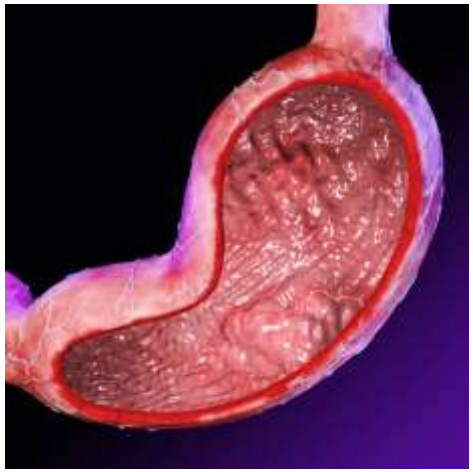
Gastric Adenocarcinoma

Bible Class

Ioannis Kapoglou

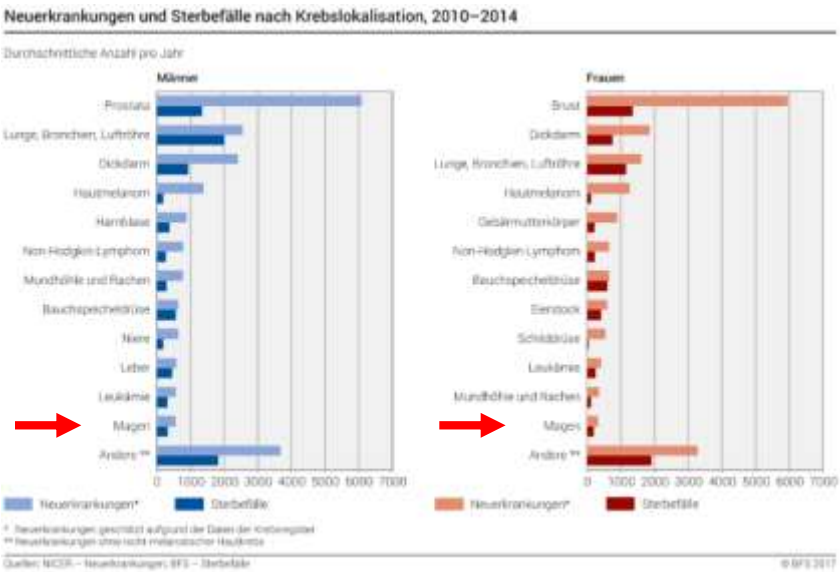
Giuglio Roncolato

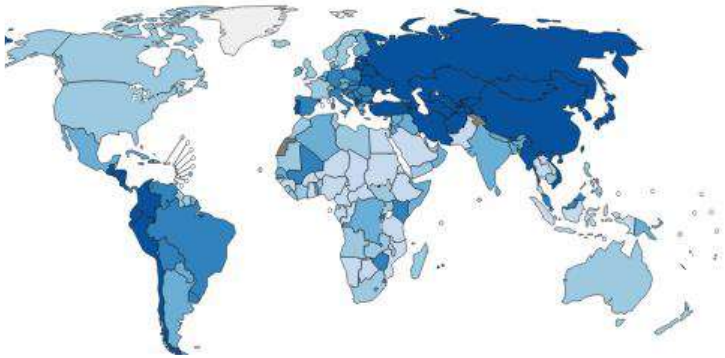


Epidemiology

- 700 new cases per year
- Constantly falling since 1986 : in Switzerland -6% due to the HP eradication for the intestinal type, augmetation of diffuse type

- Until 1980 most common cause of death by cancer.
- 5th most common cancer worldwide
- 3rd cause of mortality worldwide
- High incidence in Asia (China, Japan and Korea) eastern Europe, South America
- 5 year survival around 27%, 80% in early cancer





Bundesamt für Statistik 2017

Malvezzi M. Ann Oncol. 2016 Apr;27(4):725-31.

Köberle D. Schweiz Med Forum 2013;13(21):397–400.

Risc factors

- **Alimentary:** Alcohol, tabaco, high salt intake, nitrate
- **Infectious:** HP (Risk 2-3), EBV+ status
- **Ethnicity:** Asian>Black and Hispanic-Latino>White
- **Genetic:** Lynch syndrome, Peutz Jeghers, FAP, juvenile polyposis
- **Hereditary diffus castric carcinoma** (1%, germline mutation of CDH-1-Gen (E-Cadherin+) - life-time-risk 80%!)
- **Predisposing conditions:** partial gastrectomy >10 y, M. Ménétrier

Genetic testig in susceptible individuals

- APC/MUTHY assoc. Polyposis
- juvenile polyposis -SMAD4 or BMPR1A mutation
- Peutz-Jeghers - STK11/LKB1
- Cowden – PTEN
- Li-Fraumeni - TP53
- Gastric adennocarcinoma and Proximal polyposis of the stomach - exon 1B of APC gene

Box 1 Criteria for referring to genetic services

Suspected familial gastric cancer

- Gastric cancer in one family member before age 40.
- Or gastric cancer in two first-degree/second-degree relatives with one diagnosis before age 50*.
- Or gastric cancer in three first-degree/second-degree relatives independent of age*.

Suspected hereditary diffuse gastric cancer

- One case of diffuse gastric cancer before age 40.
- Or two cases of gastric cancer regardless of age in two first-degree/second-degree relatives, at least one confirmed diffuse gastric cancer*.
- Or personal and family history of diffuse gastric and lobular breast cancers, with one diagnosis before age 50.
- A personal or family history of cleft lip/palate in a patient with diffuse gastric cancer.
- In situ signet ring cells or pagetoid spread on gastric biopsies.

*In order to account for significant family history, the affected relatives need to be within the same side of the family (maternal or paternal).

Individuals who fulfil the family history criteria for suspected familial gastric cancer in the absence of an identified mutation could be considered for endoscopic surveillance (every 3y)

ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes
Syngal S et al. Am J Gastroenterol. 2015 Feb;110(2):223-62

Pathophysiology

Atrophic gastritis -> intestinal metaplasia ->epithelial dysplasia

Song et al. 2015:
Gastroscopy biopsy in Sweden
405'172 Patients, 1979 to 2011

- 1'599 developed gastric cancer

Initial:

- 1/256 normal
- 1/85 gastritis
- 1/50 atrophic gastritis
- 1/39 intestinal metaplasia
- 1/19 dysplasia

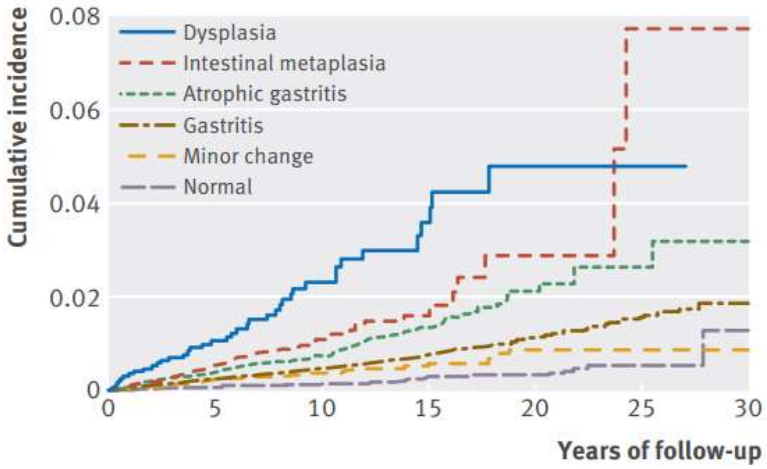


Table 3 The risk of cancer for patients with gastric atrophy and intestinal metaplasia

	5-Year incidence of gastric cancer (%)	Annual incidence (%)
All GA	1.9	0.1–0.5
Mild GA	0.7	
Severe GA	10	
All GIM		0.15–0.4 0.25
Antral GIM	5.3	
Antral and corpus GIM	9.8	
	Interval of 4–48 months	
Low-grade dysplasia	0–23	0.6
High-grade dysplasia	60–85	6

GA, gastric atrophy; GIM, gastric intestinal metaplasia.

Song H. BMJ. 2015 Jul 27;351:h3867.

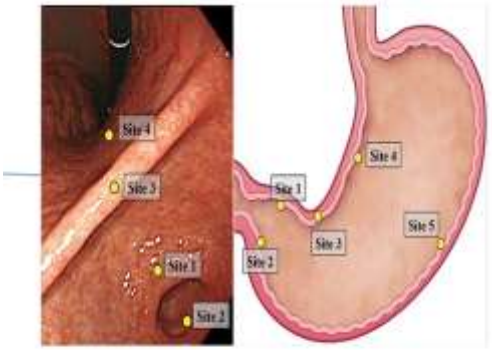
Intestinal metaplasia

- 14-25% of all Gastroscopy
- nearly a 100% of patients with intestinal-type gastric adenocarcinoma
- Only 2% in patients not infected with HP!

