

## Superficially Spreading Cancer of the Stomach

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**Background:** Superficially spreading cancer (SSC) of the stomach is rare and extends widely along the mucosa or submucosa of the stomach. This study was conducted to clarify the clinicopathologic characteristics and prognosis of patients with SSC.

**Methods:** SSC was defined as a tumor invading the mucosa or submucosa and measuring  $\geq 5$  cm in size. The clinicopathologic findings and outcomes of 36 patients with SSC were compared with those of 300 patients with early gastric cancer (EGC) measuring  $\leq 5$  cm and 271 with advanced gastric cancer measuring  $\geq 5$  cm.

**Results:** SSC was significantly different from ordinary EGC in tumor size, frequency of lymph node metastasis, lymphatic invasion, venous invasion, and stage II, III, and IV disease. The frequency of serosal invasion, lymph node metastasis, and lymphatic and venous invasions in cases of SSC was significantly lower than with advanced gastric cancer. Although tumor size of SSC evaluated before operation was smaller than that on the resected specimen, the 10-year survival rate was not different between SSC and ordinary EGC.

**Conclusions:** SSC was characterized by high frequency of lymph node metastasis and preoperative underestimation of tumor size. SSC should be treated by a gastrectomy and lymphadenectomy with sufficient resection margin.

**Key Words:** Superficially spreading cancer—Early gastric cancer—Gastric cancer—Pathology—Prognosis—Surgery.

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Recently, the detection of early gastric cancer (EGC) has increased because of improved diagnostic procedures and new widespread mass screenings.<sup>1,2</sup> The prognosis after surgery for patients with EGC is favorable,<sup>3,4</sup> and the effectiveness of endoscopic mucosal resection or laparoscopic local resection is widely accepted.<sup>5,6</sup> Among EGC cases, however, the occurrence of exceptional tumors extending widely into the mucosa, submucosa, or both has been observed.

This entity was first reported by Stout<sup>7</sup> in 1942 and was termed “superficial spreading type of carcinoma of the stomach.” This tumor type is macroscopically characterized by reddening, irregularity, and slightly nodular mucosa. Kodama et al.<sup>8</sup> and Inokuchi et al.<sup>9</sup> classified EGC into superficially spreading type and penetrating

growth type. Few comprehensive studies have evaluated the clinicopathologic characteristics and prognosis of patients with superficially spreading cancer (SSC) of the stomach.<sup>10,11</sup>

To clarify the characteristics and optimal treatment of SSC, the clinicopathologic findings and outcomes of patients with SSC were compared with those of patients with ordinary EGC and advanced gastric cancer (AGC). The features of SSC according to the major histological types were also examined.

