XXV Congreso de la Sociedad Española de Anatomía Patológica y
División Española de la International Academy of Pathology

Avances en patología gástrica. Novedades de la clasificación WHO (2010)

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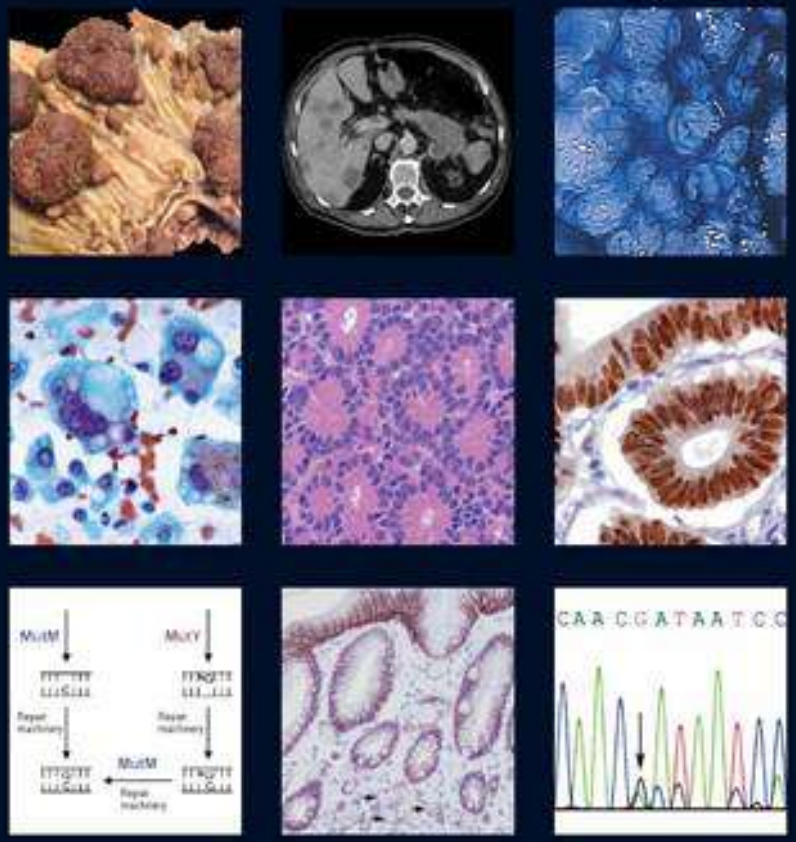
WHO Classification of Tumours of the Digestive System

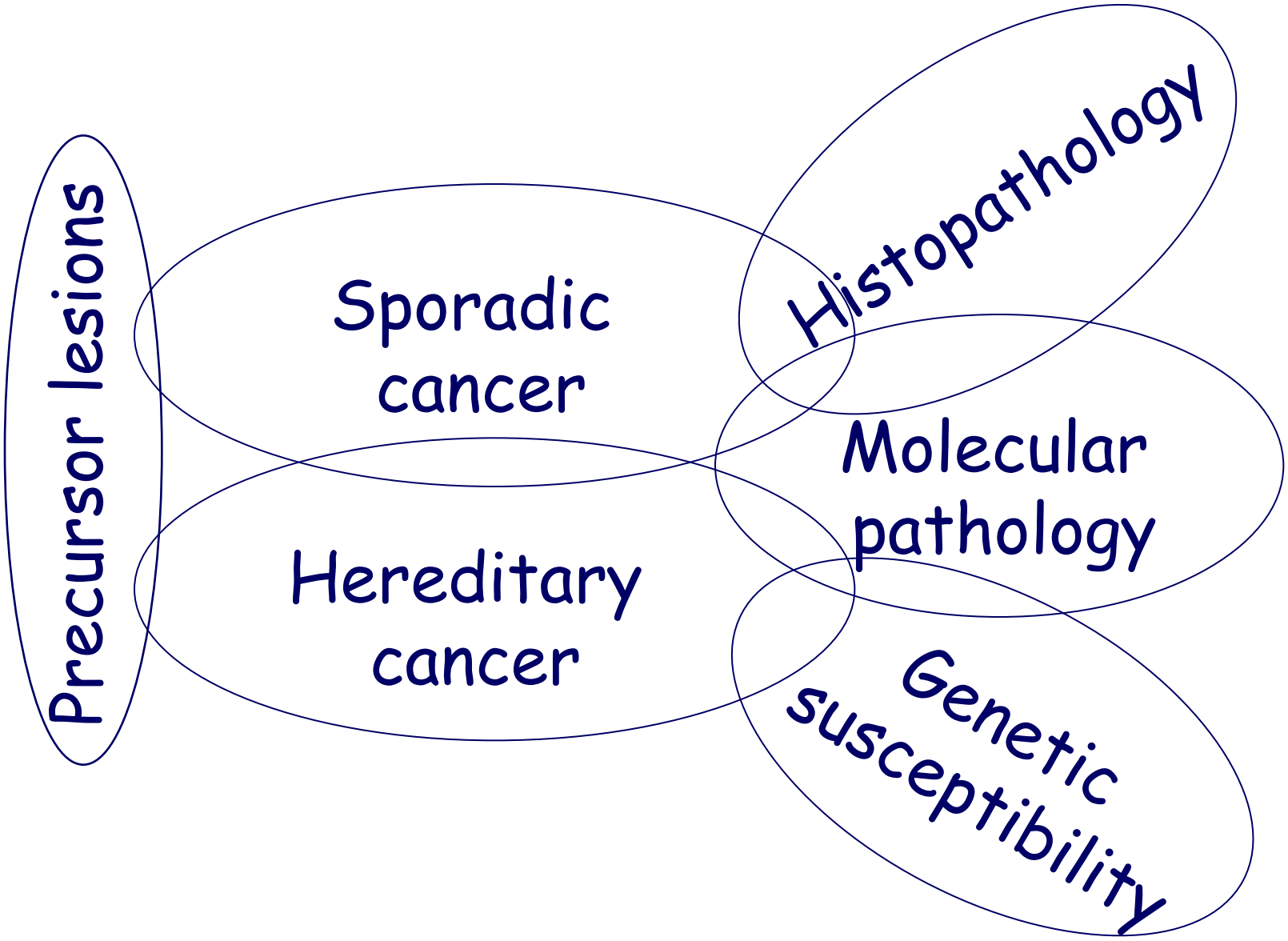
Edited by Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, Neil D. Theise



WHO

WHO Classification of Tumours of the Digestive System
Consensus and Editorial meeting
IARC, Lyon, 10-12 December 2009

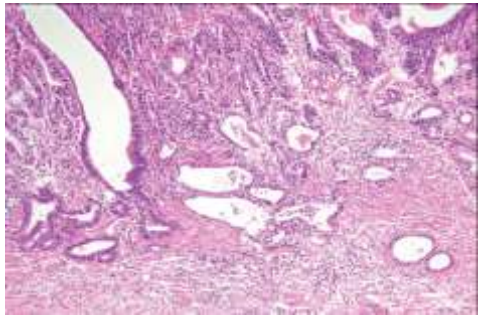
GASTRIC CANCER



Intraepithelial neoplasia *versus* Dysplasia

Recognizing that the terminology of dysplasia is entrenched in the European and particularly North-American literature, as well as in clinical practice, WHO considers that **"intraepithelial neoplasia" and "dysplasia" should be considered as synonymous terms**. The following categories should thus be considered:

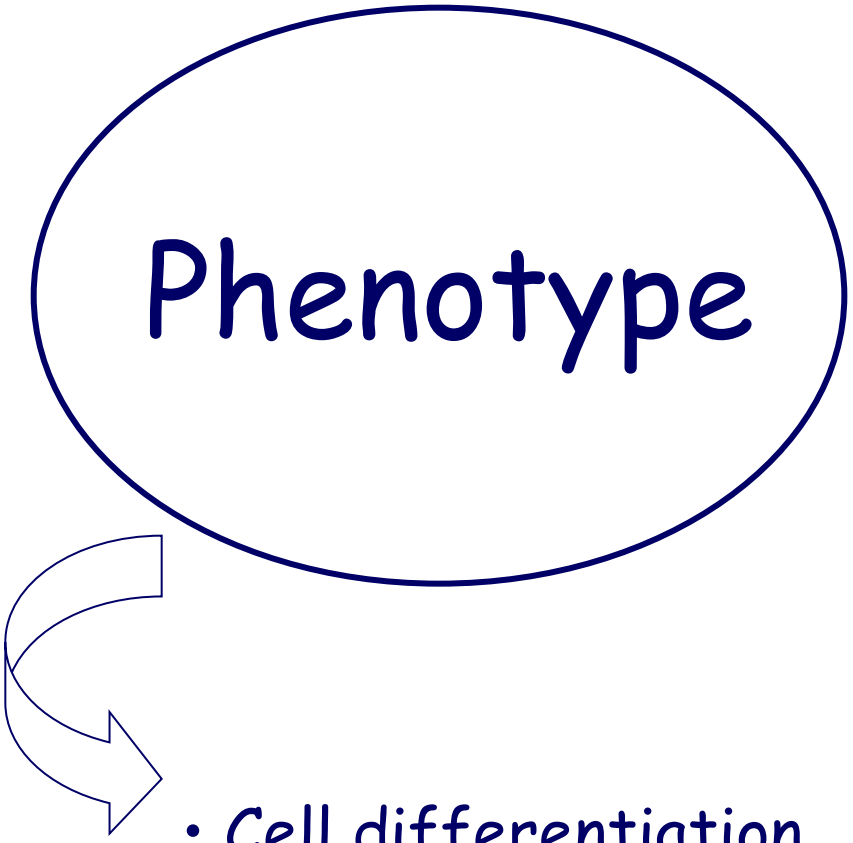
1. Negative for intraepithelial neoplasia /dysplasia*
2. Indefinite for intraepithelial neoplasia /dysplasia
3. Low -grade intraepithelial neoplasia/dysplasia
4. High-grade intraepithelial neoplasia/dysplasia
5. Intramucosal invasive neoplasia/intramucosal carcinoma



