

To the editor:

Thank you for taking the time to consider revisions to our manuscript. Please find the point-by-point response to the reviewers' comments below. Please contact me with any additional questions.

Sincerely,
Chainarong Phalanusitthepha, M.D.
On behalf of the co-authors

Reviewer 1

The paper needs minimal corrections in terms of editing, few places where there is no space between point and new word. Please clarify what would be the more aggressive treatment which you mention at the end of Discussion.

ESD is still considered an experimental treatment for early signet ring cell carcinoma. Some centers may recommend ESD, while others may wish to proceed with formal surgical excision. This has been clarified in the text.

Reviewer 2

There are good points in the manuscript; for example Fig. 3 is very beautifully illustrated. However there are some weak points and unclear descriptions. Point-by-point comments and questions;

1. Clarify in what institute(s) the patients were observed and treated; in Siriraj Hospital, Koto-Toyosu Hospital, or was the study done as a multicenter project?

The patients were treated in a single institution, Showa University Northern Yokohama Hospital (after the data were collected, the team moved to a new hospital, Showa University Koto Toyosu Hospital). This has been clarified in the text.

2. Were the pictures of Figure 1 and 2a taken from the same patient? If not, the magnification power in Figure 1c is not enough.

The images in Figure 1 are all from a single patient, which has been clarified in the caption. The image in Figure 2a is from a different patient that was chosen for clarity.

3. Concerning Figure 1d, the microscopic view; Show a picture of the resected specimen together with the lines of pathological cross section, and demonstrate which part of the lesion Figure 1d represents. In addition the magnification power of Figure 1d is not enough to identify signet ring cells.

Unfortunately, we do not have a picture of the gross specimen for this patient.

Figure 1d was intended to demonstrate the elongated and barrel-shaped glands that guide our theory of the pathophysiology in Figure 3. We have added Figure 4 to demonstrate the signet ring cells causing distortion of the gastric glands.

4. Although the authors repeatedly maintained that the "stretch sign" is useful for the diagnosis of signet-ring-cell carcinoma, but you should describe the finding more in detail. For example I do not quite understand what are the differences between the signet-ring-cell carcinoma and non-signet-ring-cell carcinoma in Figure 2. Describe the differences more in detail. I do not know if Figure 1d was taken from the same patient as Figure 2a, but I think the authors wanted to say that the NBI image of Figure 1d represents the pathological structure of signet-ring-cell carcinoma. I advise the authors to show also the microscopic view of non-signet-ring-cell carcinoma in Figure 2b for the comparison and better understanding.

The Figure 2 caption has been clarified to identify areas of normal (polygonal) glands, irregular (non-polygonal) “non-elongated” glands typical of adenocarcinoma (Figure 2b), and “elongated” glands observed in signet ring cell carcinoma (Figure 2a). We also added Figure 4 to show a side-by-side comparison of non-involved gastric mucosa (with normal glands) next to infiltration with signet ring cells (causing distortion of the gastric glands).

5. Is the “stretch sign” observed in the entire surface of the lesion, or is it identified only in a small portion of the lesion?

The “stretch sign” is observed in a portion of the lesion. In Figure 2a, for example, there is normal polygonal architecture (underlying the “a”). Proceeding toward the circle, the glands become irregular (but not yet elongated), and then within the circle is an example of an elongated gland.

The Figure 2a caption has been expanded to identify the area of normal architecture, and the results section has been updated to mention the “stretch sign” is found in only a portion of the lesion.

6. Figure 3 is very beautifully illustrated, but you should clarify that it is only an imaginary and speculative view concerning the development of signet-ring-cell carcinoma. What does the signature “Kimmy” stand for in Figure 1d and 3? Is he (or she) a pathologist or professional illustrator? Is he (or she) included in the authors?

The speculative nature of the illustration has been clarified in the Figure 3 caption.

“Kimmy” is surgeon and colleague of Dr. Phalanusitthepha in Thailand. She was included in the authors but has also been added to the acknowledgements for clarity.

7. The title had better be changed to "Endoscopic features of early-stage signet-ring-cell carcinoma of the stomach"

The title has been changed according to the reviewer’s suggestion.