### MATERIALS AND METHODS

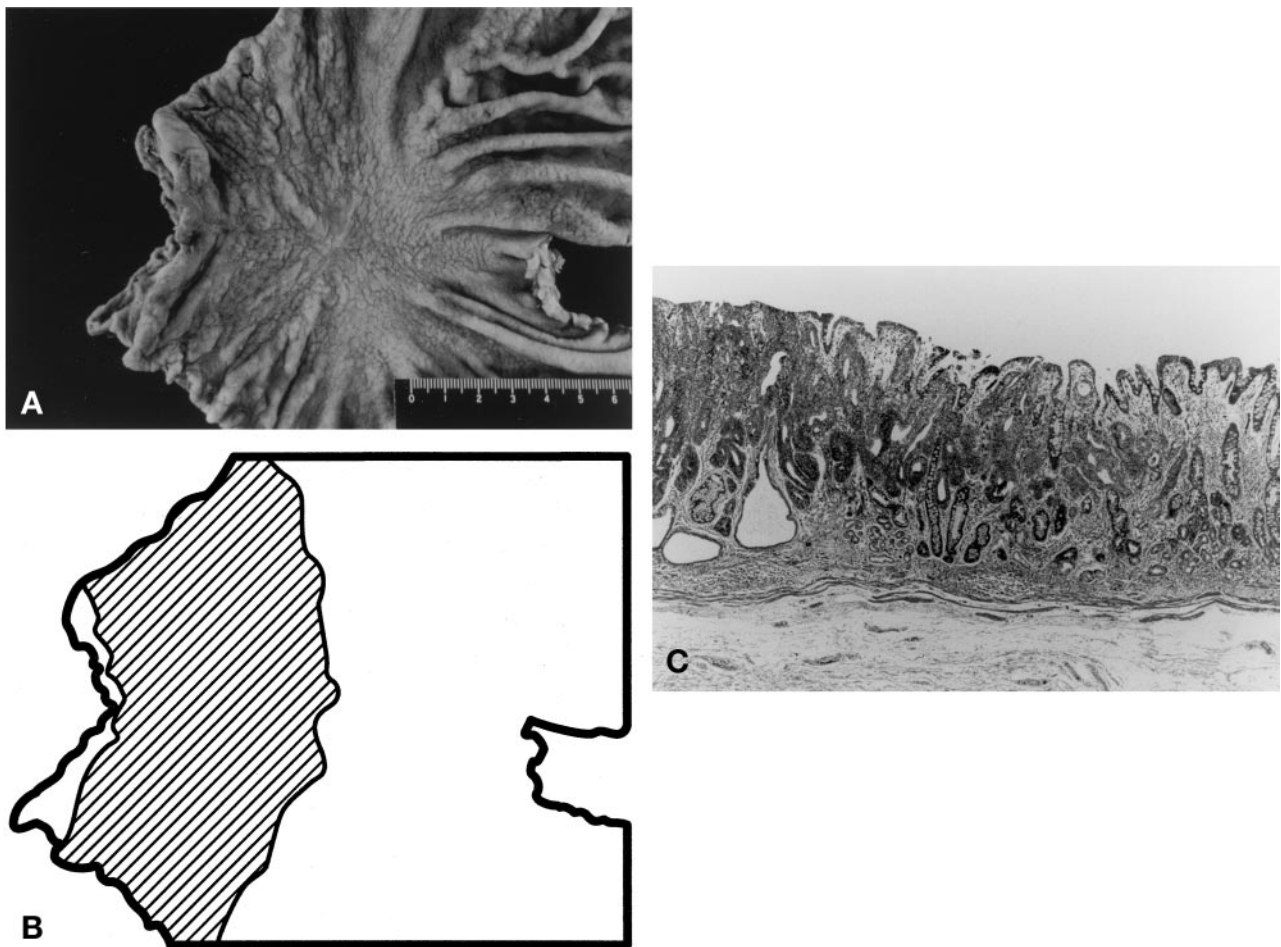
From 1982 to 1999, 696 patients with primary gastric adenocarcinoma underwent surgery at the Department of Surgery I, Oita Medical University. Of these patients, 36 had SSC, 300 had EGC measuring  $< 5$  cm, and 271 had AGC measuring  $\geq 5$  cm. SSC was defined as a tumor invading the mucosa or submucosa and measuring  $\geq 5$  cm (Fig. 1). EGC was defined as a tumor limited to the mucosa or submucosa, whereas AGC was defined as a tumor invading the muscularis propria or deeper, regard-

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**FIG. 1.** Superficially spreading cancer of the stomach. (A) Gross finding of the resected stomach. (B) Dark area shows wide area of mucosal cancer. (C) Histology revealed well-differentiated tubular adenocarcinoma widely spreading in the mucosa (hematoxylin and eosin, original magnification  $\times 10$ ).

less of the presence or absence of lymph node metastasis.<sup>12</sup>

The age and sex of patients, location, size, gross type, and histological type of tumors, depth of wall invasion, lymph node metastasis, lymphatic and venous invasions, and stage of disease were obtained from the operation records and pathology reports. Preoperative evaluation of tumor size was made by barium meal study and gastric endoscopy, and tumor size was determined by measuring the maximal diameter of the resected specimen. Histological type was divided into well-differentiated type and poorly differentiated type.<sup>13</sup> Gross appearance was classified into elevated (I, IIa) and depressed (IIb, IIc, III) type. Serosal invasion was defined as tumor invasion to the serosal surface or adjacent organs (T3). These clinicopathologic findings were based on the Japanese classification of gastric carcinoma outlined by the Japanese Gastric Cancer Association.<sup>12</sup>

All data were analyzed with the  $\chi^2$  test or Student's *t*-test. Survival rates were calculated by the Kaplan-Meier method and were assessed by the generalized Wilcoxon test. A *P* value of  $<.05$  was regarded as statistically significant.

