TITLE PAGE

1) Title

Predicting absence of lymph node metastasis of submucosal invasive gastric cancer: expansion of the criteria for curative endoscopic resection

2) Short title

Expansion of the curative condition after ESD for submucosal invasive gastric cancer

3) Author names, academic degree

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ABSTRACT

Background and study aims: The conditions upon which endoscopic resection (ER) can be considered curative for submucosal invasive gastric cancer remain controversial; thus, unnecessary surgery is sometimes performed after ER. Our purpose is to evaluate the significance of several clinicopathological factors for predicting absence of lymph node (LN) metastasis of submucosal invasive gastric cancer and thus determining cases in which ER can be considered curative.

Patients and methods: The study group comprised 220 patients with submucosal invasive gastric cancer that was resected surgically or endoscopically. Patients treated by ER underwent additional surgical resection. The presence of LN metastasis was evaluated in all patients, retrospectively.

Results: LN metastasis was detected in 37 (16.8%) of the 220 patients. Independent risk factors for LN metastasis were width of submucosal invasion >6000 μm, lymphatic involvement, undifferentiated type at the deepest invasive portion, depth of submucosal invasion >1000 μm, and tumor diameter >30 mm. The group of 36 patients with submucosal invasion to a depth of ≤1000 μm, tumor diameter ≤30 mm, differentiated type as the dominant histologic type, and absence of vessel involvement was entirely free of LN metastasis (95% confidence interval, 0-8.0%).

Conclusions: Taken together, the five independent risk factors may allow expansion of the criteria for determining whether ER for submucosal invasive gastric cancer has been curative.

KEY WORDS: submucosal invasive gastric cancer, endoscopic resection, ESD, lymph node metastasis

INTRODUCTION

Early gastric cancer is defined as tumor invasion confined to the mucosa or submucosa, irrespective of the presence or absence of lymph node (LN) metastasis. In Japan, endoscopic submucosal dissection (ESD) has become a common curative treatment for early gastric cancer [1, 2]. ESD is a new procedure that does not rely on snare techniques for dissection of submucosal tissue and allows en bloc resection of even large early gastric cancers. In comparison to endoscopic mucosal resection, ESD increases the rates of successful en bloc and complete resection and provides for detailed histopathologic examination [3]. According to the gastric cancer treatment guidelines issued by the Japanese Gastric Cancer Association, endoscopic resection (ER) is indicated for differentiated-type mucosal cancer ≤2 cm in diameter without ulceration or vessel involvement[4]. Gotoda et al. proposed expanding the indications for curative ER to the following: (1) differentiated intramucosal adenocarcinoma >2 cm in diameter but without ulceration or vessel involvement, (2) differentiated intramucosal adenocarcinoma ≤3 cm in diameter with ulceration but without vessel involvement, and (3) undifferentiated intramucosal adenocarcinoma ≤2 cm in diameter and without ulceration or vessel involvement [5]. In addition, they proposed clinical monitoring of differentiated-type early gastric cancer that is ≤3 cm in diameter and has invaded to a depth of <500 μm from the lower margin of the muscularis mucosa (SM1) but is without vessel involvement [5].

Additional surgery is recommended when the histologic findings do not match these criteria. However, the probability of LN metastasis ranges from 10.2% to 22.9% in cases of submucosal invasive gastric cancer [6 - 9]. In other words, LN metastasis is not found in 77.1% to 89.8% of patients who undergo additional surgical treatment. Thus, there are many cases of unnecessary additional surgical resection after ER.

We conducted a retrospective study to both evaluate the significance of several clinicopathologic factors for predicting LN metastasis and examine the feasibility of

expanding the criteria for determining whether ER of submucosal invasive gastric cancer can be considered curative.

