

# Early Gastric Carcinoma with Signet Ring Cell Histology

Woo Jin Hyung, M.D.<sup>1,2</sup>

Sung Hoon Noh, M.D.<sup>1,2</sup>

Jun Ho Lee, M.D.<sup>1,2</sup>

Jihun J. Huh, B.A.<sup>3</sup>

Ki Hyeok Lah, M.D.<sup>1</sup>

Seung Ho Choi, M.D.<sup>1</sup>

Jin Sik Min, M.D.<sup>1</sup>

<sup>1</sup> Department of Surgery, Yonsei University College of Medicine, Seoul, Korea.

<sup>2</sup> Cancer Metastasis Research Center, Yonsei University College of Medicine, Seoul, Korea.

<sup>3</sup> School of Medicine, Washington University, St. Louis, Missouri.

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Address for reprints: Sung Hoon Noh, M.D., Department of Surgery, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-ku, Seoul, 120-752, Korea; Fax: +82-2-313-8289; E-mail: sunghoonn@yumc.yonsei.ac.kr

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**BACKGROUND.** There has been much controversy surrounding the biologic behavior and prognosis of early stage gastric signet ring cell carcinoma (SRC). To clarify the biologic behavior of early stage gastric SRC (early SRC), we compared the clinicopathologic features and prognosis of early SRC with other histologic types.

**METHODS.** A total of 933 patients with early gastric carcinoma who had undergone gastrectomy from 1987 to 1995 were retrospectively analyzed. Among them, 263 patients with SRC were compared to 670 patients with other histologic types.

**RESULTS.** Younger patients more often had SRC than non-SRC. Additionally, the proportion of females was greater in SRC than in non-SRC. Signet ring cell carcinoma had a larger proportion of mucosa-confined lesions and a lower rate of lymph node metastasis than non-SRC. Even after stratifying the clinicopathologic characteristics, SRC showed a lower rate of lymph node metastasis than non-SRC. When the lymph node metastasis rate was compared between SRC and undifferentiated histology other than SRC, SRC demonstrated a lower lymph node metastasis rate. Multivariate analysis showed that SRC histology was a negative independent risk factor for lymph node metastasis in early gastric carcinoma. The prognosis of SRC was significantly better than that of non-SRC ( $P = 0.0104$ ).

**CONCLUSIONS.** Early gastric carcinoma with SRC is a distinct type of gastric carcinoma in terms of clinicopathologic features and prognosis. The favorable prognosis and lower rate of lymph node metastasis in early SRC suggest that the patients with early gastric carcinoma with SRC could be candidates for less invasive surgeries for an improved quality of life. *Cancer* 2002;94:78–83.

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**KEYWORDS:** early gastric carcinoma, signet ring cell carcinoma, prognosis, clinicopathologic feature.

According to World Health Organization (WHO) classification, gastric signet ring cell carcinoma (SRC) is a histologic type, primarily based on the microscopic characteristics of the tumor but not on the biologic behavior.<sup>1</sup> SRC has been classified as “diffuse type” by Lauren,<sup>2</sup> “infiltrative type” by Ming,<sup>3</sup> and “undifferentiated type” by Sugano et al.<sup>4</sup> To establish a scale of tumor aggressiveness related to prognosis, the WHO<sup>1</sup> and the Union International Contra la Cancrum (UICC)<sup>5</sup> adapted a grading system in which SRC has been classified as high grade.

Although there have been studies of the clinicopathologic characteristics including prognosis of SRC, the results were not consistent. To our knowledge, no study has focused on early stage SRC (early SRC).<sup>6–9</sup> Furthermore, few treatment strategies specific to histology for gastric carcinoma have been developed, especially for SRC, while the various types of newly developed treatment modalities have been introduced.

The purpose of this study was to clarify the biologic behavior of the early SRC by comparing the clinicopathologic features, including prognosis, with other histologic types of early gastric carcinoma. In addition, we also analyzed and compared the patterns of lymph node metastasis in patients with early SRC with other histologic types to find out the applicability of less invasive surgery for early SRC.