## RESULTS

The incidence of SSC was 11% (36 of 336) in EGCs and 5% (36 of 696) in all gastric cancers. SSC, compared with EGC, was characterized by larger tumor size (6.6 vs. 2.3 cm;  $P < .01$ ); more frequent lymph node metastasis (28% vs. 6%;  $P < .01$ ); higher percentages of positive lymphatic invasion (33% vs. 17%;  $P < .05$ ); positive venous invasion (8% vs. 2%;  $P < .05$ ); and stage II, III, and IV disease (8% vs. 1%;  $P < .01$ ; Table 1). When EGC was divided into three groups according to the tumor size ( $<1$  cm, 1–3 cm, or 3–5 cm), the

**TABLE 1.** Superficially spreading cancer (SSC) versus early gastric cancer

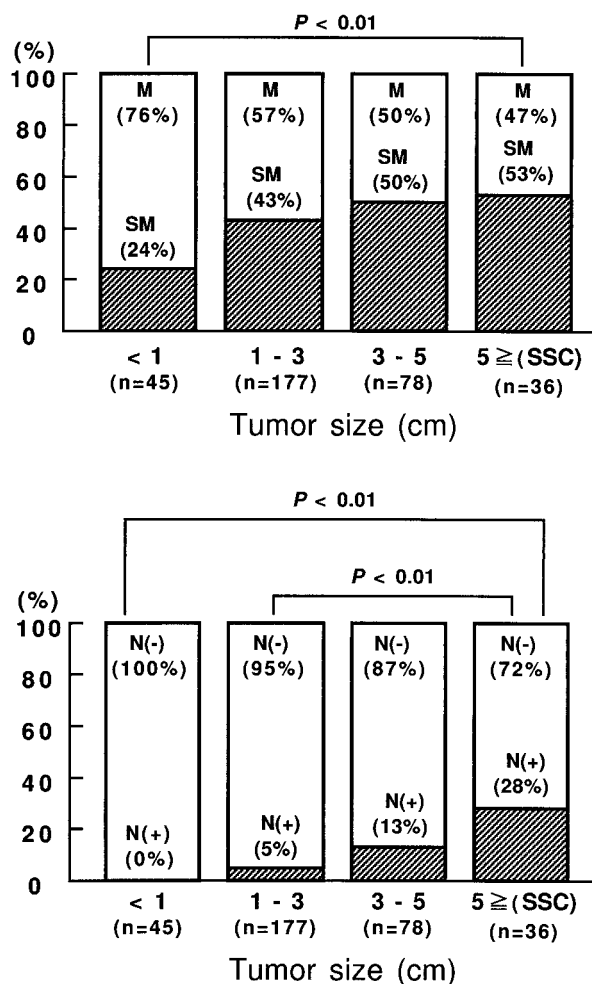
Variable	SSC (n = 36)	EGC (n = 300)	P value
Age (y), mean $\pm$ SD	62.3 $\pm$ 13.6	63.8 $\pm$ 11.4	NS
Sex			
Male	23 (64)	211 (70)	
Female	13 (36)	89 (30)	NS
Location			
Upper one third	3 (8)	43 (14)	
Lower two thirds	33 (92)	257 (86)	NS
Size (cm), mean $\pm$ SD	6.6 $\pm$ 2.0	2.3 $\pm$ 1.1	<.01
Gross type			
Elevated	8 (22)	83 (28)	
Depressed	28 (78)	217 (72)	NS
Histological type			
Well-differentiated	21 (58)	208 (69)	
Poorly differentiated	15 (42)	92 (31)	NS
Depth of invasion			
Mucosa	17 (47)	174 (58)	
Submucosa	19 (53)	126 (42)	NS
Lymph node metastasis			
Absent	26 (72)	282 (94)	
Present	10 (28)	18 (6)	<.01
Lymphatic invasion			
Absent	24 (67)	248 (83)	
Present	12 (33)	52 (17)	<.05
Venous invasion			
Absent	33 (92)	293 (98)	
Present	3 (8)	7 (2)	<.05
Stage of disease			
I	33 (92)	296 (99)	
II, III, IV	3 (8)	4 (1)	<.01

NS, not significant.

