancers (GCs). Obesity was associated with gastric cardia cancer in some case-control studies in Western countries [34, 35], but its association with distal stomach cancer has not been well examined [36]. Chow et al. [24] performed a multicenter population-based case-control study in the United States in 1998, and reported that being in the highest quartile of body mass index (BMI) compared with being in the lowest quartile was associated with an increased risk of esophageal adenocarcinoma and gastric cardia carcinoma. Lagergren et al. [27] reported similar results from a large study of the Swedish population. On the other hand, in 2003, Zhang et al. [37] reported that the BMI of patients with gastric cardia cancer was significantly lower than that of patients with noncardia GC, indicating that being underweight was positively associated with gastric cardia carcinoma. Thus, the association between obesity and gastric cardia cancer remains controversial. Kubo and Corley [38] performed a system-

atic review and metaanalysis of 14 studies and concluded that a high BMI was weakly associated with the risk of cancer in the gastric cardia.

Obesity is manifested as a markedly high volume of adipose tissue. Recent studies have demonstrated that adipocytes produce a variety of secretory peptides, named adipokines [39, 40]. More recently, some adipokines, such as leptin and adiponectin, have been shown to critically regulate the biological behavior of malignant cells [41–50], raising the possibility that adipocytes may have positive roles in the development of malignant diseases through the secretion of adipokines in an endocrine or intracrine manner. In addition, it has been suggested that the biochemical characteristics of visceral and subcutaneous adipose tissues are somewhat different [51, 52].

Taking these findings into account, we raised the hypothesis that the distribution as well as the volume of adipose tissue may have a specific association with human cancer. However, there are no reports describing adipose tissue volume or distribution in cancer patients. In this study, therefore, we measured visceral and subcutaneous fat areas separately on CT images of patients with early GC, and investigated the relationship of these findings with various clinical and pathological parameters of GC.

Patients, materials, and methods

Patients and methods

In this study, we examined the volume of visceral and subcutaneous fat in one slice of a CT scan, using Fat Scan software (N2 System, Osaka, Japan). Several studies have revealed that the visceral fat area (VFA) shown from a single scan obtained at the level of the umbilicus (the level from L4 to L5) is highly correlated with the total visceral fat volume [53–55]. Hence, we used a slice of a CT image at the umbilical level to measure VFAs and subcutaneous fat areas (SFAs). We collected the data for SFA and VFA by a previously reported technique [55, 56]. We determined the total fat area (TFA) as the sum of the SFA and VFA, and the V/S ratio, as the VFA divided by the SFA.

We retrospectively studied 550 patients whose disease was pathologically diagnosed as early GC who underwent surgical gastrectomy or endoscopic resection between April 2001 and February 2007 at the Tokyo University Hospital. Early GC, according to the classification established by the Japanese Research Society for Gastric Cancer, is defined as a lesion confined to the mucosal or submucosal layer. We selected only patients with early GC, because advanced-stage cancer may affect the volume of adipose tissue through causing diminished appetite and altered metabolism. Therefore, we also excluded patients with any other malignant diseases.

Among the 550 patients, a CT scan image of the umbilical slice was unavailable in 332 patients, who were excluded from this study. Three patients had had a previous gastrectomy and 5 patients had other advanced malignant diseases; these 8 patients were also excluded, because gastrectomy or the presence of other malignancies may affect the fat area. Finally, 210 patients (174 men and 36 women) for whom a CT image of a slice at the umbilical level was available were enrolled in this study. We also examined, in a similar manner, 147 patients (102 men and 45 women) with early colorectal cancer (CRC) as a control group in this study.

In order to analyze the associations of SFA and VFA with various parameters in cardia cancer, we used the criteria for cardia cancer proposed by Siewert and Stein [57]. According to their criteria, adenocarcinomas whose center lay within 1 cm proximal to and 2 cm distal from the gastroesophageal junction (Siewert type II) were classified as cardia cancer, and other adenocarcinomas were categorized as noncardia cancer.

This study was approved by the ethics committee of the University of Tokyo.

Statistical analysis

We performed statistical analyses of TFA, VFA, SFA, and the V/S ratio, as well as blood count data, blood chemical data, and pathological data. Spearman rank correlations were calculated to determine the relationship between nominal data and continuous data, and Mann-Whitney's *U*-test was used to determine the correlation between two kinds of continuous data. Values of $P < 0.05$ were considered to be significant.

Results

Total fat area (TFA), visceral fat area (VFA), and subcutaneous fat area (SFA) in gastric and colorectal cancers

The data for our entire patient cohort are shown in Table 1. BMI and TFA values showed no significant difference between patients with GC and those with CRC. Both BMI and TFA were the same in male and female patients. In contrast, in both GC and CRC patients, VFA was significantly larger in male patients, while SFA was larger in female patients (GC, $P < 0.001$; CRC, $P < 0.01$). This is consistent with the data of the general population without cancer [58]. However, when VFA and SFA were separately compared in each sex, both parameters mostly showed the same values. Inter-

Table 1. BMI and fat areas in patients with early gastric and colorectal cancers

Male (n = 276)	Gastric cancer (n = 174)	Colorectal cancer (n = 102)	P value
BMI (kg/m^2)	22.8 ± 2.9	22.9 ± 3.1	0.979
TFA (cm^2)	199.6 ± 89.2	185.2 ± 85.4	0.175
VFA (cm^2)	101.2 ± 52.7	91.9 ± 51.9	0.144
SFA (cm^2)	98.4 ± 45.0	93.2 ± 43.9	0.240
V/S	1.07 ± 0.41	1.05 ± 0.53	0.434
Female (n = 81)	Gastric cancer (n = 36)	Colorectal cancer (n = 45)	P value
BMI (kg/m^2)	21.9 ± 3.3	21.4 ± 3.2	0.372
TFA (cm^2)	208.7 ± 93.2	175.6 ± 82.6	0.081
VFA (cm^2)	56.6 ± 36.8	50.2 ± 29.5	0.608
SFA (cm^2)	152.1 ± 64.6	125.4 ± 60.2	0.037*
V/S	0.43 ± 0.34	0.47 ± 0.42	0.464

*$P < 0.05$
Data values are means ± SD
BMI, body mass index; TFA, total fat area; VFA, visceral fat area; SFA, subcutaneous fat area; V/S, VFA/SFA; GC, gastric cancer; CRC, colorectal cancer