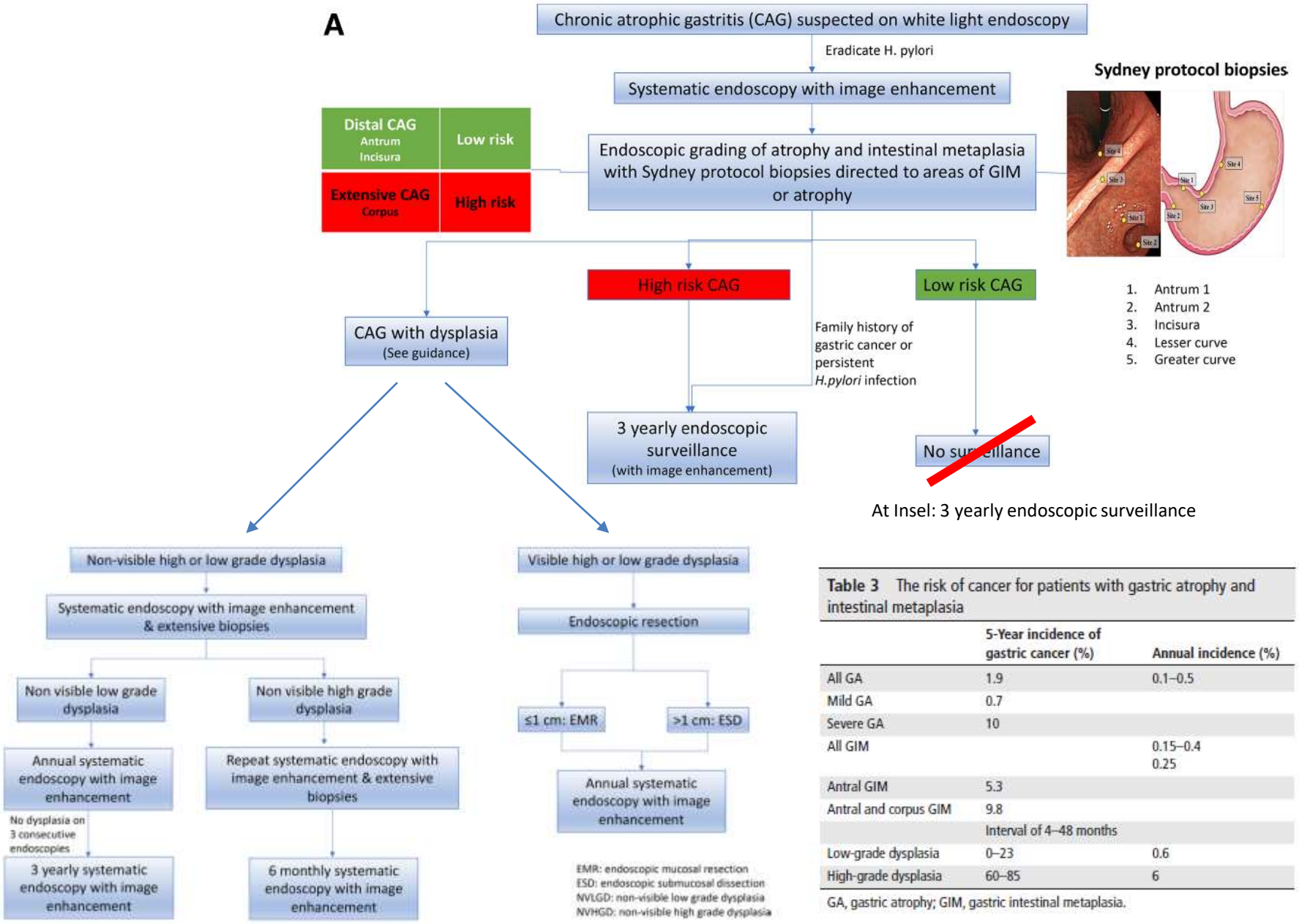
- Localisation
  - lesser curvatur and incisura, antrum

- Complete vs Incomplete = colonic
  - Immunhistochemical
  - Risk for low grade dysplasia higher in incomplete metaplasia (complete 8% vs.31% incomlete metaplasia)

Sydney protocol biopsies



1. Antrum 1
2. Antrum 2
3. Incisura
4. Lesser curve
5. Greater curve



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GA, gastric atrophy; GIM, gastric intestinal metaplasia.

What is the difference between HP pangastritis and predominant antral gastritis?

Which cell poduces acid in Stomach? Other important cells?

Cells of the stomach

Name	Region of stomach	Secretion	
Foveolar cells, Mucus neck cells			
Parietal (oxyntic) cells			
Chief (zymogenic) cells			
D-Cells			
G-Cells			
ECL-Cells			

Cells of the stomach

Name	Region of stomach	Secretion	
Foveolar cells, Mucus neck cells	Fundus, Corpus, Antrum	Mucus gel layer	Protection of mucosa
Parietal (oxyntic) cells			
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D-Cells	Fundus, Antrum	Somatostatin	Inhibition of acid
G-Cells			
ECL-Cells			

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ECL-Cells			

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ECL-Cells	Corpus	Histamin	Stimulation of acid

Helicobacter

Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 Pan-gastritis				
 Antral-predominant				

