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Red-flag Techniques for the Assessment of Pre-Neoplastic Gastric Lesions: Autofluorescence Imaging versus Virtual Chromoendoscopy

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ABSTRACT

Background/Aim: The endoscopic diagnosis of preneoplastic lesions and early gastric cancer is based on subtle morphological changes, which are difficult to recognize during routine examinations. The study was performed in order to establish the role of autofluorescence imaging (AFI) and magnifying endoscopy with narrow band imaging (ME-NBI) for the diagnosis of premalignant gastric lesions.
Methods: The study included patients with dyspeptic symptoms and/or known risk factors for gastric cancer. Imaging consisted of white light endoscopy (WLE), followed by AFI and ME-NBI. Targeted biopsies were taken from all the highlighted lesions, regardless of the method. A statistical analysis was performed to compare the results.
Results: Sensitivity of AFI (94.74%) was superior to WLE and ME-NBI (78.95%). Specificity of AFI (65.33%) was however lower than the ME-NBI and WLE, with an accuracy of 71.27%. ME-NBI has high sensitivity, a much better specificity than AFI (92%) and a diagnostic accuracy of 89.36%. Trimodal endoscopy had an accuracy of 92.55%, which was superior to all other methods. Nevertheless, ME-NBI use had reduced the percentage of false positives from 27.65% to 6.38%, thus increasing specificity.
Conclusion: Trimodal endoscopy could be proposed as a standard endoscopic technique, as it is quick, safe and accurate for the diagnosis and surveillance of premalignant and malignant upper gastrointestinal tract lesions.
Key words: pre-neoplastic gastric lesions, early gastric cancer, autofluorescence imaging, magnifying endoscopy with narrow band imaging, virtual chromoendoscopy

Abbreviations:
AFI - Autofluorescence Imaging;
ME-NBI - Magnifying Endoscopy with Narrow Band Imaging;
NBI - Narrow Band Imaging;
NPV - Negative Predictive Value;
PPV - Positive Predictive Value;
SD - Standard Deviation;
TME - Trimodal Endoscopy;
WLE - White Light Endoscopy;

INTRODUCTION

Gastric cancer is a major cause of mortality and morbidity, ranking second among the causes of cancer death, after lung cancer (1). The prognosis is poor, with a survival rate of 20% at five years, due to the fact that the vast majority of cases are diagnosed in an advanced stage of the disease. When diagnosed early, with a tumor limited to the submucosa, the prognosis improves dramatically, with five-year survival rates of up to 90% (2).

Endoscopic diagnosis of gastric cancer in the early stage is based on subtle morphological changes, which are difficult to recognize. Preneoplastic lesions,

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like atrophic gastritis and intestinal metaplasia, play an important role in gastric carcinogenesis. These are plane and diffuse lesions, with a poor correlation between endoscopic appearance and histological change (3, 4). For this reason, „red-flag" endoscopic techniques, such as autofluorescence imaging (AFI) and narrow band imaging (NBI) have been developed. They are based on interactions between light with a specific wavelength and the tissues in order to increase the accuracy of the diagnosis in early lesions (5-10).

Endoscopic autofluorescence is based on the interaction between light with a short wavelength and tissue endogenous fluorophores (collagen, nicotinamide, adenine dinucleotide, flavin and porphyrins). Normal, inflamed and neoplastic tissue have different fluorescence properties which may allow a better differentiation. Thus, normal tissues appear pseudocolored in green, blood vessels as dark green, while hypertrophic fundic mucosa of the stomach and dysplastic/neoplastic areas are magenta (5-7).

Magnifying endoscopy with narrow band imaging (ME-NBI) represents a real-time endoscopic imaging technique using narrow-bandwidth filters in a red-green-blue (R/G/B) sequential illumination system, which enhances visualization of the surface texture and the vascular network of the mucosa, with the aim of improving tissue characterization and differentiation. Haemoglobin absorbs short wavelength light, which in turn increases *in vivo* visualization of capillaries in the superficial mucosa (8,9). Consequently, a virtual chromoendoscopy image is obtained, improving the morphological analysis of surface architecture (pit-pattern) and visualization of the vascular network in the mucosa. This is especially useful in evaluating the abnormal neoangiogenesis process in high-grade dysplasia / early cancer (10).

This study was performed in order to establish the role of AFI and ME-NBI for the diagnosis of premalignant lesions and early gastric cancer in community practice settings.

METHODS

Patients with mild dyspeptic symptoms (epigastric pain, feeling of fullness, loss of appetite), without warning signs (weight loss, vomiting, anaemia, upper gastrointestinal bleeding), as well as patients with known risk factors for gastric cancer (atrophic gastritis, history of gastric polyps, gastric resection) were included in the study in order to detect preneoplastic lesions and early gastric cancer. All patients provided written informed consent prior to the procedures. Imaging included white light endoscopy (WLE) followed by examination with autofluorescence and narrow band imaging with magnification, which are usual procedures in patients with dyspepsia.

