Gastric Intestinal Metaplasia and Early Gastric Cancer

Dr. Ernst Kuipers
Erasmus University Medical Center
Rotterdam, The Netherlands

Dr. Catherine Streutker
St Michael's Hospital/Unity Health Toronto
University of Toronto

SCMD
Semaine canadienne des maladies digestives

CDDW
Canadian Digestive Diseases Week

UNITY HEALTH TORONTO

CanMEDS Roles Covered

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	**Communicator** (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Conflict of Interest Disclosure

SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

(Over the past 24 months)
Name: Ernst Kuipers

Commercial or Non-Profit Interest	Relationship
Organization: BSG and ESGE	Guideline Committee Member

Conflict of Interest Disclosure

SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

(Over the past 24 months)
Name: Catherine Streutker

Commercial or Non-Profit Interest	Relationship
Organization	
Roche	Advisory Board MSI tumours, Lung biomarkers.

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

Learning Objectives:

1. Demonstrate knowledge of the pathways leading to gastric intestinal metaplasia and the risk of progression to cancer
2. Understand the methodology and importance of adequate endoscopic and histologic assessment of the stomach
3. Integrate pathologic, endoscopic and clinical information for optimizing prevention and treatment for early gastric adenocarcinoma

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

Case:

54-year old man presents for upper endoscopy due to chronic dyspepsia

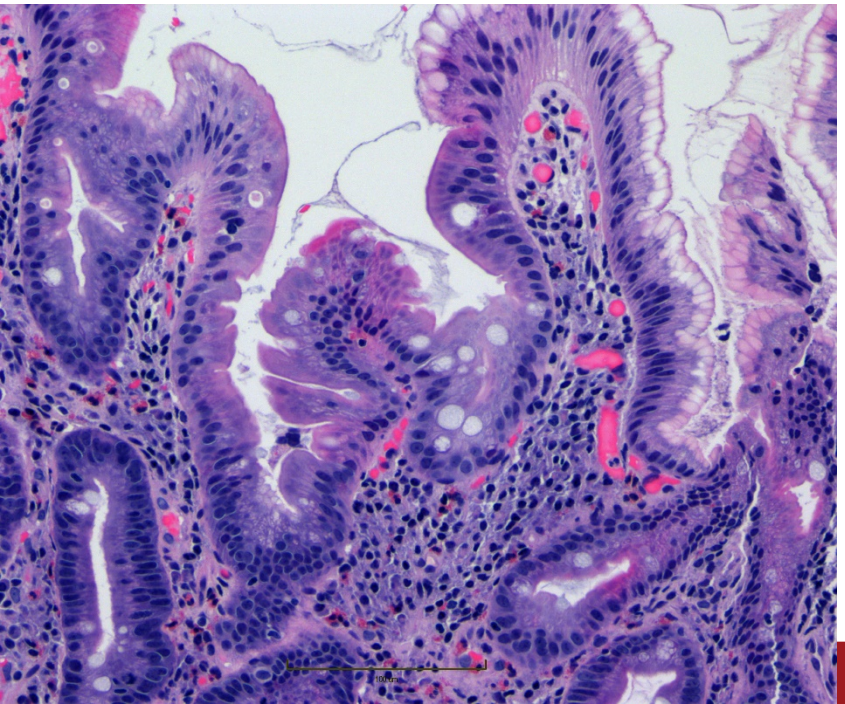
OGD mild chronic gastritis. Biopsies taken of antrum, body and incisura

Gastric Intestinal Metaplasia and Early Gastric Cancer

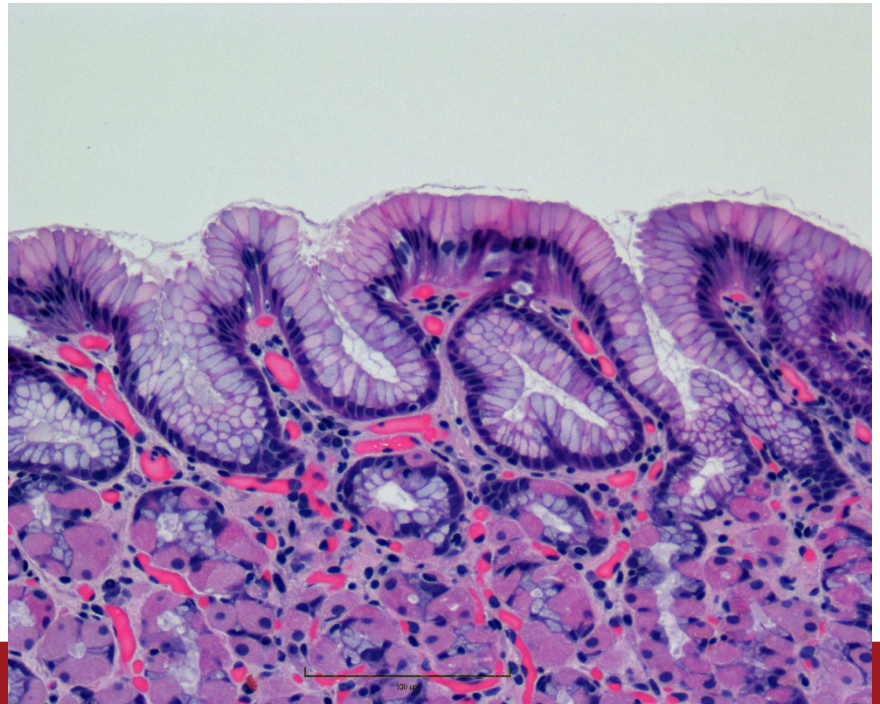
SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

Case 1:

Antrum



Body

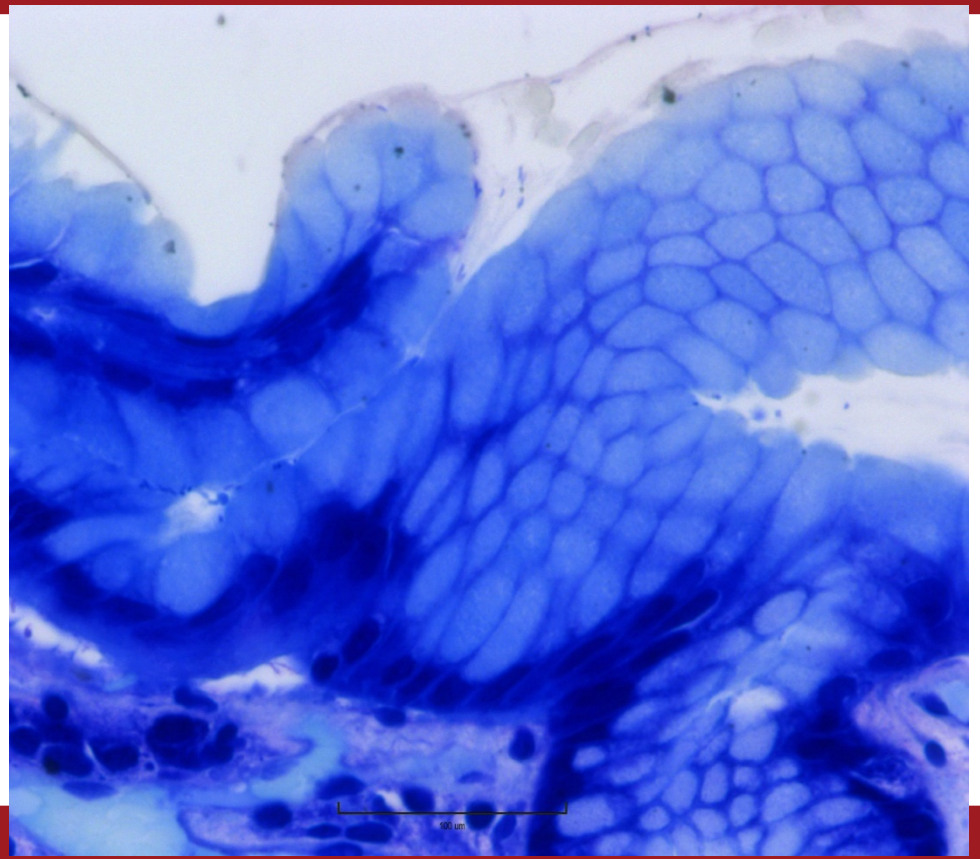


Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives[MC] | CDDW Canadian Digestive Diseases Week™

Case 1:

- Helicobacter organisms are present



Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

Questions:

- What drives the development of intestinal metaplasia?
- If you take away the inciting agent, can it regress?