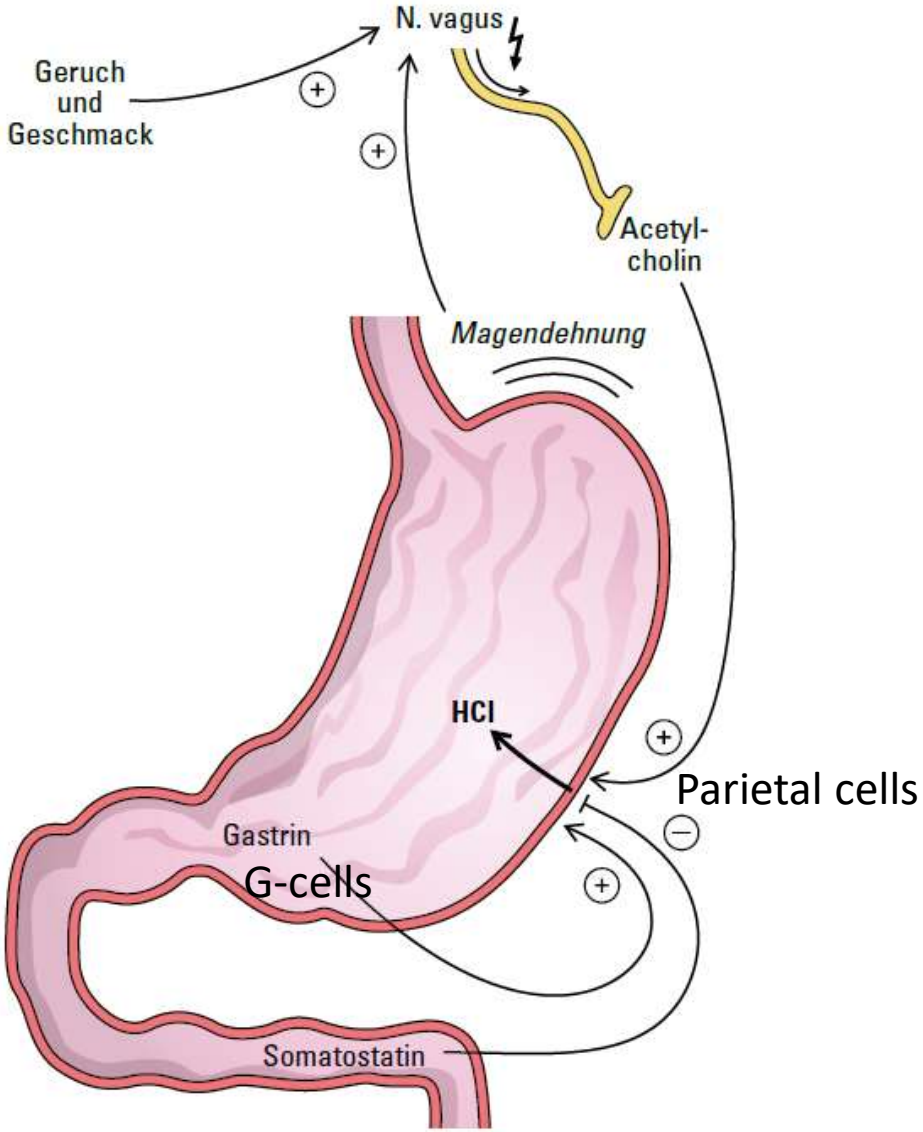


Abb. 20: Phasen der Magensäuresekretion

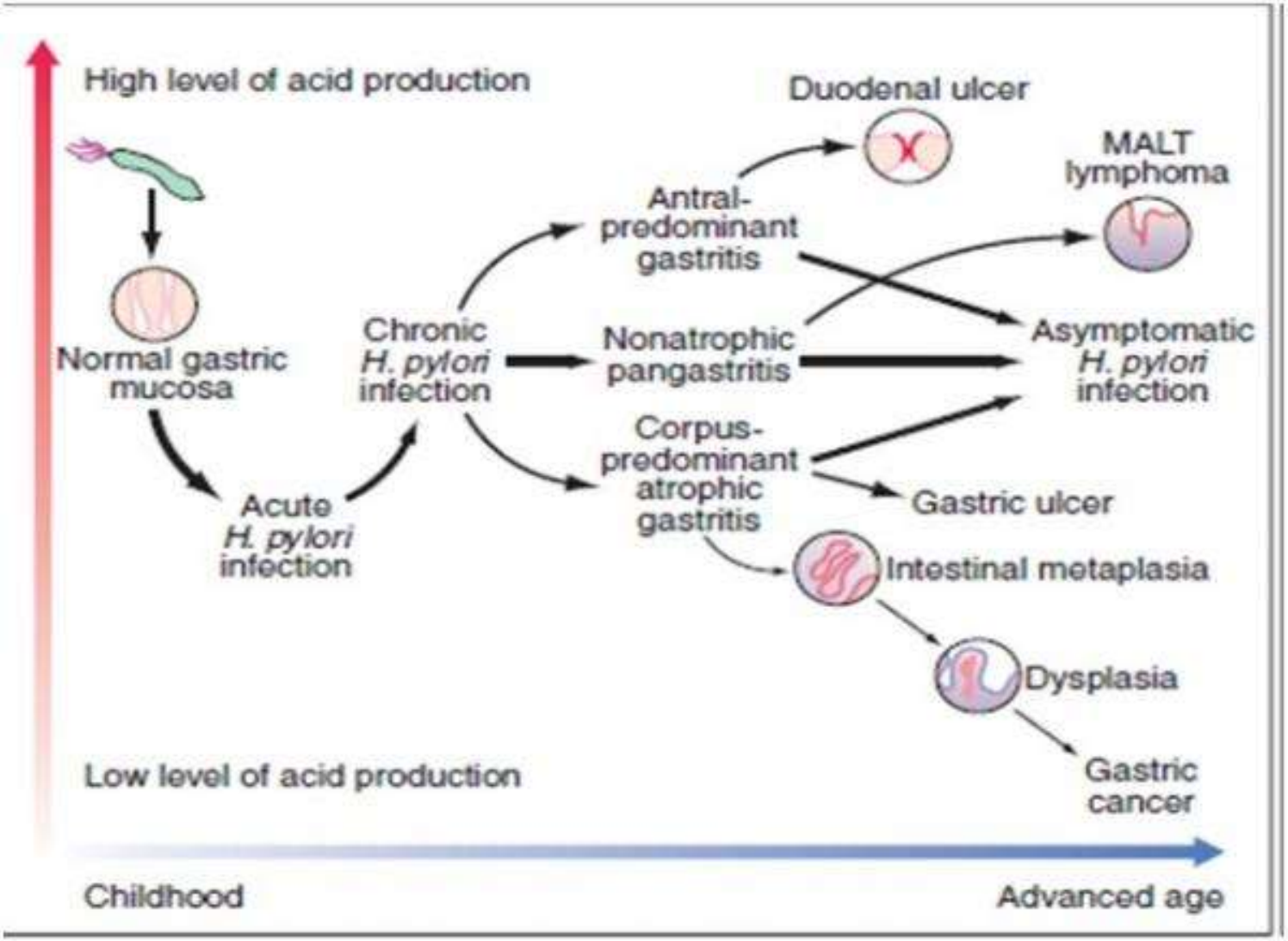
Helicobacter

Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 Pan-gastritis				
 Antral-predominant	• Chronic inflammation • Polymorph activity	• Gastric metaplasia • Active chronic inflammation	• Increased	• Duodenal ulcer

Helicobacter

Pattern of gastritis	*Gastric histology*	*Duodenal histology*	*Acid secretion*	*Clinical condition*
 Pan-gastritis	• Chronic inflammation • Atrophy • Intestinal metaplasia	• Normal	• Reduced	• Gastric ulcer • Gastric cancer
 Antral-predominant	• Chronic inflammation • Polymorph activity	• Gastric metaplasia • Active chronic inflammation	• Increased	• Duodenal ulcer

Natural history of HP-Infection

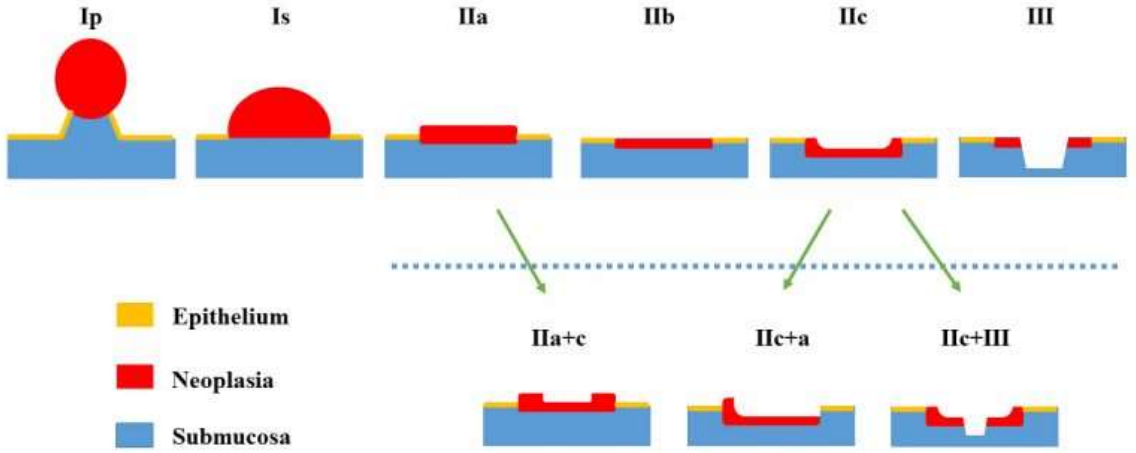


Diagnostic gastroscopy

Good Quality! Post endosopy cancer 11.3%!, at least 7min!

White light
Chromoendoscopy or virtual (NBI, FICE, i-scan)
Take 8-10 Biopsies

Paris Classification



The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon
Gastrointest Endosc. 2003 Dec;58(6 Suppl):S3-43. Review

Classification by location

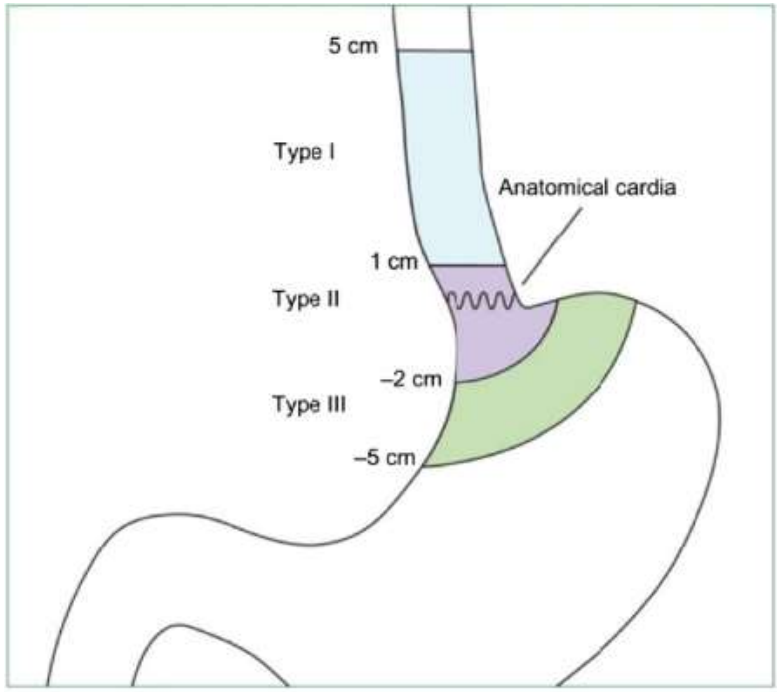


Fig. 1 The Siewert classification of GE junction adenocarcinomas.

Adenocarcinoma of esophagogastric junction = AEG

Siewert type I tumors are defined as adenocarcinomas of the distal esophagus with a center located within 1–5 cm above the anatomic EGJ

Siewert type II tumors are true carcinomas of the cardia with a tumor center within 1 cm above and 2 cm below the EGJ

Siewert type III tumors include subcardial carcinomas with centers between 2–5 cm below the EGJ.