Table 2. Fat areas in patients with cardia and noncardia cancers

Male	Cardia (n = 11)	Noncardia (n = 161)	P value
TFA (cm^2)	191.5 ± 60.8	201.0 ± 91.0	0.781
VFA (cm^2)	99.6 ± 37.9	101.8 ± 53.7	0.963
SFA (cm^2)	91.9 ± 29.9	99.1 ± 46.0	0.781
Female	Cardia (n = 2)	Noncardia (n = 33)	P value
TFA (cm^2)	307.0 ± 136.1	207.9 ± 86.1	0.256
VFA (cm^2)	88.5 ± 85.8	56.0 ± 33.5	0.670
SFA (cm^2)	218.5 ± 50.3	151.8 ± 61.0	0.136

Data values are means ± SD
Cancer locations were unclear in 2 male patients and 1 female patient; these patients were excluded from this analysis

estingly, both parameters tended to be higher in patients with GC as compared with those with CRC, although the differences were not statistically significant, except for SFA in female patients (P = 0.037).

Fat areas and age, cancer location, depth of cancer invasion, ulcer status, symptoms, and Helicobacter pylori *infection status*

Age. Because fat volumes may be associated with age, we separated the patients with early GC into two groups; a younger group (age 60 years or less) and an older group (age 61 years or more). There were no differences in TFA, VFA, or SFA values between the two groups in male patients (data not shown). However, in female patients, VFA in the older group (67.7 ± 40.1 cm^2) was significantly larger than that in the younger group (34.4 ± 12.5 cm^2; P = 0.011). SFA also tended to be larger in the older group (data not shown), and the V/S ratio in the older group (0.45 ± 0.27) was significantly higher than that in the younger group (0.39 ± 0.45, P = 0.025). This suggests that older female patients, but not male patients, tended to have more visceral fat, and this trend is consistent with the general population data [58].

Cancer location. As previously reported in Western countries, obesity is a risk factor for cancer of the gastric cardia. Therefore, we examined the fat volumes in patients with gastric cardia and noncardia cancer. Eleven male and 2 female patients had Siewert type II cardia cancer; the remainder had noncardia cancers. In both the male and female patients, there were no significant differences in TFA, VFA, or SFA between those with cardia and noncardia cancers (Table 2).

Table 3. Fat areas and depth of cancer invasion, ulcer status, presence of symptoms, and *Helicobacter pylori* infection status

Fat areas and depth of cancer invasion Male	m (n = 105)	sm (n = 69)	P value
TFA (cm^2)	203.2 ± 89.1	194.0 ± 89.6	0.561
VFA (cm^2)	103.3 ± 53.4	98.0 ± 51.8	0.672
SFA (cm^2)	99.9 ± 44.8	96.0 ± 45.7	0.568
Female	m (n = 18)	sm (n = 18)	P value
TFA (cm^2)	233.7 ± 96.8	183.7 ± 84.7	0.121
VFA (cm^2)	62.8 ± 43.1	50.4 ± 29.1	0.457
SFA (cm^2)	170.9 ± 60.6	133.3 ± 64.5	0.071
Fat areas and ulcer status	Ulcer positive (n = 55)	Ulcer negative (n = 149)	P value
TFA (cm^2)	190.0 ± 82.6	205.1 ± 92.8	0.594
VFA (cm^2)	88.6 ± 48.2	95.5 ± 54.8	0.610
SFA (cm^2)	101.5 ± 50.7	109.6 ± 54.3	0.492
Fat areas and presence of symptoms	Symptomatic (n = 42)	Asymptomatic (n = 166)	P value
TFA (cm^2)	188.6 ± 76.2	205.4 ± 92.7	0.270
VFA (cm^2)	78.8 ± 41.5	97.9 ± 55.0	0.056
SFA (cm^2)	109.9 ± 54.9	107.4 ± 52.5	0.887
Fat areas and *H. pylori* infection status	*H. pylori* positive (n = 71)	*H. pylori* negative (n = 13)	P value
TFA (cm^2)	217.6 ± 91.5	188.1 ± 79.3	0.425
VFA (cm^2)	98.9 ± 54.1	98.5 ± 47.6	0.762
SFA (cm^2)	118.6 ± 53.7	89.6 ± 48.3	0.072

Data values are means ± SD
m, mucosal cancer; sm, submucosal cancer
The ulcer status of 204 of the 210 patients was confirmed; ulcer-positive, patients with active gastric ulcer (n = 10) or ulcer within GC lesion (n = 46; 1 patient had active ulcer and ulcer within GC lesion); ulcer-negative, patients with an old ulcer scar (n = 21) or without ulcer (n = 128)
Two of the 210 patients had no records about symptoms; 166 patients were asymptomatic, and 42 patients had symptoms (epigastralgia, n = 16; epigastric discomfort, n = 9; equivocal symptoms, n = 17)
Eighty-four patients were checked for *H. pylori* infection status

Depth of cancer invasion. We compared mucosal and submucosal cancers in relation to TFA, VFA, and SFA; these parameters were not significantly different between mucosal and submucosal cancers in either sex (Table 3).

Ulcer status. Among the 210 patients, gastric ulcer status was confirmed in 204; 128 of these patients (62.7%) did not have a gastric ulcer. However, 10 patients (4.9%) had an active gastric ulcer and 21 patients (10%) had an old ulcer scar. Moreover, ulceration was detected within the early GC lesion in 46 patients (22.5%). We found no association between ulcer status and the differentiation of early GC (P = 0.283) or between *H. pylori* infection status and the differentiation of early GC (P = 0.643). We also found no association between ulcer status and TFA, VFA, or SFA (Table 3).

Symptoms. For 2 of the 210 patients with early GC there was no record of symptoms; 166 of the remaining 208 patients (79.8%) were asymptomatic, while 16 patients (7.6%) had epigastralgia, 9 patients (4.3%) had epigastric discomfort, and the other patients had equivocal symptoms. However, we could not detect significant differences between symptomatic and asymptomatic patients in the differentiation of early GC (P = 0.176), *H. pylori* infection status (P = 0.604), or in TFA, VFA, or SFA (Table 3).