Gastric Intestinal Metaplasia and Early Gastric Cancer

Intestinal metaplasia:

- Persistent inflammation and damage to the gastric mucosa leads to the development of atrophic gastritis
  - Causes: *H. pylori* infection, autoimmune gastritis, Crohn's, CVID and other disorders
- In the oxyntic mucosa, this is evident with a loss of parietal cells. Less obvious in antral mucosa
- Normal mucosa is replaced by intestinal type epithelial cells including goblet cells
- Potentiated by genetic (patient, *H. pylori cag-A* genotype) and environmental (salt intake, nitrosamines, alcohol, smoking) factors

Gastric Intestinal Metaplasia and Early Gastric Cancer

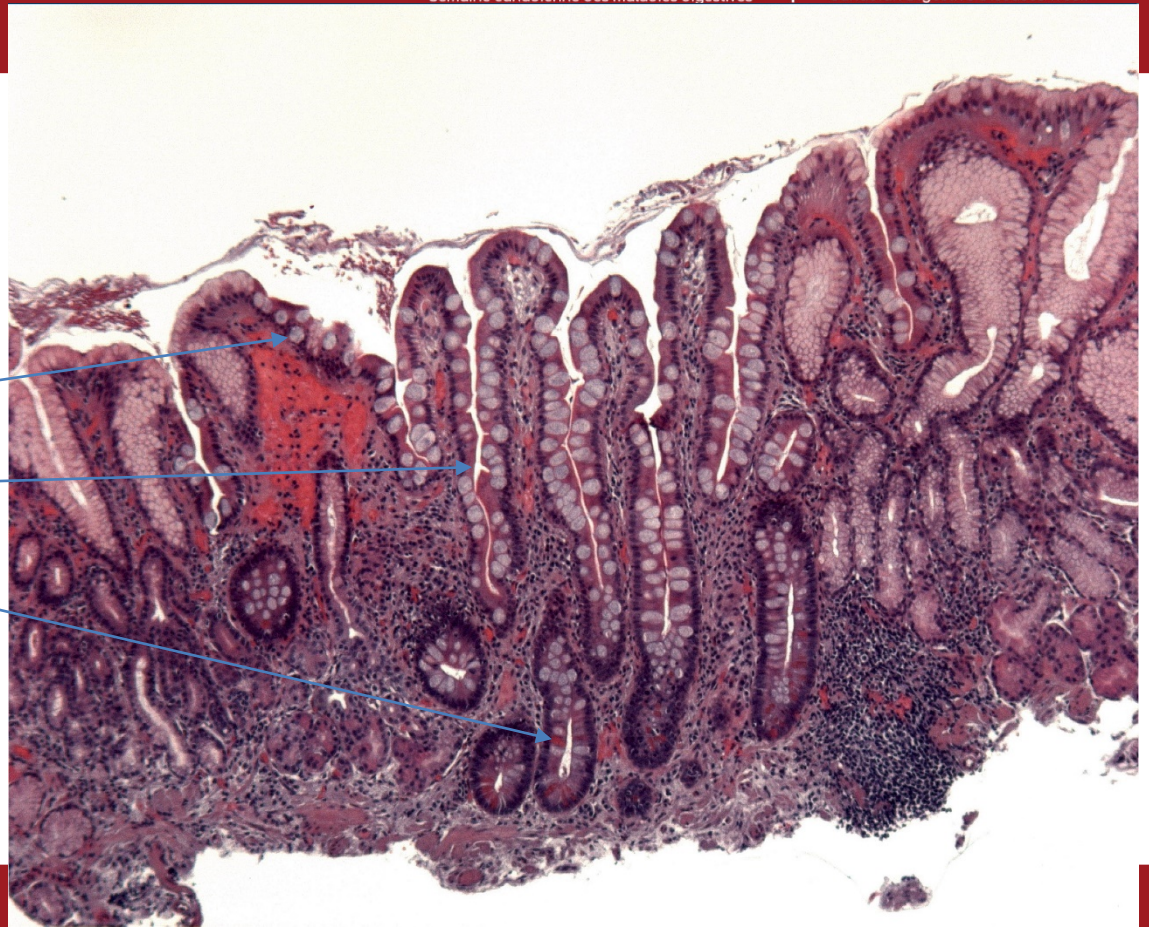
SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

Intestinal metaplasia:

As normal mucosa is lost,

it may be replaced by intestinal type epithelial cells :

- Goblet cells
- Absorptive enterocytes
- +/- Paneth cells
- May develop a more villous architecture



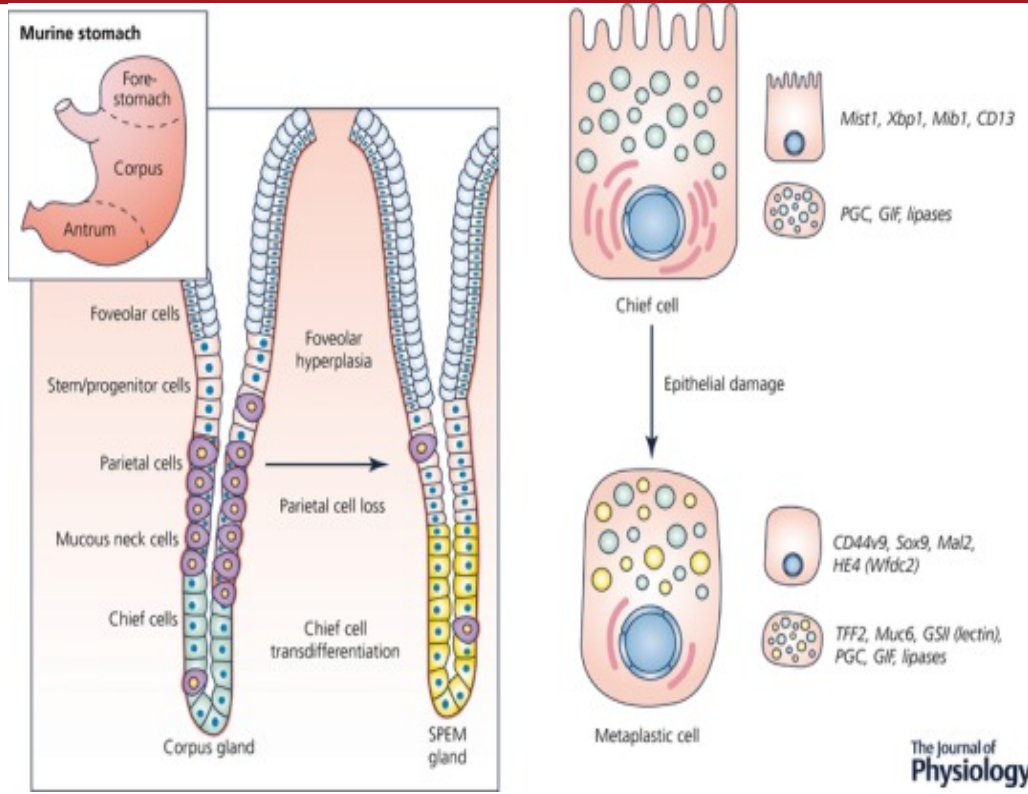
Gastric Intestinal Metaplasia and Early Gastric Cancer

Intestinal metaplasia

- Histologically, can separate IM into incomplete (more like colonic mucosa, no Paneth cells) vs complete IM (looks like small bowel mucosa)
- Theoretically less risk of development of gastric adenocarcinoma (GC) with complete IM, but it is rarely found in isolation.
- Not generally reported by pathologists.
- However, recent AGA guidelines (Gupta et al, Gastroenterology 2020) suggest that it be used to guide frequency of screening – may push pathologists into increased reporting.