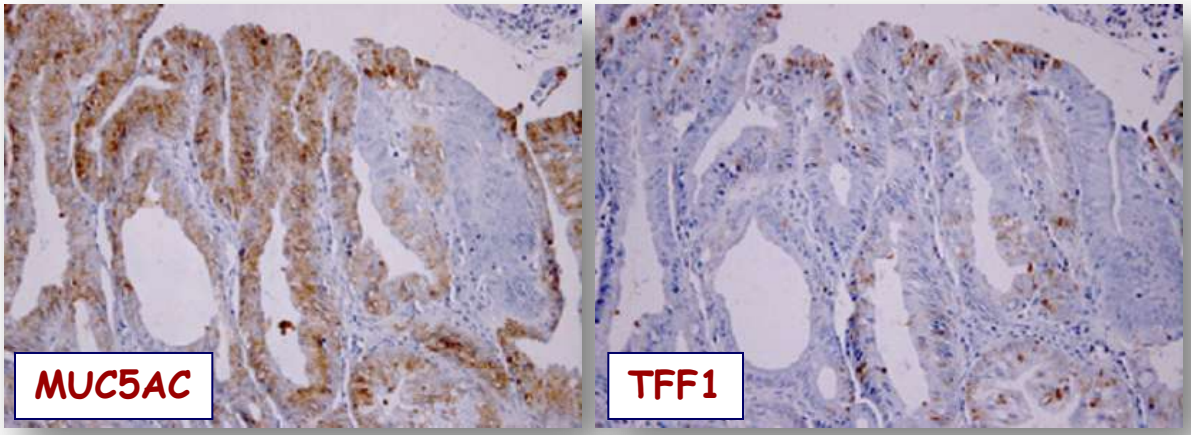
*In stomach, and as far as these guidelines is concerned, category 1 includes lesions such as atrophic chronic gastritis and intestinal metaplasia.

WHO – 4th Edition, 2010

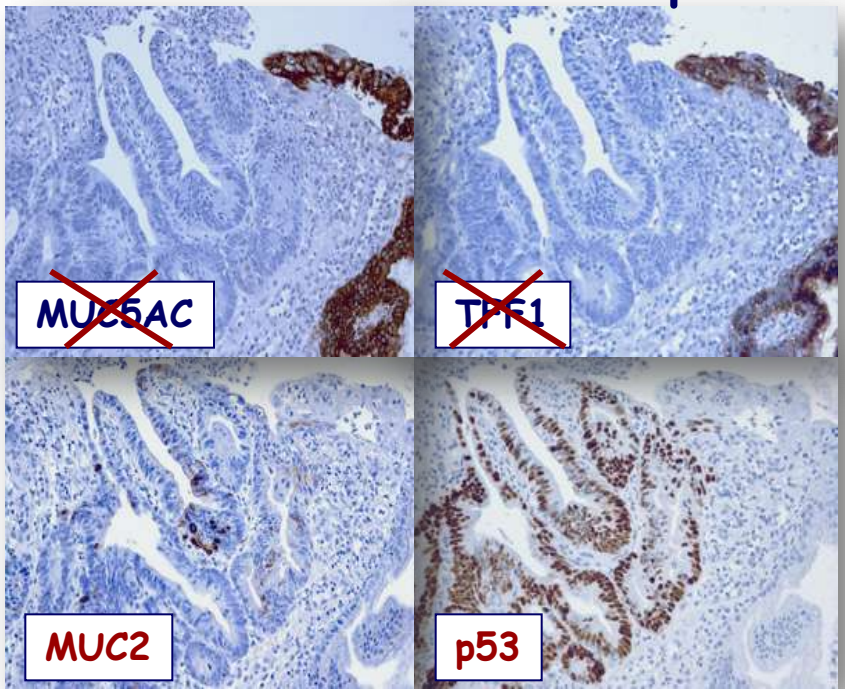
GASTRIC DYSPLASIA

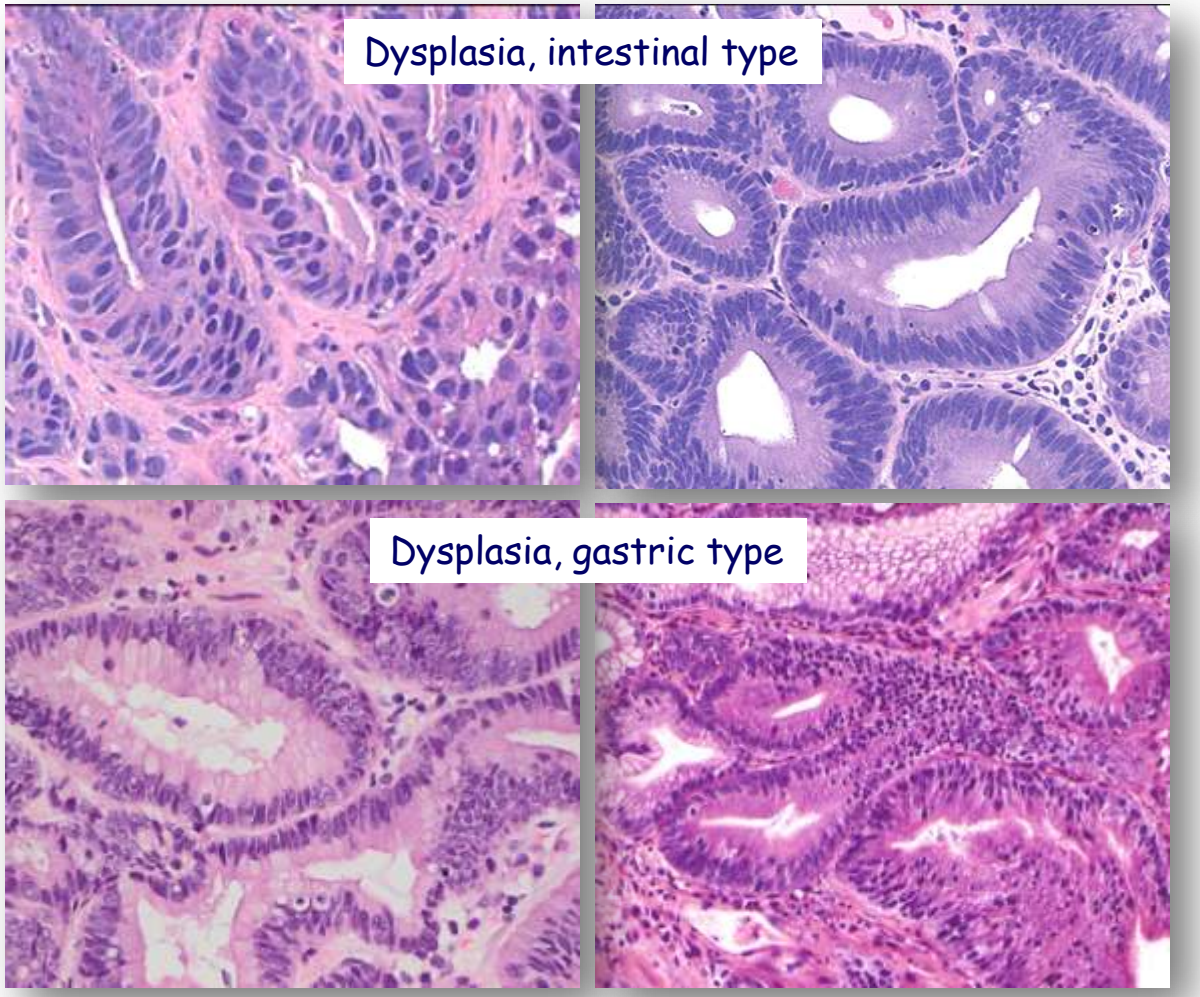


Dysplasia with gastric phenotype



Dysplasia with intestinal phenotype





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Neoplastic polyps

- Adenomatous polyps
  - Intestinal type (MUC2, CD10)
- Gastric-type adenomas
  - Foveolar type (MUC5AC)
  - Pyloric-gland type (MUC6)
- Fundic gland polyps
- Carcinoma
- Neuroendocrine tumours