METHODS

We studied 220 cases of submucosal invasive gastric cancer that was resected either surgically or endoscopically from 220 patients at Hiroshima University Hospital or an affiliated hospital during the period January 1990 through March 2009. Of the 220 cancers, 170 (77.3%) were resected surgically. The other 50 (22.7%) were treated first by ER and then surgically. In these 220 cases, D1 dissection (complete dissection of the first-tier LNs) plus either α or β gastrectomy [10], or D2 dissection (complete dissection of the first- and second-tier LNs) plus gastrectomy was performed. The entire tumor was cut into parallel 2- to 5-mm-thick sections, and all resected LNs were cut into two or three sections for evaluation of possible LN metastasis.

The following clinical variables were investigated: patient sex (male vs. female), age (≤65 years vs. >65 years), tumor location (upper vs. middle vs. lower part of the stomach), gross type (depressed vs. non-depressed), tumor diameter (≤30 mm vs. >30 mm), ulceration (present vs. absent), dominant histologic type (differentiated vs. undifferentiated), histologic type of the deepest invasive portion (differentiated vs. undifferentiated), diameter of the tumor if undifferentiated (≤20 mm vs. >20 mm), depth of submucosal invasion (500 μm, 1000 μm, or 1800 μm), width of submucosal invasion (6000 μm), infiltration (INF α vs. INF β/γ), lymphatic involvement (present vs. absent), venous involvement (present vs. absent), and LN metastasis, which was identified on hematoxylin-eosin stained slides by two pathologists. In addition, submucosal invasion depth of 1800 μm and invasion width of 6000 μm were used as cut-off values for an ROC curve analysis of LN metastasis. The predominant pattern of infiltrating growth into the surrounding tissue should be classified as

follows : INF α (Infiltration Alpha) : The tumor shows expanding growth and a distinct border with the surrounding tissue , INF β(Infiltration Beta) : This category is between Infiltration Alpha and Infiltration Gamma, INF γ (Infiltration Gamma) : The tumor shows infiltrating growth and an indistinct border with the surrounding tissue [4]. Association between clinical variables and LN metastasis was analyzed by chi-square or Fisher's exact test. Multivariate logistic regression analysis was performed to evaluate the risk factors for LN metastasis. A p value of <0.05 was considered statistically significant.

RESULTS

Incidence of LN metastasis in relation to clinicopathologic factors

LN metastasis was detected in 37 (16.8%) of the 220 patients, i.e., in 35 of the 170 patients who underwent surgical resection alone and in 2 of the 50 patients who underwent surgical resection after ER. Clinicopathological features of the 220 patients are shown in Table 1. The incidence of LN metastasis was significantly high among patients with a tumor diameter >30 mm ($p<0.0001$), undifferentiated type at the deepest invasive portion ($p<0.0001$), submucosal invasion to SM1 or more ($p=0.0010$), depth of submucosal invasion >1000 μm ($p=0.0089$), depth of submucosal invasion >1800 μm ($p=0.0001$), width of submucosal invasion >6000 μm ($p<0.0001$), INF β/γ ($p=0.0148$), lymphatic involvement ($p<0.0001$), venous involvement ($p<0.0001$). The mean depth of submucosal invasion was significantly greater among patients with LN metastasis than among those without LN metastasis (3100±2724 μm vs.1500±1194 μm, $p<0.0001$). In addition, the mean width of submucosal invasion was significantly greater among patients with LN metastasis than among those without LN metastasis (12010±8510 μm vs. 6504±6013 μm, $p<0.0001$). Sex, age, tumor location, gross type, ulceration, and the diameter of undifferentiated-type cancer were not associated with LN metastasis.

Results of multivariate logistic regression analysis

Factors predictive of LN metastasis are shown with odds ratios and 95% confidence intervals (CIs) in Table 2. Multivariate analysis showed width of submucosal invasion >6000 μm (risk ratio: 8.54, 95% CI: 2.24-41.2; p=0.0034), lymphatic involvement (risk ratio: 4.39, 95% CI: 1.55-14.1; p=0.0077), undifferentiated type at the deepest invasive portion (risk ratio: 4.30, 95% CI: 1.44-15.3; p=0.014), depth of submucosal invasion >1000 μm (risk ratio: 3.92, 95% CI: 1.07-15.5; p=0.042), and tumor diameter >30 mm (risk ratio: 3.42, 95% CI: 1.40-8.71; p=0.0078) to be independent risk factors for LN metastasis. Depth of submucosal invasion >500 μm or >1800 μm was not shown to be an independent risk factor for LN metastasis.