Classification by Histology

WHO histological classification of gastric tumours

Epithelial tumours

Intraepithelial neoplasia – Adenoma

Carcinoma

- Adenocarcinoma
  - intestinal type
  - diffuse type

  >90%
- Papillary adenocarcinoma
- Tubular adenocarcinoma
- Mucinous adenocarcinoma
- Signet-ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Others

Carcinoid (well differentiated endocrine neoplasm)

Non-epithelial tumours

- Leiomyoma
- Schwannoma
- Granular cell tumour
- Glomus tumour
- Leiomyosarcoma
- GI stromal tumour
  - benign
  - uncertain malignant potential
  - malignant
- Kaposi sarcoma
- Others

Malignant lymphomas

- Marginal zone B-cell lymphoma of MALT-type
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Others

Secondary tumours

Lauren classification

	Intestinal	Diffuse
Morphology	**Glandular** structure	**Poorly cohesive**, or dispersed single cells
Frequent sites of metastasis	Liver	Ovary, Peritoneum
Other remarks	Associated with atrophic gastritis, intestinal metaplasia	Familial variant involving ***CDH1*** germline mutation
HER2	Higher	Lower

Staging

CT Thorax/Abdomen
- Sensitivity for metastasis around 70%!

PET/CT
- Low detection rate in diffuse and mucinous tumor types (low tracer accumulation)
- Indicated when metastatic cancer is not evident but suspected, occult distant metastasis, in the posttreatment assessment for restaging, detection of recurrency, detection of synchronous cancers

Explorative laparoscopy
- To rule out M+ carcinosis- with cytology
- Indicated for clinical stage T1b or higher (especially for diffuse type)
- In 13-57% detection of metastasis not seen in CT

What are the questions to be answered when doing a gastric EUS?

Staging preoperative distantM-
EUS+/- FNP

Question	Answer
Depth of invasion, N+?	Early gastric cancer carcinoma limited to the gastric mucosa and/or submucosa regardless of the lymph node status
Lateral extension of tumor what type of surgery?	Gastrectomy: Polar, total, 4/5
FNA for all suspect nontypical findings: **lymph node, ascites, perigastric lesions**	Locoregional disease

Lambert R et al. Superficial Neoplastic Lesions in the Digestive Tract
Endoscopy 2005; 37: 570±578

Staging EUS

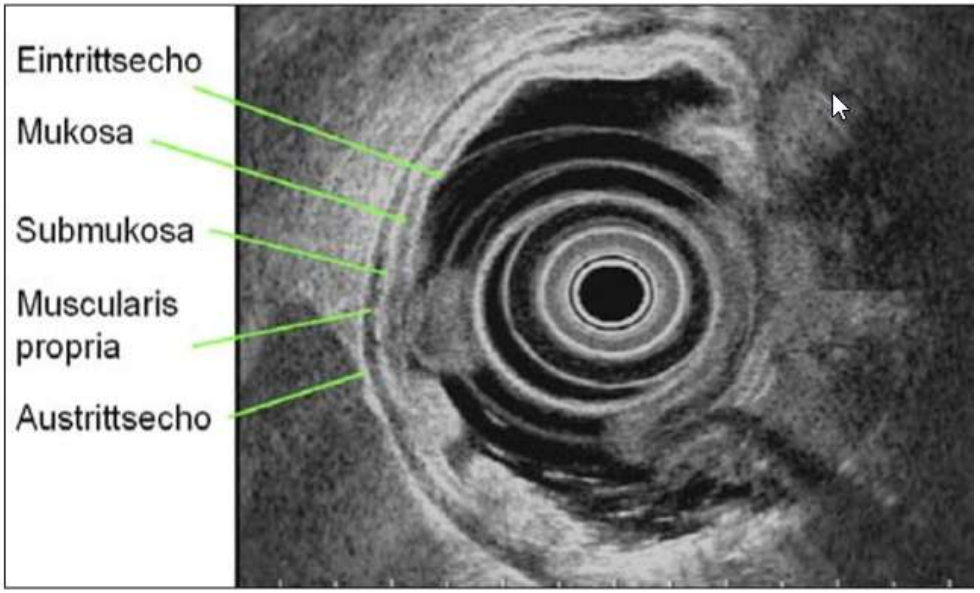
Operator depending
46-88% for T-Staging (often over-staged)
30-90% for N-staging
Detection of Ascites in 8% with normal CT

T1
Mucosa(T1a)
Submucosa (T1b)

T2 Muscularis propria

T3 Subserosa

T4 Perforation of the serosa,
T4a through the outer lining of th
T4b involving other organs



How is early gastric cancer defined?

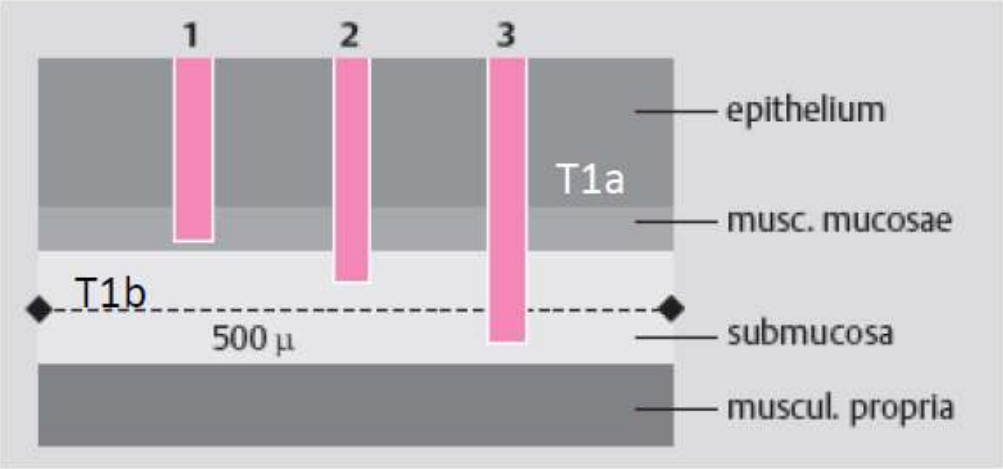


Table 17. Stomach—nodal invasion*

Size in mm	< 500 µ n/N (%)	> 500 µ n/N (%)
< 10	1/31 (3)	5/39 (13)
10-20	4/71 (6)	28/195 (14)
21-30	4/71 (6)	52/273 (19)
> 30	6/92 (7)	86/319 (27)
Total	15/265 (6)	171/826 (21)

Lambert R et al. Superficial Neoplastic Lesions in the Digestive Tract Endoscopy 2005; 37: 570±578

The histopathological features of early gastric adenocarcinoma associated with a higher risk of lymph node metastasis after endoscopic resection

1. Poorly differentiated submucosal cancer, irrespective of invasion depth below muscularis mucosae.

2. Signet ring cancer.

3. Lymphovascular invasion.

4. Depth of submucosal invasion ≥500 μm as measured in a straight line from the deepest fibre of the muscularis mucosae

When EMR/ESD/Surgery ?

