DIAGNOSTIC YIELD OF ENDOSCOPIC SCREENING FOR IDENTIFICATION OF SIGNET RING CANCER CELLS IN CARRIERS OF A PATHOGENIC VARIANT IN *CDH1*

Lady Katherine Mejía Pérez[1], Margaret O'Malley[2,4], Arjun Chatterjee[3], Lisa LaGuardia[2,4], Susan Milicia[2,4], Sarah McGee[2,4], Joshua Sommovilla[2,4], Nicholas Smith[2,4], David Liska[2,4], Carole Macaron[1,4], R. Matthew Walsh[4,5], Carol A Burke[1,2,4]

Departments of Gastroenterology, Hepatology and Nutrition[1] , Colorectal Surgery[2], Internal Medicine[3], Sanford R. Weiss MD Center for Hereditary Colorectal Neoplasia[4], and General Surgery[4,5], Cleveland Clinic, Cleveland OH

Background

- Individuals with a germline pathogenic variant in the *CDH1* gene have a high risk of signet ring cell (SRC) diffuse gastric cancer (DGC) and lobular breast cancer
- Cumulative risk of DGC by age 80 y:
  - 42-70%
  - 33-56%
- Management of the DGC risk in *CDH1* PV carrier:

Family history of DGC	Family history of breast cancer
Prophylactic total gastrectomy (PTG) If declined, annual EGD If SRC detected, total gastrectomy (TG)	Annual EGD If SRC detected, TG Consider PTG

- ***CDH1* related EGD standard: Cambridge protocol**
  - White-light HD EGD
  - Inflate and deflate
  - Targeted biopsies of endoscopically visible lesions – attention to pale areas
  - + 30 random biopsies in 5 areas of stomach
- Detection of SRC is highly variable, even in expert hands: 40-61%

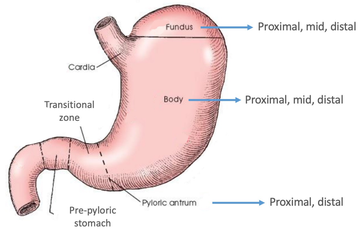
Aims

Describe the diagnostic yield of a 77-random biopsy protocol to detect SRC pre-operatively in patients with *CDH1* PV compared to their gastrectomy specimens

Secondary: Describe the anatomic locations where the SRC are most found

Methods

- Consecutive patients with *CDH1* PV seen at the Weiss Center with ≥ 1 EGD from 2007 to 2022 were included
- EGD was performed with HD white-light, and narrow band imaging
- The Weiss protocol involved a 30-minute exam with targeted biopsies of pale areas plus 7 random 4 quadrant biopsies from 11 areas



- The EGD yield was compared to surgery as gold standard

Results

61 carriers of *CDH1* PV from 39 families identified

→ Excluded 12:
6 had symptomatic DGC on 1st EGD
6 did not undergo EGD

49 patients included

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

No. Patients	N=49
Females	67%
Ethnicity	
• White	77.5%
• Black/Asian	8%/8%
• Other	6.5%
Age yrs, median [interquartile range]	
• At *CDH1* testing	45.5 [33.0-57.5]
• 1st EGD	46.5 [31.8-57.7]
• Last EGD	46.9 [32.1-58.7]
Personal History breast cancer	26%
Family history of gastric cancer	
• No	17 (35%)
• Yes	32 (65%)
• First degree relative	22 (69%)
• Second degree relative	22 (69%)
History cleft palate	2%

TABLE 2. ENDOSCOPIC CHARACTERISTICS

No. Endoscopies	N=101
Number of EGDs per patient, n (%)	
• 1	24
• 2	11
• ≥3	14
#EGDs per endoscopist, n (%)	
• Endoscopist 1	83 (82%)
• 14 other endoscopists	18 (18%)
Complications	0
Procedure time, median minutes [IQR]	29 [24-35]
IQR = interquartile range	

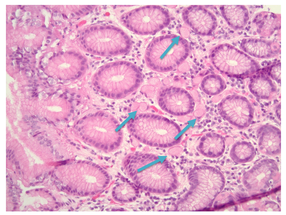


Fig 1. Signet ring cells (arrows)

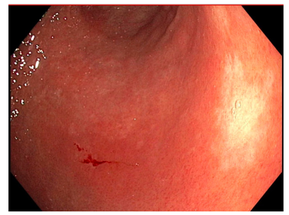
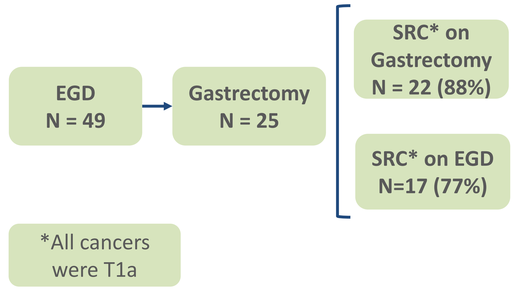
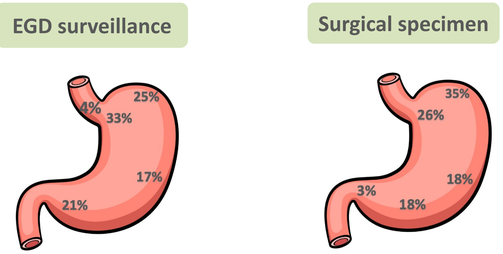


Fig 2. Suspicious pale patch

Graph 1. Diagnostic yield of 77-biopsy EGD protocol



Graph 2. Location of SRC



Conclusions

- An endoscopic protocol including targeted plus 77 random biopsies in 11 areas of the stomach increases the preoperative detection of SRC in patients with *CDH1* PV
- SRC were found diffusely in the stomach both on EGD and total gastrectomy. Two thirds of SRC were found in the proximal stomach

Contact

Lady Katherine Mejía Pérez
Department of Gastroenterology, Hepatology and Nutritrion
Cleveland Clinic, Cleveland, OH, USA
Email: mejiapl@ccf.org
Phone: 216.210.4279

References

1. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol*. 2020;21(8):e386-e397.
2. Burke A, Cruise M, LaGuardia L, et al. Technical and Endoscopic Factors in Gastric Cancer Surveillance in *CDH1* Mutation Carriers.
3. Corso G, Figueiredo J, Biffi R, et al. E-cadherin germline mutation carriers: clinical management and genetic implications. *Cancer Metastasis Rev*. 2014;33(4):1081-94.
4. Jacobs MF, Dust H, Koeppe E, et al. Outcomes of Endoscopic Surveillance in Individuals With Genetic Predisposition to Hereditary Diffuse Gastric Cancer. *Gastroenterology*. 2019; 157:87–96.
5. National Comprenhensive Cancer Network, Inc. Version 5.2017.
6. van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet*. 2015;52(6):361-74.