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RESEARCH ARTICLE

EARLY DETECTION OF GASTRIC CARCINOMA BY ADVANCE ENDOSCOPIC PROCEDURE: AN UPDATE.

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Abstract

Considerable numbers of early gastric cancers can be missed or misdiagnosed with conventional white light imaging endoscopy (WLI), thus advanced endoscopic imaging modalities have been applied to overcome the issue. High definition endoscopy can improve diagnostic accuracy, but still misses 20e25% of early gastric cancer. Magnifying endoscopy combined with narrow bandImaging (NBI) allows for very high accuracy, with sensitivity and specificity of over 95%. The algorithm for magnifying endoscopy diagnosis of gastric cancer is composed of 1) presence of demarcation line, and 2) presence of irregular microsurface and/or microvascular pattern. Ultra-high magnification of 400 times with endocytoscopy (ECS) can produce images reflecting structural and cellular atypia. Using high grade ECS atypia as the diagnostic criteria for gastric cancer, ECS achieves a high diagnostic accuracy (86% of sensitivity, 100% of specificity) although approximately 10 % of target lesions are not assessable because of poor dye staining.

Introduction:-

Gastric cancer is the fifth most common malignancy in both sexes and is the third leading cause of cancer deaths in both sexes worldwide [1]. In 2012, approximately 723,000 people died of gastric cancer worldwide, accounting for 8.8% of the total cancer death. To decrease gastric cancer death rate, primary and secondary prevention are required to reduce Helicobacter pylori (H. pylori) infection, the main cause of gastric cancer. The other major strategy is early detection of curable gastric cancer in dyspeptic patients or in a high risk population selected by efficacious serological screening tests, such as H. pylori antibody, pepsinogen testing and serum trefoil factors [2e4]. Endoscopy is exclusively used for early diagnosis of gastric cancer because of a high detection rate [5]. Despite promising data, the technique depends heavily on observational skill and a considerable % of early gastric cancer may be missed by conventional white light imaging endoscopy (WLI) [6,7]. Therefore, various endoscopic

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modalities have been newly developed to enhance the value of endoscopy in effective gastric cancer diagnosis. High definition endoscopy and image-enhanced endoscopy [8] including narrow band imaging (NBI) [9] are the key modalities, which are commercially available for an advanced endoscopy imaging in early gastric cancer. The next stage is real-time endoscopic assessment of histology (optical biopsy) by endocytoscopy (ECS) [10,11] and confocal microendoscopy [12].

High definition endoscopy; it improves the detection and diagnosis of early gastric cancerAlthough upper gastrointestinal endoscopy is more accurate than nonendoscopic modalities including integrated positron emission tomography [13] and barium meal examination, considerable numbers of superficial gastric cancers may be missed or misdiagnosed with conventional white light imaging endoscopy (WLI). High definition endoscopy (HDE) has been developed to improve the image quality and diagnostic accuracy of WLI.

To elucidate the potential of HDE, we prospectively compared ultrathin endoscopy (UTE) to HDE with respect to diagnostic accuracy of superficial gastric neoplasia [13]. A total of 57 patients were enrolled; 32 patients with early gastric neoplasia referred for endoscopic submucosal dissection (ESD), and 25 patients who underwent surveillance endoscopy after ESD. Patients with obvious advanced gastric carcinomas or cancerous lesions with deep invasion to the gastric submucosa were excluded. Each patient underwent UTE (GIF-XP260N; Olympus Medical Systems, Tokyo, Japan) and HDE (GIFH260Z; Olympus Medical Systems, Tokyo, Japan) back-to-back in a randomized order. UTE and HDE were independently performed by two different endoscopists, who did not have access to any of the patient's clinical information. The endoscopists recorded the diagnosis of neoplastic lesions as well as nonneoplastic lesions including gastric ulcers or gastric polyps. All lesions recorded were biopsied by the second endoscopist under the supervision of the study coordinator, who attended all endoscopic examinations and was aware of the diagnosis given by the two endoscopists. The pathology results from the biopsy samples were used as a gold standard for the diagnosis of gastric cancer. In 57 enrolled patients, 41 lesions (16.5 ± 13.5 mm in diameter, mean ± SD) were pathologically diagnosed as neoplasias (27 carcinomas and 14 adenomas). Eleven of the 41 pathology-confirmed neoplasias were not detected by UTE, and three were diagnosed as nonneoplasias, indicating that the missing rate and misdiagnosis rate of UTE were 26.8%, and 14.6%, respectively. In contrast, five of the 41 pathologyconfirmedneoplasias were not detected by HDE, and four were diagnosed as nonneoplasia by HDE, indicating that the miss rate and misdiagnosis rate of HDE were 12.2%, and 9.8%, respectively. Representative neoplastic lesions missed by UTE but correctly diagnosed by HDE are shown in Fig. 1.

Although UTE has emerged as an alternative to sedated endoscopy because it is well tolerated without sedation and costs less [14], our study demonstrates that the diagnostic accuracy of HDE is significantly higher than that of UTE for superficial gastric neoplasia, probably due to the differences in imaging quality. We need guidelines for selecting HDE or UTE in different clinical settings, recognizing the differences in the diagnostic accuracy and acknowledging the cost-effectiveness of unsedated screening endoscopy.

Autofluorescence endoscopy has limited clinical value in the diagnosis of early gastric cancerAlthough HDE improves diagnostic accuracy of WLI, considerable rates over 20% of superficial gastric neoplasias are still missed or misdiagnosed. Image-enhanced endoscopy, including autofluorescence endoscopy (AFE) and narrow band imaging (NBI), has emerged in the effort to overcome the limits of WLI. There has been considerable interest in the use of AFE for the detection of early digestive neoplasias, and the diagnostic relevance of the modality has been demonstrated for the detection of early neoplasias in the esophagus [15] and colon [16,17].