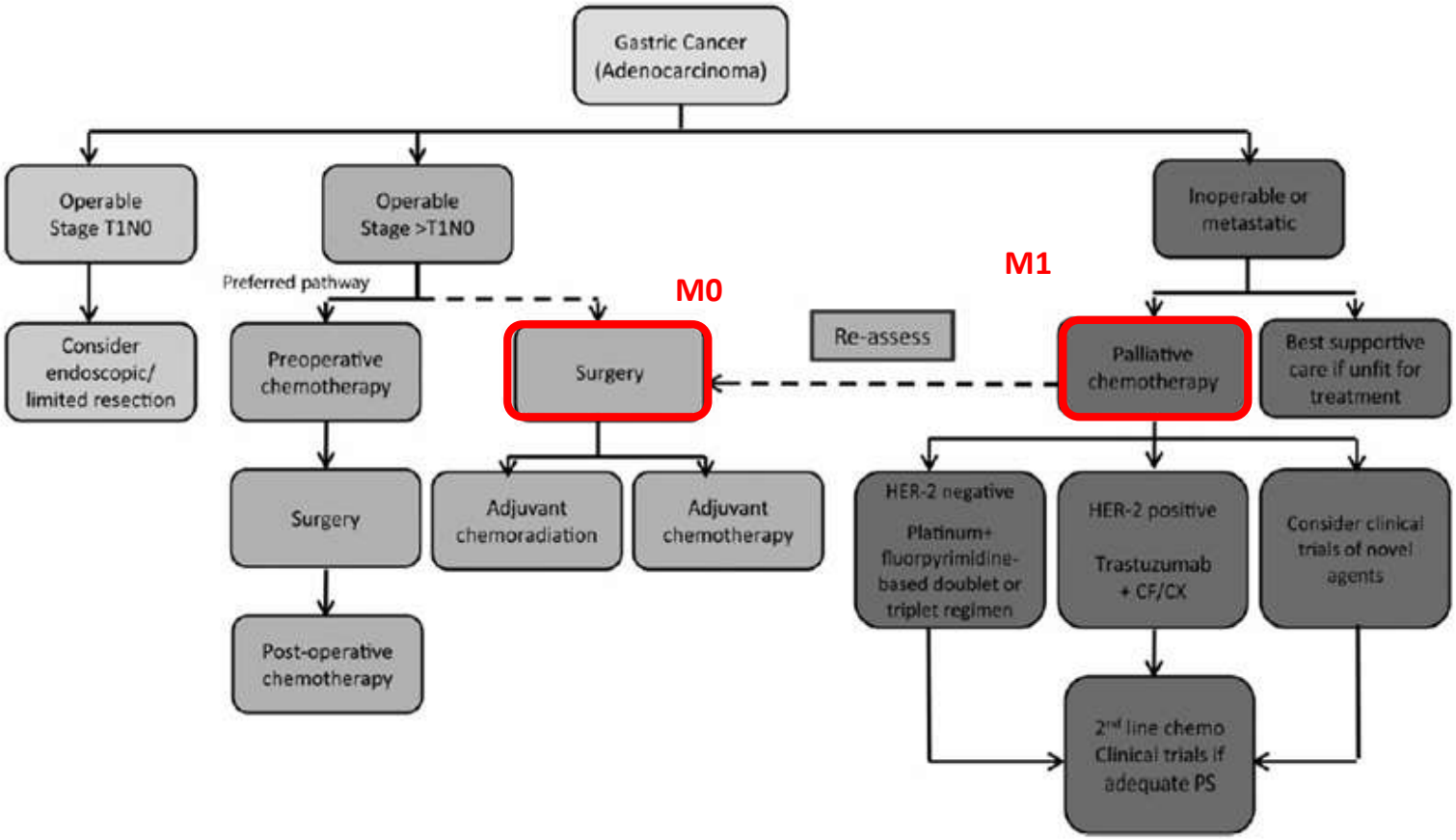
Criteria for curative endoscopic resection in early gastric cancer

	Mucosal cancer				Submucosal cancer	
	No ulcer		Ulcer present		Sm1 (<500 um)	Sm2 (>500 um)
Size (mm)	< 20	> 20	< 30	> 30	< 30	Any size
Differen-tiated cancer	EMR	ESD	ESD	Surgery	ESD	Surgery
Undiffe-rentiated cancer	Surgery considered	Surgery	Surgery	Surgery	Surgery	Surgery

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer-Digestive Endoscopy 2016; 28: 3–15

What are the indications of surgery alone?

- T1N0 not amenable to endoscopic therapy
- T1N0 incompletely resected by EMR/ESD

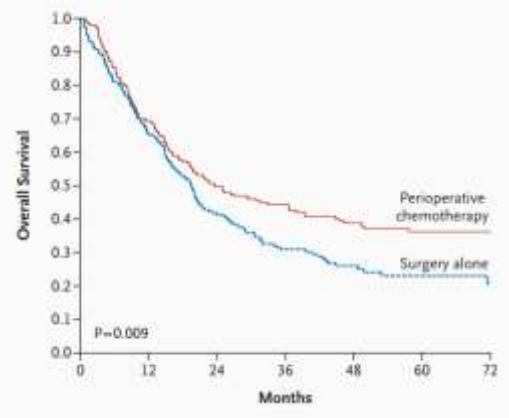


Waddell T. Ann Oncol. 2013 Oct;24 Suppl 6:vi57-63.

Chemotherapy

Perioperative – standard Cunningham et al, 2007

- Platinum/Fluoropyrimidine
- 5 year survival 36% with chemotherapy vs. 23%



Palliative - bei M1 (UICC IV) Wagner et al, 2017

- Chemotherapy +6.7 Months compared with best supportive care

Moehler M. Z Gastroenterol. 2011;49(4).

Cunningham D. N Engl J Med. 2006 Jul 6;355(1):11-20.

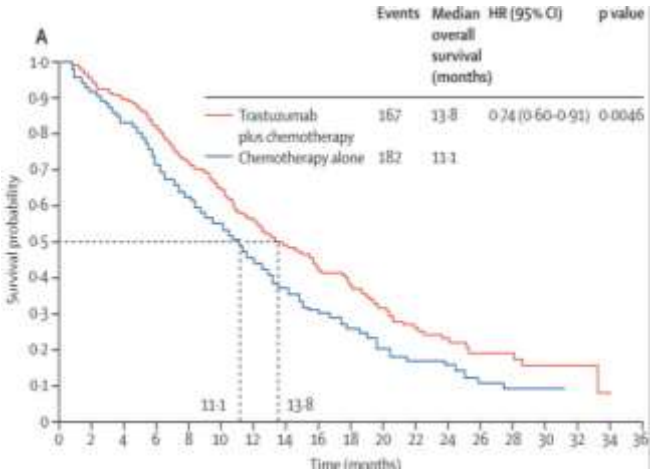
Wagner AD. Cochrane Database Syst Rev. 2017 Aug 29;8:CD004064

Targeted Therapy HER-2

22% of all castric cancers are HER2+
Trastuzumab (Herceptin®) licensed since 2010

- Median survival withTrastuzumab:
  - 13.8 Months vs. Chemotherapy alone 11.1 Months

- No more side effects



Bang et al, 2010:
ToGA-Trial (Trastuzumab for Gastric Cancer): RCT,
122 Zentren, 584 **inoperable** Patienten:
Chemotherapie vs Trastuzumab + Chemotherapie
(Capecitabine/5-FU + Cisplatin je 6x3Wo)

Prognosis after surgery alone

Over all stages 5-year survival 18% in UK

Pathological stage group	Patients (n)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Median survival
IA	10,606	99.00	96.30	93.60	Not reached
IB	2606	98.00	92.80	88.00	Not reached
IIA	2291	97.40	88.30	81.80	Not reached
IIB	2481	94.30	78.20	68.00	Not reached
IIIA	3044	89.00	64.40	54.20	Not reached
IIIB	2218	83.10	48.20	36.20	32.8 months
IIIC	1350	66.80	27.70	17.90	18.5 months

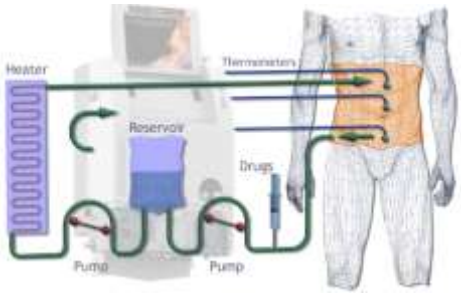
(A) Pathological stage (pTNM) and overall survival in gastric cancer patients who underwent surgical resection with adequate lymphadenectomy (D2) without prior chemotherapy or radiation therapy, stratified by pathological stage groupings, based on IGCA data (2000-2004; only patients with complete 5-year follow-up were included, n = 25,411).
(B) Pathological stage and 1-, 3-, and 5-year and median overall survivals in patients with gastric cancer who received curative surgery, stratified by pathological stage groupings, based on IGCA data.

AJCC: American Joint Committee on Cancer; IGCA: International Gastric Cancer Association.

Magenkarzinom – HIPEC

Hyperthermic IntraPEritoneal Chemotherapy

Palliative Option bei MagenCa mit Peritonealkarzinomatose:
-> Peritonektomie (sichtbare Metastasen), Peritoneallavage mit vorgewärmtem Chemotherapeutikum (Mitomycin C, Cisplatin, Fluorouracil…) in höher Dosierung.