Helicobacter pylori *infection status.* *Helicobacter pylori* infection is important when considering the carcinogenesis of GC. In our series, 84 patients were checked for *H. pylori* infection status, by the rapid urease test (RUT), serum *H. pylori* antibody, or microscopic examination. Among them, 71 patients (84.5%) were positive for *H. pylori*, and 13 patients (15.5%) were negative. In these patients, we analyzed the relationship of *H. pylori* infection status and other factors, and found that *H. pylori* infection did not have a significant association with the differentiation of early GC ($P = 0.610$), or with TFA, VFA, or SFA (Table 3).

Fat areas and histological differentiation

GC is histologically classified into two types based on the predominant morphological features: differentiated type (well and moderately differentiated adenocarcinomas) and undifferentiated type (poorly differentiated adenocarcinoma and signet ring cell carcinoma), and the biological features have been shown to be considerably different in these two types [59–63]. We focused on the histological type in relation to fat areas (Fig. 1). Interestingly, in male patients, VFA was significantly smaller in those with the undifferentiated type than in those with the differentiated type ($P = 0.016$). SFA also tended to be smaller in those with the undifferentiated type ($P = 0.07$). The trend was more prominent in female patients. VFA ($P = 0.004$) and SFA ($P < 0.001$) were markedly smaller in patients with undifferentiated GC than in those with differentiated histology. However, the V/S ratio, which is an index of body fat distribution, was not different between the differentiated and undifferentiated types in either male ($P = 0.185$) or female ($P = 0.814$) patients.

Fat areas and differentiation in mucosal and submucosal cancers

Next, we compared the fat areas in patients with mucosal and submucosal cancers in those with differentiated and undifferentiated GCs separately (Fig. 2). In differentiated GCs, TFA, VFA, and SFA did not differ according to the depth of invasion in either sex. In contrast, in undifferentiated GCs (see double-asterisks in Fig. 2), SFA was significantly smaller in submucosal cancer as compared with mucosal cancer in both male ($P = 0.024$) and female ($P = 0.025$) patients. Also, in undifferentiated GCs, the difference in TFA according to depth of invasion was also statistically significant in male patients ($P = 0.039$) and marginally significant in female patients ($P = 0.055$).

From another aspect, in male patients with mucosal cancer, TFA, VFA, and SFA did not differ between cancers with differentiated and undifferentiated type histology (Fig. 2). However, when fat volumes were examined in patients with submucosal cancer (see asterisks in Fig. 2), TFA, VFA, and SFA were significantly smaller in patients with undifferentiated cancer than in those with differentiated cancer ($P = 0.007$, $P = 0.010$, and $P = 0.022$, respectively). In female patients, a similar trend was observed; in mucosal cancer also, TFA and SFA were significantly smaller in patients with undifferentiated cancer ($P = 0.039$, $P = 0.015$).

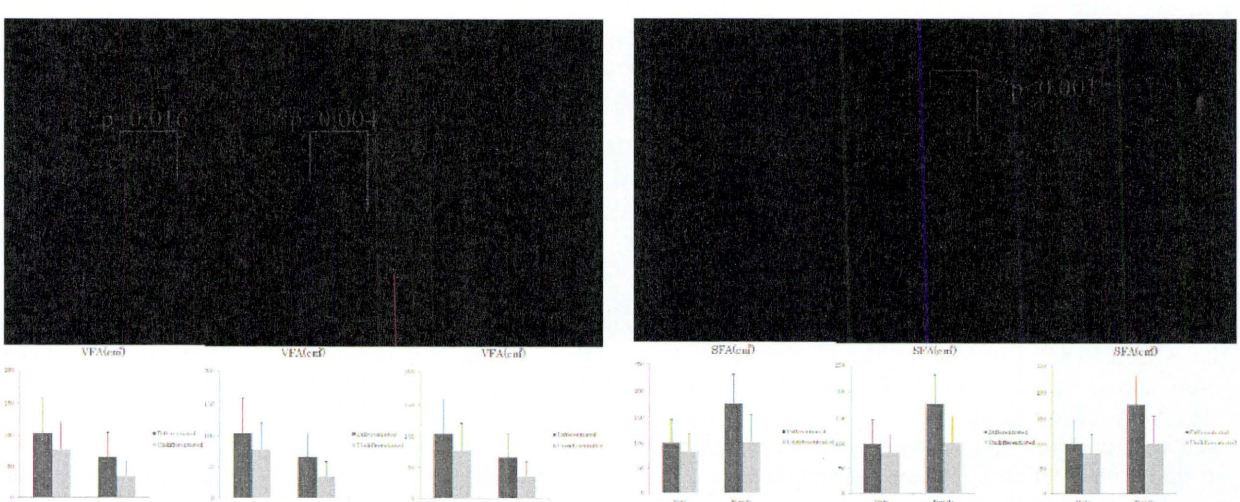

Fig. 1. Fat areas in patients with differentiated- and undifferentiated-type cancers. Male (differentiated-type cancer, $n = 151$; undifferentiated-type cancer, $n = 23$); female (differentiated-type cancer, $n = 24$; undifferentiated-type cancer, $n = 12$) $^*P < 0.05$