Gastric Intestinal Metaplasia and Early Gastric Cancer

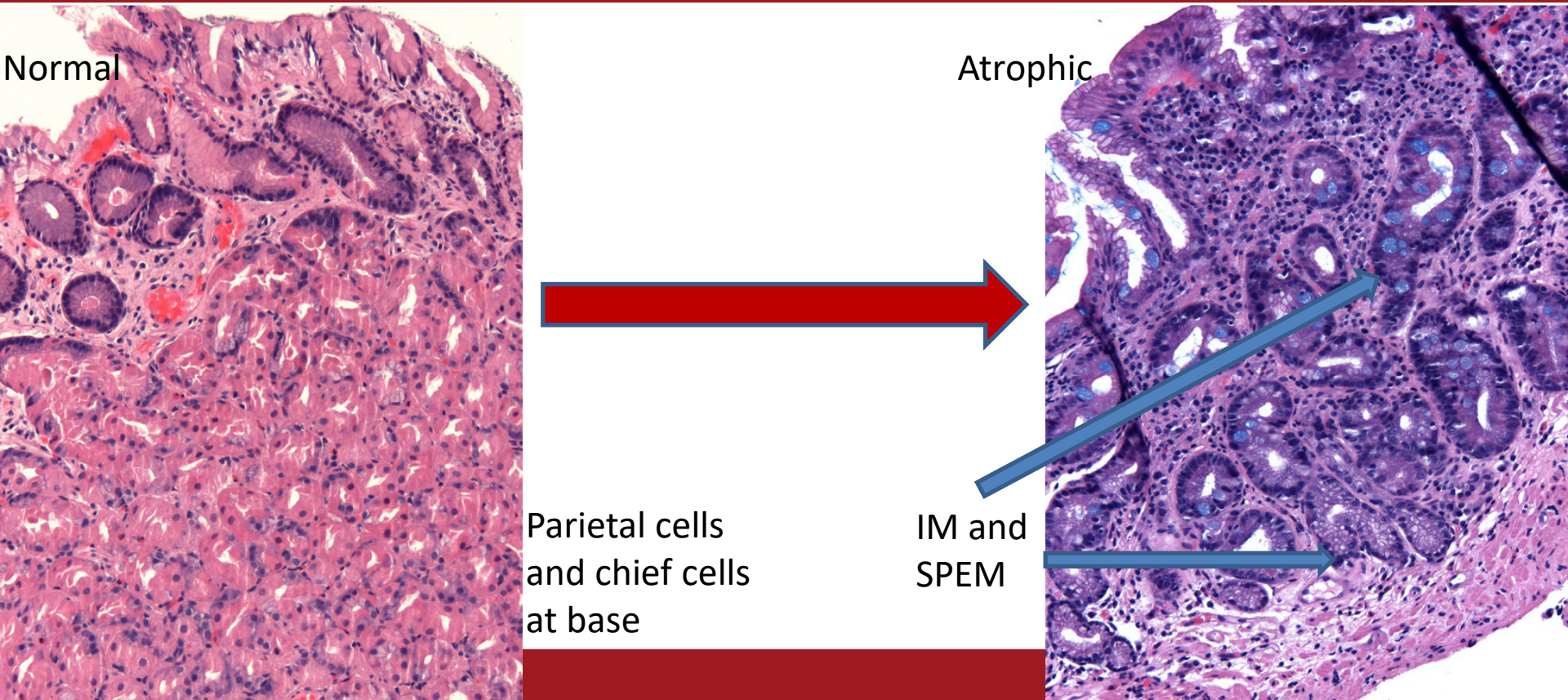
- A current theory is that IM develops secondary to Spasmolytic Polypeptide-Expressing Metaplasia (SPEM)
- In conditions of inflammation and atrophy, a 'pseudopyloric' type of simple mucous glands can be found at the base of the glands
  - Acute – wound healing
  - Chronic - ? premalignant
  - ? Site of new stem cells vs transdifferentiation of chief cells (Radyc MD et al, Gastro 2018, Nam KT et al, Gastro 2010)



Meyer and Goldenring, 2018

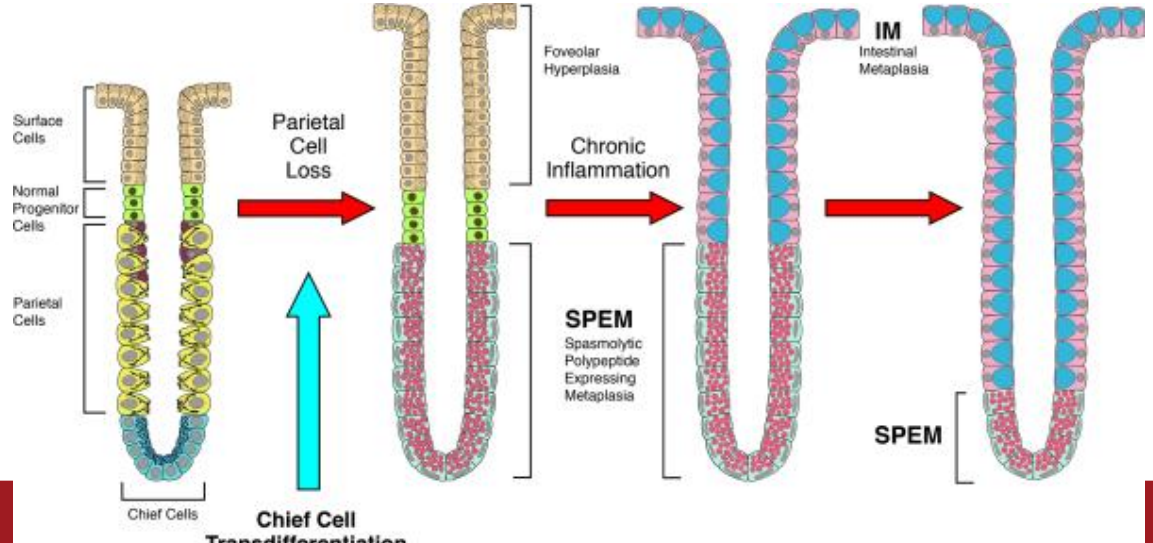
Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™



Gastric Intestinal Metaplasia and Early Gastric Cancer

- Activation of Kras in chief cells may contribute to the development of SPEM and then to IM in models (Choi et al, Gastro 2016)
- Linked to pro-inflammatory signaling through macrophages
- SPEM develops a more mitotically active phenotype which may be the precursor to IM



