Endoscopic prediction of tumor invasion depth in early gastric neoplasia: a prospective study in Peru

Predicción endoscópica de invasión tumoral en neoplasia gástrica temprana. Estudio prospectivo en Perú

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Recibido: 1-11-2016
Aprobado: 4-1-2017

ABSTRACT
Introduction: Endoscopic resection is the first option treatment of early gastric cancer with invasion to mucosa or superficial submucosa, because the risk of nodal metastasis is negligible. Then the prediction of tumor invasion is cardinal. **Objectives:** Determine the accuracy of endoscopic prediction for tumor invasion depth in early gastric neoplasia and define endoscopic characteristics associated with massive submucosal invasion. **Materials and methods:** Prospective sudy of diagnostic test validation. We included patients with early gastric neoplasias that were endoscopically or surgically resected from January 2012 to May 2016. Every lesion was looked for the presence of these features: margin elevation, central elevation, irregular surface, enlarged folds, size > 30mm and rigidity. The invasion prediction was categorized in: M-Sm1 when none feature was present, Sm2 when 2 or more features were present, and indeterminated when only one feature was present. We compared endoscopic prediction to pathological staging and determined diagnostic accuracy. **Results:** The global accuracy for endoscopic prediction was 98.2%. Sensitivity, specificity, positive and negative predictive values for M-Sm1 prediction were 97.6, 100, 100 y 92.8%, and for Sm2 prediction were 100, 97.6, 92.8 y 97.6%, respectively. Rigidity, irregular Surface, margin elevation and enlarged folds were associated with Sm2 invasion. **Conclusions:** Endoscopic prediction of tumor invasion depth in early gastric neoplasia is very accurate. The main endoscopic feature associated with Sm2 invasion is rigidity.
Keywords: Stomach neoplasms; Endoscopy; Forecasting (source: MeSH NLM)

RESUMEN
Introducción: La resección endoscópica constituye el tratamiento de elección del cáncer gástrico temprano con invasión a la mucosa o submucosa superficial, pues tiene riesgo casi nulo de metástasis ganglionar. Por tanto, la predicción de invasión tumorales cardinal. **Objetivos:** Determinar la precisión de la predicción de invasión tumoral de neoplasia gástrica temprana por endoscopía convencional y definir características endoscópicas asociadas a invasión submucosa masiva. **Material y métodos:** Estudio prospectivo de validación de una prueba diagnóstica. Se incluyeron todos los pacientes con neoplasias gástricas tempranas que fueron resecadas endoscópica o quirúrgicamente de enero 2012 a mayo 2016. En cada lesión se definió la presencia de las siguientes características: Elevación de márgenes, elevación central, irregularidad de la superficie, engrosamiento de pliegues, tamaño >30 mm y rigidez. La predicción de invasión se categorizó en: M-Sm1 cuando no tenía ninguna característica, Sm2 cuando tenía 2 o más características, e indeterminada cuando sólo tenía una característica. Se comparó la predicción endoscópica con el estadiaje patológico de los especímenes y se determinó su precisión diagnóstica. **Resultados:** La precisión global de la predicción endoscópica fue de 98,2%. La sensibilidad, especificidad, VPP y VPN para la predicción M-Sm1 fue 97,6, 100, 100 y 92,8%, y para la predicción Sm2 fue 100, 97,6, 92,8 y 97,6%, respectivamente. La rigidez, irregularidad en la superficie, elevación de los márgenes y engrosamiento de pliegues, se asociaron significativamente con invasión Sm2. **Conclusiones:** La predicción endoscópica de invasión tumoral en neoplasia gástrica temprana es muy precisa. La principal característica endoscópica asociada a invasión Sm2 es la rigidez.
Palabras clave: *Cáncer gástrico; Endoscopía; Predicción (fuente: DeCS BIREME).*

INTRODUCTION

In many western countries, the incidence of gastric cancer is declining; however, in Peru is still frequent, and it is the leading cause of cancer death, unfortunately, because most cases are diagnosed in advanced stages [1,2]. The early gastric cancer (EGC) is defined as the one that compromises the mucosa and/or submucosa, regardless of nodal involvement [3], while early gastric neoplasia involves both EGC and gastric adenomas.