## PATIENTS AND METHODS

A total of 3,104 patients who had undergone gastrectomy for histologically-proven gastric adenocarcinoma at the Department of Surgery, Yonsei University College of Medicine from January 1987 to December 1995 were reviewed retrospectively. Among the study population, 556 patients (17.9%) had SRC histology; the remaining 2548 patients (82.1%) had non-SRC histology. Of these 3104 patients, 933 patients had early gastric carcinoma. Among these 933 patients, 263 (28.2%) had early gastric carcinomas with SRC histologic type and 670 (71.8%) had early gastric carcinoma with non-SRC histologic type. Among 670 patients with non-SRC histology early gastric carcinoma, 248 (26.6% of all early gastric carcinoma patients) had early gastric carcinoma with undifferentiated histology other than SRC (poorly differentiated or mucinous adenocarcinoma). Patient follow-up lasted until death or until the cut-off date of June 30, 2000. At the time of the last follow-up, 44 patients (4.7%) had been lost to follow-up. The median follow-up interval for the 773 patients alive at the cut-off date was 84 months (range 54-161 months).

We followed the criteria of the WHO classification for histologic typing of gastric tumors: SRC was defined as "an adenocarcinoma in which a predominant component (more than 50% of the tumor) is made up of isolated or small groups of malignant cells containing intracytoplasmic mucin."<sup>1</sup> Pathologic features that might potentially influence prognosis (location and size of the primary tumor, macroscopic types, depth of invasion, and nodal status) were analyzed. Other variables analyzed included age, gender, type of operation, and stage by the fifth tumor node metastasis system of UICC.<sup>5</sup> The nodal status was evaluated using both number and extent of lymph node involvement.<sup>10</sup>

The following standardized operative procedures were performed: 1) A total or distal subtotal gastrectomy was performed depending on the location and macroscopic type of gastric carcinoma; 2) D2 lymphadenectomy was preferred according to the rules of "The Japanese Research Society for Gastric Cancer."<sup>11</sup>

## Statistical Analysis

All the statistical analyses were performed using the statistical software Statistical Package for Social Science (SPSS) version 9.0 for Windows (SPSS, Inc, Chicago, IL).<sup>12</sup> The inter-group comparisons of clinicopathologic variables were made using the two-tailed chi-square test for discrete variables.

The rates of lymph node metastasis were compared between SRC and non-SRC after stratifying the clinicopathologic characteristics. Risk factors influencing lymph node metastasis were determined by logistic regression analysis. The odds ratio in the multivariate analysis was defined as the ratio of the probability that an event (lymph node metastasis) would occur to the probability that it would not occur. The prognostic power of covariates was expressed by calculation of an odds ratio with a 95% confidence interval.

The lost cases and operative mortality cases were treated as censored data for the analysis of survival rates. The Kaplan-Meier method<sup>13</sup> was used for calculating the survival rate and the difference between the curves was assessed using the log-rank test. The accepted level of significance was  $P < 0.05$ .

## RESULTS

The incidence of SRC was 17.9% of the total cases of gastrectomies performed (556 patients out of 3104). Signet ring cell carcinoma had a higher prevalence of early gastric carcinoma (47.3%, 263 patients out of 556) than non-SRC (26.3%, 670 patients out of 2548). The incidence of early SRC was 28.2% of all early gastric carcinoma. Signet ring cell carcinoma was more common in younger patients than non-SRC. The proportion of females in the group with SRC was larger than in non-SRC (Table 1).

Signet ring cell carcinoma had a larger proportion of mucosa-confined and mid body located lesions than non-SRC among early gastric carcinoma patients. A depressed lesion was the most common macroscopic type of SRC. Signet ring cell carcinoma showed a significantly lower lymph node metastasis rate (5.7%) than non-SRC (16.0%) ( $P < 0.001$ ). Nodal status evaluated by number and extent of lymph node involvement in SRC was significantly more favorable than in non-SRC (Table 1).

In a univariate analysis, tumor size, macroscopic type, depth of invasion, and histologic type showed a significant difference in lymph node metastasis (Table 2). When lymph node metastasis was compared between SRC and non-SRC after stratifying the clinicopathologic variables, patients with SRC showed less lymph node metastasis than patients with non-SRC at