Goldenring JR et al
Exp Cell Res 2011

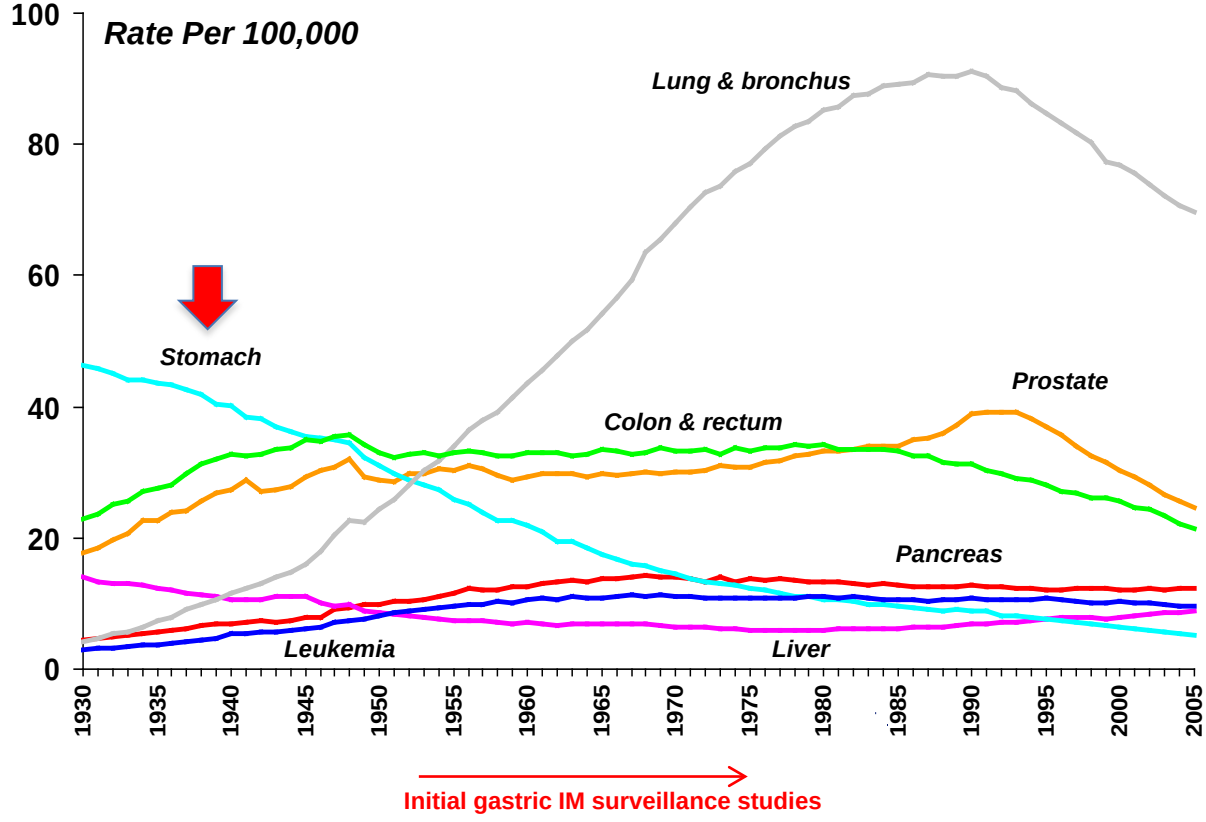
Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives[MC] | CDDW Canadian Digestive Diseases Week™

Can Metaplasia regress?

- Acute SPEM development is a response to injury and can resolve
- SPEM/IM:
  - Eradication of Helicobacter infection: conflicting results from studies with some showing decreased incidence and others no effect (Meta-analysis in Rokkas T et al, Helicobacter 2007,reviewed in Fennety MB, Gastro 2003)
- Most studies based on biopsy samples: sampling issues?

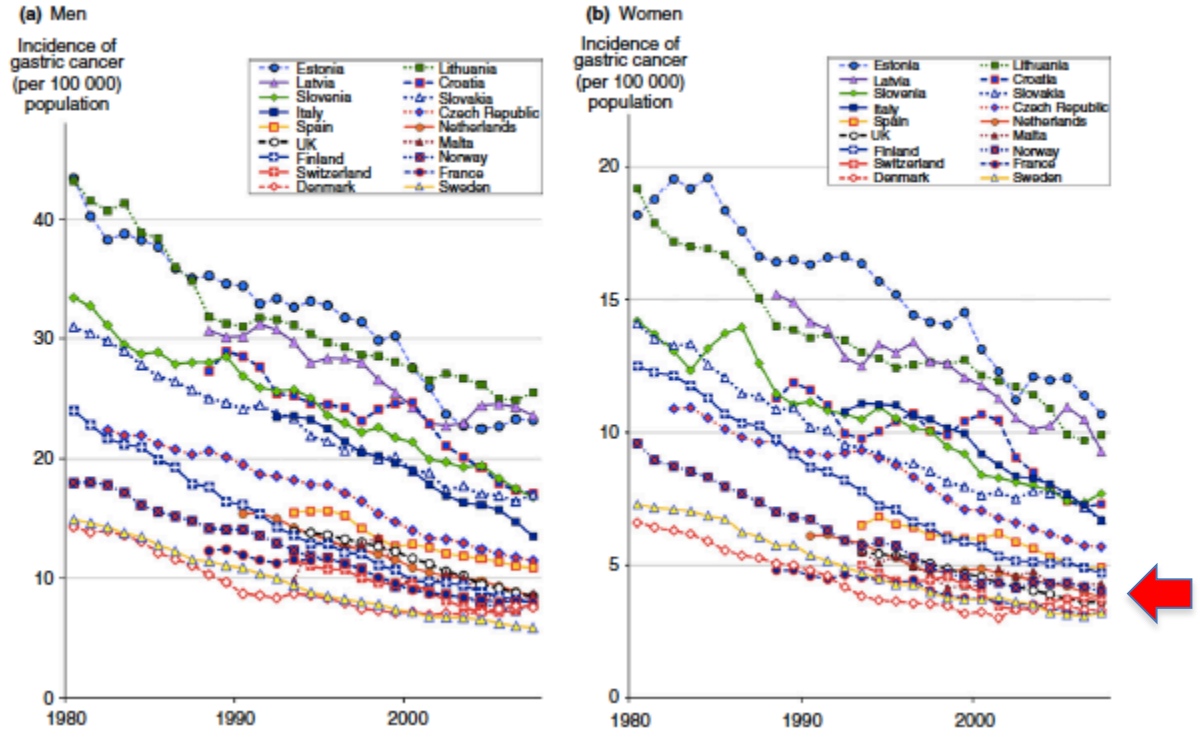
Cancer Death Rates* among men, US,1930-2005



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2005, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.

Erasmus MC

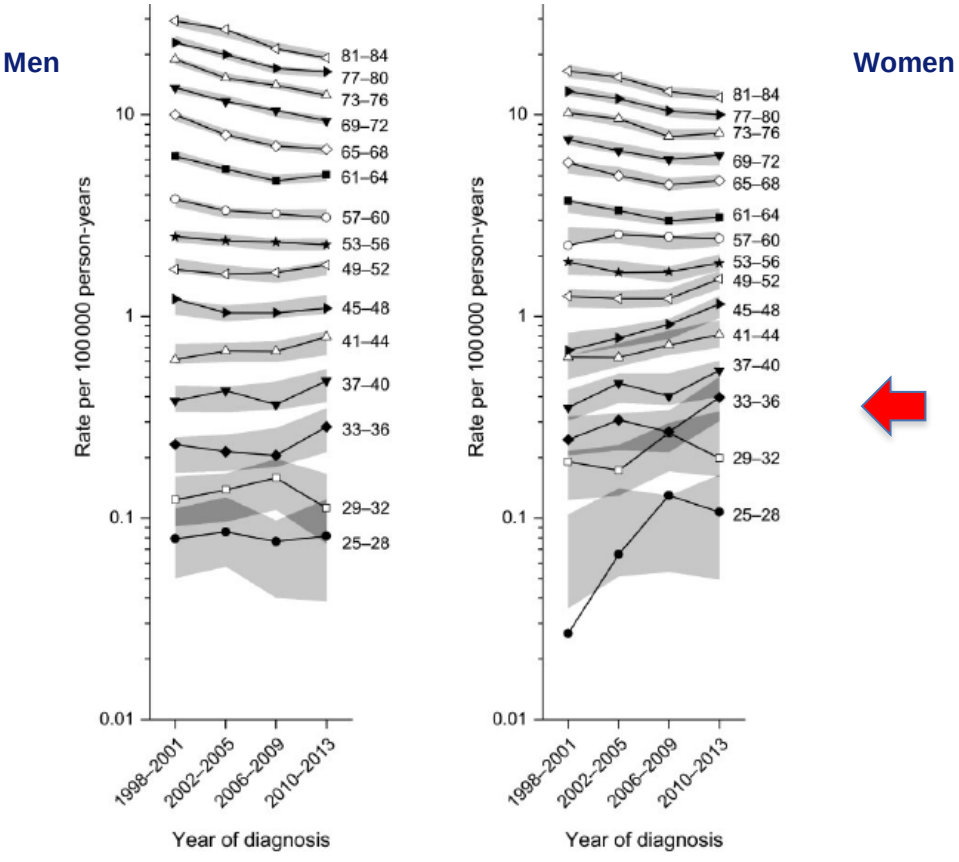
Incidence of gastric cancer in Europe; 1980 - 2015