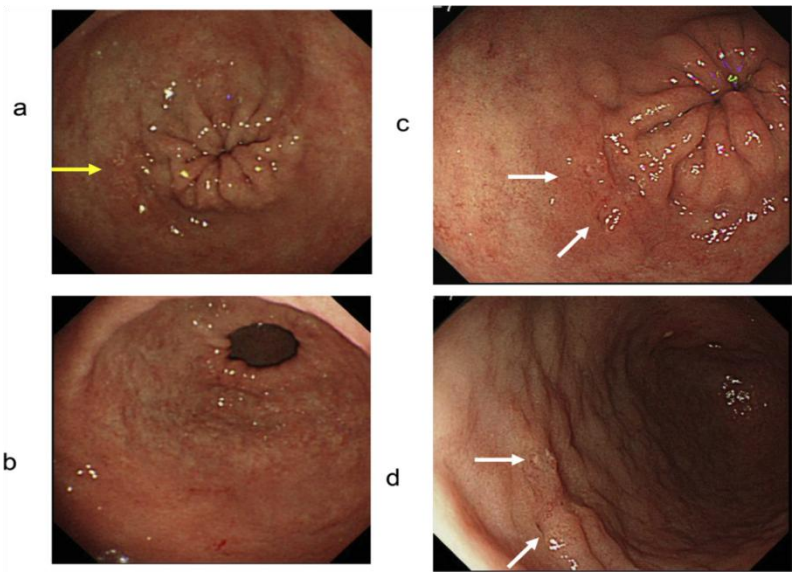

Fig. 1:-Representative endoscopic images of early gastric cancer missed by ultrathin endoscopy (UTE) but correctly diagnosed by high definition endoscopy (HDE). HDE shows an early depressed gastric cancer in the antrum indicated by white arrows (Fig. 1c and d). However, the lesion was not detected by UTE (Fig. 1a and b). A yellow arrow indicates the portion where the early cancer diagnosed by HDE may be present.

Therefore, we conducted a prospective study to compare AFE systematically with WLI for the detection of superficial gastric neoplasia [18]. A total of 51 patients were enrolled as an enriched population; 33 patients with superficial gastric neoplasia referred for ESD, and 18 control patients undergoing surveillance endoscopy after curative ESD. An autofluorescence imaging system (AFI; Olympus Medical Systems, Tokyo, Japan) and the autofluorescence imaging scope (XGIFQ240FZ; Olympus) was used for the AFE procedure. At the direction of a study coordinator, two endoscopists who were blinded to enrolled patient's information, performed WLI followed by AFE or performed AFE alone, in random order. Both endoscopists independently recorded the presence of lesions seen at AFE and WLI. All lesions identified in either test were biopsied and the pathological results were used as the gold standard. A purple or magenta area with a clear margin in a green background or a green area with a clear margin in a purple background was diagnosed as AFE-positive. A total of 39 gastric neoplasias were histologically confirmed and 52 pathological non-neoplastic lesions were found to be either WLIand/or AFE-positive. The sensitivity of WLI and AFE alone were 74.4% vs. 64.1% (n.s.) and the specificity was 82.7% vs. 40.1% (p ¼ 0.0003), respectively. WLI followed by AFE had a sensitivity of 69.2% (n.s.) and a specificity of 63.5% (p ¼ 0.046 compared to WLI alone). AFE detected 13% of all neoplasiasfinally diagnosed (23% of elevated neoplasias) which were missed by WLI. Although one quarter of elevated gastric neoplasiaswere detected only by AFE, its specificity was poor due to the high rate of detection of false-positive lesions such as intestinal metaplasia or regenerative hyperplasia.

Uedo N. et al. [19] reported data similar to our results, 1) AFE could reveal flat or isochromatic extensions that were not detected in the WLI, 2) however the diagnostic accuracy in cancer mapping was limited, probably due to ulcerations or inflammation that caused over-diagnosis in the AFE observations.

In summary, 1) AFE detected 10% more gastric neoplasias that are flat or with slight elevation and not identified by WLI, 2) the specificity of AFE in early gastric cancer diagnosis is considerably lower due to a high proportion of false-positives. Therefore, we conclude that AFE is of limited clinical value to date.

Magnifying endoscopy combined with narrow band imaging (NBI); it exert the highest accuracy in the diagnosis of early gastric cancer

Narrow-band imaging (NBI) [10] is an innovative optical technology that modifies the wave lengths and bandwidths of an endoscope's light into narrow-band illumination of 415 ± 30 nm and 540 ± 30 nm. By utilizing these narrow spectrums that fall within the hemoglobin absorption band and penetrate only into the superficial depth of the

mucosa, NBI markedly improves the contrast of vascular structures and, combined with magnifying endoscopy, yields clearer images of microvascular (MV) pattern and microsurface (MS) pattern in the gastrointestinal tract. Magnifying endoscopy combined with NBI (ME-NBI) may enable endoscopic diagnoses based on cancer-specific alterations in MS and MV patterns of the GI tract cancers [20e23], and can achieve "optical biopsy", whereby an accurate endoscopic diagnosis comparable with histopathological diagnosis can be made without biopsy sampling.