Endoscopic resection of early gastric cancer with almost no risk of nodal metastasis is the first option treatment in Japan and South Korea, as it has shown excellent short and long term oncological results (cure and survival

Citar como: Palacios Salas F, Liza Baca E. Endoscopic prediction of tumor invasion depth in early gastric neoplasia: a prospective study in Peru. Rev Gastroenterol Peru. 2017;37(2):120-8

rates), being, unlike surgery, a minimally invasive therapy [4-8]. The enthusiasm generated by these good results has made the techniques of endoscopic resection increasingly used in occidental countries, and so guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society of Gastrointestinal Endoscopy (ASGE) recommend its use [9,10].

The Japan Gastroenterological Endoscopy Society (JGES) and the Japanese Gastric Cancer Association (JGCA), published a recent guideline defining the indications for endoscopic resection of early gastric cancer as absolute and expanded [11]. The absolute indication is the differentiated adenocarcinoma, intramucosal, less than 20 mm. The expanded indications are based on the works of Gotoda and Hirasawa; and they are: (1) Differentiated intramucosal adenocarcinoma, without ulcer, any size; (2) Differentiated intramucosal adenocarcinoma, with ulcer, less than 30 mm; (3) Differentiated adenocarcinoma with superficial submucosa invasion (Sm1, <500 um depth), without ulcer, less than 30 mm; (4) Undifferentiated intramucosal adenocarcinoma, without ulcer, less than 20 mm [12,13]. The resected specimen should show lateral and vertical margins free of neoplasia, and absence of lymphovascular involvement to consider curative resection as well.

There are two techniques of endoscopic EGC resection; mucosectomy (EMR: endoscopic mucosal resection) and endoscopic submucosal dissection (ESD). The last mentioned allows en bloc resection of very large lesions, even with ulcer or scar, being able to satisfy the expanded indications proposed by Gotoda. Three recent meta-analysis have shown that ESD has significantly greater rates of en bloc and complete resections than EMR, even in small lesions with an absolute indication of endoscopic resection [14-16].

To define the indication for endoscopic resection of the early neoplasic lesions detected, the characterization of the lesions is very important. The main point of the characterization is the prediction of depth of cancer invasion or "T" stage, and the distinction between intramucosal adenocarcinoma or with minimal invasion of the submucosa (M-Sm1), with negligible risk of nodal metastasis and, therefore, candidates for endoscopic resection, and adenocarcinoma with massive invasion of the submucosa (Sm2, > 500 um), with a risk of around 20% of nodal metastasis and, therefore, candidates for surgical treatment. The accuracy of the prediction is very important, on one side, to avoid unnecessary surgery in potentially curable patients with endoscopic resection; and on the other side, to minimize retreatment after non-curative ESD.

The prediction of tumor invasion can be made by echoendoscopy with an accuracy between 41.4 and 86% [17]. The limitations of echoendoscopy are the low abailability, the ideal requirement of high-frequency miniprobesto obtain more precise results and, mainly, overstaging, being present in up to 42% of lesions categorized as Sm2, especially in those with ulcer [18]. In addition, some studies show that its precision in predicting tumor invasion is not greater than that of conventional endoscopy [19-21]. A recent meta-analysis shows a relatively low precision of the echoendoscopy in the prediction of tumor invasion in EGC, not considering it an indispensable study [18].

The easiest and most practical way to perform the prediction of tumor invasion is with conventional endoscopy and so do many experienced centers in Japan and South Korea, with a diagnostic accuracy of 73-83% [22-24]. The problem is that this prediction is based on experience and is usually done empirically without having standardized or objectively defined criteria. The endoscopic features associated with massive submucosal invasion are based on only a few retrospective studies that test their accuracy without having replicated their experience in occidental countries. Yao and col. consider that two important characteristics associated with a massive submucosal invasion are the marked elevation of the margins and the central elevation with submucosal aspect [25,26]. An attempt to objectify the prediction of invasion is given by Abe's study, after defining 4 characteristics associated with Sm2 invasion, assigns a score of 2 for the elevation of margins and size greater than 3 cm, and a score of 1 for marked redness and irregular surface, establishing, that a score of 3 or more is associated with massive submucosal invasion (Sm2), with sensitivity from 29.7 to 45.9%, specificity from 93.1 to 93.7% and accuracy from 82.5 to 84.8% [27].