<sup>a</sup> Data are presented as n (%) unless otherwise noted.

frequencies of submucosal invasion and lymph node metastasis of EGC were linked to tumor size (Fig. 2). The frequency of submucosal invasion of SSC was different from that of EGC measuring <1 cm (53% vs. 24%;  $P < .01$ ), and the frequency of lymph node metastasis of SSC was different from that of EGC measuring <1 cm (28% vs. 0%;  $P < .01$ ) and that of EGC measuring 1 to 3 cm (28% vs. 5%;  $P < .01$ ).

SSC, compared with AGC, was characterized by more frequent location in the lower two thirds of the stomach (92% vs. 72%;  $P < .01$ ), smaller tumor size (6.6 vs. 8.6 cm;  $P < .01$ ), lower percentages of serosal invasion (0% vs. 54%;  $P < .01$ ), lymph node metastasis (28% vs. 81%;  $P < .01$ ), and stage III or IV disease (8% vs. 68%;  $P < .01$ ; Table 2). Tumor size was evaluated preoperatively in 27 patients with SSC, and tumor size predicted before operation was smaller than that measured on the resected specimen (4.6  $\pm$  1.8 cm vs. 6.8  $\pm$  2.2 cm;  $P < .01$ ). However, the 10-year survival rate was not significantly different between patients with SSC and those with EGC (97.2% vs. 98.3%).



**FIG. 2.** Depth of wall invasion (top) and status of lymph node metastasis (bottom) with reference to tumor size in EGC. The frequency of submucosal invasion was different between SSC and EGC measuring <1 cm, and the frequency of lymph node metastasis was different between SSC and EGC measuring <1 cm and between SSC and EGC measuring 1 to 3 cm. SSC, superficially spreading cancer; M, mucosal; SM, submucosal; N(-), node negative; N(+), node positive.

There were 21 well-differentiated SSCs and 15 poorly differentiated SSCs (Table 3). The well-differentiated tumors were predominant in men (81%), whereas the poorly differentiated tumors were predominant in women (60%). Depressed type comprised 62% of well-differentiated tumors, whereas it comprised 100% of poorly differentiated tumors. The 10-year survival rate was not significantly different between well-differentiated and poorly differentiated SSC (95.2% vs. 100%).

## DISCUSSION

In this study, we clarified that SSC was characterized by location in the lower two thirds of the stomach,

**TABLE 2.** Superficially spreading cancer (SSC) versus advanced gastric cancer (AGC)<sup>a</sup>

Variable	SSC (n = 36)	AGC (n = 271)	P value
Age (y), mean ± SD	62.3 ± 13.6	63.5 ± 11.9	NS
Sex			
Male	23 (64)	183 (68)	
Female	13 (36)	88 (32)	NS
Location			
Upper one third	3 (8)	77 (28)	
Lower two thirds	33 (92)	194 (72)	<.01
Size (cm), mean ± SD	6.6 ± 2.0	8.6 ± 3.6	<.01
Histological type			
Well-differentiated	21 (58)	138 (51)	
Poorly differentiated	15 (42)	133 (49)	NS
Serosal invasion			
Absent	36 (100)	126 (46)	
Present	0 (0)	145 (54)	<.01
Lymph node metastasis			
Absent	26 (72)	51 (19)	
Present	10 (28)	220 (81)	<.01
Lymphatic invasion			
Absent	24 (67)	26 (10)	
Present	12 (33)	245 (90)	<.01
Venous invasion			
Absent	33 (92)	143 (53)	
Present	3 (8)	128 (47)	<.01
Stage of disease			
I, II	33 (92)	86 (32)	
III, IV	3 (8)	185 (68)	<.01

NS, not significant.

<sup>a</sup> Data are presented as n (%) unless otherwise noted.

frequent lymph node metastasis, frequent lymphatic and venous invasions, and advanced stage. Although preoperative evaluation of tumor size was often insufficient, the 10-year survival rate of patients with SSC was high and comparable with that of patients with ordinary EGC.

SSC is a relatively rare entity among gastric cancers. The previously reported incidence of SSC was only 5% to 11% of EGCs and 2% to 4% of all gastric cancers.<sup>10,11,14</sup> The incidence of SSC in our series (10% in EGC and 5% in all gastric cancers) was similar to that of these reports.