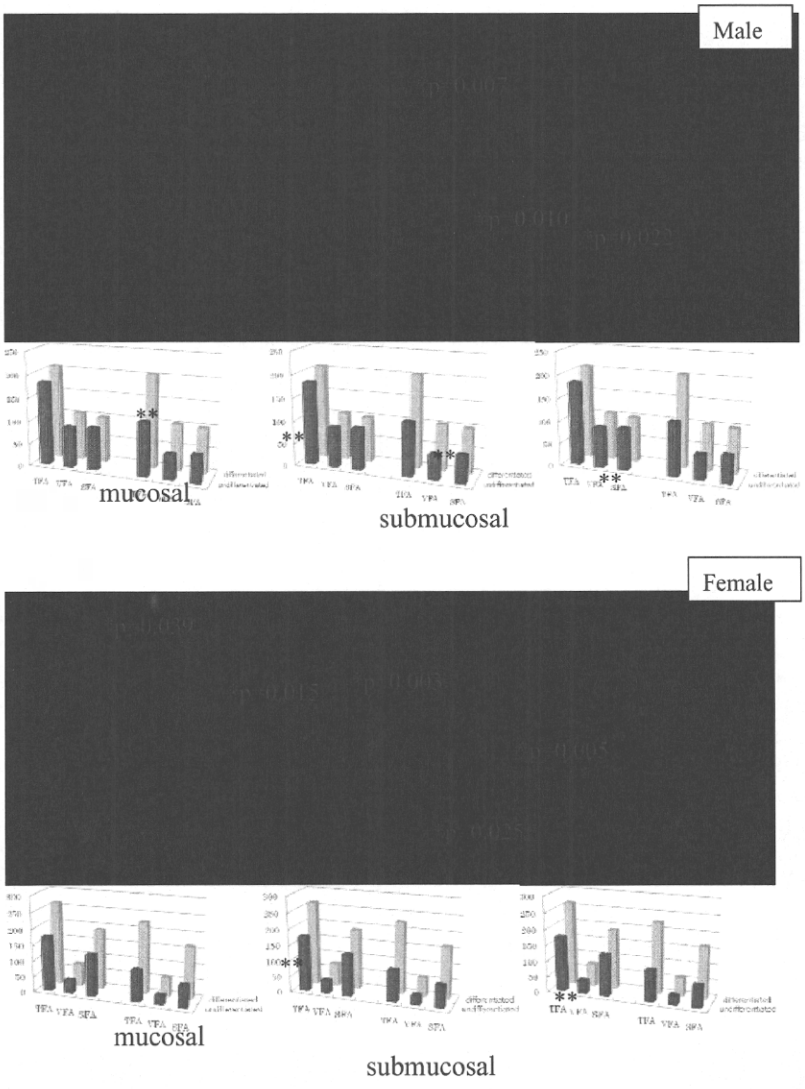

Fig. 2. Fat areas in patients with differentiated and undifferentiated cancers with invasion of different layers. Male (differentiated type of mucosal cancer, $n = 90$, undifferentiated type of mucosal cancer, $n = 15$; differentiated type of submucosal cancer, $n = 61$; undifferentiated type of submucosal cancer, $n = 8$); female (differentiated type of mucosal cancer, $n = 12$; undifferentiated type of mucosal cancer, $n = 6$; differentiated type of submucosal cancer, $n = 12$; undifferentiated type of submucosal cancer, $n = 6$) $*P < 0.05$ (comparison of differentiated and undifferentiated cancers in each depth of cancer invasion) $**P < 0.05$ (comparison of mucosal and submucosal cancers in undifferentiated-type cancer) Male total fat area (*TFA*), $P = 0.039$; subcutaneous fat area (*SFA*) $P = 0.024$; female SFA, $P = 0.025$

Fat areas and histological differentiation at different ages

In the present study, patients with undifferentiated-type GC were significantly younger than patients with differentiated-type cancer (56.3 ± 12.1 and 67.6 ± 9.1 years; $P < 0.001$). We divided the patients into two groups; those aged 60 years or less and those aged 61 years or more, and reevaluated the data. As shown in Table 4, TFA, VFA, SFA were not different between differentiated and undifferentiated type cancers in the older group in male patients. However, when these fat areas were compared in the younger group in male patients, all the values were significantly smaller in the undifferentiated type. In female patients, the difference between the younger and older groups was not so evident.

Discussion

In this study, we used a slice of a CT image at the umbilicus and separately quantified the subcutaneous fat area (SFA) and visceral fat area (VFA) in patients with early gastric cancer (GC) and patients with colorectal cancer (CRC). The values were mostly consistent with those of the Japanese general population [58]. Male patients had larger VFAs, while female patients had larger SFAs. In female patients, TFA and VFA in the older group were significantly larger than those in the younger group. The same trend was reported for BMI in the general Japanese population [64]. These data indicate that adipose tissue volume and distribution are not markedly changed by the presence of early cancer lesions in the stomach.

Table 4. Fat areas in patients with differentiated and undifferentiated cancers in the two age groups

	Age 60 years or less (n = 49)			Age 61 years or more (n = 125)		
Male	Diff (n = 36)	Undiff (n = 13)	P value	Diff (n = 115)	Undiff (n = 10)	P value
TFA (cm^2)	216.4	138.3	*0.002	202.1	189.6	0.689
VFA (cm^2)	109.4	64.9	*0.006	103.3	95.3	0.620
SFA (cm^2)	107.0	73.4	*0.007	98.8	94.2	0.920
V/S	1.04	0.90	0.365	1.10	1.04	0.604
	Age 60 years or less (n = 12)			Age 61 years or more (n = 24)		
Female	Diff (n = 5)	Undiff (n = 7)	P value	Diff (n = 19)	Undiff (n = 5)	P value
TFA (cm^2)	223.5	128.0	*0.005	250.0	149.8	0.082
VFA (cm^2)	41.7	29.2	0.088	73.7	44.7	0.082
SFA (cm^2)	181.8	98.8	*0.005	176.3	105.2	*0.043
V/S	0.23	0.50	0.223	0.42	0.58	0.915

* $P < 0.05$
Data values are averages
Diff, differentiated-type cancer; Undiff, undifferentiated cancer

In our data, VFA and SFA, as well as BMI, were not different between the patients with GC and those with CRC. Previous reports in Western countries have shown that the BMI of patients with gastric cancer was lower than that of patients with CRC [65, 66]. The patients in those studies, however, included many with advanced cancer, whereas our patients were restricted to those with early-stage cancer. Therefore, this discrepancy is not surprising, but rather suggests that the patients with GC possess the same amount of adipose tissue as those with CRC, as long as the malignant lesions are limited to an early stage.

Demographic trends in GC differ by cancer location and histology. While there has been a marked decline in distal, differentiated-type gastric cancers, undifferentiated-type cancers of the gastric cardia are increasing, particularly in Western countries [28, 67]. Japan and Korea have the highest rates of gastric cancer in the world [68, 69], and in contrast to the increasing incidence of proximal gastric cancers in the West, distal cancers continue to predominate in Japan. However, even in Japan, the proportion of proximal gastric cancers has increased among men [70].