**TABLE 1**  
Comparative Data on Early Gastric Cancer Patients

Clinicopathologic features	SRC <i>n</i> = 263 (%)	non-SRC <i>n</i> = 670 (%)	<i>P</i> value
Age (yrs)			< 0.001
< 55	184 (70.0)	276 (41.2)	
≥ 55	79 (30.0)	394 (58.8)	
Gender			< 0.001
Male	140 (53.2)	466 (69.6)	
Female	123 (46.8)	204 (30.4)	
Location			0.042
Lower	120 (45.6)	367 (54.8)	
Middle	126 (47.9)	266 (39.7)	
Upper	17 (6.5)	37 (5.5)	
Operation			0.123
Total	40 (15.2)	77 (11.5)	
Subtotal	223 (84.8)	593 (88.5)	
Tumor size (cm)			0.379
≤ 1.0	20 (7.6)	77 (11.5)	
≤ 2.0	74 (28.1)	189 (28.2)	
≤ 3.0	60 (22.8)	147 (21.9)	
≤ 4.0	40 (15.2)	108 (16.1)	
> 4.0	69 (26.2)	149 (22.2)	
Macroscopic type			< 0.001
Elevated	24 (9.1)	174 (26.0)	
Flat	39 (14.8)	83 (12.4)	
Depressed	200 (76.1)	413 (61.6)	
Depth of invasion			< 0.001
Mucosa	185 (70.3)	289 (43.1)	
Submucosa	78 (29.7)	381 (56.9)	
LN metastasis			< 0.001
Negative	248 (94.3)	563 (84.0)	
Positive	15 (5.7)	107 (16.0)	
Extent of LN metastasis <sup>a</sup>			< 0.001
N0	248 (94.3)	563 (84.0)	
N1	12 (4.9)	76 (11.3)	
N2	3 (0.8)	24 (3.6)	
N3	0 (0.0)	7 (1.0)	
Number of involved LNs			< 0.001
0	248 (94.3)	563 (84.0)	
1-2	9 (3.4)	54 (8.4)	
3-4	3 (1.1)	23 (3.4)	
≥ 5	3 (1.1)	30 (4.5)	

SRC: Signet ring cell carcinoma; LN: lymph node.

<sup>a</sup> Based on 4th UICC classification.

all variables (Fig 1). Only 1.6% of the patients with SRC confined to mucosa showed lymph node metastasis, and all the involved lymph nodes were exclusively perigastric nodes, whereas 3.5% of the patients with non-SRC confined to mucosa showed lymph node metastasis. When tumors invaded the submucosal layer, the lymph node metastasis rate of SRC was 15.4%, while that of non-SRC was 25.5%. Tumors less than 1 cm in diameter with SRC histology showed no lymph node metastasis. Lymph node metastasis rates of SRC were similar and less than

**TABLE 2**  
Comparative Data on Lymph Node Metastasis in Early Gastric Cancer Patients

Clinicopathologic features	Lymph node metastasis			<i>P</i> value
	Negative <i>n</i> = 811	Positive <i>n</i> = 122	% of Positive	
Age (yrs)				0.165
< 55	407	53	11.5	
≥ 55	404	69	14.6	
Gender				0.060
Male	536	70	11.6	
Female	275	52	15.9	
Location				0.443
Lower	422	65	13.3	
Middle	339	53	13.5	
Upper	50	4	7.4	
Tumor size (cm)				< 0.001
≤ 1.0	91	6	6.2	
≤ 2.0	246	17	6.5	
≤ 3.0	175	32	15.5	
≤ 4.0	125	23	15.5	
> 4.0	174	44	20.2	
Macroscopic type				0.001
Elevated	158	40	20.2	
Flat	114	8	6.6	
Depressed	539	74	12.1	
Depth of invasion				< 0.001
Mucosa	461	13	2.7	
Submucosa	350	109	23.7	
Histological type				< 0.001
SRC	248	15	5.7	
non-SRC	563	107	16.0	

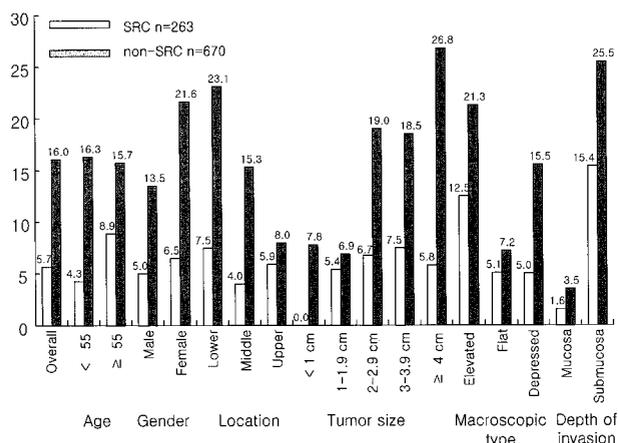
SRC: Signet ring cell carcinoma.

8%, regardless of tumor size, while those of non-SRC increased up to 26.8% when tumors were larger than 2cm (Fig. 1).