We have performed a prospective study to elucidate the superiority of ME-NBI over WLI in gastric cancer diagnosis [24]. A total of 111 patients who underwent surveillance EGD due to a high risk of gastric cancer were assigned. A total of 201 gastric lesions that were mainly superficially depressed and diagnosed by WLI as cancer or non-cancer with a slight suspicion of cancer were prospectively

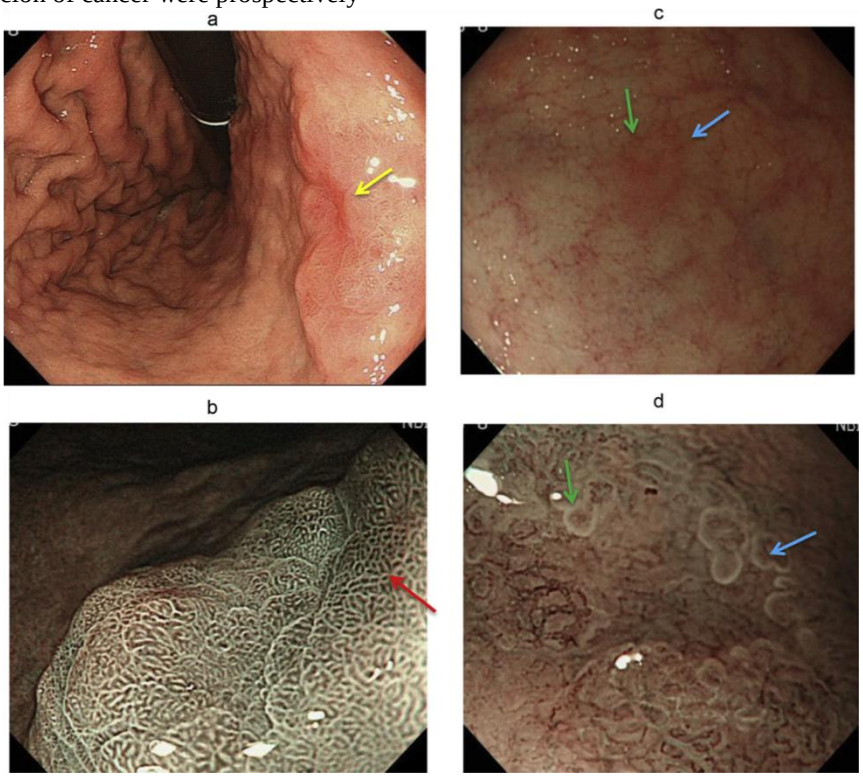

Fig. 2:-Two representative lesions enrolled in this study. A pathologically noncancerous depression was diagnosed by WLI (Fig. 2 a, yellow arrow) as cancer but by ME-NBI (Fig. 2b, red arrow) as non-cancerous. A pathologically cancer was diagnosed by WLI (Fig. 2 c, indicated by blue and green arrows) as non-cancer, but by ME-NBI as cancer (Fig. 2 d).

Enrolled, and ME-NBI was used to further characterize lesions picked up by WLI. The sensitivity and specificity of WLI and ME-NBI for the diagnosis of gastric cancer were evaluated using pathology as the gold standard. Fourteen of the 201 lesions were pathologically proven as gastric cancer; the 187 others were pathologically non-cancerous lesions (five low grade adenomas and 182 nonneoplastic lesions). Seventy-nine of 201 superficial gastric lesions were recognized or suspected as cancerous lesions with WLI. However, only six of these 79 WLI-cancers (7.6%) were determined to be cancers pathologically. Of the 79 WLI-cancers, 13% were diagnosed as NBI-cancers. The remaining 87% of WLI-cancers were diagnosed as NBI-non-cancers, and all but one WLI-cancer and one NBI-non-cancer were determined to be cancers pathologically. The sensitivity and specificity for ME-NBI diagnosis using the defined criteria were 92.9% and 94.7%, respectively, significantly better than for WLI (42.9% and 61.0 %, respectively; P <0.0001) . Fig. 2 shows two representative lesions enrolled in this study; a pathologically noncancerous depression that was diagnosed by WLI as cancer but by ME-NBI as non-cancerous, and a pathology-confirmed cancer that was diagnosed by WLI as non-cancer, but by ME-NBI as cancer.

A muticenter prospective randomized study [25] reported data very similar to those demonstrated by our study. C-WLI alone showed 64.8% diagnostic accuracy, whereas ME-NBI, in conjunction with WLI, identified small, depressed gastric mucosal cancers with 96.6% accuracy, 95.0% sensitivity, and 96.8% specificity. These data

strongly suggest that ME-NBI exerts a very high accuracy in the diagnosis of early gastric cancer, realizing optical biopsy.

Sub-classification of irregular MV patterns was proposed for predicting histological patterns of gastric cancer [26]. Fine network patterns, in which abundant microvessels are well connected to one