From these data, we raised the hypothesis that there is different association between fat volume and gastric cancers at different locations. However, in both male and female patients, TFA, VFA, and SFA, as well as BMI, did not show a significant difference between cardia and noncardia cancers. This is in contrast to previous reports in Western countries showing a strong association between obesity and cardia cancer [24, 27, 34–36]. The reason for this discrepancy is not clear. However, in the present study, the number of patients with cardia cancer was small and very obese patients were relatively rare (only 2 men out of a total of 210 patients had a BMI of more than 30). Hence, in Japan, other factors, such as salt intake or *H. pylori* infection, may have a strong contribution to the pathogenesis of gastric cardia cancer, which may mask the possible correlation with adipose tissue volume. In fact, the association between chronic *H. pylori* infection and the development of gastric cancer is well established [71–74]. In Japan, the prevalence of *H. pylori* infection is less than 20% at age 20 years, but increases to 80% in those over the age of 40 years [75]. In the present study, 84 patients were checked for *H. pylori* infection status, by the rapid urease test (RUT), serum *H. pylori* antibody, or microscopic examination. Among them, 71 patients (84.5%) were positive, and 13 patients (15.5%) were negative. We analyzed the results in relation to BMI, TFA, VFA, and SFA, and in relation to the differentiation of early GC and found that, *H. pylori* infection had no association with any of these parameters.

The most striking finding in our data is the difference in adipose tissue volumes between patients with differentiated and undifferentiated GCs. In both male and female patients, TFA, VFA, and SFA were significantly smaller in patients with undifferentiated-type cancer than in those with differentiated-type cancer, except for SFA in male patients. As compared with the general Japanese population, fat areas are considered to be reduced in patients with undifferentiated gastric cancer. These findings suggest that reduced fat volume may be mechanically related to the development of undifferentiated GC. Furthermore, the TFA, VFA and SFA values did not show a significant difference between mucosal and submucosal cancers in patients with differentiated cancer, whereas in patients with undifferentiated GC, these values tended to be lower in submucosal cancer than in mucosal cancer. With these results, we raise the

possibility that a reduced fat volume may be favorable for the submucosal invasion of undifferentiated GC. Another speculation is that undifferentiated, but not differentiated, GC may already have systemic effects inducing a reduction of subcutaneous fat volumes when invasion into the submucosal layer is present.

In our data, the difference in SFA appeared to be more prominent than that in VFA. In submucosal cancers, the differences in both SFA and VFA between differentiated and undifferentiated cancers were significant in both sexes. However, in mucosal cancers, only SFA in female patients showed a significant difference between differentiated and undifferentiated cancers. These findings suggest that SFA may be more closely related to the development and progression of undifferentiated rather than differentiated GC; this would explain the significant difference in SFA between differentiated and undifferentiated cancers in mucosal cancers only in female patients, who have, basically, larger SFAs.

In our study, in male patients, a significant difference in fat volumes between patients with differentiated and undifferentiated GCs was detected only in the younger group (60 years or less), but not in the older group (61 years or more). Thus, in male patients, the specific association between undifferentiated GC and reduced fat volume was applicable only for the younger group. This trend was not observed in female patients. The mechanisms of carcinogenesis of undifferentiated GC are markedly different according to age and sex. Many studies have suggested that GCs show considerable differences in their clinical characteristics as well as genetic background according to their histological classification [63, 76]. Our result is an additional finding on the biological difference between the two histological types of GC.

In summary, we demonstrated that the differentiated- and undifferentiated-type GCs showed different associations with adipose tissue volume. The mechanisms are not clear yet and require further investigation. However, recent studies have provided evidence that adipose tissue can produce many cytokines (adipokines), such as leptin and adiponectin, which can potently affect the biological behavior of malignant cells [41–50]. Our data support the hypothesis that these adipose tissue-derived factors are differently associated with the caricinogenesis or progression of GC of each histological type.

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CLINICAL PRACTICE GUIDELINE

Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria. The major advantages of the technique in comparison with polypectomy and endoscopic mucosal resection are controllable resection size and shape and *en bloc* resection of a large lesion or a lesion with ulcerative findings. This technique is applied for the endoscopic treatment of epithelial neoplasms in the gastrointestinal tract from the pharynx to the rectum. Furthermore, some carcinoids and submucosal tumors in the gastrointestinal tract are treated by ESD. To determine the indication, two aspects should be considered. The first is a little likelihood of lymph node metastasis and the second is the technical resectability. In this review, practical guidelines of ESD for the gastrointestinal neoplasms are discussed based on the evidence found in the literature.

Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Gastrointestinal neoplasm; Treatment guideline; Lymph node metastasis

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GENERAL CONCEPT TO APPLY ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTROINTESTINAL NEOPLASMS

Endoscopic submucosal dissection (ESD) is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria in three steps: injecting fluid into the submucosa to elevate the lesion from the muscularis propria, precutting the surrounding mucosa of the lesion, and dissecting the connective tissue of the submucosa beneath the lesion. The major advantages of the technique in comparison with polypectomy and endoscopic mucosal resection (EMR) are these: the resected size and shape can be controlled; *en bloc* resection is possible even for a large lesion; and the lesions with ulcerative findings are also resectable[1,2]. Retrospective analyses of the comparison between ESD and EMR for the stomach epithelial neoplasms showed that ESD increased *en bloc* and histologically complete resection rates compared with EMR but was associated with longer average operation times and a higher incidence of intraoperative bleeding and perforation[3,4].

Two aspects are considered to determine the application of ESD for each lesion by each operator (Figure 1). The first is a little likelihood of lymph node metastasis and the second is the technical resectability. The former has been determined by the large numbers of surgically resected cases in each organ before establishment of ESD and the latter may be determined by the applied technique, the expertise of the operators, the location of the lesions or their characteristics. In terms of technical resectability, *en bloc* resection is more desirable than piecemeal resection for accurate assessment of the appropriateness of the therapy, because the depth of invasion and lymphovascular infiltration of cancer cells (that are considerable risk factors for nodal metastasis) are not accurately assessed by piecemeal resection. Almost all possible node-negative epithelial neoplasms can be resected *en bloc* by

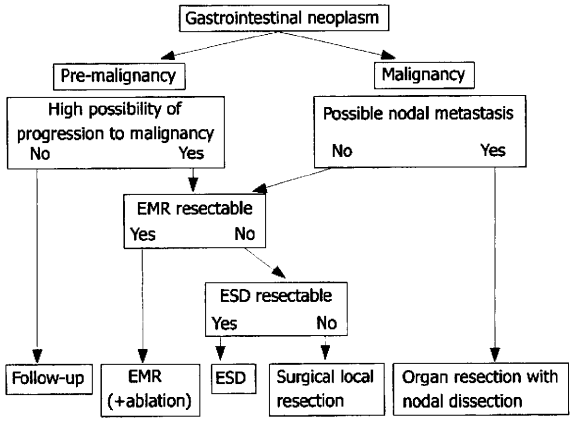

Figure 1 Algorism for endoscopic submucosal dissection of gastrointestinal neoplasms.

