RESPONSE LETTER

Name of journal: *World Journal of Gastroenterology*

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Title: Treatment for gastric 'indefinite for neoplasm/dysplasia' lesions based on predictive factors

Reviewer's code: 03765064

Dear Reviewers and editor

Thank you for the very kind and insightful comments on the manuscript. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes to the manuscript are shown in yellow highlighted text. A "Comments" section was also added according to the retrospective study guideline. We would be very honored if our manuscript is now considered acceptable for publication in the journal.

Sincerely,
Ho Suk Kang

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Comment 1) The prevalence of carcinoma is extremely high in this cohort and the authors should address how similar histologic findings in a low prevelance population would need to be interpreted with great caution.

Response 1) Thank you for your comment. I have inserted additional discussion in the text.

Discussion
Our study has some limitations. This was a retrospective, correlative study in a single center that was not based on a trial and lacked strictly regulated, periodical follow-up data or data on *H. pylori* infection and intestinal metaplasia. There may be a selection bias enrolled in a single, tertiary medical center located at the gastric cancer-endemic country. Nevertheless, our study has some strengths. This is among the rare reports describing the clinicopathologic features associated with repeated IFND diagnosis;

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Comment 2) What is the definition of atypia vs regernative atypia and how good is the concordance between pathologists to identify these findings

Response 2) Thank you for your comment. I have changed the sentence in Methods ,

Results and Discussion section

Method

IFND lesions were divided into two subgroups: 'atypical epithelia' and 'regenerating atypia[2,19,20]. The regenerating atypia was favored when the a few gland/epithelium had immature cells with basophilic cytoplasm and nuclear atypia (hyperchromatic nucleus, variable nuclear size and shape, basally non-located nuclei, increased nucleocytoplasmic ratio) showing pseudostratification, reduced or absent mucus secretion, and less maturation and differentiation toward the surface [2,19,20]. The atypical epithelium was favored when the above mentioned features were added with moderately distorted architecture (localized cellular crowding or irregular shaped glands) and haphazardly arranged dystrophic goblet cells with compressed nuclei showing loss of nuclear polarity [2,19,20]. In this study, gastritis and adenoma cases were categorized into the non-carcinoma group and adenocarcinoma cases into the carcinoma group.

Results

whereas that of gastritis showed no statistically significant agreement between the first and second biopsies (κ=0.117, P=0.463). Therefore, overall concordances between pathologists in the review of IFND lesions were 50% for gastritis, 66.7% for gastric adenoma, and 50.7% for gastric cancer.

Discussion

Previous studies have also raised this concern, with 30–50% of the original diagnostic biopsies incorrectly interpreted[21-23]. Likewise in this study, the overall concordances between pathologists in IFND lesions were not satisfactory (50-67%). However, the problem of interpretation lies not in the ability of the endoscopist or pathologist, but in the structural and cytologic features of the lesion

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Comment 3) Would recd to use either the Paris classification or at least the variables considered in this to correlate clinical findings.

Response 3) Thank you for your comment. Table 1, 3, and Supplementary Table e1 contains information on Paris classification. And more detailed classification for Paris classification was difficult to analyze.

Ex) Table 1.

Gross type	0.585

Elevated (type I and IIa)	181 (39.3)	136 (38.1)	45 (43.3)
Flat (type IIb)	168 (36.4)	134 (37.5)	34 (32.7)
Depressed (type IIc and III)	112 (24.3)	87 (24.4)	25 (24.0)

Comment 4) Would separate out IMCA from invasive carcinoma?

Response 4) Thank you for your comment. Our institute consider surgery first in EGC with undifferentiated cell, even if it is confined in mucosa. We made an Appendix Table X like your comment, and did not make a big difference from Table 3. Therefore if you don't mind, we want to present it as a classification of the original form.

Appendix Table X. Clinicopathologic factors of invasive carcinoma in the submucosal layer or deeper in the subgroup analysis of the carcinoma group

Initial Dx		Carcinoma Group		
Final Dx	Total	Intramucosal carcinoma	Invasive carcinoma in the submucosal layer or deeper	*P*
	N=104	n=81 (%)	n=23 (%)	
Sex				0.880
Male	71 (68.3)	55 (67.9)	16 (69.6)	
Female	33 (31.7)	26 (32.1)	7 (30.4)	
Age (y)				**0.045**
<60	32 (30.8)	21 (25.9)	11 (47.8)	
≥60	72 (69.2)	60 (74.1)	12 (52.2)	
Endoscopic size (mm)				0.081
<10	35 (33.7)	31 (38.3)	4 (17.4)	
≥10	69 (66.3)	50 (61.7)	19 (82.6)	
Gross type				**0.032**
Elevated (type I and IIa)	45 (43.3)	36 (44.4)	9 (39.1)	
Flat (type IIb)	34 (32.7)	30 (37.0)	4 (17.4)	
Depressed (type IIc and III)	25 (24.0)	15 (18.5)	10 (43.5)	

Single lesion				0.605
No	7 (9.3)	6 (7.4)	1 (4.3)	
Yes	97 (93.3)	75 (92.6)	22 (95.7)	
Ulcer				**0.024**
No	70 (67.3)	59 (72.8)	11 (47.8)	
Yes	34 (32.7)	22 (27.2)	12 (52.2)	
Spontaneous bleeding				0.554
No	73 (70.2)	58 (71.6)	15 (65.2)	
Yes	31 (29.8)	23 (28.4)	8 (34.8)	
Fold change				**0.003**
No	91 (87.5)	75 (92.6)	16 (69.6)	
Yes	13 (12.5)	6 (7.4)	7 (30.4)	

Dx, diagnosis; IFND, indefinite for neoplasm/dysplasia; Bx, biopsy;

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Comment 5) If there is no difference in survival of the early and late diagnosis groups why separate these out

Response 5) Thank you for your comment. According to your comment, we are considering how to solve this in the next study. I have inserted additional discussion in the text.

However, because the endoscopically-suspected gastric cancers in our retrospective study tended to lead to earlier diagnosis and resection than endoscopically-undetermined lesions; thus, less-aggressive gastric cancers may remain undiagnosed or have a delayed diagnosis, our results of no prognostic differences between the early and late diagnosis groups might be due to the possible selection bias. Therefore, our findings concerning the prognostic impact of prolonged diagnostic delays in indefinite lesions should not be considered conclusive and further prospective studies are necessary.

Thank you you wonderful comment. I look forward to good results.
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