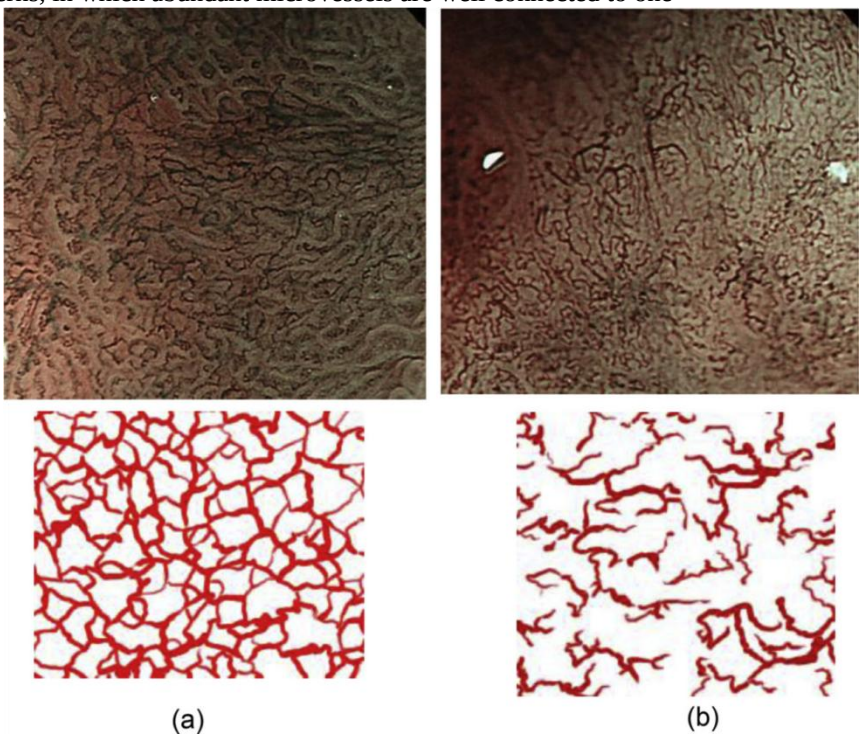

Fig. 3:-Sub-classification of microvascular (MV) patterns of early gastric cancer. (a) Fine network pattern looks like a mesh, in which abundant microvessels connect with one another, is characteristic of differentiated adenocarcinoma. (b) Corkscrew pattern has isolated and tortuous microvessels, in which scanty microvessels do not connect with one another, and is characteristic of poorly differentiated adenocarcinoma.

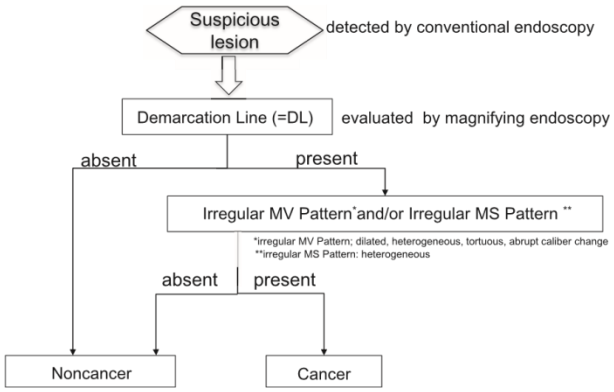

Fig. 4:-The main schema of the algorithm for the diagnosis of early gastric cancer using magnifying endoscopy.

Another like a mesh, are characteristic of differentiated adenocarcinoma. A corkscrew pattern, in which tortuous microvessels are isolated like a corkscrew, is characteristic of poorly differentiated adenocarcinoma (Fig. 3).

Previous studies showed that the clinical experience did not prove to be an advantage in learning curves for NBI diagnosis, and a short training program with minimal clinic practice may enable less experienced endoscopists to become competent in NBI magnification [27,28].

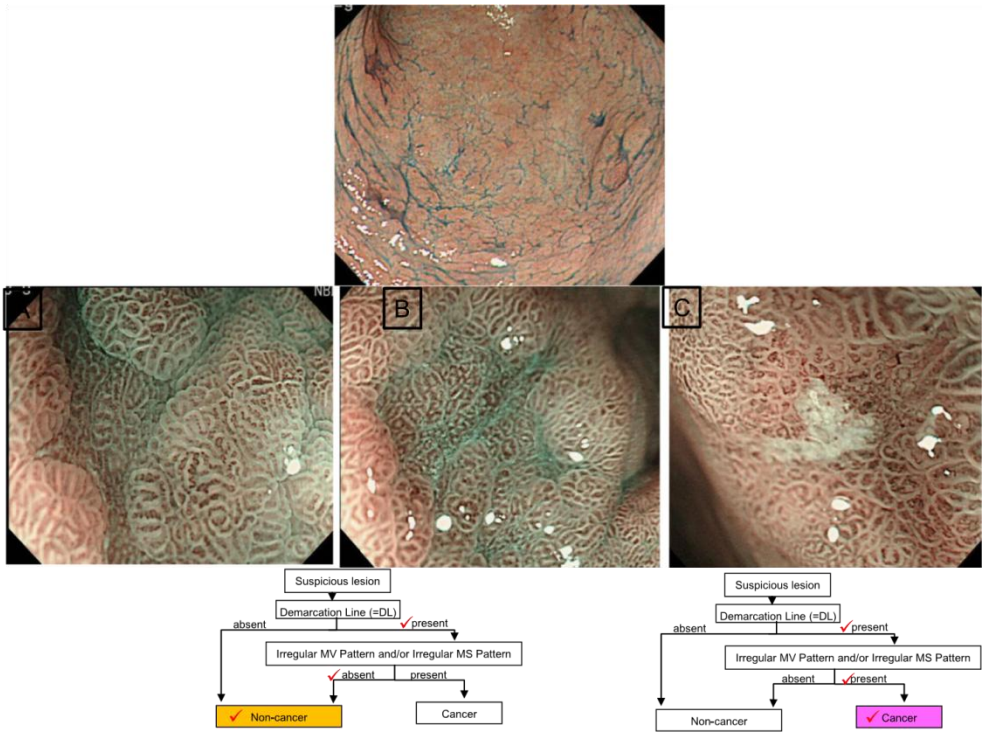

Fig. 5;-Representative endoscopic images of early gastric cancer and non-cancerous depressions mimic to cancer with chromoendoscopy. Because lesion A and B show the presence of a demarcation line, but the absence of irregular MV and MS pattern, the diagnoses of the both lesions are non-cancer. In contrast, because lesion C shows the presence of a demarcation line and the presence of irregular MV and MS pattern, the diagnosis is cancer.
Diagnostic algorithm for early gastric cancer using magnifying endoscopy

Accumulating evidence indicates that magnifying endoscopy is a highly accurate technique and the key for diagnosing early gastric cancer. However, because many different criteria or algorithms for the magnifying endoscopy diagnosis have been proposed, there is controversy about which criteria or algorithm should be used. A unified algorithm is necessary for wide-spread general use of magnifying endoscopy and enhanced the efficacy of the diagnosis of early gastric cancer in the clinical setting. Multiple societies concerned with this issue, including the World Endoscopy Organization, have devised a unified international algorithm for ME diagnosis of early gastric cancer using an evidencebased approach [29].