Upper endoscopy was performed à jeun, using a high-resolution endoscope with optical zoom (CV-260SL LUCERA, Olympus Medical System Co, Tokyo, Japan). This device possesses trimodal examination capabilities: classic white light endoscopy, autofluorescence imaging, and narrow band imaging magnification, respectively.

During AFI, a suspected neoplasia (AFI-positive lesion) was defined as any area that is different in colour from the surrounding mucosa, and which has a defined circumferential margin.

In the narrow band imaging mode, an optical zoom with 80x magnification was used during examinations. Neoplasia was defined as a superficial lesion with a different mucosal pit-pattern and/or microvasculature as compared to the surrounding tissues, based on the disappearance of the regular mucosal structure, irregular pattern and/or microvascular dilation, tortuosity with irregular size and shape of the vessels. Trimodal endoscopy (TME) non-neoplasia consisted of lesions diagnosed as WLE neoplasia and/or AFI neoplasia but did not comply with the criteria for ME-NBI neoplasia. ME-NBI visualisation has also been performed for lesions diagnosed as WLE- and AFI-endoscopy non-neoplasia, although it targeted WLE and/or AFI neoplastic lesions. TME neoplasia also included cases with WLE and AFI non-neoplasia which complied with criteria of ME-NBI neoplasia.

Targeted biopsies were taken for pathology exam from all lesions visualised by any of the three methods. For patients without any lesions, random biopsies were taken from the fornix, body and gastric antrum. Several gastric biopsy specimens obtained during endoscopy were fixed in buffered formalin and embedded in paraffin. The specimens were sectioned at 4µm thickness, and stained by haematoxylin and eosin. An expert pathologist blinded to endoscopic and clinical findings reviewed the sections. Inflammation, atrophy, metaplasia and dysplasia were classified according to the revised Vienna classification (11).

The final diagnosis of preneoplastic or neoplastic lesion was based on imaging features and pathology confirmation, considered the "gold standard".

Descriptive statistics was also performed using Statistical Package for the Social Sciences (SPSS), version 17.0 (IBM, New York, USA). The results were expressed as mean ± standard deviation (SD). For each imaging method, sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value

(NPV) were calculated compared with the final pathological diagnosis.

RESULTS

The study included a total of 94 patients with dyspeptic symptoms and known risk factors for gastric cancer. The mean age was 55.77 years (± 13.82) with a range between 20 and 84 years. Most patients were in the fifth (30 patients) and sixth (22 patients) decade of life. Gender distribution was approximately equal, with a slight predominance of males (51.07%).

Distribution of cases diagnosed in the study group was as follows: 5 patients diagnosed with early gastric cancer (5.32%), 19 (20.21%) patients with gastric polyps, 3 with MALT lymphoma (3.19%), 13 with diffuse atrophic gastritis (13.83%), 5 with focal atrophic gastritis (5.32%), 18 with Barrett's oesophagus (19.15%), 5 with gastric/duodenal ulcers (5.32%) and 26 with normal appearance (27.66%).

WLE had a sensitivity of 72.73% (95% CI, 55.78% - 84.93%), a specificity of 80.33% (95% CI, 68.69% - 88.37%) and an accuracy of 77.65% with a negative predictive value of 84.48% and a positive predictive value of 66.67% (*table 1*).

The sensitivity of AFI (94.74%, 95% CI: 75.36% - 99.06%) was superior to both the classical examination and ME-NBI. The specificity of AFI was 65.33% (95% CI: 54.05% -75.12%), lower than ME-NBI and WLE, with a positive predictive value of 40.91%, negative predictive value 98% and a diagnostic accuracy of 71.27%.

The ME-NBI examination has lower sensitivity (78.95%, 95% CI , 56.67% - 91.49%), but with a much better specificity (92%, 95% CI, 83.63% - 96.28%) as compared to AFI. It also displayed a positive predictive value of 71.43%, negative predictive value of 94.52% and a diagnostic accuracy of 89.36%, above the other two methods (*table 1*).

In the per-patient analysis, trimodal endoscopy had a sensitivity of 94.74% (95% CI 75.36% - 99.06%), a specificity of 92% (95% CI 83.36% -96.28%%), and an accuracy of 92.55%. Its positive predictive value was 75%, while its negative predictive value was 98.57%, which is superior to all other methods of examination. Moreover, ME-NBI use had reduced the percentage of false positives from 27.65% to 6.38%, thus increasing specificity.