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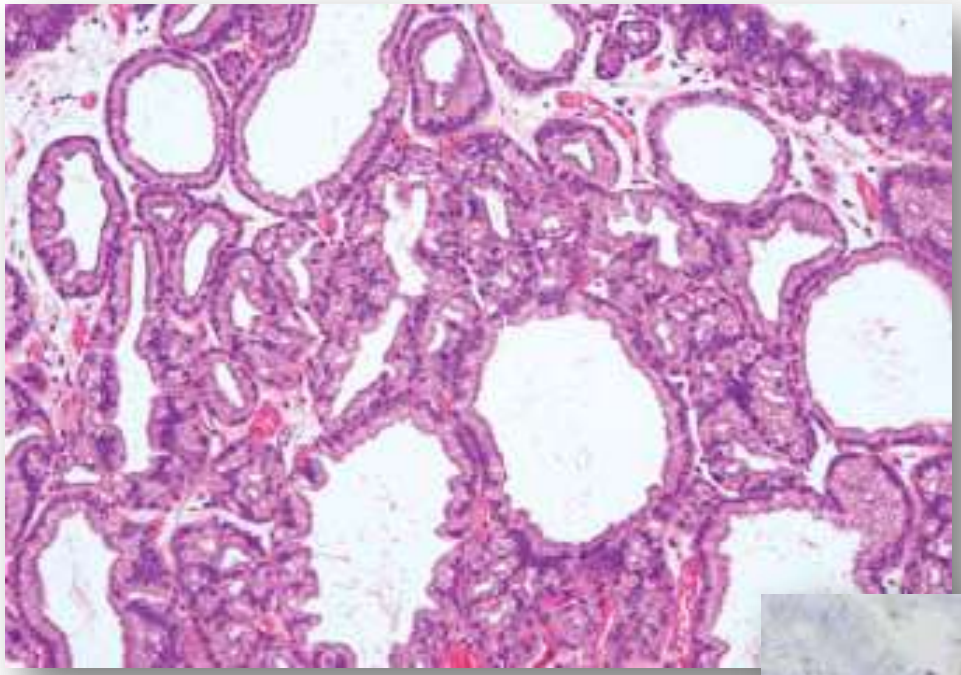
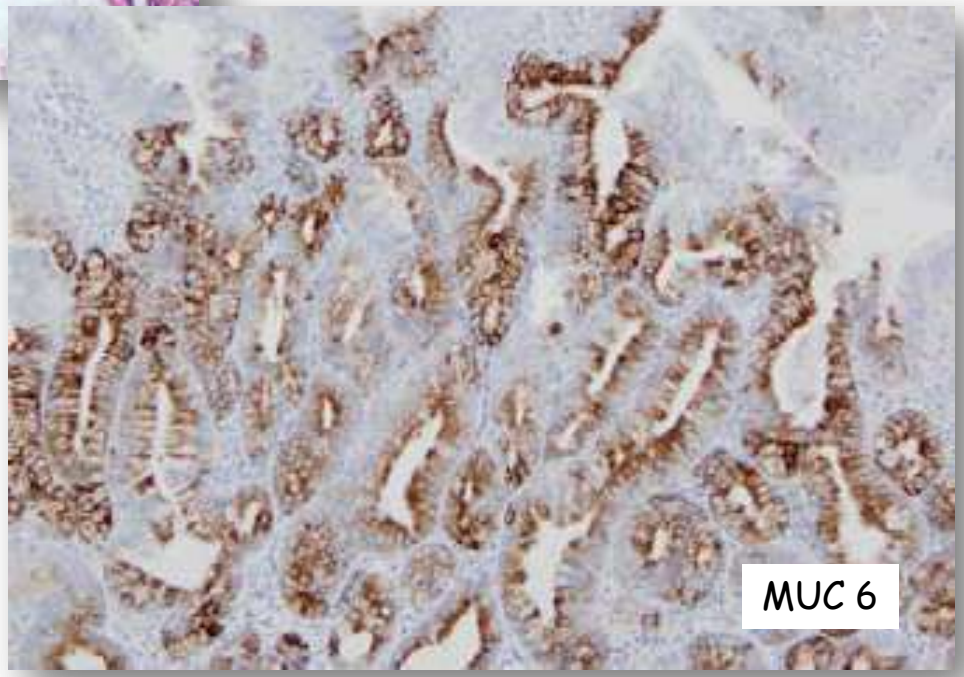