Identification of cases without LN metastasis by combining independent predictors

We examined the value of combining the following five independent clinicopathologic factors to predict LN metastasis: width of submucosal invasion >6000 μm, lymphatic involvement, undifferentiated type at the deepest invasive portion, depth of submucosal invasion >1000 μm, and tumor diameter >30 mm. The incidence of LN metastasis is shown in relation to the number of positive clinicopathologic factors in Table 3. Lesions that were either negative for all factors or positive for only one factor were without LN metastasis. As the number of positive clinicopathologic factors increased, the incidence of LN metastasis increased.

Conditions surrounding absence of LN metastasis of submucosal invasive gastric cancer

When we took 1000 μm as the cut-off value for vertical submucosal invasion, the group of 36 patients with submucosal invasion to a depth ≤1000 μm, a tumor diameter ≤30 mm, dominant differentiated type histology, and lack of vessel involvement was entirely free of LN metastasis (95% CI, 0-8.0%).

Relations between depth of submucosal invasion and width of submucosal invasion and other factors

Correlation was found between depth of submucosal invasion and width of submucosal invasion (correlation coefficient, 0.54) (Figure1). In addition, correlation was found between tumor diameter and width of submucosal invasion (correlation coefficient, 0.36) (Figure 2). No correlation was found between depth of submucosal invasion and other factors or between width of submucosal invasion and other factors.

DISCUSSION

Independent risk factors for LN metastasis of submucosal invasive gastric cancer identified in this study comprised width of submucosal invasion >6000 μm, lymphatic involvement, undifferentiated type at the deepest invasive portion, depth of submucosal invasion >1000 μm, and tumor diameter >30 mm. Our findings suggest that it may be possible to predict absence of LN metastasis in cases of submucosal invasive gastric cancer by evaluating these five risk factors in combination.

Son, et al. examined 124 cases of submucosal invasive gastric cancer, conducted a multivariate analysis, and cited lymphatic involvement and SM2 infiltration as risk factors for LN metastasis [11]. Shimoyama, et al. reported, on the basis of their study of 294 submucosal invasive gastric cancers, that tumor diameter was significantly greater in cases of LN metastasis than in cases without LN metastasis. They also reported a significantly higher incidence of lymphatic involvement and invasion into SM2 in cases of LN metastasis [12]. In Japan, the following criteria have been applied in determining whether ER can be considered curative in cases of submucosal gastric cancer: a tumor diameter ≤30 mm; differentiated-type cancer; invasion into SM1 (up to 500 μm); and absence of vessel involvement [5]. These criteria are based on data obtained from the pathological findings of reported surgical resections. One of the characteristics of the present study is that sections 2-5 mm in size were examined by hematoxylin and eosin staining for a detailed analysis of all cases, including an analysis of the deepest invasive portions containing infiltrating cancer cells.

Histopathologic type is one of the main factors involved in LN metastasis of gastric cancer [13 - 16], and we reported previously on outcomes after ER of undifferentiated gastric cancer and expansion of the criteria for determining whether ER can be considered curative in such cases[17, 18]. Moreover, Park, et al. examined 234 cases of undifferentiated early gastric cancer and reported that it might be possible to expand the criteria establishing whether ER can be considered curative for tumors with a diameter of 15 mm or less and invasion to SM1 [19]. Kunisaki, et al. studied 573 cases of undifferentiated early gastric cancer and reported that it may be possible to expand the criteria to mucosal gastric cancer tumors 20 mm or more in diameter without vascular invasion, as well as to cases of SM1 cancer less than 20 mm in diameter and without vessel involvement [20]. With regard to cancers of mixed differentiated and undifferentiated types, Hanaoka, et al. reported that those of undifferentiated-type-predominant mixed type have a higher incidence of LN metastasis compared to differentiated type submucosal invasive gastric cancers [21]. In the present study, submucosal invasive gastric cancers of both differentiated and undifferentiated types were examined; there was no significant difference between these two main histologic types in terms of the incidence of LN metastasis. Moreover, because the reported criteria for determining that ER is curative includes lesions of the undifferentiated type, mucosal cancer without ulceration or vessel involvement, and a diameter within 2 cm [5, 22], we divided our sample cases into two groups (undifferentiated cancers >20 mm in diameter and differentiated cancers of any size or undifferentiated cancers ≤20 mm in diameter) to compare the incidences of LN metastasis. There was no significant difference between these two groups. However, examination of the histologic type of the deepest invasive portion with infiltrating cancer cells revealed a significantly higher incidence of LN metastasis in the group of undifferentiated-type cancers than in the group of differentiated-type cancers, and we thus conclude that the presence of the undifferentiated type in the deepest invasive portion is an independent risk factor for LN metastasis. This is similar to findings in cases of submucosal invasive colorectal cancer, in which the histologic type of the deepest invasive