Roberts SE et al. APT 2016; 43: 334-45

Erasmus MC

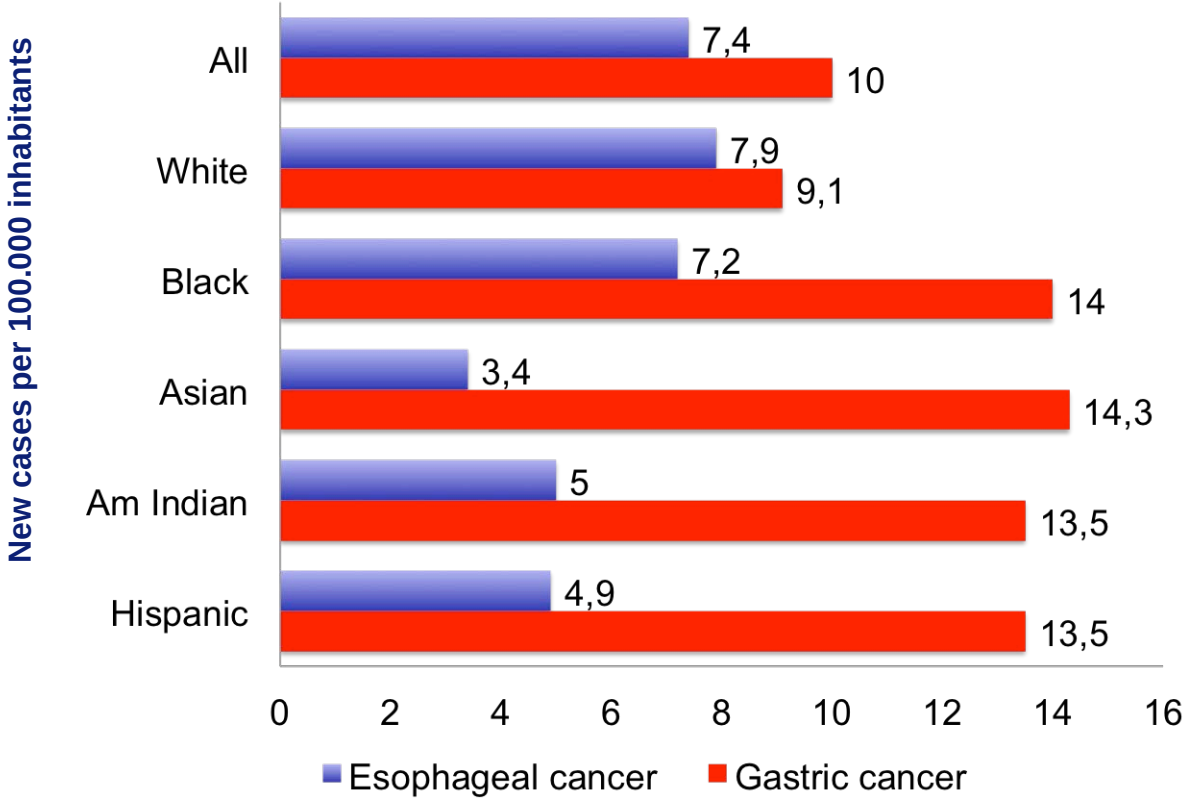
Age-related time-trends in US incidence of gastric cancer in the US; 1980 - 2015



Anderson WF et al. JNCI 2018

Erasmus MC

Esophageal and gastric cancer cases in US males by race / ethnicity



Erasmus MC

Data from SEER 13; www.seer.cancer.gov

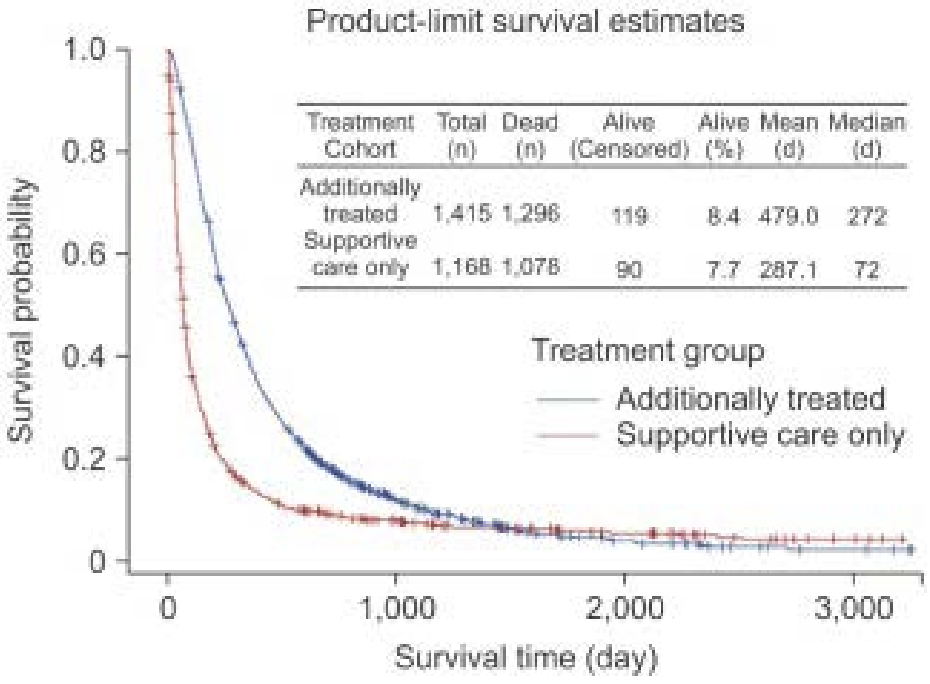
Estimated esophageal and gastric cancer cases in the United States in 2020