The main objective of the present research is to determine the accuracy of prediction of tumor invasion depth in early gastric neoplasia by conventional endoscopy, in relation to the pathological analysis of endoscopically or surgically resected specimens. The secondary objectives are to define which endoscopic features are associated with massive submucosal invasion and what clinical-pathological features affect the accuracy of prediction of tumor invasion depth.

MATERIALS AND METHODS

Patients and treatment

Prospective study to validate a diagnostic test at the Edgardo Rebagliati Martins National Hospital (Lima - Peru) between January 2012 and May 2016. Patients with endoscopic and histological diagnosis of early neoplasic stomach lesions (gastric adenoma and early gastric cancer) in who were resected endoscopically or surgically were included. Patients with lesions with a clear endoscopic appearance of advanced gastric

cancer, lesions greater than 20 mm whose histology was undifferentiated adenocarcinoma, and lesions resected more than 3 months after endoscopy for staging were excluded. All patients with lesions that fulfilled the absolute and expanded indications of endoscopic resection were treated with endoscopic submucosal dissection by one operator. If the specimen showed lateral and vertical margins free of neoplasia, as well as absence of lymphovascular involvement, it was considered curative resection. In any other case, the resection was considered non-curative, and the patient was oriented to surgical treatment.

Patients with early gastric neoplasia whith either difficult localization or had not absolut or expanded criteria for endoscopic resection (mainly prediction of Sm2 invasion) or who had incomplete or non-curative endoscopic resections, were treated surgically.

All patients signed informed consent prior to staging endoscopy and resection procedure.

Endoscopic assessment of depth of invasion

The equipment used was FUJINON EG-590WR gastroscopes, EPX-4400 video processor or EPX-4450 HD (FUJINON Co. Ltd., Tokyo - Japan). The examination was performed by one endoscopist with more than 10 years of experience and trained at the Keio University Hospital and at the National Cancer Center, Tokyo - Japan. The endoscopic evaluation was performed with white light and in some cases with FICE to highlight the characteristics of the surface; chromoendoscopy with contrast stain was not routinely used for not having indigo carmine. The macroscopic type of the neoplasias was defined according to the Japanese and Paris classification, as Type I (protruded), Type IIa (slightly elevated), IIb (flat), IIc (slightly depressed), III (excavated) and combinations [3,28]. Types I, IIa, and IIa + I were classified as elevated; types IIc, III, and IIc + III were classified as depressed; type IIb as flat; and types IIa + IIc or IIc + IIa as mixed. The location of the lesions was defined in upper thirds (fundus and upper body), middle (remaining body and angle) and lower (antrum). The scar or active ulcer was considered as a positive ulcer finding (UL+) [3].

In gastric lesions, the following features were evaluated as potential indicators of submucosal invasion:

- Size greater than 30 mm: This feature was only evaluated in protruding lesions.
- Marked margin elevation (with submucosal aspect): The discrete margin elevation, which almost flattened with maximum insufflation, was not considered.
- Central elevation (with submucosal aspect): Manifested with maximum insufflation.
- Pronounced irregular surface.
- Enlarged folds (drumstick, fused): Each distorted fold feature was evaluated separately. We did not consider the folds that converge to the lesion and gradually decrease in thickness, as well as those that are amputated without being thickened.
- Rigidity: This feature is dynamic and it was evaluated with changes of insufflation and with peristaltism.

The prediction of the depth of invasion in lesions considered as early gastric neoplasias was performed as follows:

- Intramucosal lesions or with superficial invasion of the submucosa (M-Sm1): Absence of submucosal invasion indicators (Figure 1).