portion with infiltrating cancer cells is an important risk factor for LN metastasis [23 - 25]. As we reported previously [26], when examining cases of submucosal invasive gastric cancer, it is important to take into account the histologic type of the deepest invasive portion with infiltrating submucosal invasive cancer cells in addition to the main histologic type. With regard to width of submucosal invasion, Hanaoka, et al. have reported that, of submucosal invasive gastric cancers of mixed differentiated and undifferentiated types, undifferentiated-type-predominant mixed type showed a significantly higher incidence of LN metastasis with significantly greater depth of submucosal invasion compared to the differentiated type [21]. Meanwhile, with regard to colorectal submucosal invasive cancer, Ueno, et al. reported absence of LN metastasis among cases of submucosal invasion to a width <2000 μm and a high incidence of LN metastasis among cases of submucosal invasion to a width >4000 μm [24]. The benefit of examining the width of submucosal invasion has been discussed, with some investigators reporting that cases of LN metastasis involve greater submucosal invasion widths [27] and others arguing that cases with high budding involve greater submucosal invasion widths [28]. Ours is the first study to identify submucosal invasive gastric cancer with a submucosal invasion width exceeding 6000 μm as an independent risk factor for LN metastasis. Thus, we believe it is important to measure the width of submucosal invasion in cases of gastric cancer.

With regard to depth of submucosal invasion, there have been few reports on the incidence of LN metastasis of submucosal invasive gastric cancer according to measured depths of submucosal invasion exceeding 500 μm [19]. In our study, depth of submucosal invasion exceeding 1000 μm was identified as an independent risk factor for LN metastasis of submucosal invasive gastric cancer. Whereas some investigators have reported that it is difficult to establish a pretreatment determination of whether submucosal invasion exceeds 500 μm [29, 30], others have reported that depth of submucosal invasion up to 1000 μm can be established with the use of endoscopic ultrasound [31, 32]. Thus, we believe that it would be clinically more useful to distinguish submucosal invasion at a depth of 1000 μm rather

than 500 μm. Yao, et al. reported that pretreatment diagnoses of SM2 invasion in cases of depressed-type submucosal invasive gastric cancer could become more precise with depth of submucosal invasion ≥600 μm and width of submucosal invasion ≥2500 μm [33]. In recent years, ESD has been established as a standard endoscopic treatment for early gastric cancer, and a high success rate has been achieved for en block resection [3, 34]. As such, ESD should be performed first for cases in which the depth of submucosal invasion is determined to be within 1000 μm; the aim would be total excisional biopsy, and the resection should be followed by pathological examination to predict absence of LN metastasis on the basis of the five criteria described herein, i.e., width of submucosal invasion <6000 μm, no lymphatic involvement, differentiated type at the deepest invasive portion, depth of submucosal invasion <1000 μm, and tumor diameter <30 mm. In this way, unnecessary additional surgeries after ER for submucosal invasive gastric cancer can be avoided.

