Editorial Commentary

Non-targeted biopsies in hereditary diffuse gastric cancer: Necessary, but not enough

Kole H. Buckley[1], Rashmi Tondon[2], Parry Guilford[3], Bryson W. Katona[1]

[1]Division of Gastroenterology and Hepatology, Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Pathology and Laboratory Medicine, Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA, USA; [3]Cancer Genetics Laboratory, Centre for Translational Cancer Research (Te Aho Matatū), Department of Biochemistry, University of Otago, Dunedin, New Zealand

Correspondence to: Bryson W. Katona, MD, PhD. Division of Gastroenterology and Hepatology, Perelman School of Medicine at University of Pennsylvania, 3400 Civic Center Blvd., 751 South Pavilion, Philadelphia, PA 19104, USA. Email: bryson.katona@pennmedicine.upenn.edu.

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Hereditary diffuse gastric cancer (HDGC) is caused by germline pathogenic/likely pathogenic (P/LP) variants in the *CDH1* and *CTNNA1* genes (1-6). Carriers of P/LP *CDH1* variants have an estimated 33–42% risk of diffuse gastric cancer by age 80 years old (7,8). Risk management strategies in HDGC are largely confined to two options: annual upper endoscopic surveillance or prophylactic total gastrectomy (9). While prophylactic total gastrectomy is currently the only definitive method to eliminate future gastric cancer risk, yearly endoscopic surveillance may offer value by informing the timing of total gastrectomy in patients who do not wish to immediately pursue surgery. Endoscopic surveillance may also offer value in carriers of *CDH1* or *CTNNA1* P/LP variants who do not have a family history of gastric cancer, a subgroup where future risk of diffuse gastric cancer remains particularly uncertain.

The principal goal of upper endoscopic surveillance is to use targeted and non-targeted biopsies to identify foci of signet ring cell carcinoma (SRCC) while still at an early stage (10). However, the reliability of this method is problematic given its high false negative rate, as demonstrated by gastrectomy specimens frequently showing SRCC despite negative endoscopic findings (11-13). The recent study by Lee *et al.*, published in *Lancet Oncology*, aimed to determine whether non-targeted biopsies improve endoscopic detection of SRCC by evaluating the diagnostic yield of SRCC in targeted versus non-targeted biopsies and assessing the cumulative incidence of cancer during longitudinal follow-up (14). This study was conducted at the Cambridge University Hospitals National Health Service (NHS) Foundation Trust between June 1, 2005 and July 31, 2021. The patient cohort included 145 individuals from 76 families who fulfilled HDGC testing criteria according to the International Gastric Cancer Linkage Consortium (IGCLC) (9,14).

A major finding of this study was that non-targeted biopsies acquired during endoscopic surveillance provided a higher diagnostic yield of SRCC compared to targeted biopsies (14). Indeed, of 58 patients diagnosed with SRCC, 50% were first diagnosed via only non-targeted biopsies while 26% were first diagnosed via only targeted biopsies (14). Of the remaining patients, 10% were first diagnosed with SRCC observed by both non-targeted and targeted biopsies, 9% had macroscopic tumors that were directly visualized, and 5% were first diagnosed only after a total gastrectomy was performed (14). SRCC positive targeted biopsies were most frequently found in the antrum, whereas SRCC positive non-targeted biopsies were more often found in the cardia and fundus (14). This is likely due to better mucosal visualization in the antrum given the lack of rugae, therefore allowing better visualization of pale lesions of mucosa that are associated with SRCC

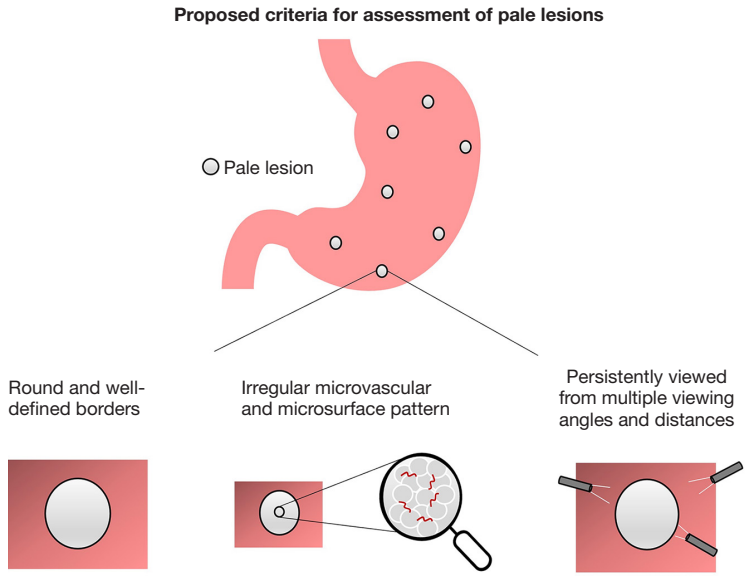

Figure 1 Proposed criteria for assessment of pale lesions.