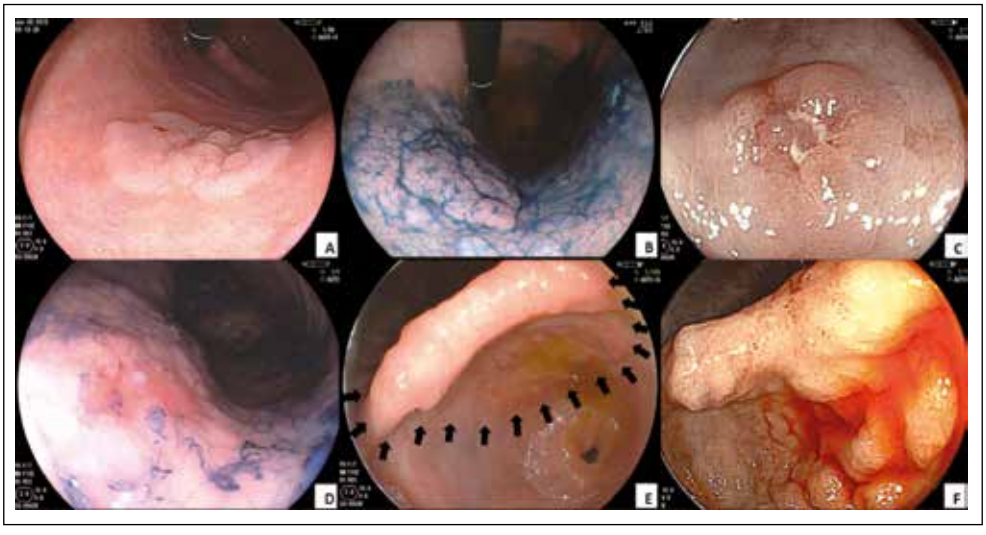

Figure 1. Lesions with prediction of M-Sm1 invasion (without Sm invasion indicators).

A and B) Type 0-IIa lesions with 25 mm and 20 mm in diameter, in body, with very discrete surface irregularity. C) Type 0-IIc+IIa lesion with 9 mm in diameter, in antrum, with slightly elevated margins. D) Type 0-IIc lesión with 16 mm in diameter, in body, with regular surface. E and F) Type 0-IIa with 55 mm in diameter, in angle and antrum, with regular granular surface.

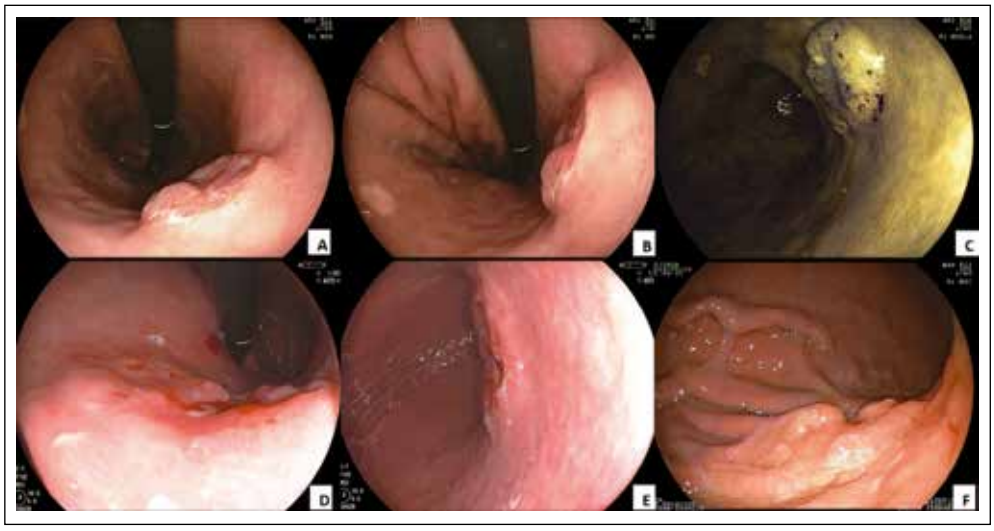

Figure 2. Lesions with prediction of Sm2 invasion (presence of 2 or more Sm invasion indicators).

A and B) Type 0-IIc lesion with 22 mm in diameter, in body, with irregular surface, marked central elevation and margins elevations with submucosal appearence. C) Type 0-Is lesion with depression with 25 mm in diameter, in body, with irregular surface and rigidity. D and E) Type 0-IIc lesion with 32 mm in diameter, in body, with very irregular surface, margin elevation with submucosal appearence and rigidity. F) Type 0-IIc lesion with 30 mm in diameter, in body, with

- Lesions with massive invasionof the submucosa (Sm2): Presence of 2 or more indicators of submucosal invasion (Figure 2).
- Lesions with indeterminate invasion prediction: Presence of only 1 indicator of submucosal invasion (Figure 3).