The algorithm is composed of, 1) magnifying endoscopic imaging of non-neoplastic mucosa, including chronic gastritis and intestinal metaplasia, and 2) diagnostic algorithm for the diagnosis of early gastric cancer using magnifying endoscopy. Fig. 4 shows the main schema of the diagnostic algorithm for early gastric cancer using magnifying endoscopy. The algorithm is mainly based on the VS classification system [30]. A suspicious lesion detected by WLI is assessed by magnifying endoscopy. A key component of the algorithm is whether a demarcation line is present or not; a border between the lesion and surrounding areas, discernible through an abrupt change in MV and/or MS patterns. If a demarcation line is present, the next step is to assess whether an irregular MV pattern and/or an irregular MS pattern are present. The diagnosis of the lesion is cancer if an irregular MS pattern and/or MV pattern are present. Fig. 5 demonstrates representative endoscopic images of early gastric cancer and non-cancerous depressions mimicking cancer with chromoendoscopy. Because lesion A and B show the presence of a demarcation line, but the absence of irregular MV and MS pattern, the diagnosis

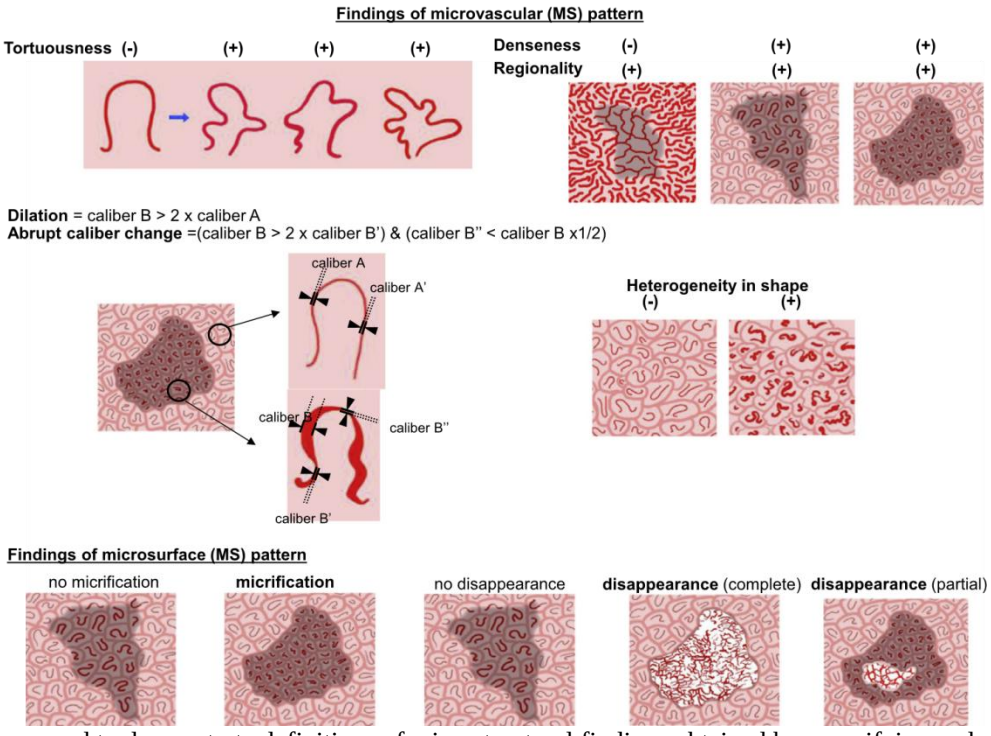

Fig. 6:-Schema used to demonstrate definitions of microstructural findings obtained by magnifying endoscopy combined with NBI (ME-NBI). Republished with permission from the publishers of Endoscopy 2009; 41: 310e315.of both lesions is non-cancer. In contrast, because lesion C shows the presence of a demarcation line and the presence of irregular MV and MS patterns, the diagnosis is cancer.

The key of this algorithm is the assessment of irregular MV and MS patterns, which can be expressed as cancer-specific microstructural findings. Because the word, 'irregular', is subjective and difficult to define, more descriptive technical terms are required precisely to recognize it with less interobserver differences. Using more objective terms of microstructural findings predefined (Fig. 6) , we have done a study to elucidate which are cancer-specific MS and MV findings obtained with ME-NBI [31]. A ME-NBI image catalog composed of 100 lesions (55 depressed gastric cancers and 45 noncancerous depressions) was constructed, and all assigned ME-NBI images were reviewed by 11 endoscopists who answered as to the presence or absence of predefined findings. Multivariate logistic regression analysis demonstrated significant associations between gastric cancer and five microstructural findings; dilation, heterogeneity in shape, tortuousness and abrupt caliber alteration of MV patter and disappearance of MS pattern (Fig. 6). In our other studies [32,33], micrification (small mucosal structure) and heterogeneity in shape of MS patterns (Fig. 7A) are cancer-specific findings especially in elevated types of early gastric cancer, and intrastructural irregular vessels (ISIV) (Fig. 7B) is a cancer specific finding in flat types of early gastric cancer. The evidence indicates that irregular (cancer-specific) MS patterns can vary according with macroscopic appearance of early gastric cancer.