The per-lesion analysis found 40 gastric lesions (41.49%): 8 elevated circumscribed lesions, 10 ulcerated lesions, three depressed lesions and 19 gastric polyps. Of these 19 polyps, 9 were adenomas without dysplasia, 5 were polyps with low dysplasia, three lesions exhibited high grade dysplasia, while one polyp displayed adenocarcinoma changes.

All 19 polyps were positive in AFI mode examination (magenta on a green background), with a high number of 9 (47.36%) false positive results. After ME-NBI examination was performed, the number of false positive results decreased to two (10.52%, p=0.0052).

AFI diagnosed 8 (20%) circumscribed lesions in addition to WLE: two cases of gastric cancer, two lesions with high grade dysplasia changes, two with intestinal metaplasia and two false-positive results. The latter two cases were confirmed by ME-NBI and pathological examination as inflammatory lesions.

Basically, at the per-lesion analysis of the study group, WLE had a sensitivity of 65% (95% CI, 43.29%-81.88%), a specificity of 70% (95% CI, 48.1 %-85.45%) and an accuracy of 67.75%. The negative predictive value was 66.67%, while the positive predictive value was 68.42%. The sensitivity of AFI was superior to WLE (88.89%, 95% CI, 67.2%-96.9%) and NBI-ME (83.33%,

Table 1 - Per patient analysis

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Accuracy
WLE	72.73% (55.78%-84.93%)	80.33% (68.69%-88.37%)	66.67%	84.48%	77.65%
AFI	94.74% (75.36%-99.06%)	65.33% (54.05%-75.12%)	40.91%	98%	71.27%
ME-NBI	78.95% (56.67%-91.49%)	92% (83.63%-96.28%)	71.43%	94.52%	89.36%
TME	94.74% (75.36%-99.06%)	92% (83.36%-96.28%)	75%	98.57%	92.55%

CI: confidence interval, WLE: white light endoscopy; AFI: autofluorescence endoscopy: ME-NBI: magnifying endoscopy with narrow band imaging; TME: trimodal endoscopy

95% CI, 60.78% -94.16%), respectively. The specificity of AFI was however very low (27.27% 95% CI, 13.15%-48.15%), lower than ME-NBI and WLE as a matter of fact. AFI had a positive predictive value of 50%, a negative predictive value of 75% and a diagnostic accuracy of only 55%. ME-NBI examination had a higher specificity (90.91%, 95% CI, 72.19%-97.47%), with a positive predictive value of 88.24%, negative predictive value of 86.96% and a diagnostic accuracy of 87.5%, above the other two methods (*table 2*).

Overall, trimodal examination had a sensitivity of 94.44% (95% CI 74.24%-99.01%), a specificity of 90.91% (95% CI 72.19%-97.47%), and an accuracy of 92.5%. Its positive predictive value was 89.47% and the negative predictive value was 95.24%, which is superior to all other modes of examination separately. Compared to the total number of lesions, the percentage of false positive results was 40% for AFI and decreased to only 5% after these lesions were examined with ME-NBI, therefore increasing the specificity of the method (p=0.0099).

Only 5 cases (5.32%) of early gastric cancer were diagnosed in the study group: type I elevated (one case), depressed type IIc (2 cases) and type III excavated (2 cases), respectively. Conventional endoscopy showed only 3 of the lesions, as the two cases of type IIc early gastric cancer were only diagnosed with AFI. In ME-NBI mode, all early gastric cancer lesions had an irregular mucosal pit pattern and vascular pattern characterized by the presence of irregular calibre and corkscrew neoformation vessels.

DISCUSSION

Most of the recent literature studies have investigated the role of these imaging techniques used separately for detection of early neoplastic lesions, especially in patients with Barrett's esophagus. So far, there is scarce information about the combined use of those techniques. A total of 94 patients with minimum digestive symptoms and no alarm signs were included in the current study, with the aim of looking at both early cancer diagnosis and preneoplastic lesions involved in gastric carcinogenesis.

WLE had a sensitivity and specificity of 72.73% and 80.33%, respectively, which confirms to a certain extent its limited diagnostic value. This study clearly demonstrated the superiority of trimodal examination (WLE + AFI + NBI), which increased the detection rate by 22% (sensitivity 94.74%), with a very good negative predictive value (98.57%) as compared to conventional examination.