Histopathological analysis

Endoscopic or surgical specimens were fixed with formalin and sectioned every 2 or 5 mm, respectively, and stained with hematoxylin - eosin.

Figure 3. Lesions with prediction of indeterminate invasion (only one Sm invasion indicator).

A, B and C) Type 0-IIc+IIa lesions with 26 mm and 10 mm in diameter, in antrum, with only margin elevation. D) Previous lesion with magnification and FICE, clear demarcation line, slight irregularity of microstructure and microvasculature (this lesion was recategorized as M-Sm1 due to these findings and resected by ESD).

The following features were determined:

- Tumor size: <20 mm; 20 - 30 mm, >30 mm.
- Degree of differentiation: Differentiated (tubular well or moderately differentiated and papillary adenocarcinoma) and undifferentiated (poorly differentiated adenocarcinoma, signet-ring or mucoid cell). Adenomas were categorized as differentiated.
- Invasion depth: Mucosa (M), superficial submucosa (Sm1 <500 um), deep or massive submucosa (Sm2 >500 um) and muscularis propia (Mp). Then, two categories were regrouped for the correlation with endoscopic prediction; M-Sm1 and Sm2-Mp.
- Lymphovascular invasion: Present or absent.

Statistic analysis

The accuracy of the endoscopic prediction of tumor invasion depth was determined by comparing it with histopathology findings. The sensitivity, specificity, PPV and NPV of both the endoscopic prediction of M-Sm1 lesions and the endoscopic prediction of Sm2 invasion were also determined. For this analysis only these two categories were used, and the group of patients with undetermined prediction was not included. Bivariate analysis (chi-square test) was then performed to determine which endoscopic features were significantly associated with Sm-2 invasion. Finally, we determined which clinical and pathological features affected the precision of the endoscopic prediction of tumor invasion depth. All analysis were performed using the statistical package (SPSS) version 23.0, considering as level of statistical significance any value of $P < 0.05$.

RESULTS

Clinical - pathological features

Clinical-pathological features of patients and lesions are shown in Table 1. A total of 61 patients, female most of them (61.5%) with an average age of 69.5 years, in which 65 lesions compatible with early gastric neoplasia were identified. Regarding the macroscopic type of lesions, 42 (62.7%) had a depressed component, and 15 (23.1%) had an ulcerative finding (ulcer or scar). The average lesion size was 23.95 mm, range 5-80 mm. Endoscopic resection of 46 lesions (70.8%) and surgical resection of 19 (29.2%) were performed. From the resected lesions 17 were adenomas with high grade dysplasia and 48 were EGC. About the histological type, 87.7% of lesions were differentiated and 12.3% were undifferentiated. In terms of tumor invasion depth, 48 (73.8%) lesions were intramucosal, 4 invaded Sm1, 11 invaded Sm2 and 2 infiltrated the Mp.

Table 1. Clinical pathological features in 61 patients with 65 neoplasic early gastric lesions.

Characteristics	N (%)
Demographic data	
Gender	
Male	23 (37.7)
Female	38 (62.3)
Age, average years (SD)	69.5 (±13.7)
Macroscopic findings	
Localization	
Upper third	3 (4.6)
Middle third	22 (33.8)
Lower third	40 (61.6)
Specific macroscopic type	
I	5 (7.7)
IIa	16 (24.6)
IIb	2 (3.1)
IIc	23 (35.4)
III	1 (1.5)
Mixed type	18 (27.7)
General macroscopic type	
Elevated (I+IIa)	21 (32.3)
Flat (IIb)	2 (3.1)
Depressed or mixed (IIc + III + mixto)	42 (64.7)
Size. average mm (range)	23.95 (5-80)
≤20 mm	33 (50.8)
21-30mm	19 (29.2)
≥31mm	13 (20.0)
Ulceration	
Absent	50 (76.9)
Present	15 (23.1)
Treatment	
Endoscopic	46 (70.8)
Surgical	19 (29.2)
Histological findings	
Degree of differentiation	
Undifferentiated	8 (12.3)
Differentiated	57 (87.7)
Depth of invasion	
Mucosa (M)	48 (73.8)
Superficial submucosa (Sm1)	4 (6.2)
Deep submucosa (Sm2)	11 (16.9)
Muscularis externa (Mp)	2 (3.1)