Endocytoscopy; it enables an optical biopsy of early gastric cancer with a high accuracy

In order to achieve real-time endoscopic assessment of histology (optical biopsy), endoscopic modalities are required to attain endoscopic images that correspond to the key histopathological

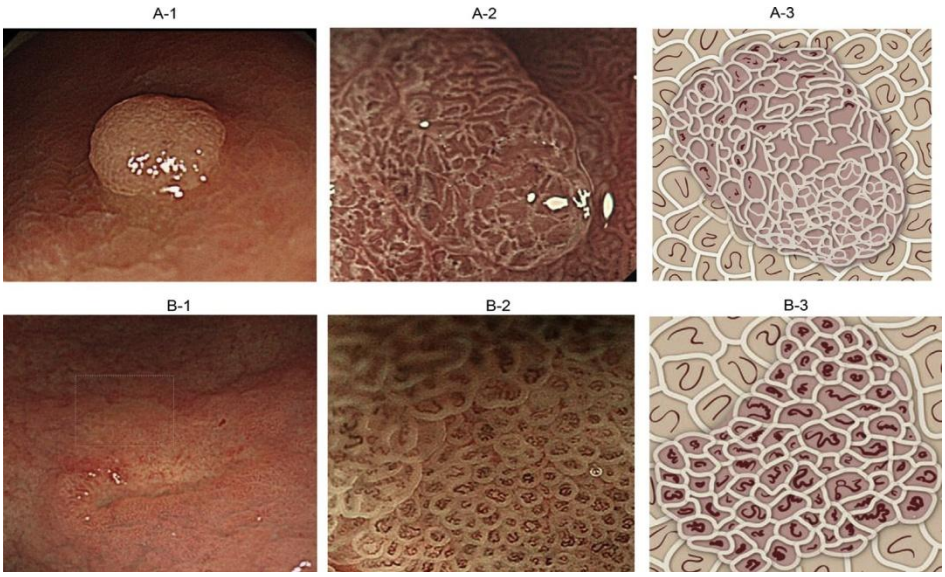

Fig. 7:-Variations of irregular microsurface (MS) pattern; heterogeneous in shape (Fig. 7A) and regular MS pattern with intrastructural irregular vessels (ISIV, Fig. 7B). A: White light imaging endoscopy (WLI) shows discolored a small and white elevated lesion (Fig. 7A-1). Microvascular (MV) pattern was not observed by magnifying endoscopy with NBI (ME-NBI) (Fig. 7A-2), but MS pattern appears heterogeneous in shape (Fig. 7A-3), one of gastric cancer specific findings often observed in elevated type of early gastric cancer. B: WLI shows a white shallow depression (Fig. 7B-1). Magnifying endoscopy with NBI (ME-NBI) at the area of white square of Fig. 7B-1 shows regular MS pattern with intrastructural irregular vessels (ISIV), one of gastric cancer specific findings often observed in flat type (0-IIb) of early gastric cancer. In ISIV, irregular MV patterns defined by dilation, heterogeneity in shape, tortuousness and abrupt caliber alteration, are recognized in tubular or papillary MS, which seems relatively regular.

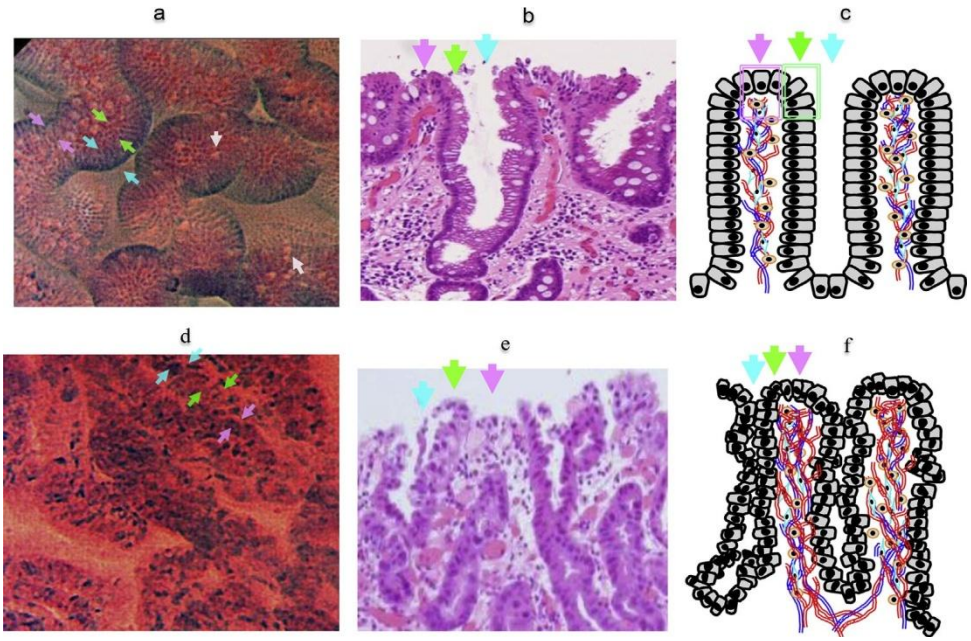

Fig. 8:-An Endocytoscopic (ECS) image (Fig. 8a) of early gastric cancer of well differentiated adenocarcinoma, and corresponding pathological image (Fig. 8b) and schema (Fig. 8c) of glandular structure. Unstained round areas indicated by white arrows in Fig. 8 a were sometimes observed, which were compatible with those recently reported as goblet cells of intestinal metaplasia. An Endocytoscopic (ECS) image (Fig. 8d) of early gastric cancer of well differentiated adenocarcinoma, and corresponding pathological image (Fig. 8e) and schema (Fig. 8f) of glandular structure. Reproduced with permission from the publishers of Endoscopy 47:19e25, 2015.

findings for cancer diagnoses; structural atypia and cellular atypia. Endoscopic magnifications of 80e100 times produce optical images reflecting structural atypia and ultra-high magnification of 400e1000 times can produce images reflecting cellular atypia [34,35].

