

Early diagnosis of hereditary diffuse gastric cancer: (not only) an endoscopic challenge!

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Bibliography

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Gastric cancer still represents a major cause of death worldwide mostly due to late diagnosis [1]. Moreover, given an aging and increasing global population, the number of cases is expected to increase during the next decade even as incidence declines [2].

For the intestinal subtype of gastric cancer according to Lauren's classification, together with *Helicobacter pylori* eradication and diet changes, early endoscopic diagnosis is considered to be the main cornerstone of overcoming the dismal prognosis of patients who harbor gastric cancer [3,4]. However, endoscopic diagnosis of diffuse gastric cancer (DGC), even in advanced stages, has always been considered a (*our first!*) challenge due to its scattered cell clusters and infiltrative behavior with very often no or only minor luminal changes.

One percent to 3% of all gastric cancers may be considered hereditary diffuse gastric cancer (HDGC). CDH1 germline mutations encoding the cell-to-cell adhesion protein E-cadherin cause HDGC and are detected in 25% to 40% of tested families [5]. According to the most recent guidelines, criteria for testing CDH1 mutation include the presence of 2 cases with gastric cancer, regardless of age, at least 1 with confirmed DGC; 1 case of gastric diffuse cancer before 40; or a personal or family story of DGC or lobular breast cancer, with 1 case diagnosed before age 50. In addition, this testing could be considered in patients with bilateral or familial lobular breast cancer, patients with DGC and cleft lip/palate and those with precursor lesions for signet ring cells carcinoma [6].

Management options for asymptomatic mutation carriers are (*our second!*) challenge. On one hand, prophylactic gastrectomy is recommended because of the significant risk of suffering of gastric cancer and, as discussed above, because neoplastic cells infiltrate the mucosa while preserving normal surface epithelium, making it easy to

miss diffuse cancer on endoscopy [7]. On the other hand, a significant number of patients will never develop cancer and surgical options may lead to complications and significantly impact an individual's quality of life.

As an answer to these challenges, diverse attempts have been made to improve gastroscopy. These would serve endoscopic evaluation a) to screen all first-degree relatives of patients meeting criteria for CDH1 testing; and b) during annual endoscopic surveillance that may be proposed to patients who want to delay surgical treatment or have significant contraindications to surgery.

As for other organs (eg, Barrett's, ulcerative colitis), the lines of thoughts were: to inspect and clean the mucosa, to identify mucosal lesions and, even in the (most probable) absence of malignancy, to perform a (significant) number of biopsies (to overcome the multiple foci of neoplastic lesions) [8]. In 2010 the Cambridge protocol was published as a way to standardize procedures and improve cancer foci detection [9]. That protocol recommended that all endoscopically visible lesions be targeted and biopsies be taken of 6 random sample in each anatomical zones, including the antrum, transitional zone, body, fundus, and cardia (i.e., at least 30 biopsies). Nevertheless, Fujita H [10] reported an interesting study aimed at modeling bioptic diagnostic yield on the basis of the topographic distribution of cancer foci in a series of 10 gastrectomies in CDH1-mutation carriers. They concluded that on the basis of the number of sampled glands per biopsy in routine surveillance preoperative endoscopy, the theoretical number of biopsies necessary for a 90% rate of detection of (at least 1) neoplastic foci would be 1768 (ranging from 50 to 5832). Also, and contradicting the predilection for the distal stomach and the body-antral transitional zone noted by Charlton A et al. [11], Fujita H et al. suggested that the highest density of neoplastic foci was found in the anterior proximal fundus and cardia/proximal fundus.

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In summary, our (*third!*) challenge is performing an adequate gastroscopy that includes at least 30 biopsies. As was the case with precancerous lesions in the intestine [12–14], methods of improving conventional endoscopy have been studied. Shaw D et al. performed 99 surveillance procedures in 33 patients using only targeted biopsies. Using white light endoscopy plus congo red-methylene blue chromoendoscopy if no lesions were found in white light endoscopy, 56 pale lesions (post dye application) were identified during 24 procedures (in 18 patients). Signet ring cell carcinoma (SRCC) was detected in 41% of these lesions and when a highly suspicious lesion was seen the targeted biopsy confirmed carcinoma in 91% of cases. Although this protocol may facilitate early detection of gastric cancer, its benefit may be limited to lesions greater than 4 mm because pale lesions identified at chromoendoscopy appear to correspond to the larger foci of 4 mm to 10 mm [15]. Lim et al. studied 29 patients who fulfilled criteria for HDGC, but used high-resolution white light endoscopy with autofluorescence (AFI) and narrow band imaging (NBI), and both random and targeted biopsies were performed. Targeted biopsies identified 7 SRCC whereas in the 696 random biopsies, 22 SRCC foci (in line with Fujita data) were found. The additional use of targeted biopsies together with random biopsies identified a further 3 cases (19%). The authors concluded that high-quality white light endoscopic examination with random and targeted biopsies can identify early lesions and define surgical timing. However, only a limited utility was found for AFI and NBI and these findings together should be analyzed with caution because very few targeted biopsies correspond to SRCC [16].

In this issue of *Endoscopy International Open*, Huneburg et al. report on their attempt to improve endoscopic detection of HDGC by using high-resolution white light endoscopy and pan-gastric chromoendoscopy with indigo carmine combined with targeted and random biopsies in a case series of 7 patients with a proven CHH1 germline mutation scheduled for a presurgical (screening) procedure. Cambridge protocol was applied but only a single focus of SGCC was detected during random biopsies (i.e., 1 cancer for >250 biopsies performed, again in line with Fujita A). Also, most foci would be detected in corpus and proximal body, as stated in **Table 2** of the Huneburg et al. manuscript, which is not an easy position for any endoscopic procedure and again in line with histopathology studies by Fujita.

Taken together and with Huneberg's data, these reports suggest that: a) It will be extremely difficult to collect large series of patients (due to the rarity of this disease and also to the infrequent option of endoscopic surveillance); b) Standard high-quality gastroscopy should be performed and targeted biopsies performed whenever minute changes are seen, particularly in the proximal stomach; and c) Current virtual and standard chromoendoscopy do not provide additional information because they were developed/conceived to target other types of pathologic processes. Further research should focus on determining predictive features

of endoscopic changes (e.g., preferred location, type, size, etc.) and potentially to test ways of performing targeted biopsies vs. random (to overcome the enormous number of biopsies), for instance with magnification methods incorporated in most endoscopes of the most recent generations or even confocal methods.

Competing interests: None

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