AFI thus proved to be a highly sensitive method for the diagnosis of preneoplastic lesions and early cancer (88.89%). It was proven capable to detect 15% more lesions than conventional endoscopy (which included two cases of early gastric cancer). The results were similar to those in the literature, as most studies are proving the superior sensitivity of AFI compared to conventional endoscopy. The higher sensitivity of AFI was demonstrated in previous studies, both in patients with Barrett's oesophagus, dysplastic lesions (12-17) as well as chronic atrophic gastritis (18) or early gastric cancer. In the latter category, 13% of lesions were detected solely by AFI, particularly in the case of elevated lesions (7). The results are better in patients with Barrett's oesophagus than in those with gastric disease. A possible explanation for this would consist of the differences between target organs and the study design. Due to the small diameter of the oesophagus,

Table 2 - Per lesions analysis

	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Accuracy
WLE	65% (43.29%-81.88%)	70% (48.1%-85.45%)	68.42%	66.67%	67.75%
AFI	88.89% (67.2%-96.9%)	27.27% (13.15%-48.15%)	50%	75%	55%
ME-NBI	83.33% (60.78%-94.16%)	90.91% (72.19%-97.47%)	88.24%	86.96%	87.5%
TME	94.44% (74.24%-99.01%)	90.91% (72.19%-97.47%)	89.47%	95.24%	92.5%

CI: confidence interval, WLE: white light endoscopy; AFI: autofluorescence endoscopy: ME-NBI: magnifying endoscopy with narrow band imaging; TME: trimodal endoscop

the quality of the image is much better compared to the stomach, where brightness is lower, and multiple artefacts tend to occur.

The main disadvantage of AFI is a reduced specificity and consequently a low positive predictive value due to the high number of false positives result. This is the reason why it was considered of limited value for clinical practice (19). Nevertheless, in trimodal endoscopy this disadvantage is surmounted by using NBI with magnification in order to characterize lesions visualized by AFI. This strategy in turn reduces the number of false positives and thus increases specificity (16, 17, 20). In the current study, the percentage of false positive results was 40% for AFI and decreased to only 5% after these lesions were examined in ME-NBI, thus increasing the specificity of the method to 90.91%. The overall analysis of the study group, using ME-NBI, reduced the percentage of false positives from 27.65% to 6.38%. This is illustrative for the very good sensitivity and specificity (94.74% and 92%, respectively) of trimodal examination, which delivers a diagnostic accuracy of premalignant and malignant lesions of 92.55%.

Examination using ME-NBI has the advantage of good visibility of mucosal pattern and microvascular network, showing specific changes in neoplasia (10, 21-25). Unfortunately, there is no clear diagnostic criteria to differentiate changes of varying degrees of dysplasia and early gastric cancer, which is needed for further studies. In this study we considered as positive lesions the ones characterised by the presence of an irregular mucosal pit pattern, disappearance of the fine mucosal structure and vascular pattern of irregular type with dilated vessels, tortuous, irregular in size and shape. Using these criteria, ME-NBI had a good diagnostic accuracy. However, it was not able to accurately differentiate dysplasia from early gastric cancer.

While most of the studies published in the literature consisted of relatively homogeneous groups of patients, with a specific condition (Barrett oesophagus, atrophic gastritis, early gastric cancer), in this study we included patients who were not previously diagnosed with gastric pathology, showing minimal symptoms and no warning signs, in order to determine the role of trimodal endoscopy in the routine practice of a gastroenterology department. One of the weaknesses of the present study is the small number of patients included in order to validate the results. However, the percentage of premalignant lesions involved in gastric carcinogenesis (40%) and early gastric cancer (5.32%) diagnosed in the study fits in the literature data from our country (26).

CONCLUSION

In conclusion, AFI can be used as a "red flag" technique in order to identify certain lesions which are difficult to visualize in WLE. AFI is most useful when it is used as part of a multimodal examination, thus increasing the number of lesions detected. However, this technology needs improvements regarding image resolution, reduction of artefacts and contrast enhancement. Quantitative analysis of the images and the establishment of an autofluorescence index might improve diagnostic accuracy, completing the visual interpretation of images. Moreover, ME-NBI is an additional technique able to better characterize the mucosal and vascular pit pattern of the lesions, significantly reducing the number of false positive lesions detected by AFI.

Trimodal endoscopic examination including WLE, AFI and NBI with magnification could be practiced as a standard endoscopic technique. It is quick, safe and accurate for the diagnosis and surveillance of premalignant and malignant digestive tract lesions. However, larger randomized controlled studies are needed in order to establish the role of these techniques in evaluating different subgroups of patients, before introduction in routine endoscopic examination.

Author contributions

Concept – F.M.M., S.A.; Design - F.M.M., S.A.; Supervision – S.A.; Data collection and/or Processing – F.M.M., I.S., B.E.D., C.M., S.A.; Analysis and/or interpretation - F.M.M., I.S., B.E.D., C.M., S.A.; Literature Review - F.M.M., S.A.; Writer - F.M.M., S.A.; Critical Review - F.M.M., I.S., B.E.D., C.M., S.A.

Informed consent statement

Written informed consent was obtained from all patients who participated in this study.

Conflict of interest and Source of Funding statement

The authors declare they have no conflict of interests. The authors declared that this study has received no financial support.

Data sharing statement

No additional data are available.

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