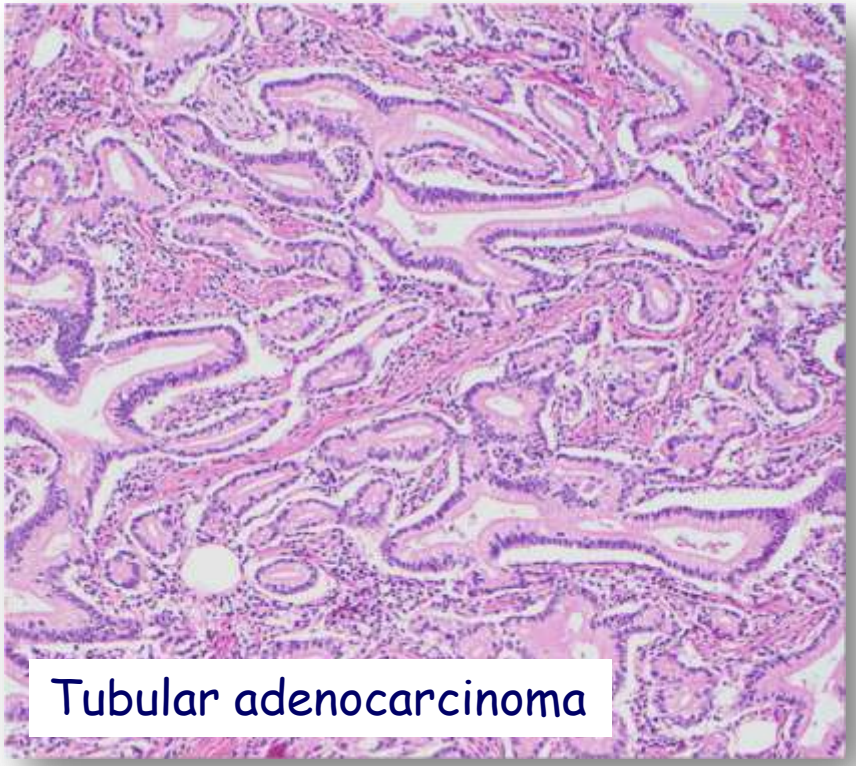
Pyloric gland adenoma

Gastric carcinoma

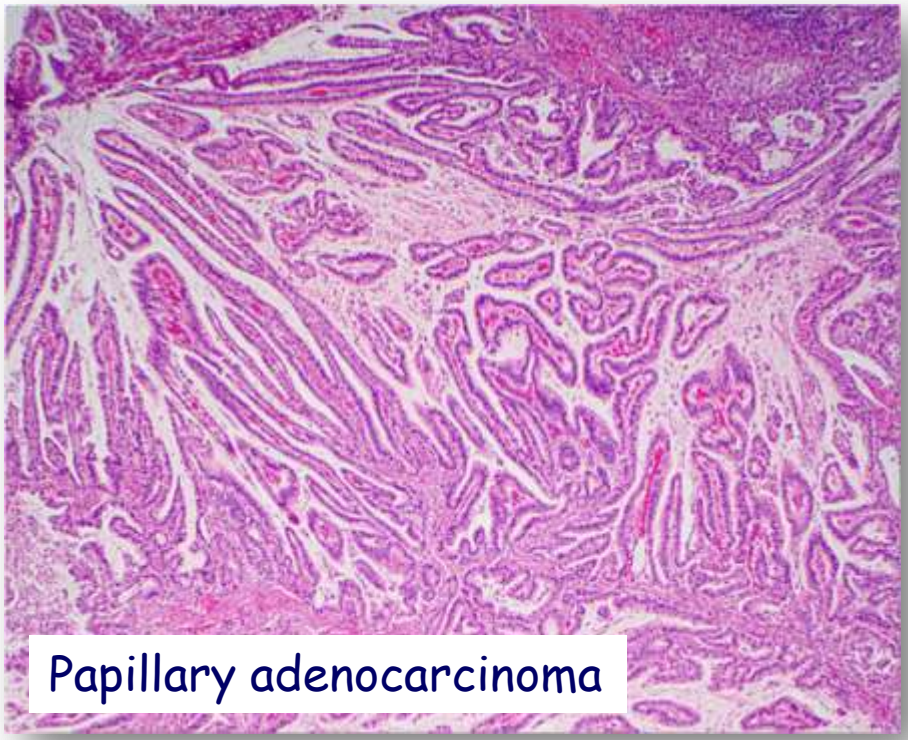
4-1-02 - ICD-O Code

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3

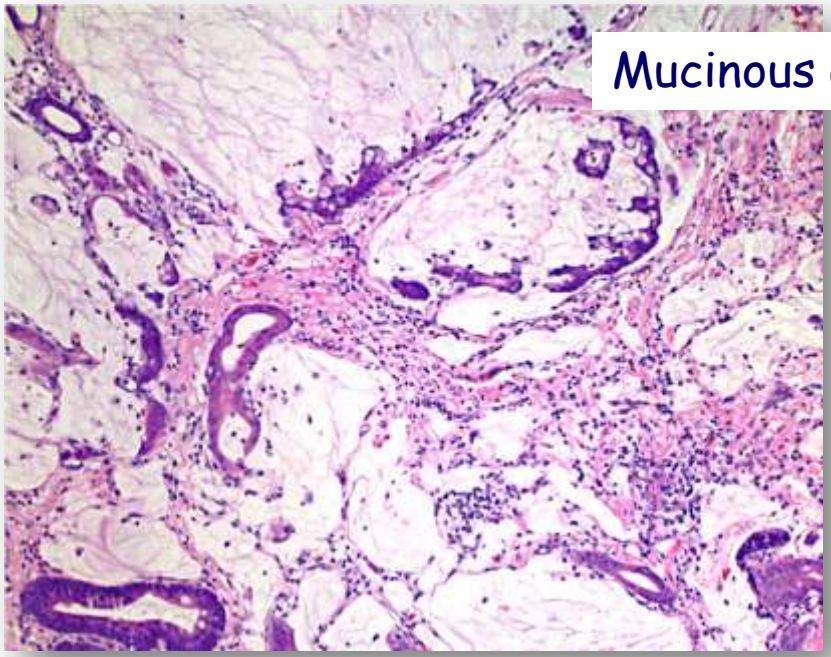
WHO – 3rd Edition, 2000



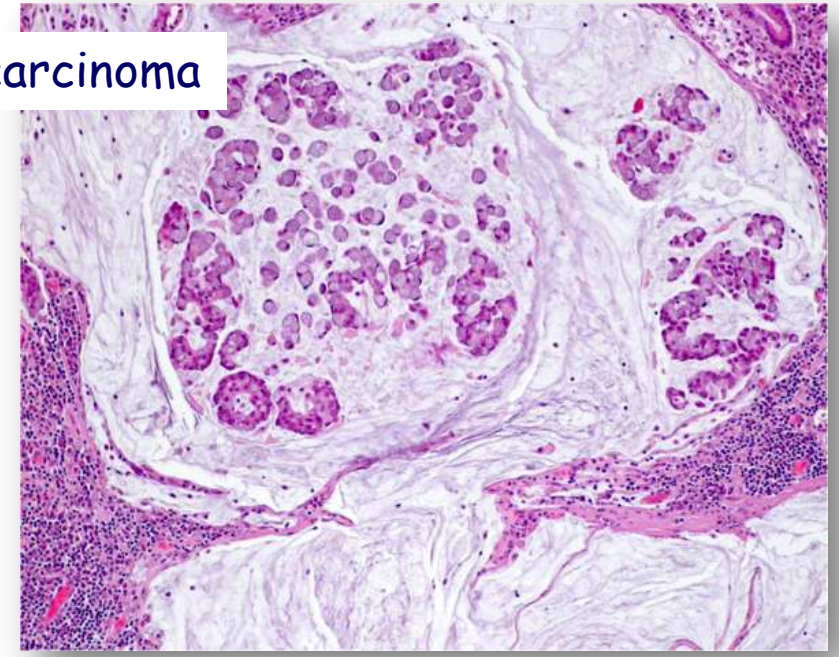
Tubular adenocarcinoma

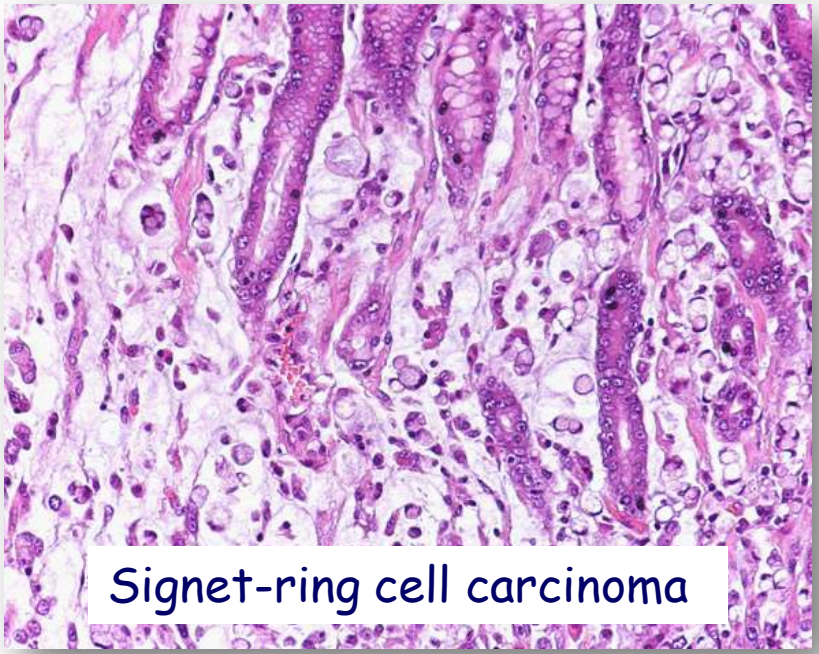


Papillary adenocarcinoma



Mucinous adenocarcinoma





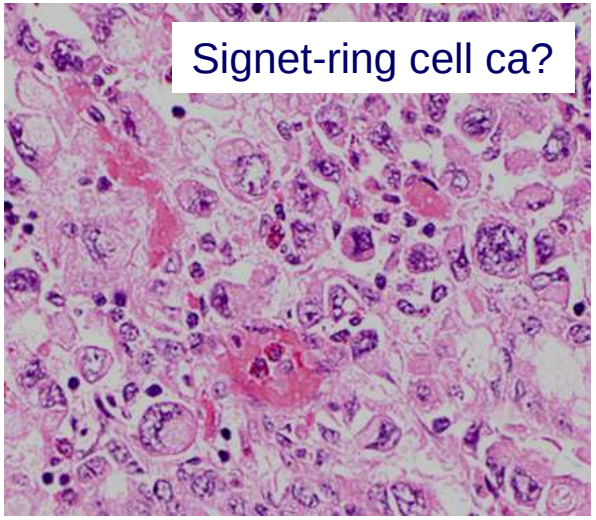
Signet-ring cell carcinoma

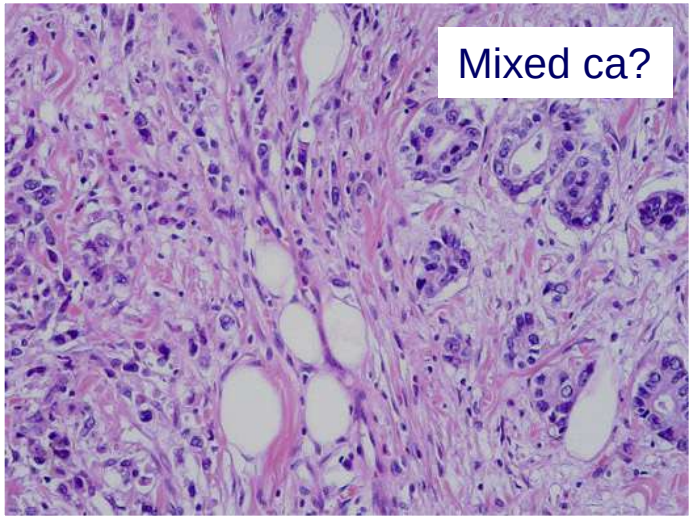
4-1-02 - ICD-O Code

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3

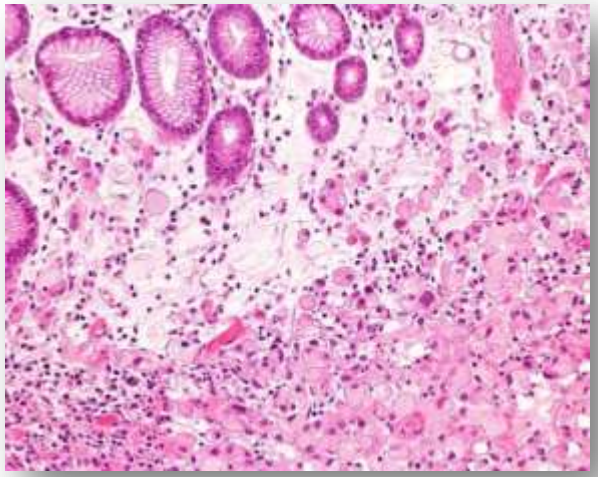
WHO – 3rd Edition, 2000

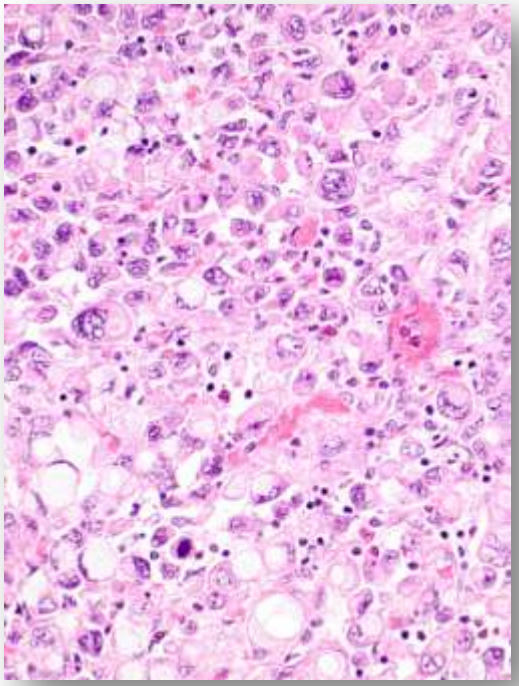
Shortcomings:

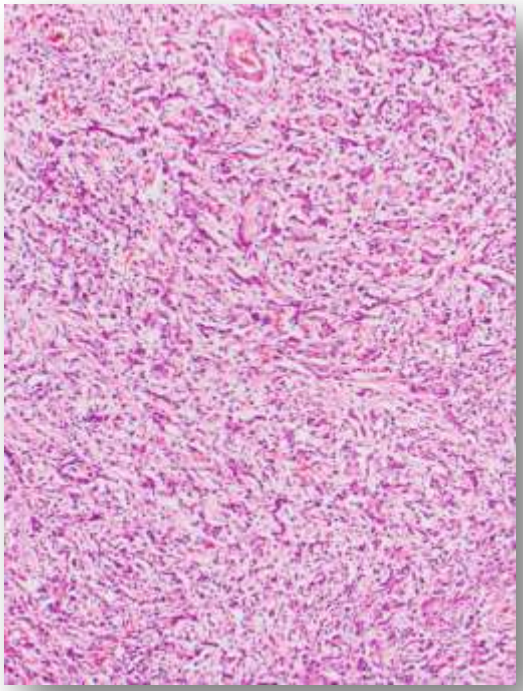


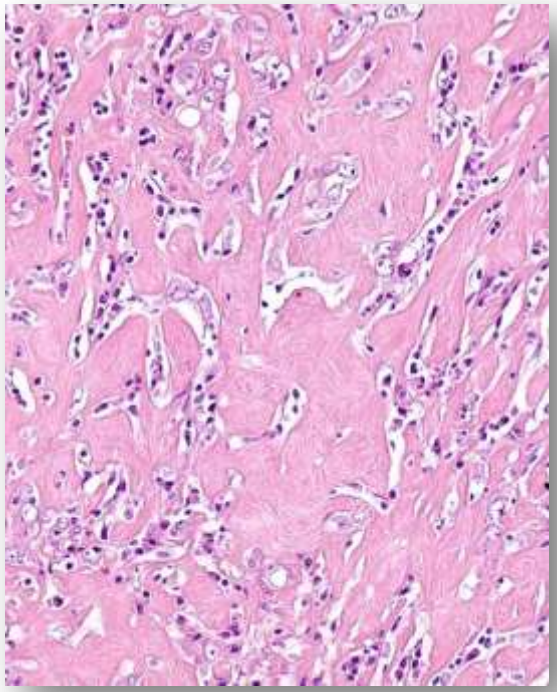


Signet-ring cell carcinoma



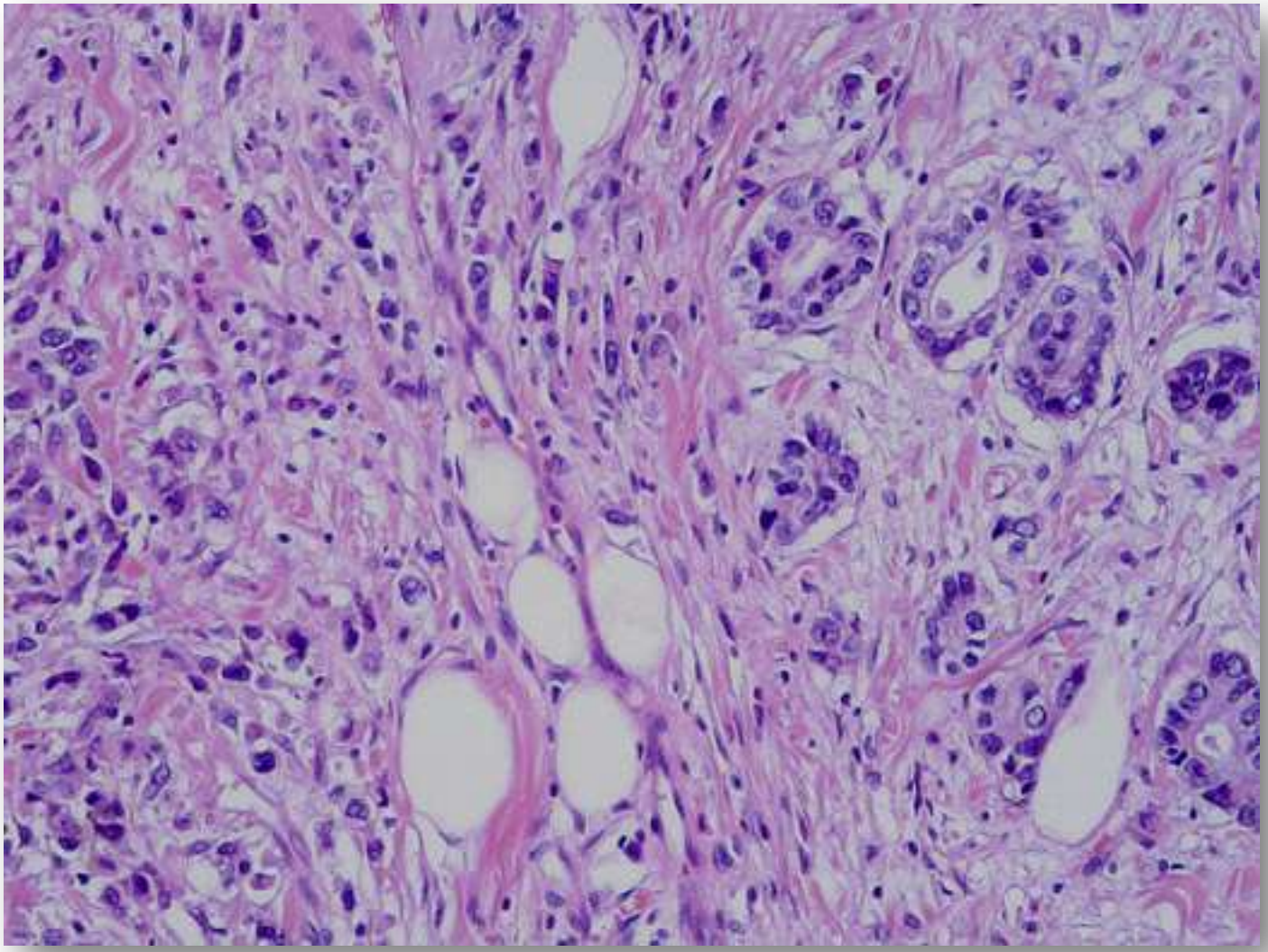


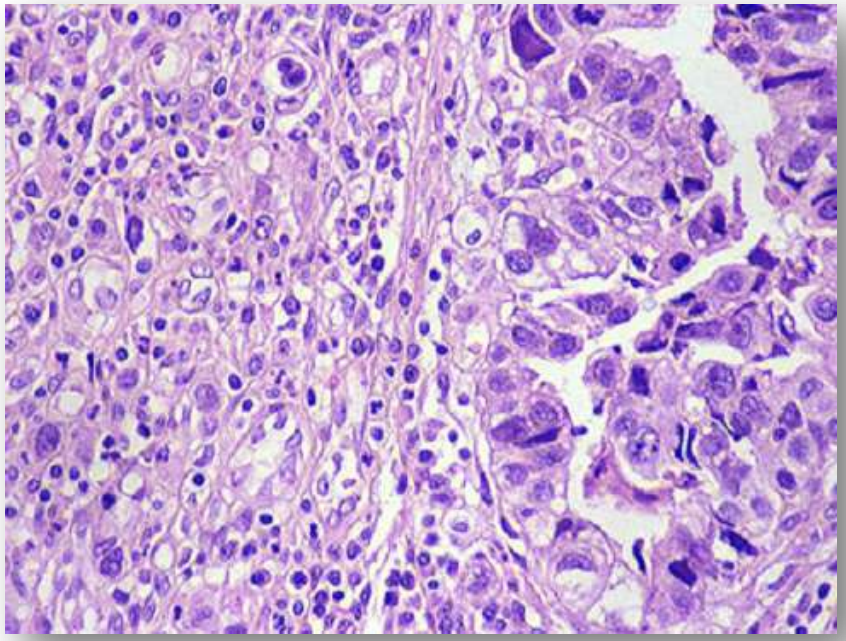


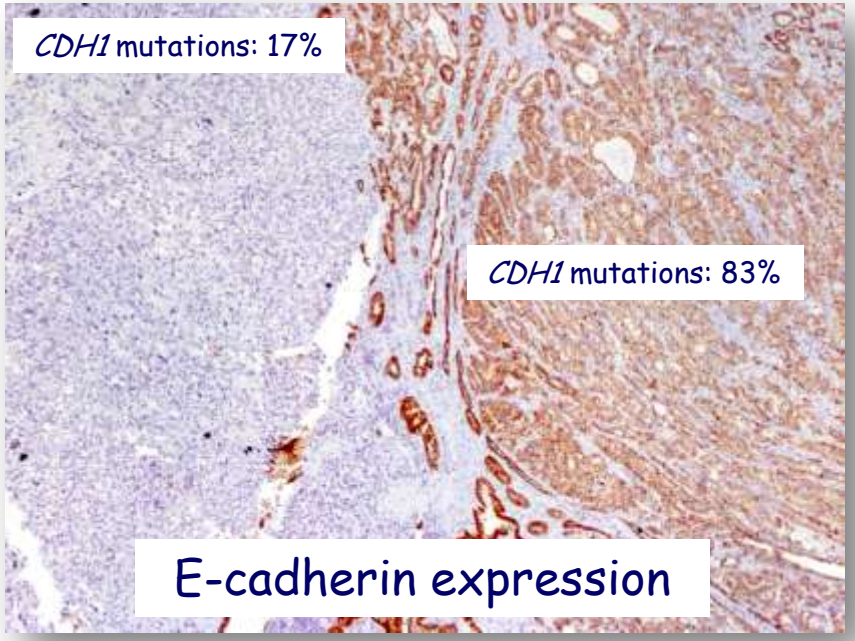


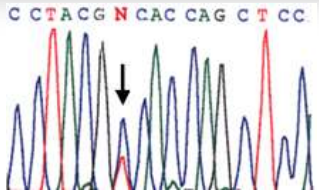
Signet-ring cell carcinoma without signet-ring cells…

What about the mixed type of gastric carcinoma?