Evaluation of the prediction of tumor invasion by conventional endoscopy

Table 2 presents data from evaluation of the prediction of tumor invasion depth by conventional endoscopy in relation to histopathological evaluation. From 65 lesions, the prediction of tumor invasion depth by conventional endoscopy was: M-Sm1 in 42 (64.62%), Sm-2 in 14 (21.54%) and indeterminate in 9 (13.85%). The 9 lesions with prediction of indeterminate invasion belong to superficial lesions, which in the histopathological evaluation showed M invasion in 5 cases and Sm1 invasion in 4. The overall accuracy of the prediction of tumor invasión depth by conventional

Table 2. Accuracy of the prediction of tumor invasion by conventional endoscopy.

	Depth of invasion by conventional endoscopy		
	M-Sm1 (n=42)	**Indeterminate (n=9)**	**Sm2 (n=14)**
Depth of invasion by histology			
Mucosa (M) (n=48)	42	5	1
Superficial submucosa (Sm1) (n=4)	0	4	0
Deep submucosa (Sm2) (n=11)	0	0	11
Muscularis propia (Mp) (n=2)	0	0	2
Global accuracy	*55/56**	*98.2 (94.5 – 100)*	
M-Sm1 accuracy	*55/56**	*98.2 (94.5 – 100)*	
Sm2accuracy	*55/56**	*98.2 (94.5 – 100)*	
Overestimation. %	*1/56**	*1.8 (-1.7 – 5.3)*	
Underestimation. %	*2/56**	*3.6 (-0.01 – 0.08)*	
Sensitivity			
M-Sm1	*42/43*	*97.6 (93.1 – 100)*	
Sm2	*13/13*	*100*	
Specificity			
M-Sm1	*13/13*	*100*	
Sm2	*42/43*	*97.6 (93.1 – 100)*	
PPV			
M-Sm1	*42/42*	*100*	
Sm2	*13/14*	*92.8 (79.3 – 100)*	
NPV			
M-Sm1	*13/14*	*92.8 (79.3 – 100)*	
Sm2	*42/43*	*97.6 (93.1 – 100)*	

95% of confidence interval (CI 95%); PPV: positive predictive value; NPV: negative predictive value

*The 9 indeterminate cases were excluded for the calculation

endoscopy was 98.2% with overestimation in one case (1.8%) and underestimation in two cases (3.6%). The sensitivity, specificity, PPV, and NPV for the prediction of M-Sm1 invasion were 97.6%, 100%, 100% and 92.8%, respectively; while the prediction of Sm2 invasion were 100%, 97.6%, 92.8%, and 97.6%, respectively.

Endoscopic features associated with massive submucosal invasion

Table 3 shows the endoscopic features of lesions associated with massive submucosal invasion in histopathology. Bivariate analysis showed that rigidity, irregular surface, margin elevation, central elevation, and enlarged folds were associated with significant submucosal invasion; the association was greater with rigidity.

Clinical pathological features affecting the accuracy of endoscopic staging

Table 4 shows the accuracy of the endoscopic staging in relation to the macroscopic and histological features of the lesions. The accuracy of endoscopic staging is lower in lesions located in the upper third of the stomach, with protruded morphology and size more than 20 mm. The histological type of the lesions, differentiated or undifferentiated, was not associated with an impairment of the accuracy of endoscopic staging. The lesions that invade Sm1 are very difficult to define as such by endoscopy, which is why they are categorized together with intramucosal lesions.

Table 3. Association between endoscopic features and massive submucosal invasion.

	Bivariated analysis * OR (IC 95%)	*P*
Rigidity		
Absent	1	<0.05
Present	6.4 (3.5 – 9.2)	
Irregular surface		
Absent	1	<0.05
Present	3.9 (2.1 – 5.7)	
Margin elevation		
Absent	1	<0.05
Present	3.2 (1.6 – 4.8)	
Enlarged folds		
Absent	1	<0.05
Present	3.06 (1.2 – 4.8)	
Central elevation		
Absent	1	<0.05
Present	2.7 (0.3 – 5.1)	
Tumor size		
< 30 mm	1	0.47
> 30 mm	-	

95% of confidence interval (CI 95%)
* Bivariated analysis: Chi-square Test. OR: Odds Ratio