Kitamura et al.<sup>10</sup> investigated 32 SSCs and reported that the frequencies of submucosal invasion (63%), lymph node metastasis (22%), and lymphatic invasion (16%) were higher in SSC than in cancers measuring ≤2 cm. The Japanese-language literature contains several reports of SSC. Honda et al.<sup>14</sup> examined 44 cases of SSC and showed higher frequencies of lymph node metastasis (16%) and lymphatic invasion (27%) in SSC than in ordinary EGC. Morita et al.<sup>15</sup> studied 29 cases of EGC measuring >8 cm in size and found that SSC was associated with frequent submucosal invasion (66%) and lymph node metastasis (38%). Our study confirmed that the frequencies of lymph node metastasis (28%), lym-

**TABLE 3.** Well- versus poorly differentiated type of superficially spreading cancer<sup>a</sup>

Variable	Well (n = 21)	Poorly (n = 15)	P value
Age (y), mean ± SD	65.6 ± 12.0	57.5 ± 14.7	NS
Sex			
Male	17 (81)	6 (40)	
Female	4 (19)	9 (60)	<.05
Location			
Upper one third	1 (5)	2 (13)	
Lower two thirds	20 (95)	13 (87)	NS
Size (cm), mean ± SD	7.0 ± 2.4	6.2 ± 1.3	NS
Gross type			
Elevated	8 (38)	0 (0)	
Depressed	13 (62)	15 (100)	<.01
Depth of invasion			
Mucosa	9 (43)	8 (53)	
Submucosa	12 (57)	7 (47)	NS
Lymph node metastasis			
Absent	16 (76)	10 (67)	
Present	5 (24)	5 (33)	NS
Lymphatic invasion			
Absent	14 (67)	10 (67)	
Present	7 (33)	5 (33)	NS
Venous invasion			
Absent	18 (86)	15 (100)	
Present	3 (14)	0 (0)	NS
Stage of disease			
I	20 (95)	13 (87)	
II, III, IV	1 (5)	2 (13)	NS

NS, not significant.

<sup>a</sup> Data are presented as n (%) unless otherwise noted.

phatic invasion (33%), and submucosal invasion were higher in SSC than in ordinary EGC.

Even when the depth of wall invasion is limited to the mucosa or submucosa, SSC has a high potential for metastasis to the lymph nodes. We previously showed that tumor size was closely linked to the degree of lymph node metastasis<sup>16</sup> and that tumor size was correlated with the frequency of lymph node metastasis in EGC invading the submucosa.<sup>17</sup> Therefore, gastrectomy with lymph node dissection is recommended for patients with SSC.<sup>11</sup>

Tumor size of SSC in our series was often underestimated preoperatively. The accuracy of preoperative evaluation of the extent of SSC is 90% by radiological examination and 79% by endoscopic examination.<sup>15</sup> When treating SSC by gastrectomy, a sufficient resection margin is important.<sup>11</sup> In SSC, the poorly differentiated type showed a female predominance and was associated with the grossly depressed type. These features are similar to those of ordinary EGC<sup>13,18</sup> and are useful in the radiological or endoscopic diagnosis of SSC.

Clarification of the histogenesis and development of SSC is important. Bamba et al.<sup>19</sup> studied the clonality of SSC and indicated that seven of nine SSCs were of monoclonal origin. Kodama et al.<sup>8</sup> and Inokuchi et al.<sup>9</sup>

showed that the growth pattern of EGC was associated with clinical outcome: superficially spreading type had a favorable prognosis, whereas penetrating growth type had a poor outcome because of frequent liver metastasis. Haraguchi et al.<sup>20</sup> studied the relationship between growth pattern and DNA ploidy and found that the superficially spreading type showed lower DNA ploidy more often than did the penetrating growth type. Recently, Tomoda et al.<sup>21</sup> detected a lower microvessel density and less vascular endothelial growth factor in superficially spreading type than in penetrating growth type. Some gastric carcinomas with low DNA ploidy and weak secretion of vascular endothelial growth factor may spread widely in the mucosa without vertical invasion through the gastric wall. Further investigations, including molecular and biological studies, are required to clarify the morphogenesis and growth mechanism of SSC.

In conclusion, SSC was characterized by a high frequency of lymph node metastasis and preoperative underestimation of tumor size. The optimal treatment for SSC is gastrectomy and lymph node dissection with sufficient resection margin. Endoscopic mucosal resection or laparoscopic local resection should not be applied to SSC.<sup>22</sup>

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