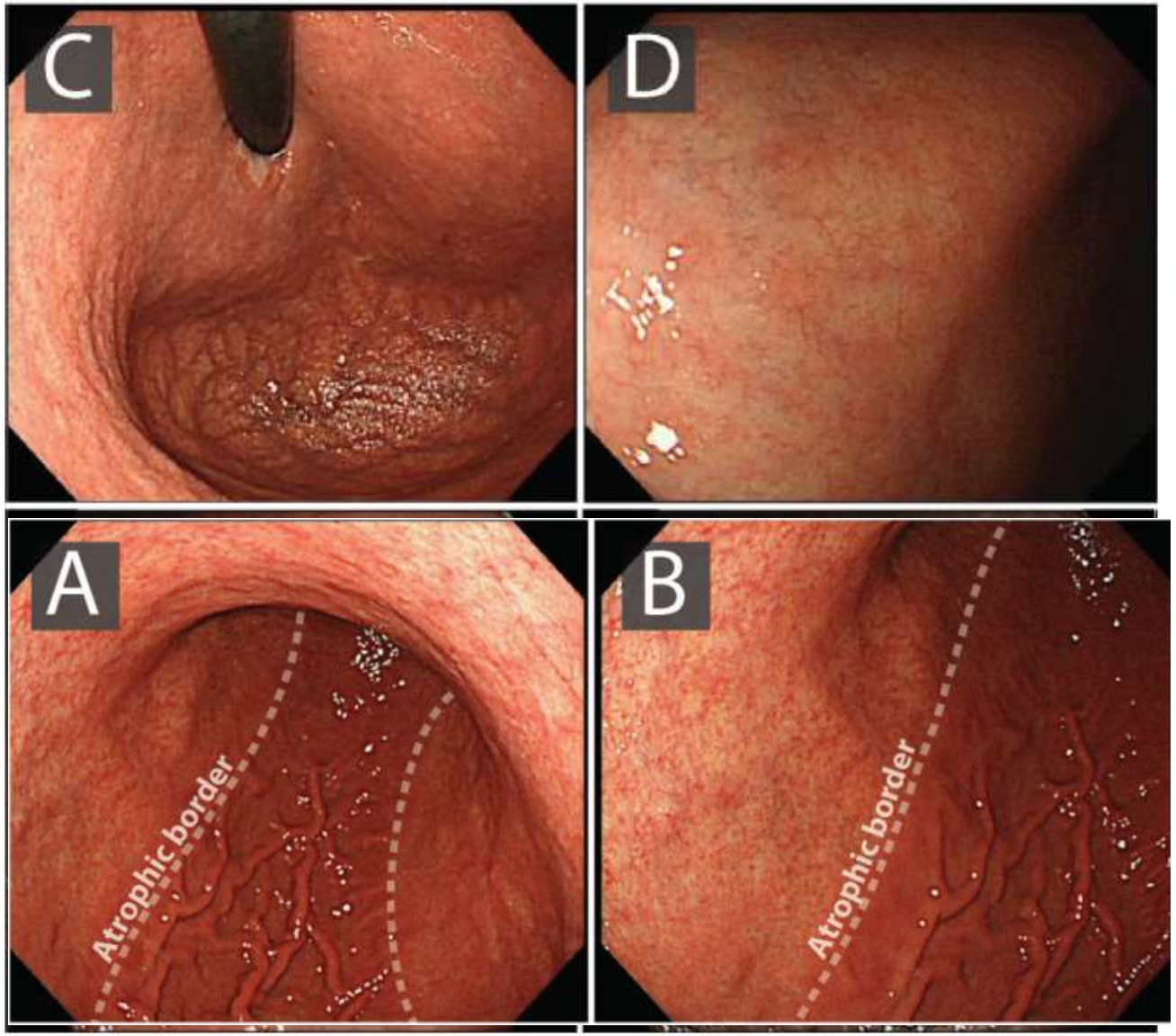


Desiderio et al, 2017:
Meta-Analyse, 11 RCTs, 21 Non-RCTs seit 1985, 2520 Patienten mit fortgeschrittenem MagenCa (T3-T4): **Gastrektomie + HIPEC vs. Gastrektomie**

- Insgesamt verlängertes Überleben von 4 Monaten mit HIPEC: 11.1 Monate vs 7.06 Monate
- Langzeit-Überleben nicht besser HIPEC vs. palliative Chemo

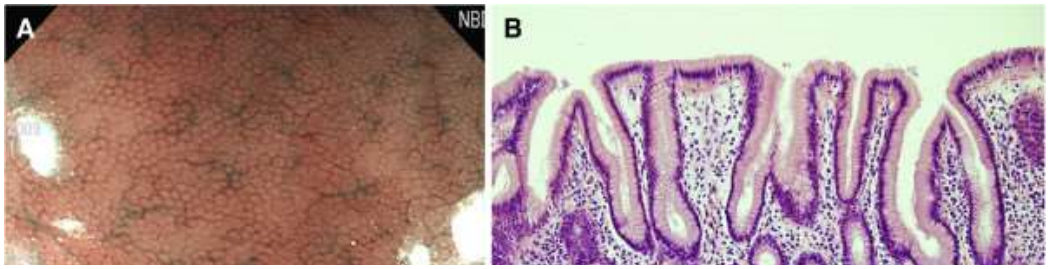
Moehler M. Z Gastroenterol. 2011;49(4).
Desiderio J. Eur J Cancer. 2017 Jul;79:1-14.

Quiz



Chronic atrophic gastritis

There are four principle endoscopic features of CAG: palor, loss of gastric folds, prominence of the vessels and the atrophic border.



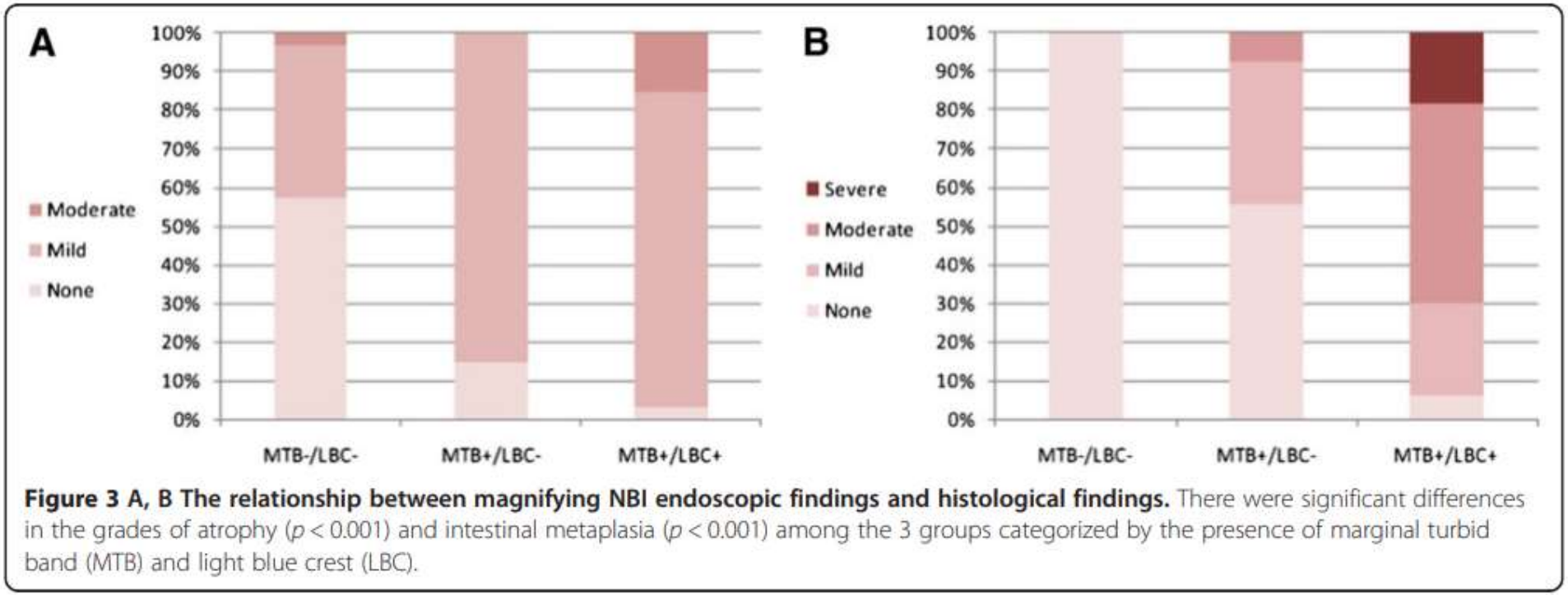
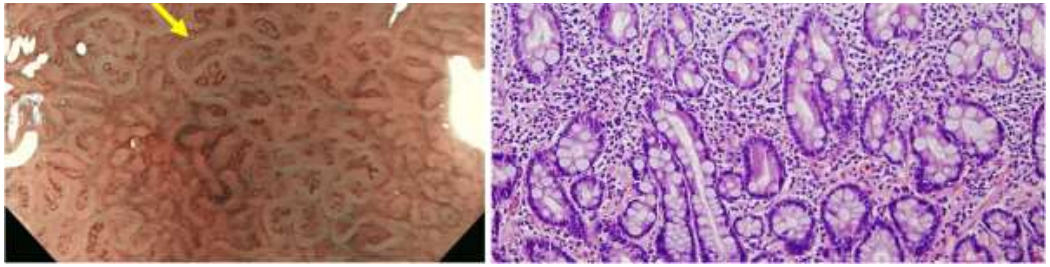
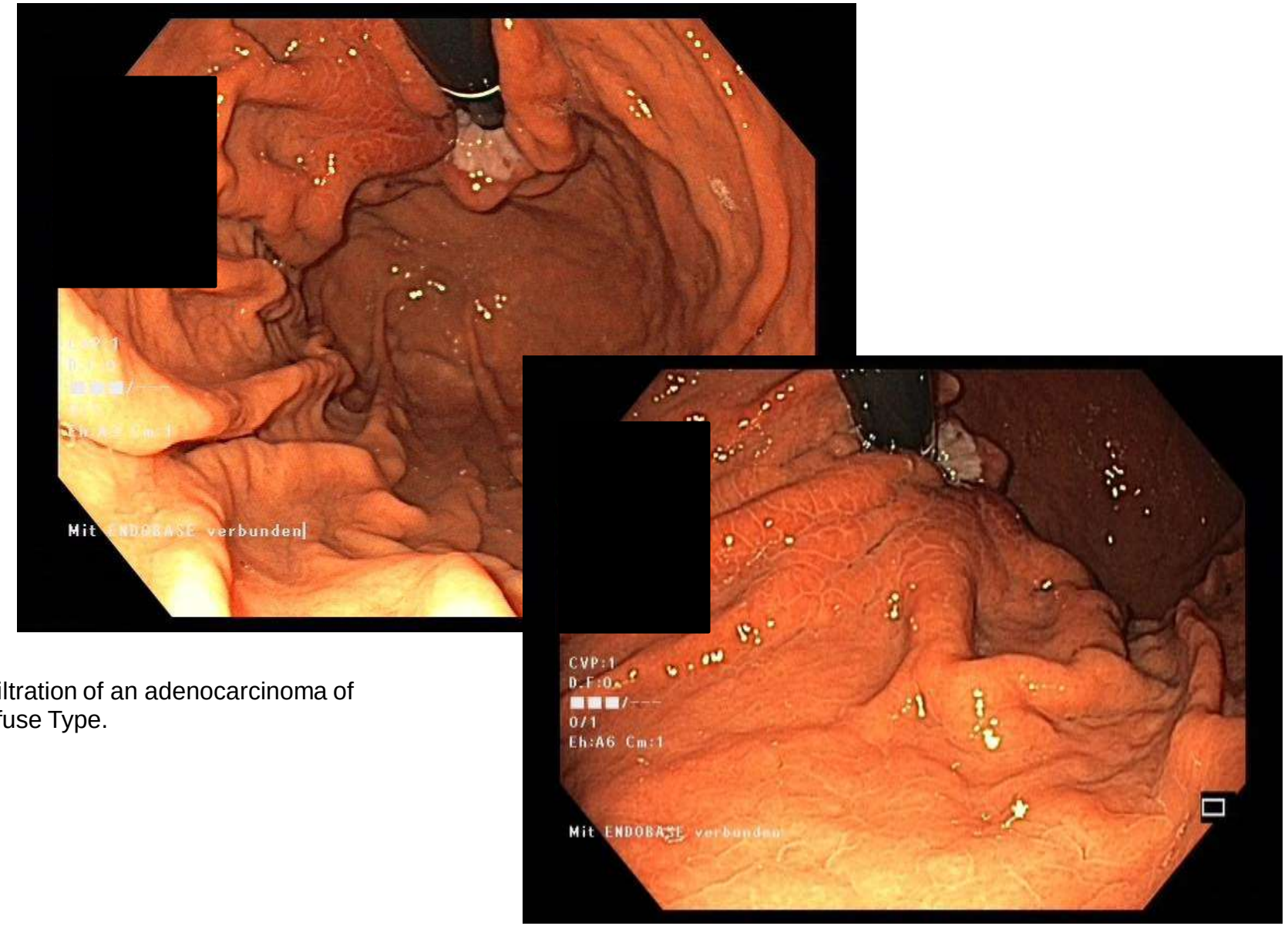