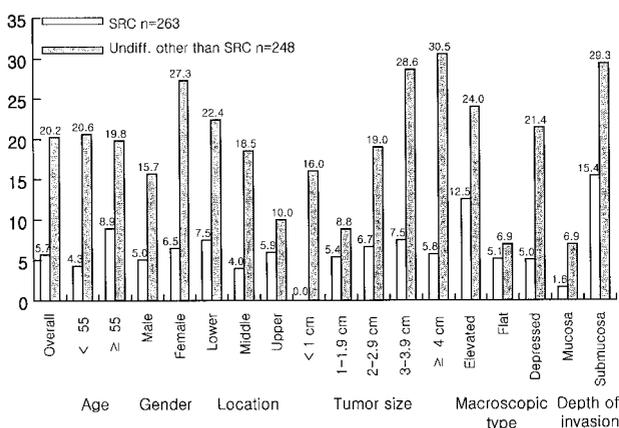
In a comparison of lymph node metastasis rates between SRC and undifferentiated histology other than SRC (poorly differentiated or mucinous adenocarcinoma) according to clinicopathologic features, less lymph node metastasis rates, were noted in SRC at all variables (Fig. 2).

Multivariate analysis using logistic regression analysis showed that male gender, a larger tumor size, submucosal invasion, and non-SRC histology were independent risk factors for lymph node metastasis (Table 3).

The cumulative survival was significantly higher in patients with SRC histology than those with non-SRC histology (*P* = 0.0104). The 5-year and 10-year survival rates were 94.2% and 89.7% for patients with SRC histology, 91.6% and 79.1% for those with non-SRC histology (Fig. 3).



**FIGURE 1.** Histogram showing the rate of lymph node metastasis according to clinicopathologic features in early gastric carcinomas with or without signet ring cell carcinoma (SRC) histology. Tumors with SRC histology show a lower lymph node metastasis rate after stratifying all clinicopathologic variables.



**FIGURE 2.** Histogram showing the rate of lymph node metastasis according to clinicopathologic features in early gastric carcinomas with signet ring cell carcinoma (SRC) histology or with undifferentiated histology other than SRC (Undiff. other than SRC). Tumors with SRC histology show a lower lymph node metastasis rate after stratifying all clinicopathologic variables.

**DISCUSSION**

The main findings of this study are: 1) early gastric carcinoma with SRC histology had a larger proportion of mucosa-confined, midbody located, depressed lesions and a lower rate of lymph node metastasis than non-SRC; and 2) patients with SRC histology showed a better survival rate than patients with non-SRC.

A higher prevalence in female patients and in younger patients and predominance of macroscopically depressed lesions are consistent characteristics of early SRC compared to previous studies. Distribution of depth of invasion and lymph node metastasis, which are important prognostic factors, are inconsistent with previous studies. These contradictory results

may arise through small sample sizes of patients with early SRC, lack of accurate staging of patients, or inadequate interpretation of statistical analysis.<sup>6-9</sup> Sugihara et al. suggested that SRC forms more frequently in the intramucosal section than the extramucosal section of the lesion.<sup>14</sup> A higher proportion of depressed lesions and easily detectable histologic features of enriched intracytoplasmic mucin with peripherally compressed nucleus enables early detection of SRC by an endoscopic exam and biopsy.<sup>8</sup> In a study of clarifying the significance of the intestinalization in the growth of signet ring cell carcinoma, the expression of the intestinal phenotype is a time-dependent and unstable phenomenon probably based on the accumulation of genetic changes; this intestinal phenotype expression plays a role in progression of signet ring cell carcinoma as the depth of invasion proceeds.<sup>15</sup> These biologic and histologic natures of SRC could be the reasons for a larger proportion of mucosa-confined lesions in early SRC.

Another peculiar characteristic of early SRC is the pattern of lymph node metastasis. Early SRC had low probabilities of lymph node metastasis, and no early SRC smaller than 1cm in tumor size had lymph node metastasis. Unlike other histologic types, the lymph node metastasis rate of SRC did not increase as the size of the tumor increased. Only 1.6% of early SRC confined to mucosa showed lymph node metastasis, and all the involved lymph nodes were perigastric nodes. Signet ring cell carcinoma-invaded submucosal layer also showed less lymph node metastasis (15.4%) than non-SRC (25.5%). SRC histology was negatively associated with lymph node metastasis in a multivariate analysis. Therefore, a patient with early SRC histology would be a good candidate for less invasive surgery.