CONCLUSION

We found independent risk factors for LN metastasis of submucosal invasive gastric cancer to include the following: width of submucosal invasion >6000 μm, lymphatic involvement, undifferentiated type at the deepest invasive portion, depth of submucosal invasion >1000 μm, and tumor diameter >30 mm. Taking these conditions into account may expand the criteria for curative ER of submucosal invasive gastric cancer. We recognize the need to establish our findings in a larger patient population.

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Table 1. Relation Between Clinicopathological Factors and LN Metastasis

Variable	No. of Cases	LN metastasis present (%)	*p* - value
Sex			
Male	149	20 (13.4)	NS
Female	71	17 (23.9)	
Age (years)			
≤ 65	98	15 (15.3)	NS
> 65	122	22 (18.0)	
Tumor location			
Upper stomach	58	4 (6.9)	
Middle stomach	107	19 (17.8)	NS
Lower stomach	55	14 (25.5)	
Gross type			
Depressed	187	32 (17.1)	NS
Non-depressed	33	5 (15.2)	
Tumor diameter (mm)			
≤30	141	11 (7.8)	< .0001
>30	79	26 (32.9)	
Ulceration			
present	79	16 (20.3)	NS
absent	141	21 (14.9)	
Histologic type (dominant)			
differentiated	152	24 (15.8)	NS
undifferentiated	68	13 (19.1)	
Histologic type at the deepest invasive portion			
differentiated	104	6 (5.8)	< .0001
undifferentiated	116	31 (26.7)	
Size of undifferentiated tumor (mm)			
≤20	172	25 (14.5)	NS
>20	48	12 (25.0)	

Number of cases is shown unless otherwise indicated.
LN = lymph node, NS = not significant

Table 1. Relation Between Clinicopathological Factors and LN Metastasis (cont)

Variable	No. of Cases	LN metastasis present (%)	*p* - value
Depth of SM invasion			
SM1 (≤ 500μm)	43	0 (0)	.0010
SM2 (> 500μm)	177	37 (20.9)	
Depth of SM invasion (μm)			
≤ 1000	90	8 (8.9)	.0089
> 1000	130	29 (22.3)	
Depth of SM invasion (μm)			
≤ 1800	144	14 (9.7)	.0001
> 1800	76	23 (30.3)	
Width of SM invasion (μm)			
≤ 6000	117	5 (4.3)	< .0001
> 6000	103	32 (31.1)	
INF α	52	3 (5.8)	.0148
β / γ	168	34 (20.2)	
Lymphatic involvement			
present	102	31 (30.4)	< .0001
absent	118	6 (5.1)	
Venous involvement			
present	40	17 (42.5)	< .0001
absent	180	20 (11.1)	
Total	220	37 (16.8)	

Number of cases is shown unless otherwise indicated.
LN = lymph node, NS = not significant
SM = submucosal, INF = infiltration

Table 2 Multivariate Analysis of Risk Factors for LN Metastasis of Submucosal Invasive Gastric Cancer

Variable	Odds ratio (95% CI)	*p* - value
Width of SM invasion >6000 μm	8.54 (2.24 – 41.2)	.0034
Lymphatic involvement	4.39 (1.55 – 14.1)	.0077
Undifferentiated histologic type at the deepest invasive portion	4.30 (1.44 – 15.3)	.014
Depth of SM invasion >1000 μm	3.92 (1.07 – 15.5)	.042
Tumor diameter >30 mm	3.42 (1.40 – 8.71)	.0078
Venous involvement	-	NS
INF β/γ	-	NS

LN: lymph node, CI: confidence interval, SM: submucosal, INF: infiltration, NS: not significant