The Endocytoscopy System (ECS), based on ultra-high magnification endoscopy, visualizes living gastrointestinal cells using live staining, making it possible to differentiate between cancerous and non-cancerous tissue. ECS findings of non-neoplastic gastric mucosa showed a wide lumen or regular linear lumen (indicated by blue arrows, Fig. 8a) between glands composed of regular-cell linings (indicated by green arrows, Fig. 8a). As shown in a corresponding histopathological picture (Fig. 8b) and schema (Fig. 8c), the gland lumen is well preserved and mucosal cells regularly align in non-neoplastic mucosa, which corresponds to the findings of ECS. Unstained round areas indicated by white arrows in Fig. 8a were sometimes observed, which were compatible with those recently reported as goblet cells of intestinal metaplasia [36]. In cancerous lesions, ECS shows irregular glandular structures defined as lumen absence or fusion (Fig. 8d), and irregular cellular structures. Fig. 8e and f depicts a corresponding histopathological picture and schema, respectively.

In the first study conducted recently [10], we defined high-grade ECS atypia as the consistent observation of any of the following features: lumen absence, lumen fusion, or irregular nuclei showing the three typical features (heterogeneous shape, swelling, and disarrangement) (Fig. 9). A total of 100 lesions evaluated by ECS and histopathology were enrolled to create an ECS image catalog (44 early cancers, ten low-grade adenomas, 46 non-neoplastic lesions). Four endoscopists (two trainees and two experts) independently reviewed the catalog images and evaluated each of them for the presence or absence of ECS atypia. Using the defined high-grade atypia as a diagnostic criterion of cancer, the sensitivity, specificity, accuracy, and positive and negative predictive values for cancer diagnosis by endocytoscopy were 78.4%, 93.3%, 87.3%, 85.4 %, and 87.3%, respectively. The concordance rate for the diagnosis of high-grade endocytoscopicatypia was good among the four endoscopists (k value 0.682). No significant difference in diagnostic accuracy or concordance was observed between trainee and expert endoscopists. Thus, we concluded that, using the defined high-grade atypia as a diagnostic criterion of cancer, ECS provided a satisfactory level of accuracy and concordance for the diagnosis of early gastric cancer, regardless of endoscopic expertise. Although training remains a crucial point in gaining assessable ECS images, learning curves in the step of ECS diagnosis may be rapid in endoscopists with various experiences.

Based on the results of the first study, we conducted the second study to examine the feasibility of ECS in diagnosing early gastric cancer using high grade ECS atypia as the diagnostic criteria of gastric cancer (Fig. 9) [11]. Gastric lesions that were the targets of histopathological diagnosis by ESD or biopsy specimen were prospectively enrolled and evaluated with ECS following double staining with crystal violet and methylene blue. A total of 82 lesions were investigated including 23 early gastric cancers, ten gastric adenomas, and 49 non-neoplastic lesions. Ten lesions could not be well observed by ECS because of poor staining due to viscous mucus or plaque, thus assessability rates with ECS were 88% in total and 91% for gastric cancer. High-grade ECS atypia was observed in 86% of assessable gastric cancers, but not in any cases with gastric adenomas or non-neoplastic lesions. Based on this criterion, the sensitivity, specificity, PPV, and NPV of gastric cancer diagnosis was 86 %, 100%, 100%, and 94%, respectively. Fig. 10 shows a representative case with a small early gastric cancer observed by ECS. A high magnification-ECS image of the depressed area demonstrates the existence of high grade ECS atypia; lumen absence, lumen fusion, and irregular nuclei (heterogeneous shape, swelling, and disarrangement). In contrast, a high magnification-ECS image of the