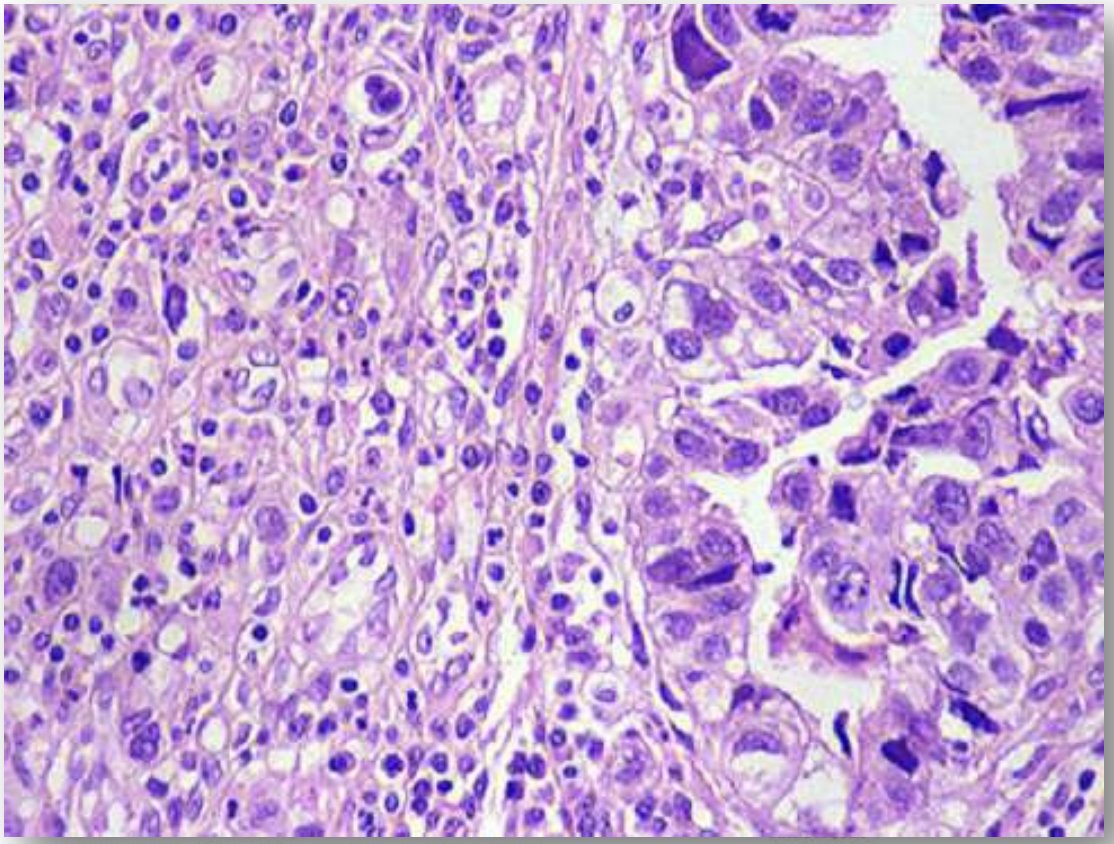


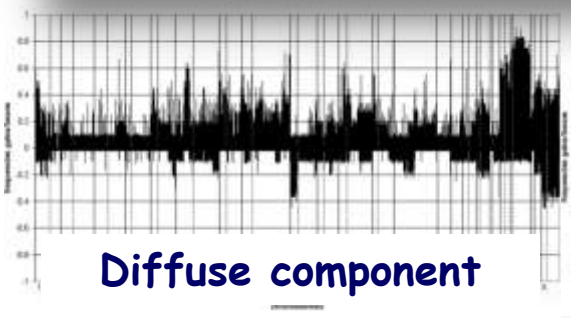
CDH1 mutations

E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas

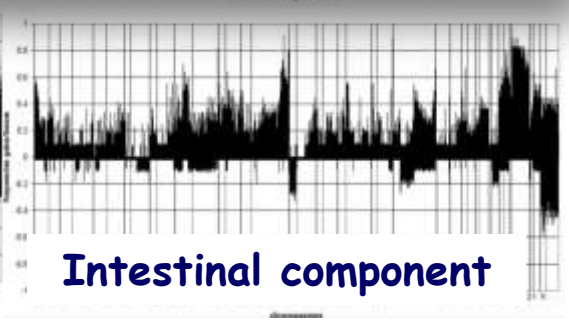
Machado J et al: Lab Invest 79: 459, 1999

Laser microdissection



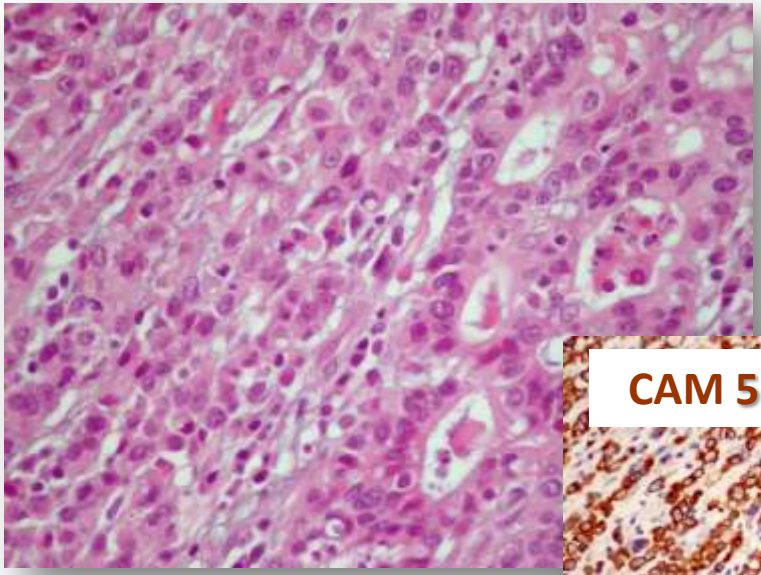


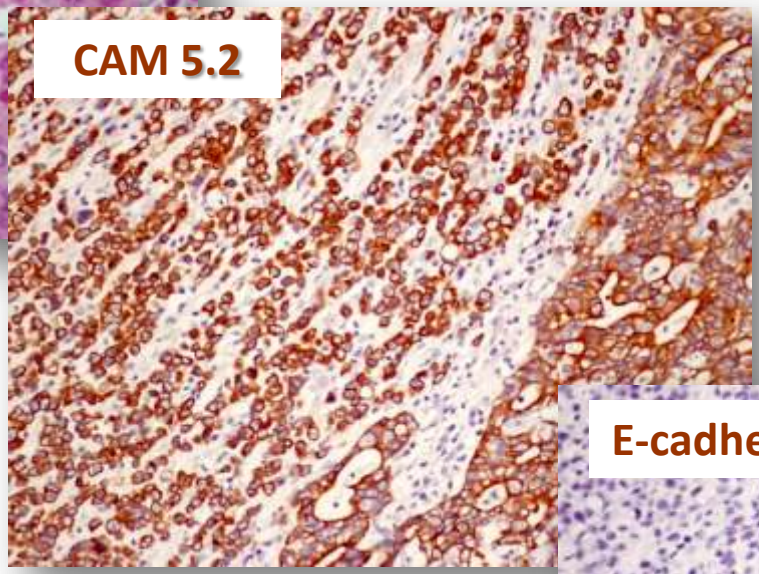
Diffuse component

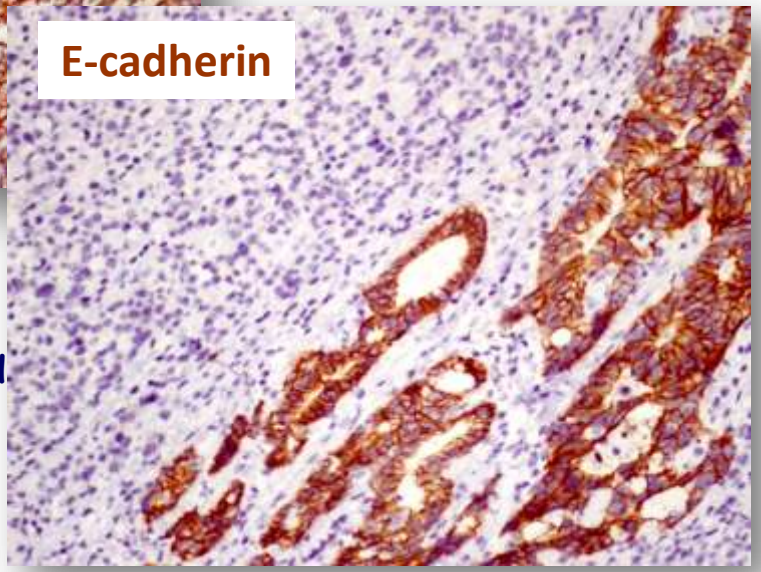


Intestinal component

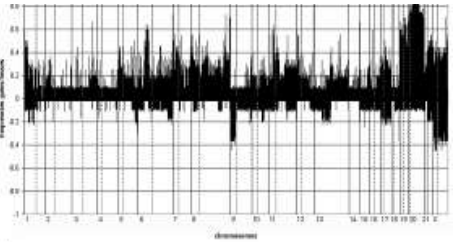
Mixed gastric carcinomas



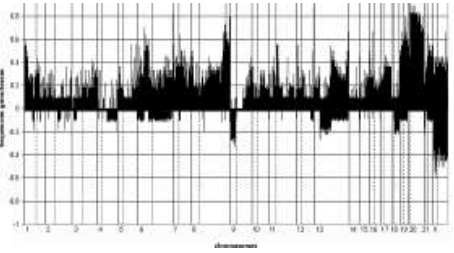




Diffuse component



Intestinal component



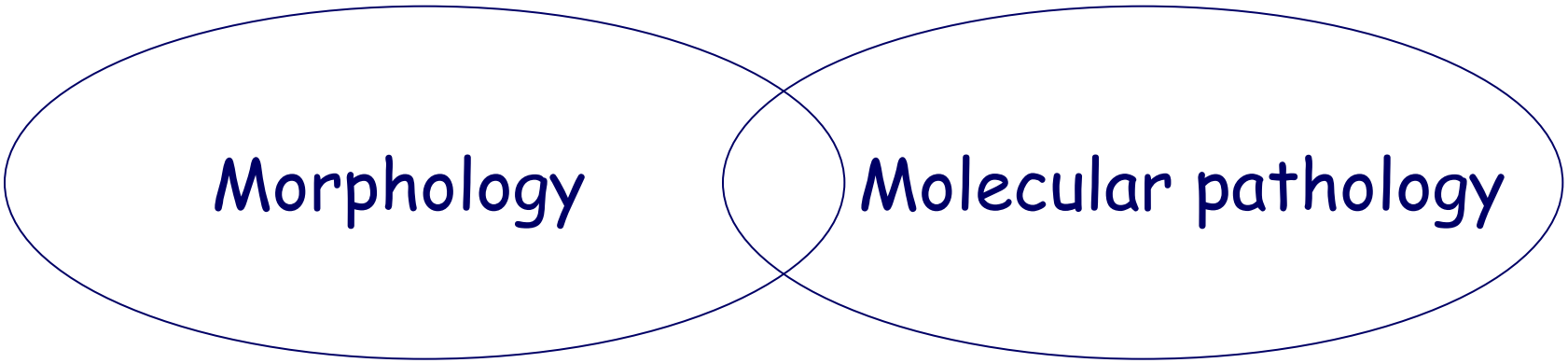
Carvalho B *et al:* **Mixed gastric carcinomas show similar chromosomal aberrations in both their diffuse and glandular components**
Cellular Oncology 28:283, 2006

Park SY *et al*: **Mixed-type gastric cancer and its association with high-frequency CpG island hypermethylation**. *Virchows Archive* 456, 2010

Histological type	5-year survival rate
Glandular (n=89)	52%
Isolated cell (n=14)	67%
Solid (n=28)	48%
Mixed (n=82)	16%