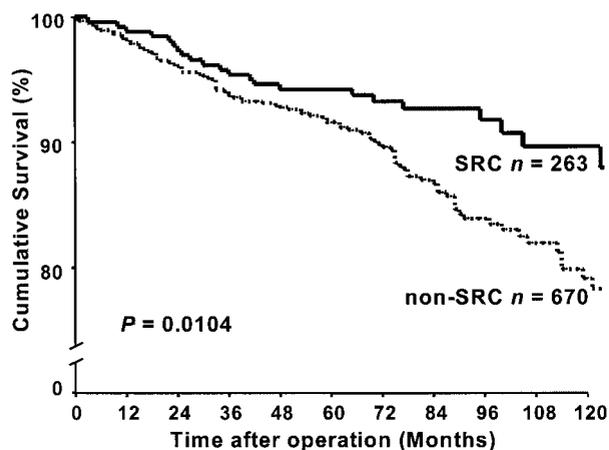
To our knowledge, no study had attempted to clarify the applicability of less invasive surgery for early SRC, despite the previous studies on clinicopathologic features or biologic behavior of SRC. As SRC was classified as undifferentiated or diffuse type in many studies about less invasive surgeries, SRC was considered a histologic type of contraindication or a limited indication for the application of less invasive surgery.<sup>16-18</sup> In this study, SRC showed a significantly lower lymph node metastasis rate than undifferentiated histology other than SRC.

Japanese researchers have reported that the prognosis of early gastric carcinoma with SRC was significantly better than that of other types,<sup>6,8</sup> while Kim et al.<sup>7</sup> reported that prognosis of early gastric carcinoma with SRC patients was similar to other types of carcinomas. In the current study, the survival rate in patients with early SRC was higher than that in patients

**TABLE 3**  
Multivariate Analysis of the Risk Factors for Lymph Node Metastasis

Clinicopathologic features	Coefficient	Standard error	Odds ratio	95% Confidence interval	P value
Age (yrs)					0.814
< 55			1		
≤ 55	0.05	0.22	1.05	0.69-1.61	
Gender					0.026
Male			1		
Female	-0.49	0.22	0.61	0.40-0.94	
Macroscopic type					0.473
Elevated			1		
Flat	-0.37	0.45	0.69	0.29-1.65	
Depressed	-0.28	0.24	0.76	0.47-1.22	
Location					0.477
Lower			1		
Middle	0.13	0.22	1.14	0.74-1.75	
Upper	-0.53	0.56	0.59	0.20-1.77	
Tumor size (cm)					0.035
≤ 1.0			1		
≤ 2.0	-0.25	0.51	0.78	0.29-2.15	
≤ 3.0	0.39	0.49	1.47	0.56-3.86	
≤ 4.0	0.53	0.51	1.70	0.63-4.64	
> 4.0	0.75	0.48	2.11	0.81-5.47	
Histological type					0.017
SRC			1		
non-SRC	0.76	0.32	2.13	1.14-3.98	
Depth of invasion					< 0.001
Mucosa			1		
Submucosa	2.19	0.31	8.95	4.85-16.52	

SRC: Signet ring cell carcinoma.

**FIGURE 3.** Cumulative survival curves for early gastric carcinoma patients with or without signet ring cell (SRC) histology. The early gastric carcinoma patients with SRC histology showed a significantly more favorable survival over those patients without SRC histology ( $P = 0.0104$ ).

without SRC. The better prognosis of early SRC than non-SRC is related to a lower lymph node metastasis rate and a higher prevalence of mucosa-confined lesions in SRC.

Advanced gastric carcinoma with SRC is charac-

terized by the potential to infiltrate the gastric wall diffusely and a unique type of SRC, linitis plastica, which indicates carcinomas involving the entire stomach, a higher rate of peritoneal dissemination than non-SRC.<sup>19,20</sup> Advanced gastric carcinoma with SRC showed a rate of lymph node metastasis similar to or higher than other types of carcinoma.<sup>6-8</sup> Unlike advanced cancer, early gastric carcinoma with SRC has characteristics of favorable clinicopathologic features and good prognosis.

Taking into consideration the clinicopathologic features and prognosis, we suggest that early signet ring cell carcinoma of the stomach should be regarded as a distinct type of gastric carcinoma. Based on these results, early SRC can be a candidate for less invasive surgery for an improved quality of life.

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