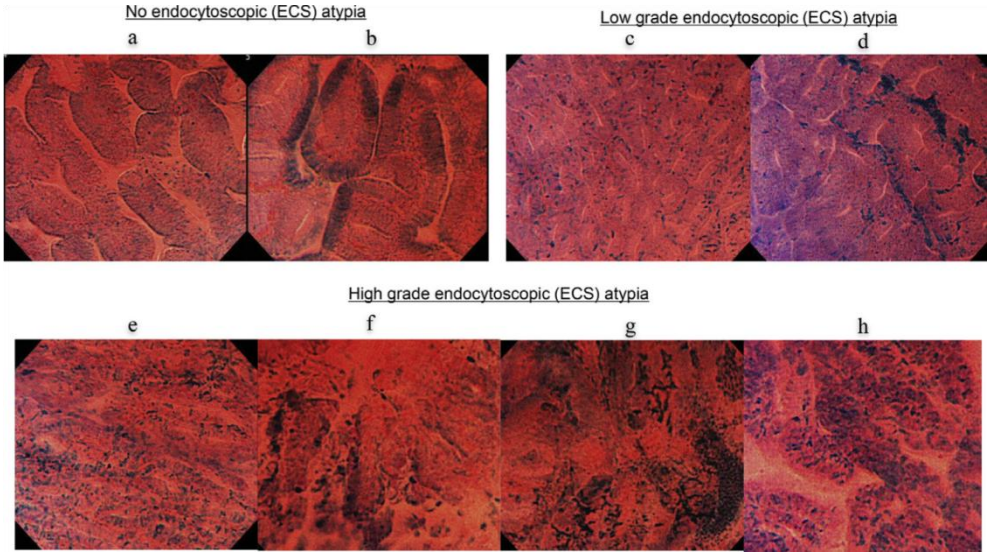

Fig. 9:-The classification of endocytoscpic (ECS) atypia. ECS findings of non-neoplastic gastric mucosa (Fig. 9a and b) show a wide lumen or linear lumen between glands composed of regularly lined cells, indicating no ECS atypia. ECS findings of early gastric cancers (Fig. 9eeh) show high-grade ECS atypia defined by any of the following features being consistently observed: lumen absence or fusion, and irregular nuclei showing the three typical features (heterogeneous shape, swelling, and disarrangement). Fig. 9c and d shows low-grade ECS atypia defined by consistently observed lumen shortening and narrowing or absence and fusion of lumen observed in part. Some of these figures are reproduced with permission from the publishers of Endoscopy 46; 827e832, 2014.

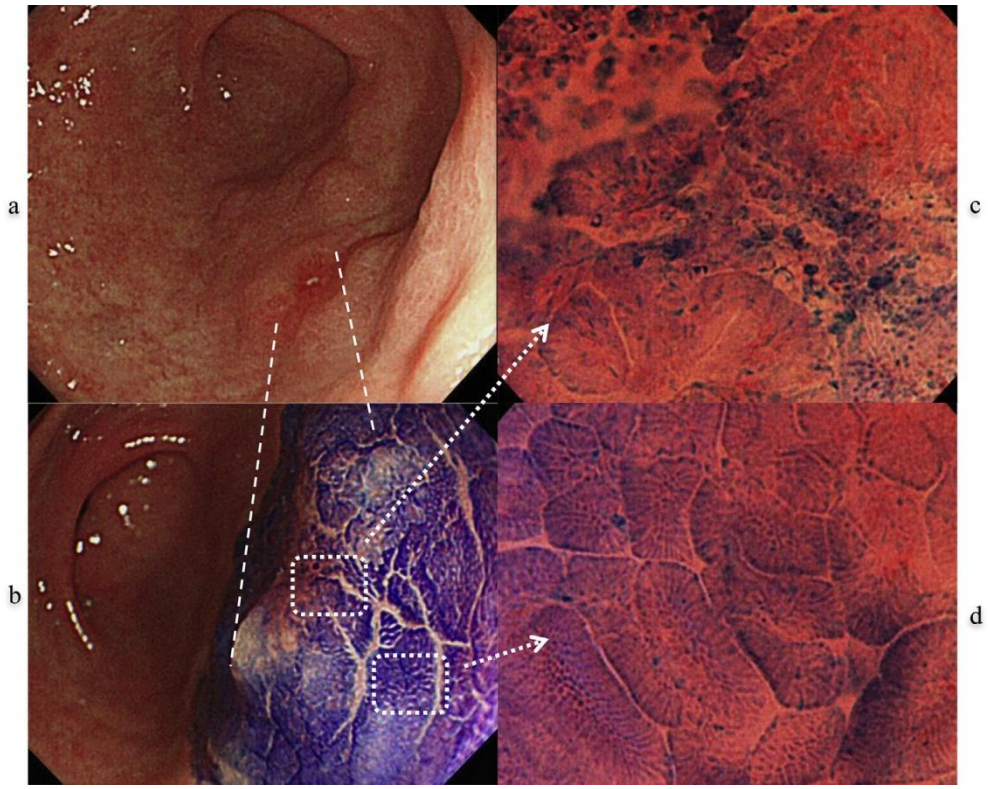

Fig. 10:-Type 0-IIc type early gastric cancer, well demonstrated by endocytoscopy (ECS). Fig. 10a shows a small depressed gastric lesion located on posterior wall of the antrum. Fig. 10b is a low magnification-ECS image around the depressed lesion after double staining with 0.05% crystal violet and 0.1% methylene blue. A high magnification-ECS image of the depressed area (Fig. 10c) demonstrates the existence of high grade ECS atypia; lumen absence, lumen fusion, and irregular nuclei (heterogeneous shape, swelling, and disarrangement). In contrast, a high

magnification-ECS image of the surrounding area (Fig. 10d) shows linear lumens between glands composed of regularly lined cells, indicating no ECS atypia in the area.

Surrounding area shows linear lumens between glands composed of regularly aligned cells, indicating no ECS atypia in the area. ECS is a clinically feasible modality to obtain in vivo histology with high diagnostic accuracy in gastric cancer although approximately 10% of target lesions were not assessable because of poor dye staining.

Practice points
20e40% of early gastric cancer may be missed by white light imaging endoscopy.
High definition endoscopy can improve diagnostic accuracy, but still misses 20e25% of early gastric cancer.
Magnifying endoscopy combined with narrow band imaging exerts very high accuracy, sensitivity, and specificity over 95 %.
Algorithm for magnifying endoscopy diagnosis of gastric cancer is composed of 1) presence of demarcation line, and 2) presence of irregular microsurface and/or microvascular pattern.
Ultra-high magnification of 400 times with endocytoscopy (ECS) can produce images reflecting structural atypia and cellular atypia of early gastric cancer.

Research agenda
Further evaluations of various types of gastric cancers are necessary to confirm if ECS can achieve real-time histology (optical biopsy).
The improvement in vital staining of gastric lesion is required to realize true optical biopsy by ECS.

Conflict of interest statement:None.

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