ESD, when they are treated by very experienced hands. This does not mean that all endoscopic resection should be performed as ESD. Polypectomy or endoscopic mucosal resection (EMR) are beneficial for patients with pedunculated neoplasms or small neoplasms because of the little invasiveness[5]. If the lesions are apparently pre-malignant neoplasms, piecemeal resection by using EMR may be permissible with the best balance of risks and benefits. Surgical organ resection with lymphadenectomy should be applied to those neoplasms with high probability of positive lymph nodes or failure in complete removal by ESD. Recurrent lesions can be also indicated for ESD, if they fulfill the criteria of no nodal metastasis, but indication should be carefully determined considering the risks of accompanying complications.

STOMACH EPITHELIAL NEOPLASMS

Aspects of nodal metastasis

Pre-malignant stomach epithelial neoplasms, gastric adenomas, have no nodal metastases. It is still controversial whether we should treat gastric adenomas endoscopically or follow them. A series with a small number of cases with a preoperative diagnosis of pre-malignant lesion revealed that 37% (16/43) of them were finally diagnosed as adenocarcinoma and a lesion > 1 cm was considered to pose a risk of malignancy[6]. Another study revealed that 6.8% (8/118) of cases were finally diagnosed as adenocarcinoma and high-grade dysplasia by endoscopic biopsy was considered to be an independent risk factor for malignancy[7]. Furthermore, preoperative diagnosis of depressed adenoma is considered to represent a higher risk of malignancy than protruding adenoma[8]. So, when the lesions have these characteristics, endoscopic treatments are recommended, similarly to intramucosal carcinomas. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques to remove the apparent gastric adenomas is allowed.

In terms of malignant stomach epithelial neoplasms, the following types of early gastric cancers without lymphovascular infiltration of cancer cells may have little likelihood of nodal metastases: (1) intramucosal, differentiated adenocarcinoma without ulcer findings of any size; (2) intramucosal, differentiated adenocarcinoma with ulcer findings when the lesion is ≤ 3 cm; (3) intramucosal, undifferentiated adenocarcinoma without ulceration when the lesion is ≤ 2 cm; and (4) differentiated adenocarcinoma with minute submucosal penetration (500 micrometers below the muscularis mucosa; sm1) when the lesion is ≤ 3 cm[9].

Technical aspects

When the endoscopists are well trained for ESD, the technical aspects may not restrict indications to perform ESD, based on the above criteria of no nodal metastasis. However, in our opinion, cases of ulcer findings with fusion of the muscle layer and the mucosal layer and cases of undifferentiated adenocarcinoma may be excluded from the indication or be carefully resected, at least until now. The former cases occur in cancers that previously had a deep ulcer extending into the proper muscle layer, where it is difficult to identify the gastric wall plane during submucosal dissection, which increases the possibility of perforation or incomplete resection by ESD[10]. In the latter cases, first, the margin is very unclear and the possibility of incomplete resection is fairly high, second, the clinical course after recurrence may be more miserable than that of differentiated-type, and third, the differentiation between ulcerative finding or biopsy-inducing fibrosis is sometimes difficult, even though small intramucosal undifferentiated adenocarcinoma with ulcer findings may be associated with nodal metastases[9].

ESOPHAGEAL SQUAMOUS EPITHELIAL NEOPLASMS

Aspects of nodal metastases

Low- and high-grade squamous intraepithelial neoplasms, including carcinoma *in situ* (m1), have no nodal metastases. It is still controversial whether one should treat these intraepithelial neoplasms endoscopically or just follow them. However, when the lesions are diagnosed as high-grade intraepithelial neoplasms, endoscopic treatment is recommended, to avoid future development of invasive carcinoma or to contain foci of invasive carcinoma[11,12]. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques to remove the apparent intraepithelial neoplasms is allowed[13-15].

Esophageal squamous cell carcinomas invading the lamina propria (m2) pose little risk of nodal metastases. For those invading the muscularis mucosa (m3) and those with minute submucosal invasion (< 200 micrometers below the muscularis mucosa; sm1), the nodal metastases rate is 9.3% and 19.6%, respectively. The nodal metastases rate of m3 or sm1 cancers with 0-II type, < 5 cm, well or moderately differentiated type, and no lymphovascular infiltration of cancer cells is 4.2%[16]. It has been reported that no nodal metastasis was found in patients with sm1, low

histologic grades, and no lymphovascular infiltration of cancer cells[17]. Therefore, for patients unwilling to undergo esophagectomy or chemoradiation and patients with comorbid diseases, ESD may be applied taking into consideration the risks of nodal metastases and treatment-related morbidity.

Technical aspects

When the endoscopists are well trained for ESD, the technical aspects by themselves may not restrict indications to perform ESD, except in special circumstances, such as lesions located in the diverticulum. When lesions spreading > 3/4 of circumference are resected as circular or semi-circular resection, post-operative stricture occurs to a high rate[18]. So, it is controversial to treat these lesions endoscopically. However, intensive balloon dilatations or tentative stent insertion may rescue from the stricture.

ESOPHAGEAL BARRETT NEOPLASMS

Aspects of nodal metastasies

Columnar intraepithelial neoplasms have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and additional ablation therapy to remove the apparent intraepithelial neoplasms is allowed[19-23].

There are no data about nodal metastases from the large numbers of surgically resected cases due to limited number of cases of esophageal columnar epithelial carcinomas at an early stage, although a small number of cases revealed no nodal metastasis for the intramucosal and sm1 cancer, where sm1 was determined by upper third of the submucosa[24]. There is no consensus whether one should apply to this kind of malignancy the same criteria that are applied to stomach epithelial neoplasms or esophageal squamous epithelial neoplasms as far as the depth of sm1 to be measured. International workshops of esophagogastric neoplasms adopted the cut-off line of 500 micrometers below the deeper muscularis mucosae, similarly to the stomach[25,26].