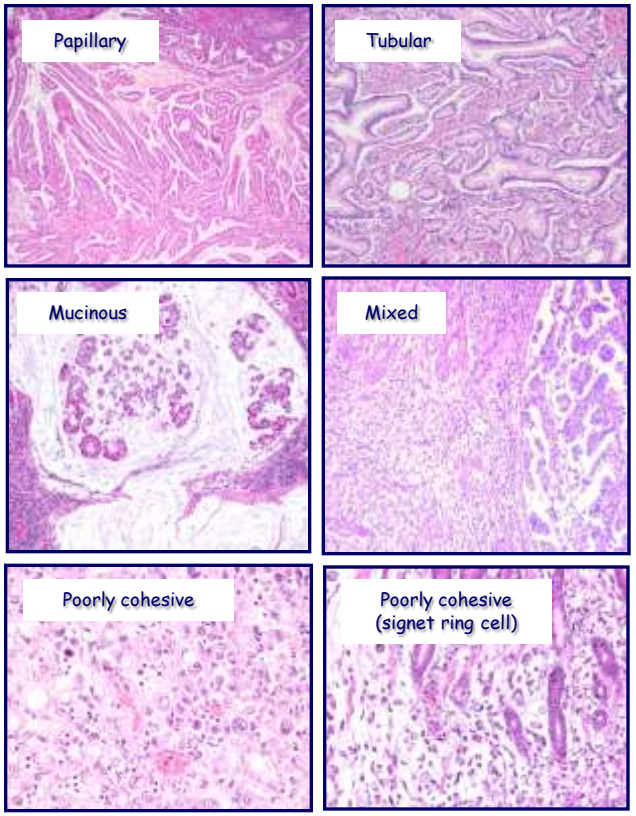
Carneiro F *et al*: Pathol Res Pract 191: 571, 1995

More recently confirmed:
Zheng HC *et al*. Mixed-type gastric carcinomas exhibit more aggressive features and indicate the histogenesis of carcinomas. *Virchows Archive* 452, 2008


Morphology
Molecular pathology

4-1 Gastric carcinoma

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori



4-1-02 - ICD-O Code

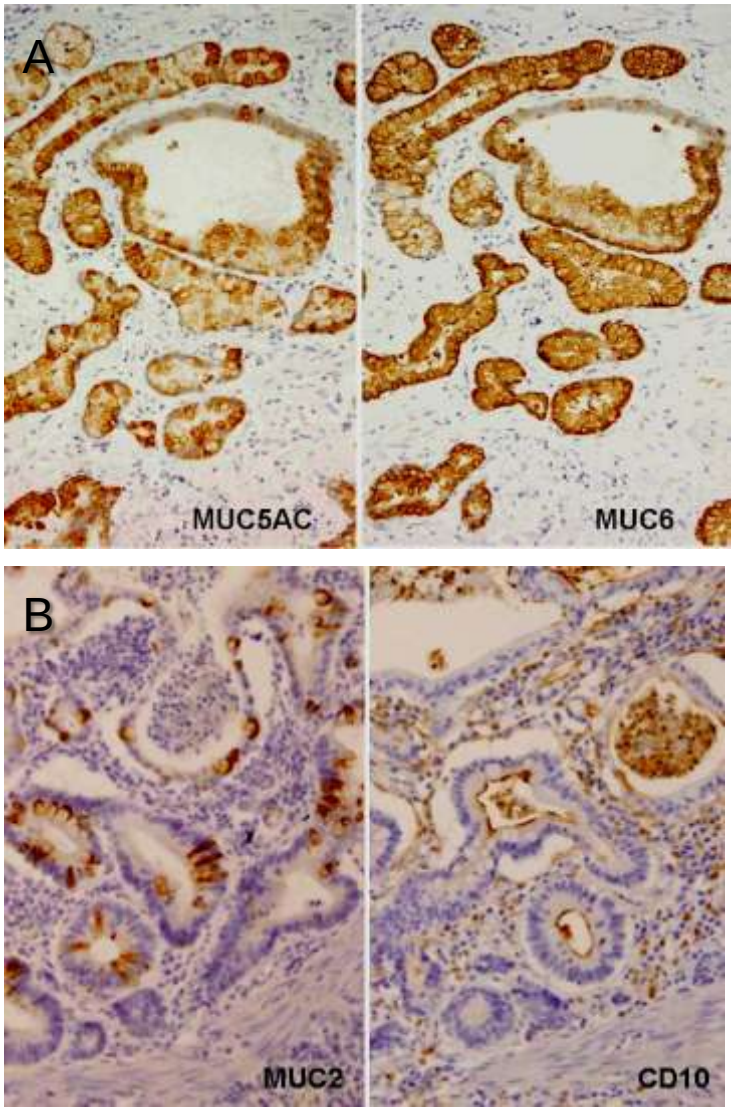
Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Poorly cohesive carcinoma (Signet-ring cell carcinoma and other variants)	8490/3
Mixed carcinoma	8255/3

WHO – 4th Edition, 2010

The dawn of phenotypic classification of gastric adenocarcinoma

Gastric type

Intestinal type



Despite acknowledging the existence of different phenotypic types, the WHO booklet does not recommend (yet?) it's utilization in daily practice

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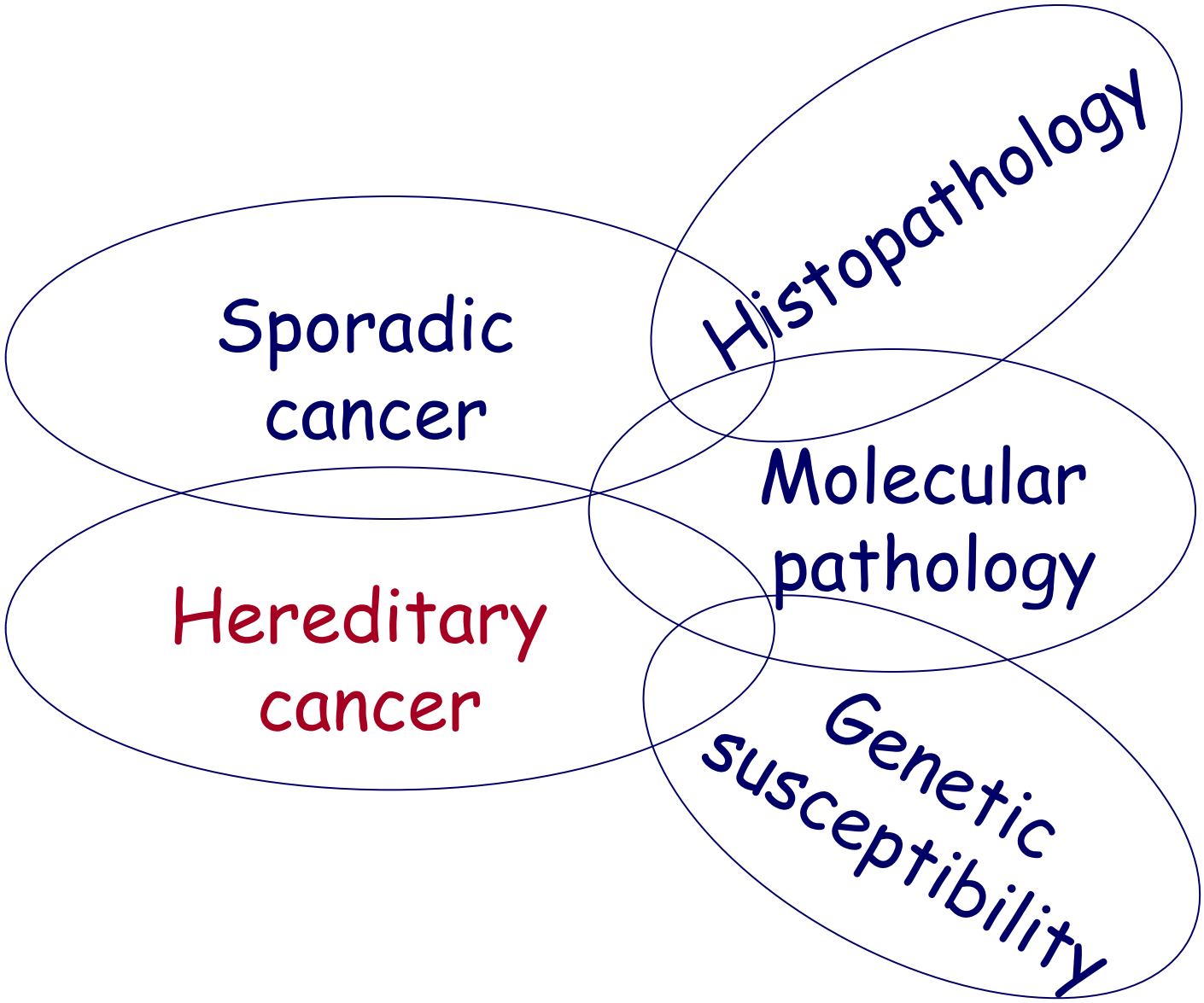
Sporadic cancer
Hereditary cancer
Histopathology
Molecular pathology
Genetic susceptibility

New Chapter on:

Hereditary diffuse gastric cancer

F. Carneiro
A. Charlton
D.G. Huntsman

Definition

Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant cancer-susceptibility syndrome that is characterized by signet-ring cell (diffuse) gastric cancer and lobular breast cancer. The genetic basis for this syndrome was discovered in 1998 by Guilford *et al.* [1081], who identified germline mutations of the E-cadherin (*CDH1*) gene (MIM No. 192090) by linkage analysis and mutation screening in three Maori kindreds with multigenerational, diffuse gastric cancer in New Zealand.

MIM No.: 137215

Diagnostic criteria

In families with an aggregation of gastric cancer, the histopathology of the tumours is often unknown; these cases are designated as familial gastric cancer (FGC). When the histopathological type of one or more gastric cancers is known, discrete syndromes/diseases can be diagnosed; these include HDGC, familial diffuse gastric cancer (FDGC) and familial intestinal gastric cancer (FIGC) [397].