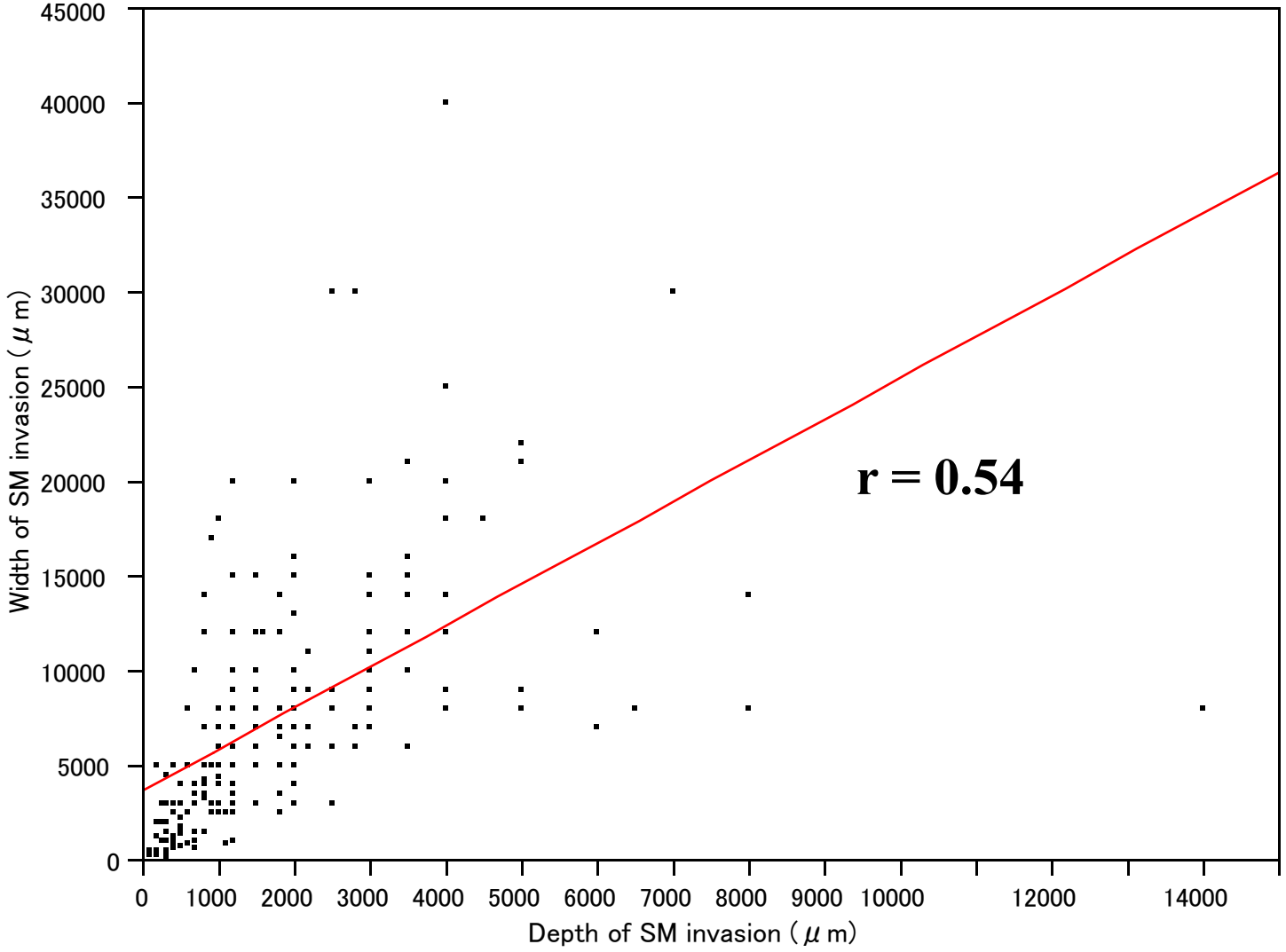
Table 3 Incidence of LN Metastasis of Submucosal Invasive Gastric Cancer in Relation to Number of Positive Factors*

No. of positive factors*	No. of cases	No. of cases with LN metastasis
0	30	0 (0)
1	50	0 (0)
2	32	3 (9.4)
3	48	10 (20.8)
4	31	6 (19.4)
5	29	18 (62.1)
Total	220	37 (16.7)