Technical aspects

Similarly to esophageal squamous epithelial neoplasms, the technical aspects by themselves may not restrict indications to carry out ESD, when the endoscopists are well trained for ESD. When lesions spreading > 3/4 of the circumference of the esophagus (a situation which commonly occurs in long segment Barrett epithelium) are resected (with circular or semi-circular resection), post-operative strictures occur at a high rate[19-23].

RECTAL EPITHELIAL NEOPLASMS

Aspects of nodal metastases

Pre-malignant rectal epithelial neoplasms, rectal adenomas, have no nodal metastases. From the standpoint of adenoma-carcinoma sequence, all adenomas, including diminutive polyps, are targets for endoscopic resection[27,28], although some investigators agree with endoscopic removal only if the size is > 5 mm[29]. *En bloc* resection is not always necessary for rectal adenoma or intramucosal carcinoma. However, higher rate of local recurrence was reported when multiple resections were performed[30-32]. Intramucosal carcinomas and those with slight submucosal invasion (< 1000 micrometers below the muscularis mucosa; sm1) without lymphovascular infiltration have little risk of nodal metastasis[33].

Tumor morphology and surface pit pattern are good endoscopic indicators for submucosal invasion. From this aspect, depressed lesions, laterally spreading tumors of non-granular type (LST-NG) and large protruding tumors are considered as good candidates for ESD because these lesions have a high risk of submucosal invasion, which may be difficult to diagnose preoperatively, and a thorough histopathological assessment of the resected specimen is essential. It is controversial whether one should perform ESD or piecemeal EMR for laterally spreading tumors of granular type (LST-G), because most lesions are intramucosal and the endoscopic prediction of invasiveness is highly feasible[34].

Technical aspects

Even for lesions that meet the criteria above, laparoscopic or open surgery may be selected in some institutions considering the location and size of the lesion. The lesions with submucosal fibrosis due to previous endoscopic treatment or biopsy are also resectable by ESD, even though the indication should be carefully weighed considering risks and benefits of ESD *vs* surgery[35,36]. The rectum is fixed to the retroperitoneum, therefore the endoscope is more easily manoeuvered than in other organs of the gastrointestinal tract. Furthermore, panperitonitis may be less likely than in the rest of the colorectum, even if the muscularis propria is teared, although penetration leads to air accumulation in the retroperitoneal space, which may then spread to a wider area[37,38].

COLONIC EPITHELIAL NEOPLASMS

Aspects of nodal metastases

The criteria for absence of nodal metastases are the same as those of rectal epithelial neoplasms (see above).

Technical aspects

There are several tortuous folds in the colon. Peristalsis and residual feces may sometimes disturb ESD procedure. So it is commonly believed that the technical difficulty of colon ESD exceeds those of the stomach, the esophagus, and the rectum, although there are many differences. In all cases, should one consider the substantial risks and expected benefits of ESD. However, promising results of ESD are reported from very experienced endoscopists at advanced institutions, similarly to those of the rectal epithelial neoplasms[39-43].

EPITHELIAL NEOPLASMS IN THE SMALL INTESTINE, INCLUDING DUODENUM

Aspects of nodal metastases

Pre-malignant epithelial neoplasms in the small intestine have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and ablation therapy to remove the apparent intraepithelial neoplasms is allowed[44]. There are no data about nodal metastases from the large numbers of surgically resected cases due to limited number of cases of epithelial carcinomas in the small intestine. There is no consensus whether one should apply the same criteria of stomach epithelial neoplasms or colorectal epithelial neoplasms to this malignancy.

Technical aspects

The small intestine, including the duodenum, is considered to be the most difficult organ where to perform ESD. The endoscope does not easily reach the target lesion and the organ is not fixed tightly except at the level of the duodenum, which results in fairly bad maneuverability. Peristalsis is the most active and the wall is the thinnest among the other gastrointestinal organs. Even is the resection is completed successfully, pancreatic juice and bile cause chemical damage to the mucosal wound, which may lead to prolonged bleeding and perforation. In our opinion, closure of the mucosal wound is recommended after ESD. When considering these issues, indication to perform ESD in the small intestine should be carefully assessed and limited. Due to the structural specificity of the papilla, ESD for ampullary neoplasms is not performed.

PHARYNGEAL EPITHELIAL NEOPLASMS

Aspects of nodal metastasis

Pre-malignant epithelial pharyngeal neoplasms have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and ablation therapy to remove the apparent intraepithelial neoplasms is permissible[45]. There are no data about nodal metastasis from the large numbers of surgically resected cases due to limited number of cases of pharyngeal epithelial carcinomas at an early stage. So, indication for invasive carcinoma is still controversial due to the lack of data. Owing to the structural differences, it is impossible to apply the criteria of esophageal squamous epithelial carcinomas for this malignancy.

Technical aspects

ESD is technically possible in this organ, and ESD may be the optimal endoscopic treatment not only because it enables an *en bloc* resection but also because it can prevent removal of excess mucosa of the pharynx, which is a very narrow and important organ related to swallowing and speech[46].

CARCINOID

Aspects of nodal metastasis

Carcinoids are classified based on organ site and cell of origin and occur most frequently in the gastrointestinal tract (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%)[47]. Primary size > 2 cm, serosal penetration, and primary site in the small intestine are considered to be risk factors for metastases in the case of gastrointestinal carcinoids[48].

Nodal metastases are most commonly found with small intestine carcinoids (20%-45%), providing the rationale for an extended resection including the adjacent lymph node drainage area. Carcinoids of the appendix < 1 cm rarely metastasize, simply requiring appendectomy for treatment. Rectal carcinoids < 2 cm rarely metastasize, directing local excision, including endoscopic resection[49]. Another group revealed that colorectal carcinoids < 1 cm without lymphovascular infiltration could be curatively treated by local resection, but others would need radical nodal dissection[50]. Duodenal carcinoids < 2 cm may be excised locally because they rarely metastasize[51].