Figure 3 A, B The relationship between magnifying NBI endoscopic findings and histological findings. There were significant differences in the grades of atrophy ($p < 0.001$) and intestinal metaplasia ($p < 0.001$) among the 3 groups categorized by the presence of marginal turbid band (MTB) and light blue crest (LBC).

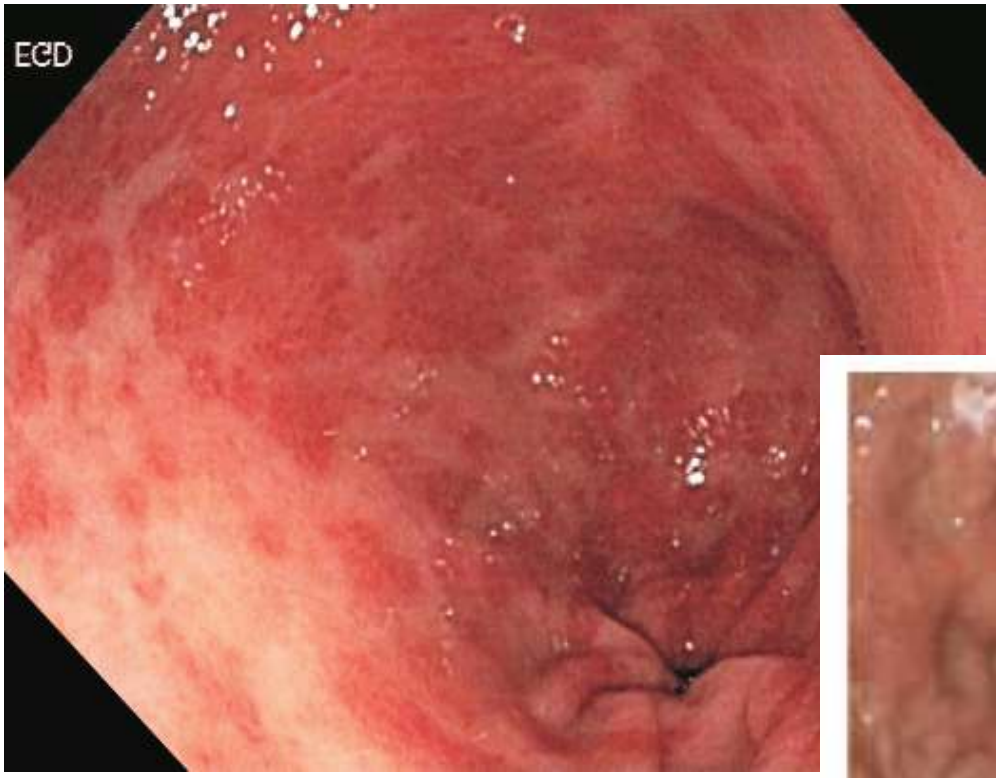


Schematic figure for marginal turbid band and light blue crest. The marginal turbid band is defined as an enclosing, white turbid band on the epithelial surface/gyri, and light blue crest is defined as a fine, blue-white line on the crest of the epithelial surface/gyri.