	Incidence
Esophageal cancer	18.440
Gastric cancer	27,600

Erasmus MC

Siegel RL et al. US Cancer Statistics 2020. Cacancerjournal.com

Gastric cancer survival in the US Medicare population

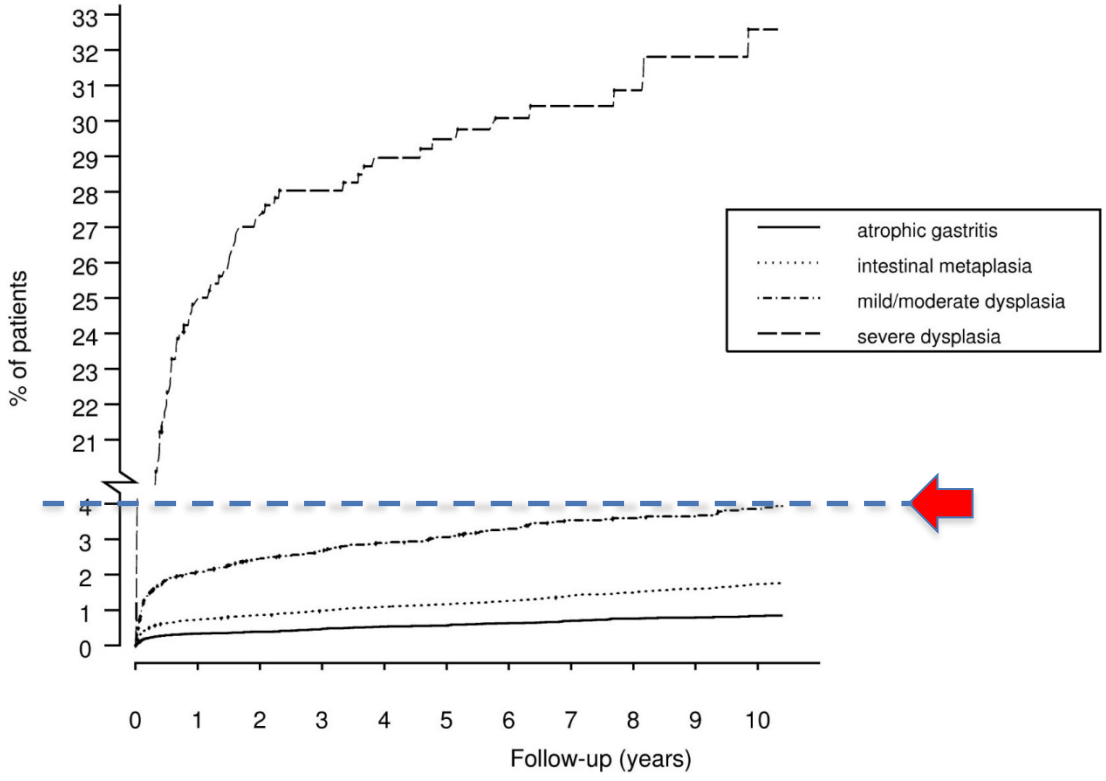


Treatment Cohort	Total (n)	Dead (n)	Alive (Censored)	Alive (%)	Mean (d)	Median (d)
Additionally treated	1,415	1,296	119	8.4	479.0	272
Supportive care only	1,168	1,078	90	7.7	287.1	72

Karve S et al. J Gastric Cancer 2015

Erasmus MC

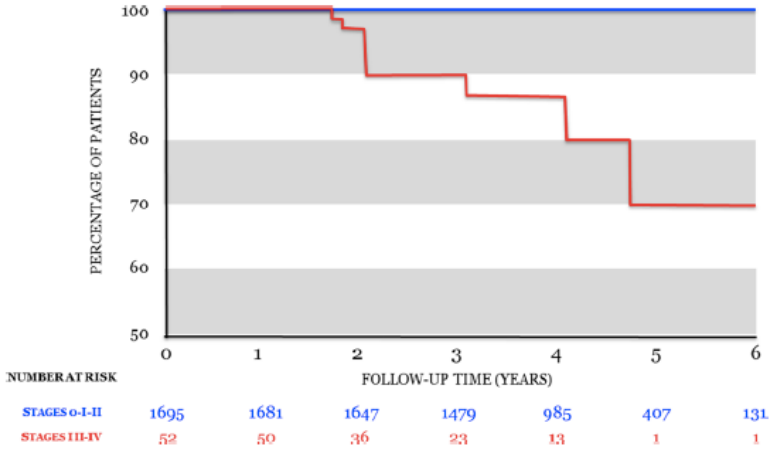
Time-related progression of pre-malignant lesions to gastric cancer in 97.837 Dutch subjects with atrophy / IM



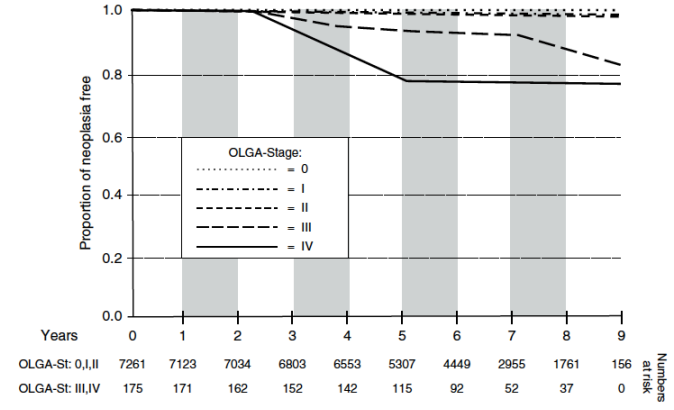
de Vries AC et al. Gastroenterology 2008

Erasmus MC

Progression to dysplasia and cancer in particular occurs in patients with OLGA stage III / IV



Rugge M et al. Gut 2019



Rugge M et al. AJG 2018

Erasmus MC

Barrett's esophagus: progression to esophageal adenocarcinoma (EAC) in nationwide population-based studies

	N	Pat years follow-up	EAC / 1000 pats / yr	95% CI
Netherlands	42.207	234.821	1.4	0.12-0.16
Ireland	8.522	59.784	1.6	0.10-0.16
Denmark	11.028	56.782	1.2	0.09-0.15

De Jonge PJ et al. Gut 2010, Bhat et al. JNCI 2011, Hvid-Jensen et al. NEJM 2011

- Irish Study: EAC incidence 2.7 / 1000 / yr in pts with IM, vs 0.7 in those without IM
- Danish Study: all histologically confirmed IM

Erasmus MC

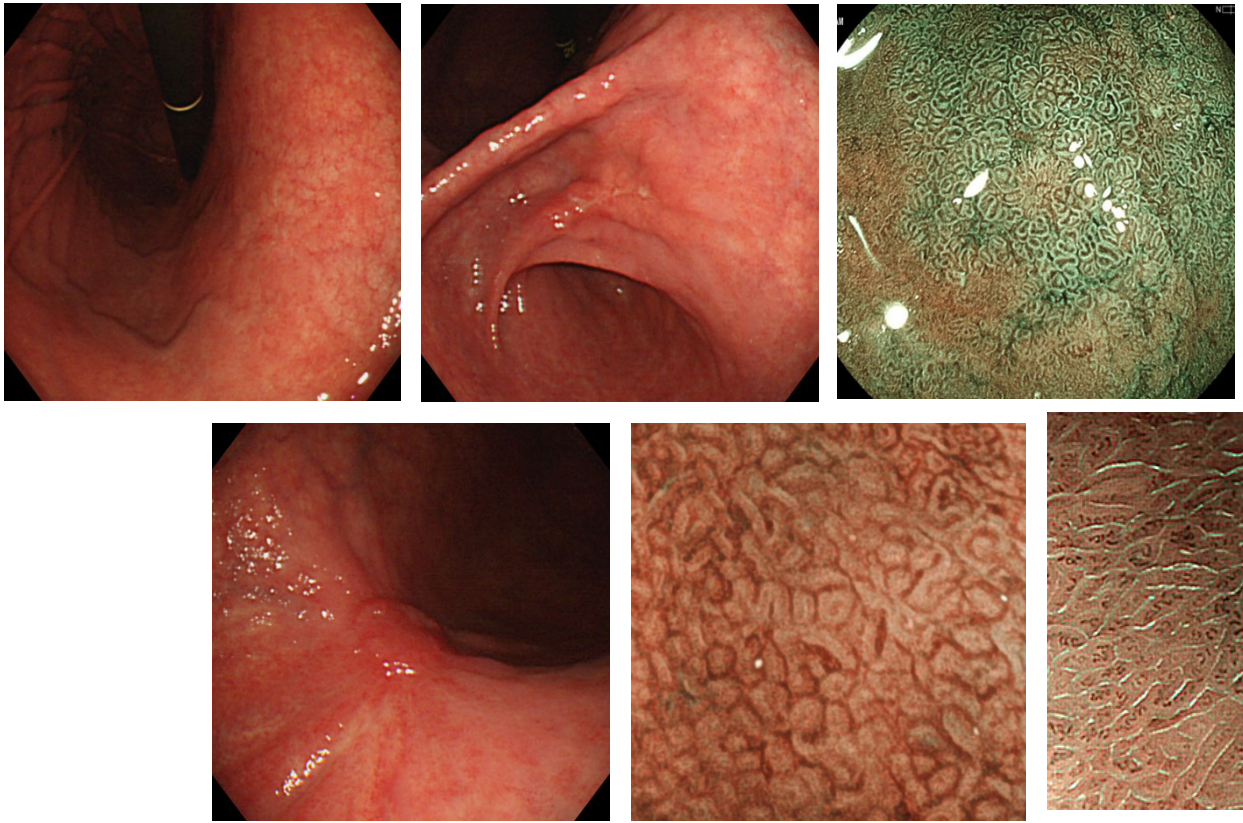
Impact of endoscopic screening on gastric cancer mortality in Korea