Multiple gastric carcinoids, usually no more than 1 cm, can be followed up by endoscopy and biopsy[52,53]. Sporadic gastric carcinoids should be treated by gastrectomy with lymphadenectomy, because some of those have nodal metastases even when they have a small size[54-56]. However, differentiation of types of gastric carcinoids is not always easy, so endoscopic resection, as a first step to obtain histology, may be acceptable for small gastric carcinoids < 1 cm to predict nodal metastases.

Technical aspects

Because almost all lesions for local resection are less than 1 cm in all the gastrointestinal organs, band ligation resection[57,58], cap-technique[59] or strip biopsy[60-62] result in good outcome. So the application of ESD for carcinoids may be limited. When the lesions are in intermediate size, such as 1-2 cm, or invade massively the submucosal layer, which may result in tumor-positive margin resection, ESD should be applied[36,63].

SUBMUCOSAL TUMOR

Aspects of metastases

Submucosal tumors (SMTs) are mesenchymal tumors, which may have very diverse origins. SMTs are classified and defined as benign or malignant based on a combination of size, histological, immunohistochemical, and ultrastructural criteria. The majority of them are classified into gastrointestinal stromal tumor (GIST), of muscular origin, of neurogenic origin, of vascular origin, and of adipose tissue origin. SMTs < 3 cm are generally considered benign tumors. SMTs > 3 cm with high mitotic counts are considered tumors at high-risk of malignancy. In case of GIST, the cutoff of the size between pre-malignancy and malignancy may be

2 cm. Sarcomas including malignant GIST generally do not metastasize to regional lymph nodes, but instead spread hematogenously to the liver or metastasize to the peritoneum[64]. Benign SMTs should generally only be treated if they are symptomatic. So the SMTs > 2 cm or 3 cm without evidence of metastasis may be candidates for local resection[65].

Technical aspects

From the rationale of ESD, the targets should originate from over the muscularis propria. The lesions originating from the inner layer of the muscularis propria may be resectable by careful resection over the outer layer of the muscularis propria, but the high probability of perforation and the artificial peritoneal dissemination by tear of the tumor capsule should be taken into consideration. When considering that the small size lesions located in the mucosal or submucosal layers are mostly benign, the indication of ESD for SMTs is quite limited, although some investigators reported promising results of ESD for SMTs[66,67].

FUTURE PERSPECTIVES

The perspectives on the current indication of ESD are described based on a review of data available in the literature until the end of 2007. Further investigations in both aspects, the assessment of nodal metastases and the technical innovations, may change widely the above perspectives in the future. Recently, a new application of ESD is being investigated in cooperation with laparoscopic surgeons for the treatment of possible node-positive gastric carcinoma and gastric GIST[68,69]. There is no doubt that these attempts will expand ESD into a new field, which will be added to the upcoming practical guidelines for ESD.

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Technical Feasibility of Endoscopic Submucosal Dissection of Gastrointestinal Epithelial Neoplasms With a Splash-Needle

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Abstract: Endoscopic submucosal dissection (ESD) permits the resection of large gastrointestinal epithelial neoplasms and neoplasms with submucosal fibrosis in an en bloc manner. However, the high frequency of complications accompanying ESD and its complex processes suggests that the process requires improvement. A total of 22 consecutive patients with gastrointestinal epithelial neoplasms were enrolled during a 6-month period to evaluate a novel endosurgical knife for ESD. This novel knife is known as the "splash-needle," and it is thin, short needle with a water-irrigation function. The technical results revealed that the rates of bloc resection and en bloc resection with tumor-free lateral/basal margins (R0 resection) were 91% (20/22) and 82% (18/22), respectively. There was no significant bleeding or perforation during or after ESD. The median operation time was 60 minutes (range, 20 to 210). The splash-needle is a promising novel endosurgical knife that is useful for less complicated ESD. The accumulation of knowledge and cases verifying its usefulness is necessary, and a study comparing the knife with first-generation endosurgical knives is also warranted.

Key Words: endoscopic submucosal dissection, ESD, endoscopic treatment, gastrointestinal neoplasm, needle knife, water irrigation

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The endoscopic submucosal dissection (ESD) technique is a new endoscopic treatment that uses a cutting device and a submucosal fluid cushion. By using this technique, it has become possible to resect large gastrointestinal (GI) epithelial neoplasms and neoplasms with submucosal fibrosis endoscopically in an en bloc manner. Although recent reports describing advanced ESD techniques with these different knives[1–7] and submucosal fluid cushions[8–10] at Japanese institutions are favorable, no perfect knife or submucosal fluid cushion has thus far been created. In this background, Pentax Co has invented a novel second-generation endosurgical knife with a water-irrigation function. This new knife, known as the "splash-needle" (DN-2618A, Pentax Co, Tokyo, Japan), reduces the high frequency of complications accompanying ESD and its complex processes. In this study, we investigated the technical feasibility of ESD using the newly developed endosurgical knife for superficial GI epithelial neoplasms.

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PATIENTS AND METHODS

A total of 22 consecutive GI epithelial neoplasms in 22 patients were resected by ESD with a splash-needle between November 2006 and May 2007 at the University of Tokyo Hospital in Tokyo, Japan. All patients had a preoperative diagnosis of node-negative carcinoma, which is defined by intramucosal or slight submucosal invasive carcinoma based on the criteria of each organ.[11–13] Diagnoses were made using chromoendoscopy, endoscopic biopsy, and occasionally endoscopic ultrasonography or magnifying endoscopy for lesions suspicious for submucosal invasion. All patients were informed of the risks and benefits of several treatment options including ESD, conventional endoscopic mucosal resection (EMR), ablation therapy, and conventional surgery. Written informed consent was obtained from all the patients preoperatively. From the reports of the enrolled patients, the efficacy (defined as the rates of en bloc resection and complete resection), safety (defined as the rates of complication), and convenience (defined as the operation time) of ESD were investigated. The operation time was defined as the duration from the beginning of lesion observation after endoscope insertion to the completion of treatment for artificial mucosal defect after resection.

The Splash-Needle

The splash-needle (Fig. 1) was used as described below for phases of the procedure from marking to submucosal dissection. The characteristics of the novel knife include: (1) a short needle adjustable in length (maximal length is 2.5 mm), (2) a thin needle (0.3 mm in diameter) that makes it possible to resect using only a coagulation current for both mucosal incision and submucosal dissection (in cases with a great deal of