On the basis of clinical criteria, the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 defined families with the HDGC syndrome as those fulfilling one of the following features:

(1) two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one being diagnosed before the age of 50 years; or (2) three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of diagnosis [397]. Women in these families also have an elevated risk of lobular breast cancer [341, 1501, 1513, 2855, 3136]. IGCLC criteria for genetic testing, updated in 2009 [871] are shown in Table 4.2.01. An alternative genetically-based nomenclature, proposed by the New Zealand group, in which the term "HDGC" is restricted to families with germline mutations in the *CDH1* gene [1081, 1082]. The IGCLC definition for HDGC will be used for the remainder of this section [871].

Epidemiology

The vast majority of gastric cancers are sporadic, but approximately 1–3% result from an inherited predisposition [870, 2396, 2439].

The prevalence of HDGC is uncertain, partly due to the recent identification of this syndrome. In a review of 439 families with aggregation of gastric cancer [2395], *CDH1* mutations were preferentially observed in families fulfilling the clinical criteria for HDGC (36.4%). In FDGC, the frequency of germline mutations in *CDH1* was much lower (12.5%) [2396]. *CDH1* mutations have not been found in families with weaker histories of gastric cancer; however, mutation rates of up to 10% have been described in individuals with no family history but DGC diagnosed at less than age 35 years, from populations with a low incidence of gastric cancer [1501, 3136]. There are striking population-specific differences regarding the fraction of families with aggregation of gastric cancer and frequency of *CDH1* germline mutations. In countries with a low incidence of gastric cancer, the frequency of germline alterations in the *CDH1* gene is > 40%, while in countries with a moderate or high incidence of gastric cancer, the frequency of alterations in *CDH1* is about 20% [2396]. These observations in moderate- or high-incidence countries are probably related to clustering of gastric cancer attributable to environmental risk factors (lifestyle, diet) and/or variation in genes conferring a weak susceptibility [2396].

Localization

Most index cases with HDGC present with cancers that are indistinguishable from sporadic diffuse gastric cancer, often with linitis plastica, which can involve all topographic regions within the stomach. Systematic complete mapping of total gastrectomies from asymptomatic carriers

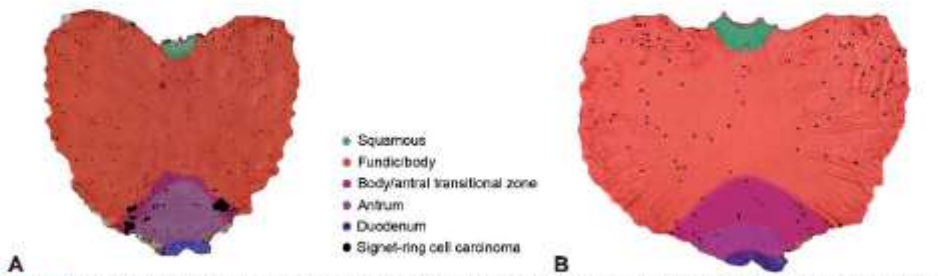

Fig. 4.2.01 Mapping of gastric mucosal zones (semi-opaque colours) and location of foci of stage T1a signet-ring cell (diffuse) carcinoma (black circles) on photos of two stomachs. Adapted from Charlton *et al.* (493). A Asymptomatic *CDH1*-mutation carrier, aged 15 years; the map indicates the location of 318 foci and mucosal zones. B Asymptomatic *CDH1*-mutation carrier, aged 19 years, from the same family; the map indicates the location of 115 foci and mucosal zones.

GASTRIC CARCINOMA

- Sporadic (90%)
- Familial Aggregation (10%)
  - Familial Gastric Cancer (FGC)
  - Familial Intestinal Gastric Cancer (FIGC)
  - Familial Diffuse Gastric Cancer (FDGC)
- Hereditary (1%)*
  - Hereditary Diffuse Gastric Cancer (HDGC)

* Most caused by E-cadherin alterations

Criteria for testing for E-cadherin gene mutation: updated recommendations from the International Gastric Cancer Linkage Consortium (IGCLC)*

1. Two or more documented cases of gastric cancer in first degree relatives, with at least one documented case of diffuse gastric cancer diagnosed before the age of 50 years

2. Three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of onset

3. Diffuse gastric cancer before the age of 40 years without a family history

4. Families with diagnoses of both diffuse gastric cancer and lobular breast cancer, with one case before the age of 50 years

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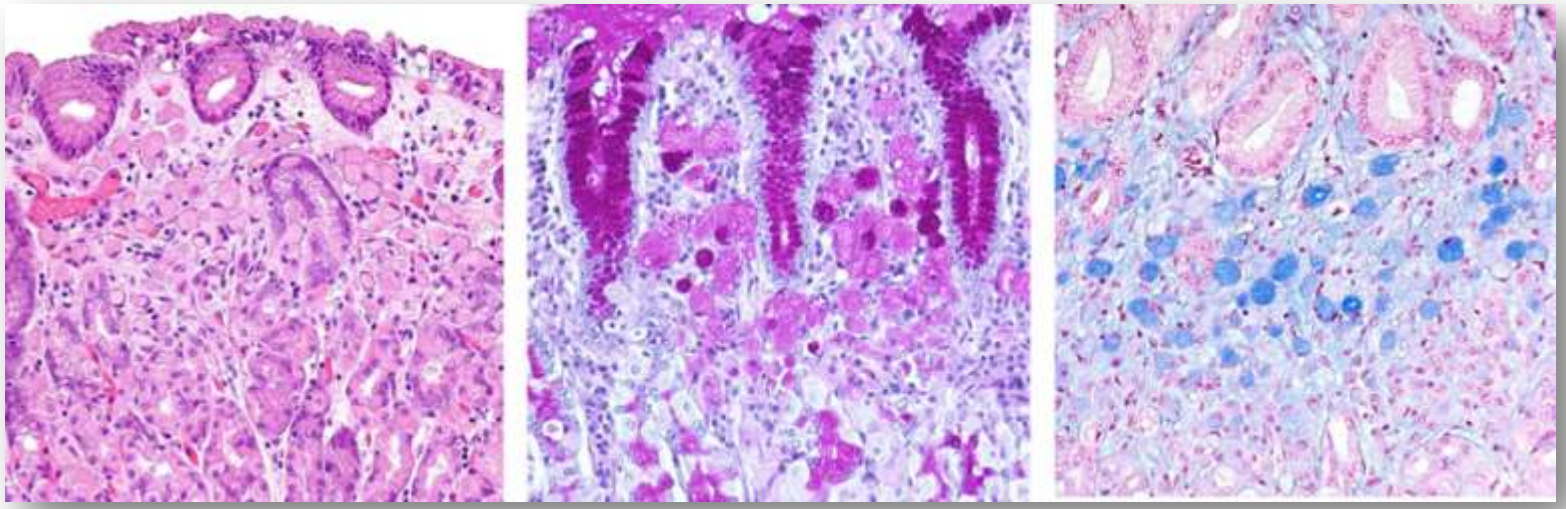
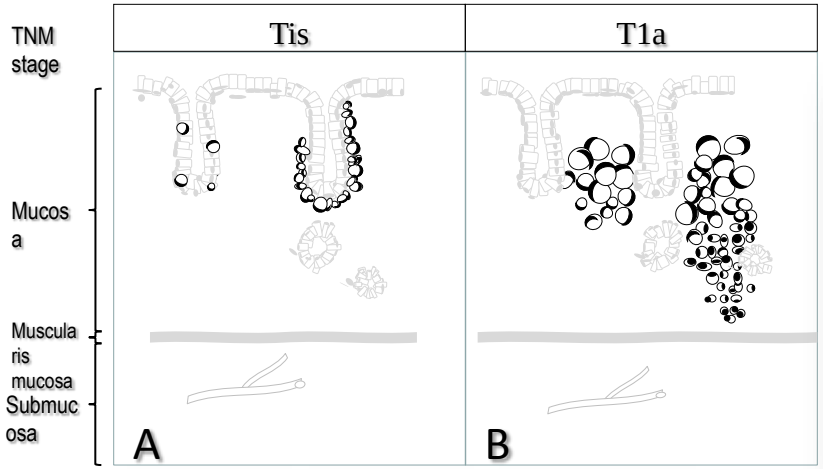
*In addition, in cases where expert pathologists detect carcinoma *in situ adjacent to diffuse-type gastric* cancer, genetic testing should be considered since this is rarely, if ever, seen in sporadic cases.

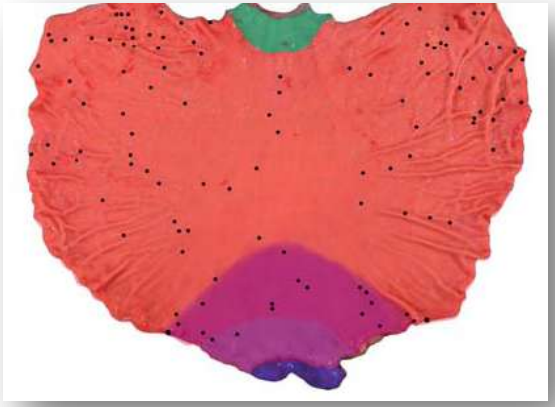
Hereditary Diffuse Gastric Carcinoma

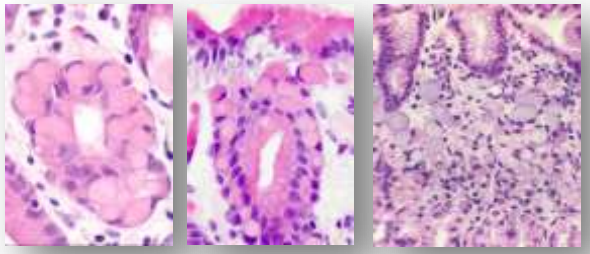


4-3 Hereditary Diffuse Gastric Cancer

Fátima Carneiro
Amanda Charlton
David Huntsman







In situ carcinoma | Pagetoid spread | T1a intramucosal signet-ring cell

WHO – 4th Edition, 2010

Thanks for your attention