(15,16). Importantly, when compared to targeted biopsies, the anatomical distribution of SRCC detected from non-targeted biopsies more closely mimicked the distribution of SRCC in total gastrectomy specimens (14). These findings provide support for the utilization of non-targeted biopsies during endoscopic surveillance in HDGC, a practice that has long been endorsed by the IGCLC (9).

Endoscopically detected flat pale lesions have previously been recognized to be associated with foci of SRCC (15,16). However, biopsy of pale lesions has a low positive predictive value, as demonstrated in this study where only 12% of pale lesions biopsied revealed foci of SRCC (14). While the characteristics of pale lesions that are suspected to contain SRCC can be challenging to define, it is important to establish such criteria as lesions with a similar appearance will accumulate with continued surveillance due to scarring of the gastric mucosa after repeated biopsy. Previous studies have indicated that pale patches with an irregular microvasculature and microsurface may be indicative of underlying SRCC (17,18). Building off this, the authors of the current study identified three additional criteria, including that pale lesions associated with SRCC are more round (rather than irregularly shaped), have well-defined borders, and are likely to be persistently observed from multiple different viewing angles as well as multiple viewing distances (*Figure 1*) (14). These new criteria were able to predict SRCC in pale flat lesions with a sensitivity of 67%, with only 16 of 386 (4%) non-suspicious lesions showing SRCC histology (14). As patients with a predisposition for HDGC may undergo multiple surveillance endoscopies, using these criteria to differentiate SRCC-associated pale lesions from previous biopsy scars or other non-malignant lesions could become increasingly important. This would be of particular importance when a high number of biopsies are taken annually, such as in the Bethesda protocol where four non-targeted biopsies are taken from each of 22 separate anatomic sites (11).

Current IGCLC guidelines recommend annual endoscopic surveillance for carriers of P/LP *CDH1* variants with a family history of diffuse gastric cancer who do not immediately pursue a prophylactic total gastrectomy (9). Of the longitudinal patient cohort in this study, 55 patients were diagnosed with SRCC via endoscopic surveillance. Between one and eight annual endoscopies were required to find SRCC in each of the 55 patients (14). Out of this group, 34/55 (62%) were diagnosed on the first endoscopy and 44/55 (80%) by the second endoscopy, demonstrating that SRCC are most likely to be identified within the first couple of surveillance endoscopies (14). However, these data do not take into account the other 43 *CDH1* P/LP carriers in which SRCC were not identified (14). Given that SRCC are detected in gastrectomy specimens in greater than 95% of *CDH1* P/LP carriers (12,19,20), it is likely that despite repeated upper endoscopies, there will always remain a subgroup of *CDH1* P/LP carriers in whom foci of SRCC will not be detected. The authors of this study suggest

that after five consecutive annual surveillance procedures with negative findings, the surveillance interval could be increased to every 2 years, particularly for individuals older than 35 years of age (14). However, without a better understanding of the time required for an undetected stage T1a SRCC to progress to ≥ stage T2 disease, such a decision might present substantial additional risk. This risk is amplified by the poor understanding we currently have of individual genetic or environmental risk factors for disease progression.

Regardless of endoscopic findings, the current IGCLC guidelines recommend total gastrectomy for *CDH1* P/LP variant carrying patients with a family history of diffuse gastric cancer (9). While this study (14) provides evidence to support the use of non-targeted gastric biopsies during upper endoscopy, more reliable techniques and/or technologies are still needed to better detect and quantify SRCC in *CDH1* carriers. Furthermore, and more importantly, further investigations to distinguish between foci of SRCC that are genuinely indolent and those with a higher likelihood of progression are needed (9). For P/LP variant carriers to avoid a total gastrectomy, treatments to prevent the development of and/or eliminate foci of SRCC are also needed. While no proven treatments are currently available, data from preclinical models suggest that E-cadherin-deficient cells may be susceptible to specific multikinase inhibitors and histone deacetylase (HDAC) inhibitors (21,22).

In conclusion, Lee *et al.* present data on the enhanced detection of early stage SRCC using targeted and non-targeted gastric biopsies in carriers of P/LP *CDH1* variants. These data show the benefit of endoscopic surveillance for informing optimal decision-making around the timing of a total gastrectomy for individual carriers of P/LP *CDH1* variants. This data is also an important component of the goal of reducing the need for prophylactic gastrectomies in HDGC families, a goal that will be further advanced by ongoing research on personalized risk stratification, chemoprevention and new endoscopic imaging modalities.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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