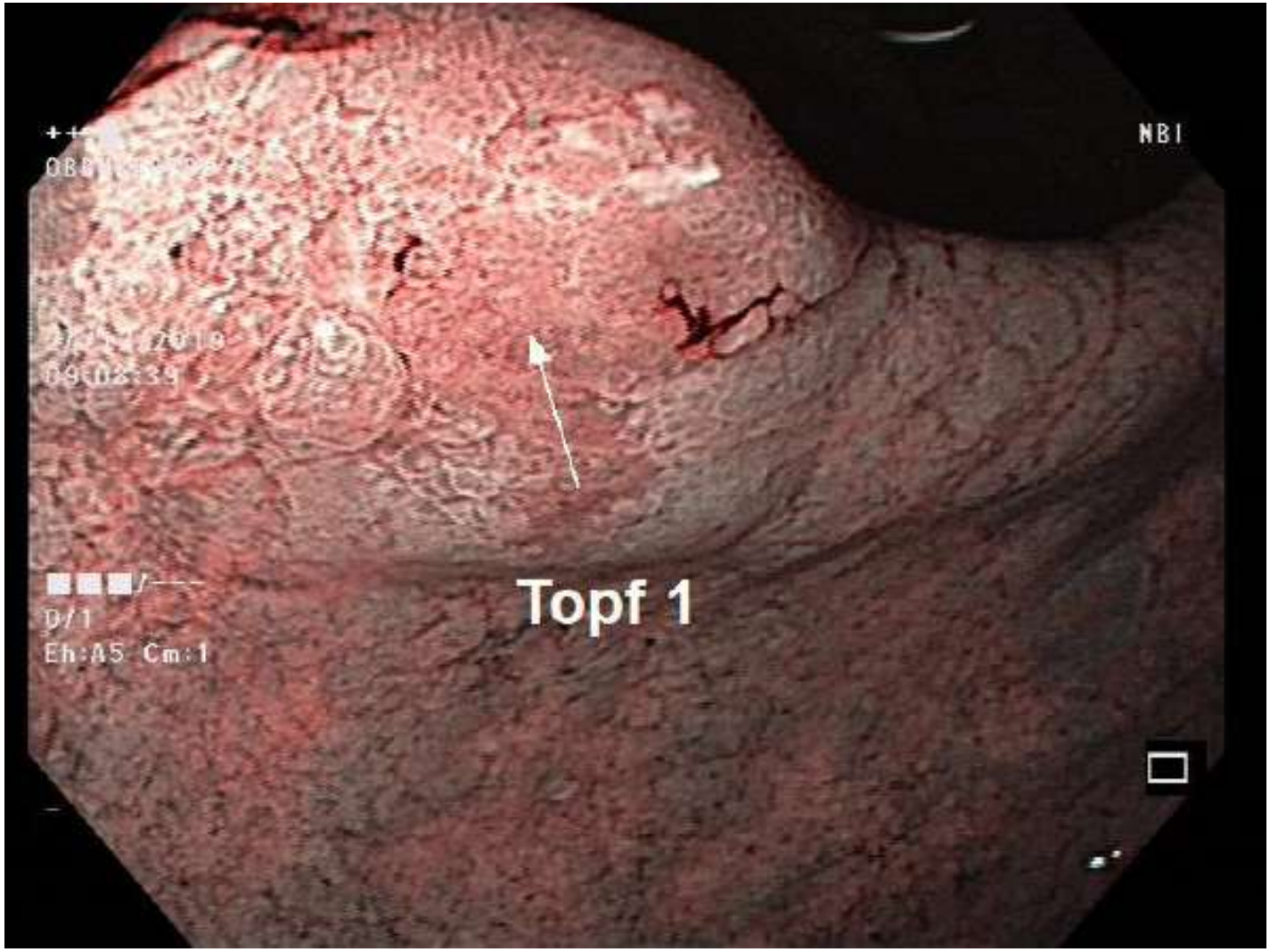
Portal hypertensive gastropathy



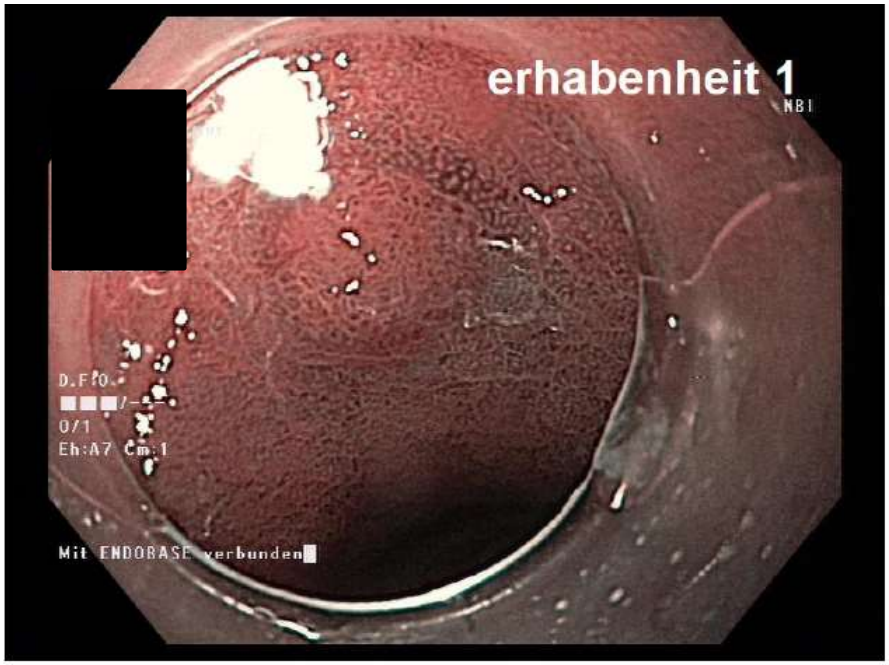
Infiltration of an adenocarcinoma of diffuse Type.

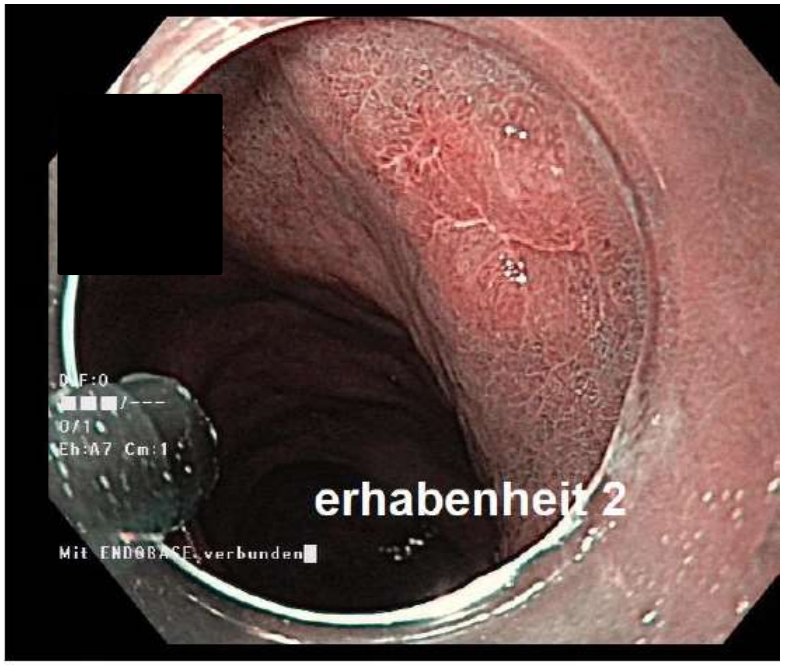


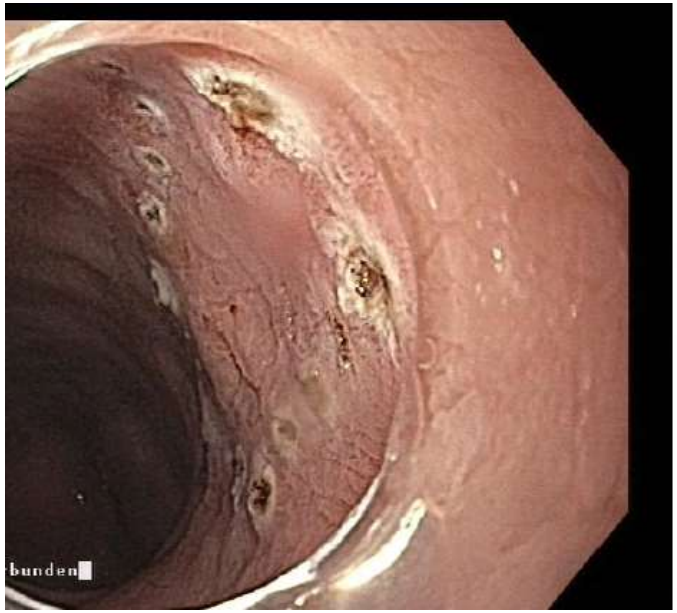
Linitis plastica
(type of adenocarcinoma) spreads to the muscles of the stomach wall and makes it thicker and more rigid.

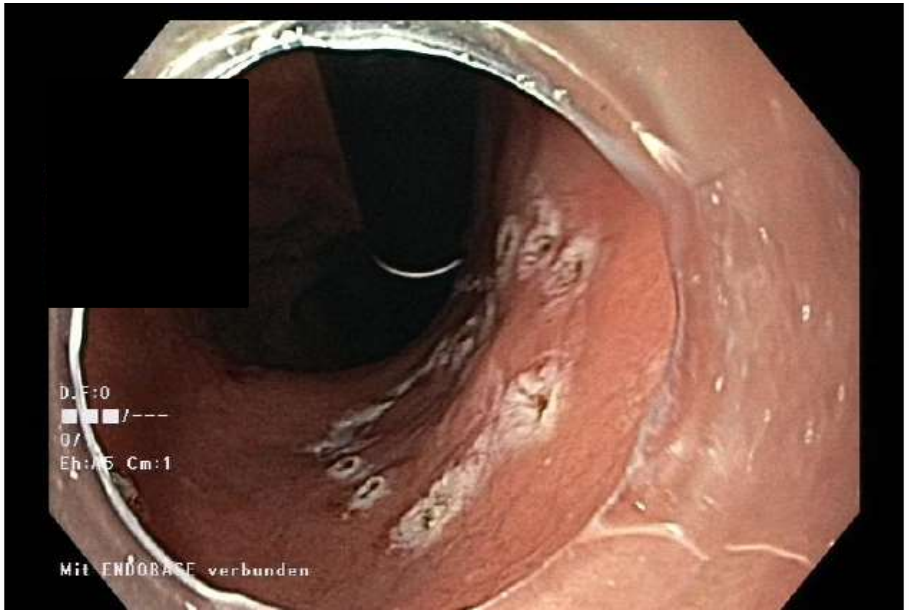


Adenocarcinoma









Adenocarcinoma

Thank you for your attention