DISCUSSION

Endoscopic resection of early gastric cancer is the first option treatment in Japan and South Korea, and its use has been spreading throughout the world [9-11]. Only lesions that have negligible or almost negligible chance of nodal metastasis are the chosen for endoscopic resection, and the most important feature associated with that is the depth of the tumor invasion, since superficial lesions, wich compromise only the mucosa or superficial submucosa, that meet other criteria proposed by Gotoda *et al*., have low risk of nodal metastasis; however, when the lesions invade the deep submucosa (Sm2), the risk increases significantly.[12] For this reason, the prediction of tumor invasion or T staging of the EGC is crucial, and in Japan and South Korea, it is usually done by endoscopy, but without standardized criteria or prospective research that support its use.

Table 4. Endoscopic staging accuracy in relation to macroscopic and histological findings.

	Endoscopic staging			
	Total	Corrects	%	*p*
Macroscopic findings				
Localization				
Upper third	3	2	66,6	
Middle third	22	19	86,3	<0,05
Lower third	40	35	87,5	
Specific macroscopic type				
I	5	3	60,0	
IIa	16	16	100	
IIb	2	2	100	<0,05
IIc	23	19	82,6	
III	1	0	0,0	
Mixed type	18	16	88,8	
General macroscopic type				
Elevated (I+IIa)	21	19	90,4	
Flat (IIb)	2	2	100	<0,05
Depressed or mixed (IIc + III + mixto)	42	35	83,3	
Size. average mm (range)				
<21mm	33	31	93,9	
21-30 mm	19	15	78,9	<0,05
>30 mm	13	10	76,9	
Ulceration				
Absent	50	44	88,0	
Present	15	12	80,0	0,06
Histological findings				
Degree of differentiation				
Undifferentiated	8	7	87,5	0,1
Differentiated	57	49	85,9	
Depth of invasion				
Mucosa (M)	48	43	89,5	
Superficial submucosa (Sm1)	4	0	0	<0,05
Deep submucosa (Sm2)	11	11	100	
Muscularis propia (Mp)	2	2	100	

In our research, we showed that the endoscopic prediction of tumor invasion has a high accuracy, estimated at 98.2%, which is higher than that reported in previous studies, in which it fluctuates between 73 and 83% [19-24]. This favorable difference is due to several factors: (1) The design of our research, in which endoscopic prediction of tumor invasion categorizes the lesions in 3 groups: M-Sm1, Sm2 and indeterminate; this last group comprised only 9 lesions (13.85%), was not considered in the statistical analysis. A sub analysis of our data, classifying the lesions in only 2 groups, M-Sm1 and Sm2, would reduce our accuracy to 84.6%, a rate similar to that reported in previous studies in centers of great experience. (2) Being a prospective research, all lesions were examined in vivo, not in photos, allowing better discrimination of endoscopic features, including rigidity, which we consider to be very important in the prediction of submucosal invasion. A recent study determined that the "non-extension sign" was associated with Sm2 invasion, with an accuracy of 96.9% [29]. (3) Endoscopist that performed a training at the Keio University Hospital and at the National Cancer Center, Tokyo-Japan, which gained experience by observing a large number of gastric lesions and experts making an evaluation of them.

The M-Sm1 tumor invasion prediction showed high sensitivity, specificity, PPV and NPV (97.6%, 100%, 100% and 92.8%, respectively). Therefore, based on our research, this category in clinical practice would have clear indication of endoscopic resection. The prediction of Sm2 tumor invasion also showed high sensitivity, specificity, PPV and NPV (100%, 97.6%, 92.8% and 97.6%, respectively). Therefore, this group of lesions would have justified indication of surgical resection in clinical practice.

The endoscopic features we are looking for to make the prediction of tumor invasion are simple and identifiable with conventional endoscopy: size greater than 30 mm, irregular surface, marked margin elevation, central elevation of lesion with submucosal appearence, enlarged folds and rigidity. In the bivariate analysis, all of them, except size, showed a significant association with Sm2 invasion. The different Asian studies have also shown similar results [21-24,27,29]. However, since our research is prospective, it allowed to assess the rigidity, not evaluated in previous studies, and this is the characteristic that showed greater association with Sm2 invasion (OR 6.4; 95% CI: 3.5-9.2).