LN: lymph node

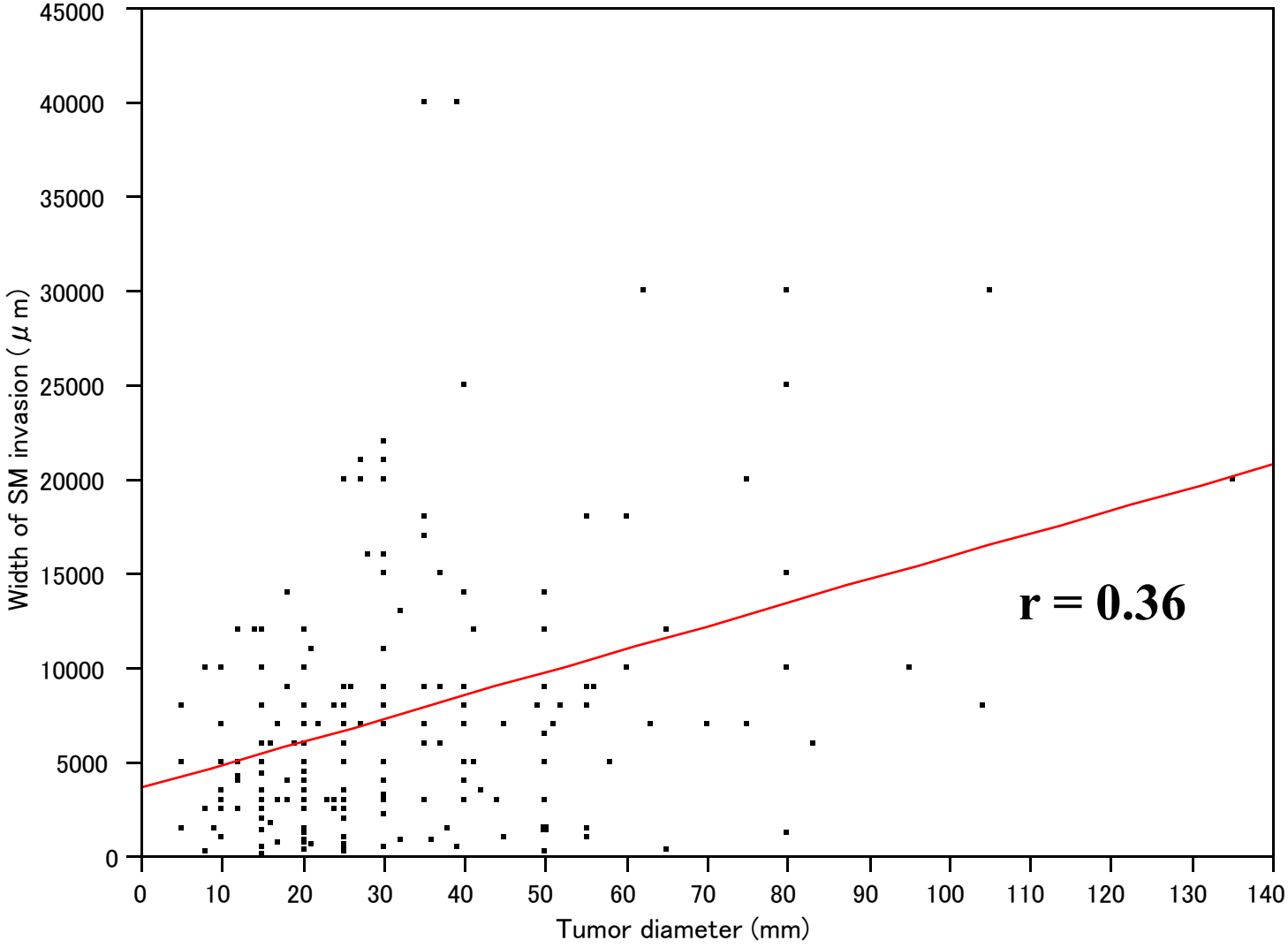
*Factors identified by multivariate analysis = width of SM invasion >6000 μm, lymphatic involvement, undifferentiated histologic type at the deepest invasive portion, depth of SM invasion; >1000 μm, tumor diameter ; >30 mm

Figure 1. Relation Between SM Depth and SM Width



SM: submucosal

Figure 2. Relation Between Tumor Diameter and SM Width



SM: submucosal