Clinical outcomes of CDH-1 mutation carrier patients undergoing open vs. MIS prophylactic total gastrectomy – The Mayo Clinic experience

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Background

- Inherited cancers occur in 1-3% of gastric cancer patients. Hereditary diffuse gastric cancer (HDGC) is a genetic syndrome predisposing carriers to developing early onset diffuse gastric cancer and lobular breast carcinoma (LBC).
- The CDH1 gene (and a small percentage of mutations in the CTNNA1 gene) is implicated in the majority of HDGC cases.
- Penetrance of pathogenic mutations/lifetime risk of developing gastric cancer is estimated at 33-70%.
- Prophylactic gastrectomy is recommended for patients and affected family members before age 40. If gastrectomy is undesired, annual surveillance endoscopy with chromoendoscopy is recommended.

Study Aim

As the percentage of CDH mutation carriers who possess occult foci of in situ carcinoma is not well defined, this study was designed to:

- Compare the incidence of in situ and invasive gastric adenocarcinoma in preoperative endoscopic biopsy vs surgical resection specimens in CDH-1 mutation carriers who undergo open and MIS (laparoscopic or robotic) prophylactic gastrectomy.

Materials and methods

- Retrospective review of 56 patients with CDH-1 gene mutations undergoing prophylactic total gastrectomy w/ D1+ lymphadenectomy and Roux-en-Y reconstruction from January 2000 to January 2021 by five surgeons
- 25% of patients underwent concurrent procedures (adrenalectomy, salpingo-oophorectomy, appendectomy, hysterectomy, hiatal hernia repair, umbilical hernia repair etc)
- Statistical analysis was performed using Pearson's Chi-square tests and Kruskal-Wallis rank sum tests.

HDGC Testing Criteria

CDH1 (or *CTNAA1,* if *CDH* negative*)* testing is recommended when <u>one</u> of the following criteria have been met and /or following confirmation of cancer diagnoses.

Family criteria

≥2 cases of gastric cancer in family regardless of age, with at least one DGC

≥1 case of DGC at any age and ≥1 case of LBC <70yrs in different family members

≥2 cases of LBC in family members <50yrs

Individual criteria

- DGC <50yrs
- DGC at any age in individuals of Māori ethnicity
- DGC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate
- History of DGC and LBC, both diagnosed <70yrs
- Bilateral LBC, diagnosed <70yrs
- Gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in individuals <50yrs

* Family members must be 1st or 2nd degree blood relatives of each other.

Results

	MIS (n = 38)	Open (n=18)	*p* value
Age (SD), years	39.4 (12.7)	42.7 (12.4)	*0.4*
Sex (%), female	27 (71.1%)	13 (72.2%)	*1.0*
Race			*0.5*
White	36 (94.7%)	18 (100%)	
Native- American	2 (5.3%)	0 (0%)	
Pre-op BMI (SD), kg/m²	33.3 (9.7)	29.2 (5.6)	*0.2*
Preop Endoscopy (%), n	35 (92.1%)	7 (41.2%)	***<0.001***
Operative time (SD), mins	243 (86)	210 (57)	*0.2*
Blood loss (SD), cc	83 (77)	97.5(97)	*1.0*
Lymph node harvest (SD), n	16.3 (12.8)	14.6 (13.9)	*0.5*
Length of stay (SD), days	4.2 (2.8)	6.7 (4.1)	***<0.001***

Pathology Positivity rate

Endoscopic pathology	MIS (n = 38)	Open (n=18)	*p* value
Tis	2 (4%)	1 (5.6)%	**<0.001**
T1+			
Surgical Pathology	**MIS (n = 38)**	**Open (n=18)**	***p* value**
			<0.001
Tis	1(2%)	10 (56%)	
T1a	10 (26.3%)	0 (0%)	
T2 and above	0 (0%)	1 (5.6%)	
Lymphoma	0 (0 %)	1 (5.6%)	

Complications

30-day complications	MIS (n = 38)	Open (n=18)
Esophagojejunostomy leak	1 (2.6%)	1 (5.6%)
Esophagojejunostomy stricture	2 (5.3%)	0 (0%)
Intra-abdominal Abscess	1 (5.6%)	0 (0%)
Port Site hernia	2 (5.3%)	0 (0%)
Roux limb obstruction	1 (2.6%)	0 (0%)
Ischemic Colitis	1 (2.6%)	0 (0%)

Conclusions

- Surgical pathology specimens had a 7.5-fold positivity rate for in-situ and invasive cancer when compared to endoscopic specimens.
- MIS operations allowed for shorter length of stay but were otherwise comparable to open operations.

Early prophylactic gastrectomy remains recommended over serial endoscopic surveillance in CDH-1 positive patients.

Limitations

- Preoperative endoscopy with biopsy was conducted in 76.8% (42/56) of patients.
- Retrospective study with small sample size
- Variability of operative techniques between surgeons

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