In our research, prediction of tumor invasion was performed as follows: Mucosa (M-Sm1) when they had none of the above features; massive submucosa (Sm2) when it had two or more of these features; indeterminate when only had one endoscopic feature. In most Asian studies, only two categories, M and Sm2, are considered, and one feature present is enough to consider the lesion as Sm2. However, we wanted to improve the accuracy of the prediction, particularly the specificity of the group that is categorized as Sm2, with the main objective of not referring patients to whom the surgical specimen finally reveals only M-Sm1 invasion, since they can benefit from endoscopic resection, which provides equal cure rates, but with less invasiveness and a better quality of life. There is only one antecedent of a similar approach, in which Abe *et al*. perform a logistic regression analysis and mainly determined that tumor size greater than 3 cm, margin elevation, irregular surface, and marked redness are associated with Sm2 invasion. Then, they establish a diagnostic model in which they assign 2 points to the presence of any of the first two features and one point for either of the last two; thus, lesions with 3 or more points evaluated by 3 different observers, categorize them as Sm2, with an accuracy of 82,5 to 84.8%, specificity from 93.1 to 93.7%, but with a low sensitivity of 29.7 to 45.9% [27]. We believe that in our research the prediction of Sm2 invasion is simpler, achieving a high specificity of 97.6%, and also a high sensitivity of 100%.

Like other studies, we found that some macroscopic factors, such as the location of lesions in the upper third, the protruded or depressed shape, size larger than 20 mm may affect the accuracy of the prediction [23,30]. Regarding the histological characteristics, we found that the accuracy was lower in Sm1 lesions, which are very difficult to differentiate endoscopically, that's why they are usually categorized together with intramucosal lesions, since in addition their risk of nodal metastasis is negligible and the suggested treatment in both cases is usually the same, endoscopic resection. However, we did not find that the accuracy was lower in the undifferentiated type, as other studies suggest [23,30].

The importance of our research is that, except for the Asian studies, it is the first one that evaluates the T staging endoscopic accuracy through simple endoscopic features, and is also performed with conventional endoscopy (although with high resolution and definition). In addition, we sought a greater accuracy of the prediction of tumor invasion Sm2, which was a weak point in previous studies, not to send to surgery patients who could benefit from ESD. We thus created a small sub group of indeterminate prediction, 9 cases that eventually all turned out to be M-Sm1 lesions. We believe this sub group deserves a special strategy and management in centers of reference or greater complexity through: (1) Echoendoscopy with miniprobes: although most studies do not conclude on the benefits or advantages from the echoendoscopy over the conventional endoscopy in defining the T stage of the EGC, some studies show that both techniques can be complemented, and even echoendoscopy can redefine the staging of the lesions categorized as Sm2 by conventional endoscopy, so some algorithms

suggest its use in this sub group of patients [19-21,24,29-31]. (2) Magnifying endoscopy: Kikuchi *et al*. showed that the presence of dilated vessels within the lesions was associated with submucosal invasion in 6/18 (33.3%), with diagnostic accuracy, sensitivity and specificity of 81.5%, 37.5%, and 88.3%, respectively [32]. Other studies show that features such as loss of glandular microstructure, scattered and scarce vessels, and multi-caliber vessels were associated with Sm2 invasion [33-34]. Then, if these indicators are present, the patient must be referred for surgery, and if they are not present, for endoscopic resection. (3) Diagnostic ESD: especially if the lession is not very large, its location is affordable and there is a small risk of complications.

The limitations of this research are to have being performed in a single center, by a single endoscopist with training in Japan, and a not so large number of neoplastic gastric lesions. We suggest training in the evaluation of the endoscopic features of gastric lesions directed to non-expert endoscopists in different medical centers, using photos and videos, and then seek to replicate the research, at a multicentric level and with a large number of lesions, that also allow to perform a multi variate analysis to define individual endoscopic features as predictors of Sm2 invasion.

In conclusion, the endoscopic prediction of tumor invasión depth in early gastric neoplasia is highly accurate. In addition, marked margin elevation, central elevation, irregular surface, enlarged folds, and rigidity are associated with massive submucosal invasion.

Thanks: To Professor Naohisa Yahagi and Dr. Toshio Uraoka from University Hospital of Keio

Conflict of interests: the authors have declared that no competing interests exist.

Funding: none.

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