- Nested case-control study
  - i. Study period 2004 – 2012
  - ii. 54.418 gastric cancer cases and 217.672 controls
  - iii. OR for gastric cancer death 0.53 (0.51 – 0.56) with endoscopic screening
  - iv. OR ranging from 0.60 to 0.19 with 1- to 3- or more screening procedures
  - v. Effect noted in all age groups
  - vi. Effect most pronounced with screening intervals between 12 – 36 months

Erasmus MC

Jun JK et al. Gastroenterology 2017; 152: 1319-28

Enhanced imaging



Guideline recommendations for surveillance of patients with gastric intestinal metaplasia (IM)

Guideline	Surveillance	Patient category	Interval	Evidence	Strength
Asia-Pacific[1]	Yes	More extensive & severe	not specified	not graded	strong
Thailand[2]	Yes	Affecting both A + C	3 yrs	IIC	not graded
Taiwan[3]	Yes	Advanced OLGIM	1 - 3 yrs	IIB	strong
ESGE[4]	Yes	OLGIM III / IV	3 yrs	low	strong
BSG[5]	Yes	Affecting both A + C	3 yrs	low	strong
AGA[6]	No	-	3 – 5 yrs	very low	conditional

[1] Sugano K et al. Gut 2015
[2] Mahachai V et al. Asian Pac J Ca Prev 2016
[3] Sheu BS et al. Helicobacter 2017
[4] Pimentel-Nunes P et al. Endoscopy 2019
[5] Banks M et al. Gut 2019
[6] Gupta S et al. AGA online, Gastroenterology, Feb 2020

Erasmus MC

AGA guideline for management of gastric IM

- In patients with gastric IM, the AGA recommends test and treat for *H. pylori*

- In patients with gastric IM, the AGA recommends against *routine* use of endoscopic surveillance
    i. Patients may reasonably select to enroll in surveillance if they put:
        - a high value on potential reduction in gastric cancer
        - and a low value on potential risks of repeat surveillance

    ii. Risk assessment should be personalized. Higher risk includes incomplete IM, family history of gastric cancer, and extensive IM affecting antrum and corpus

Gupta S et al. AGA online, May 2019

Erasmus MC

AGA guideline for management of gastric IM

- Patients could reasonably choose short-interval repeat endoscopy:
    - To determine the anatomic extent of IM
    - To establish histologic IM subtype
    - To exclude prevalent cancer
    - If they have concerns about the quality of the baseline endoscopy
    - If they have an overall high risk of gastric cancer based on ancestry
    - If they have visually detected abnormalities

Gupta S et al. AGA online, May 2019

Erasmus MC

Differential recommendations to individual patients with preneoplastic lesions of the GI tract

i. 50-year old male with 3 cm non-dysplastic BE segment

i. 50-year old female with 2 small non-dysplastic colorectal adenomas

ii. 40-year old female with 10-year history of now quiescent colitis

- Reassurance to all three:
  - individual cancer risk low (<1 in 500 pts / yr)
  - Use high-resolution equipment, trained to detect lesions, spend much time on quality assurance, and follow guidelines

- Recommendation to all three: Surveillance

Erasmus MC

Differential recommendations to individual patients with preneoplastic lesions of the GI tract

iv. 50-year old male who underwent routine upper GI endoscopy with gastric biopsy sampling for dyspepsia. Histology shows no signs of *H. pylori,* but extensive IM in both antrum and corpus

- Reassurance:
  - We saw no macroscopic lesions
  - No need for intervention or surveillance

- But:
  - Equipment not used to its full potential
  - Biopsies random instead of targeted
  - Cancer risk likely higher than previous three patients
  - Outcome of cancer worse than for colorectal cancer

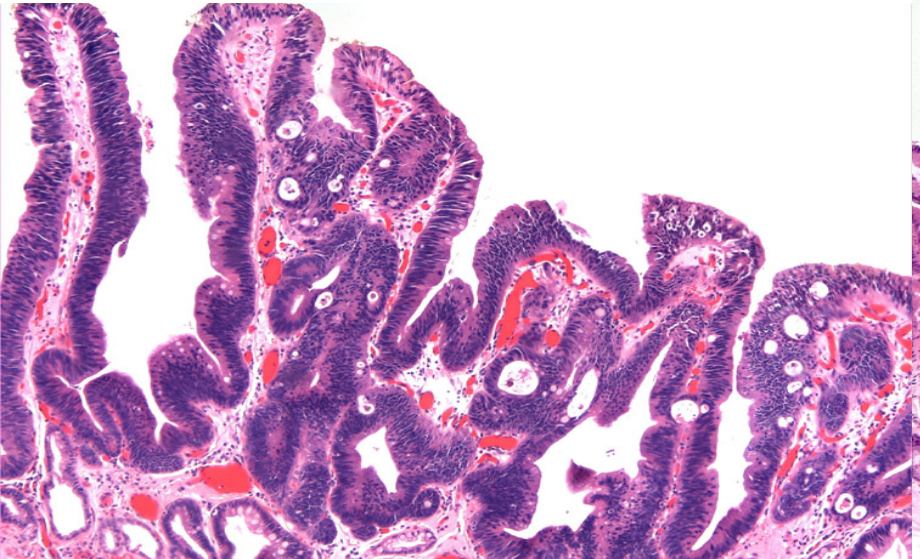
Erasmus MC

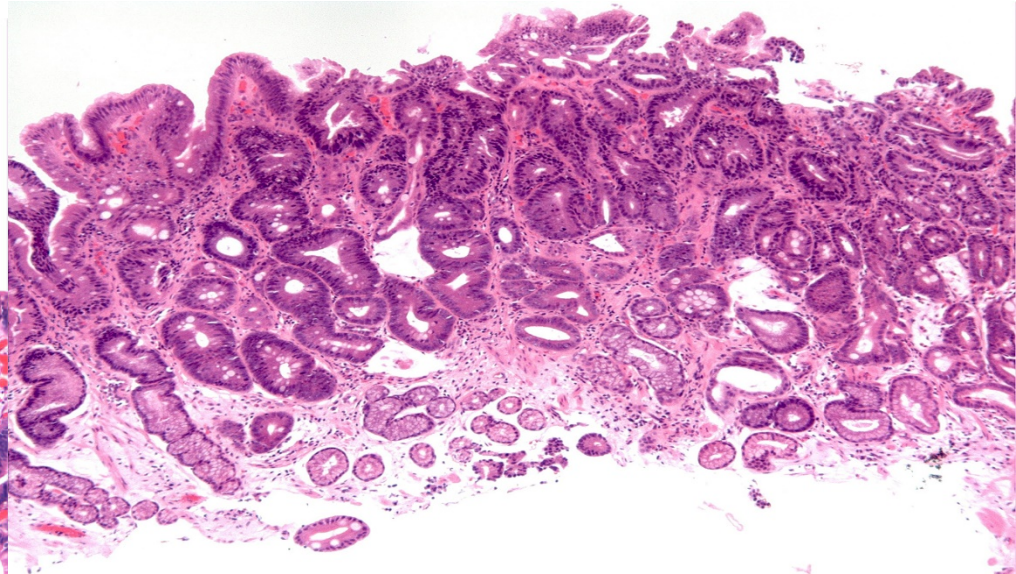
Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

Case continues:

- After 5 years of follow-up, foci of low grade dysplasia (LGD) are noted in the background of intestinal metaplasia
- What is the next step?





Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week

Early neoplastic lesions of the stomach:

- After random biopsy diagnosis in cases with no visible lesion, high definition endoscopy with chromoendoscopy
- If no lesion detected, perform biopsies for staging IM/atrophy if not already done
- Surveillance at 12 months for LGD, 6 months for High grade dysplasia (HGD) (Pimentel-Nunes P et al, Endoscopy 2019, European recommendations)
  - HGD – consider discussion with surgeon?
- Visible lesions: Endoscopic mucosal resections or endoscopic submucosal resections, depending on size/site of lesions

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week

- Gastric dysplasia suffers from the same issues of interobserver variability as seen in Barrett's associated dysplasia, particularly since there is often background inflammation (Kushima R and Kim KM, J Gastric Cancer 2011)
  - Kappa values for agreement range from 37-80% for gastric lesions (Schlemper RJ et al, J Gastroenterol 2001)
- In Barrett's esophagus, if 2 or more pathologists agree on LGD, it has a significantly higher risk of progression (Moole H et al, World J Gastroenterol 2016)
  - Currently no similar guidelines for gastric dysplasia.
- No useful biomarkers or molecular testing to aid in differentiating reactive from neoplastic changes.

Gastric Intestinal Metaplasia and Early Gastric Cancer

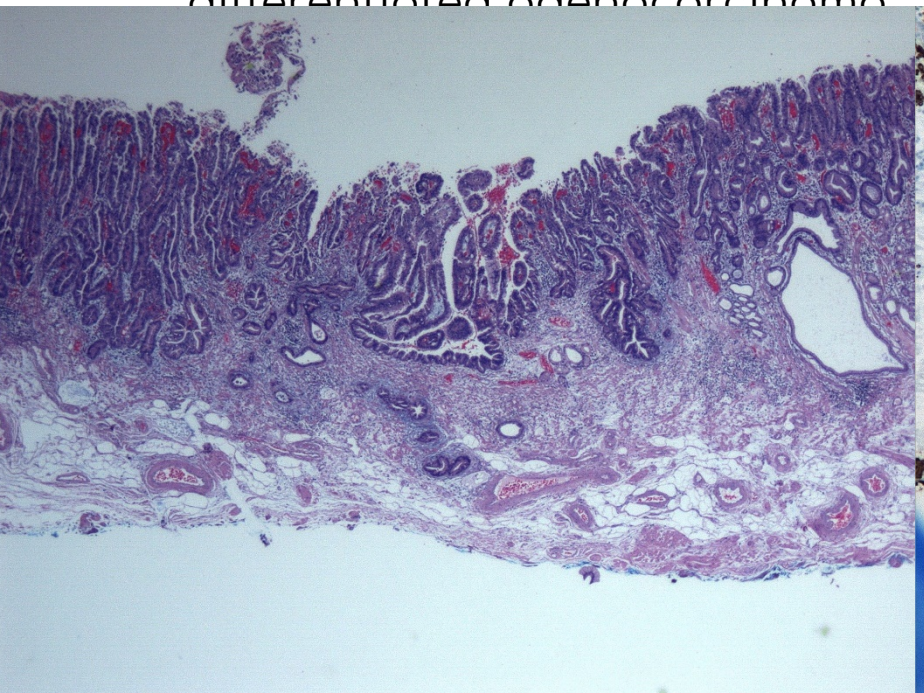
SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

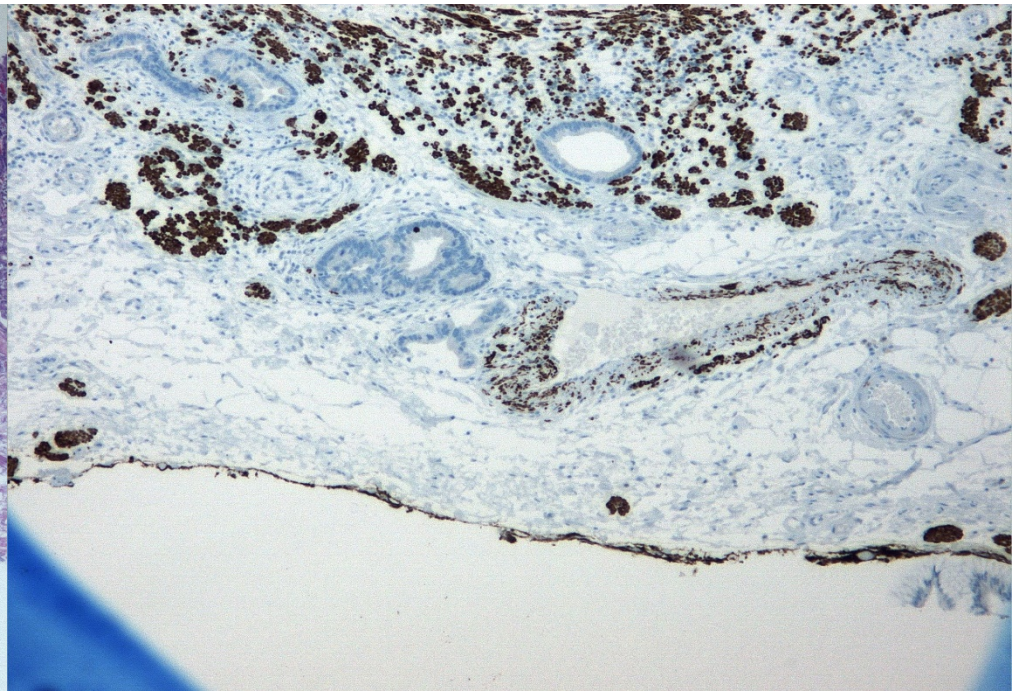
- Question: If the lesions are completely excised, is the patient still at risk of developing cancer?
- Consider the mucosal changes as a 'field effect'; the presence of any grade of dysplasia is linked to an increased risk of synchronous and metachronous adenocarcinoma (Moon HS et al, World J. Gastroenterol 2017)
- Risk of progression to carcinoma for unexcised LGD - up to 23% progress to malignancy over 10-48 months, compared to HGD with a risk of 60-85% over 4-48 months (Sung JK, Jorean J Intern Med 2016)
- Ongoing surveillance is necessary

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- Case where there was progression to High grade dysplasia was found on biopsies: ESD – intramucosal and focally submucosally invasive well differentiated adenocarcinoma





Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives MC | CDDW Canadian Digestive Diseases Week™

- What are the clinical indications for mucosa resection therapies vs surgical modalities?
- What findings on histology of EMRs/ESDs are considered high risk?

- Generally, if endoscopic/ultrasound evaluation of gastric neoplastic lesions indicates dysplasia/early adenocarcinoma, EMR/ESD should be attempted
- Lesions with high risk pathology (ie, poorly differentiated/diffuse subtypes) – may consider going straight to surgery

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives^MC | CDDW Canadian Digestive Diseases Week™

- In mucosal resections where only intramucosal adenocarcinoma (pT1a) is present, the major risk factors will be tumour size, completeness of resection, tumour histologic type/grade and lymphatic/vascular space invasion.
- Submucosal invasion can have a risk of lymph node metastasis up to 15%

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week

- One way to stratify risk – eCura system
  - 1 point each for:
    - tumor size >30 mm,
    - positive vertical margin,
    - venous invasion,
    - SM2 (depth submucosal invasion ≥500 µm
  - 3 points for lymphatic invasion
  - Total risk score: low risk (0–1 point), intermediate risk (2–4 points) or high risk (5–7 points)
  - Hatta W et al, Am J Gastroenterol 2017

Conclusions

- Pre-neoplastic lesions of the stomach remain common in certain populations
- Patients with advanced lesions (extensive IM, dysplasia) are at notable risk for progression to cancer
- The miss rate of these lesions is higher than accepted for lower GI endoscopy
- Training and awareness can increase detection
- Surveillance can reduce mortality
- Advanced lesions require treatment; EMR/ESD for early carcinomas
- Awareness of factors in early carcinomas that should lead to surgery is needed.

Erasmus MC

Gastric Intestinal Metaplasia and Early Gastric Cancer

SCMD Semaine canadienne des maladies digestives | CDDW Canadian Digestive Diseases Week™

- Questions?

Erasmus MC