Lezioni di Patologia Sistematca I - 2010

Patologia Esofagea

Giuseppe Zamboni
giuseppe.zamboni@univr.it

Esophagitis

1. **Gastroesophageal reflux disease (*GERD)***
2. **Infectious Esophagitis**
   Viral Esophagitis
   Cytomegalovirus Esophagitis
   Fungal Esophagitis
   Bacterial Esophagitis
   Parasitic Esophagitis
3. **Pill/Drug/Toxic Esophagitis**
   Pill Esophagitis
   Corrosive Esophagitis
4. **Primary Eosinophilic Esophagitis**

Primary Eosinophilic Esophagitis

Clinical features

May mimic GERD clinically, endoscopically, and histologically

Normal pH and failure to antireflux therapy

Children or young adults, with a strong male predominance

Allergic history/peripheral eosinophilia

GERD-like symptoms, the most characteristic findings are dysphagia and food impaction

60% to 75% are associated with bronchial asthma

1. Gastroesophageal reflux disease (*GERD*)

Pathology

Patchy changes: distal 8 to 10 cm

Erosions

Ulcers

Strictures

50% to 60% normal mucosa or only mild hyperemia

Endoscopic/pathologic discrepancies

Biopsy: >2.0 cm above the GEJ

Barrett's Esophagus

- Very few cases are congenital
- Most are acquired
- Caused by chronic GERD
- It predisposes to dysplasia and adenocarcinoma
- Endoscopic surveillance is highly recommended

Pathologist has to be as accurate as possible with regard to distinguishing reactive changes from dysplasia and dysplasia from carcinoma in mucosal biopsy specimens

DEFINITION OF BE (Am Coll Gastroent-2008)

1. Endoscopically recognizable columnar metaplasia of the esophageal mucosa

2. Pathological confirmation of intestinal metaplasia, defined by the presence of goblet cells

- BE does not include patients who have IM of the gastric cardia

The consequences of over-diagnosis are serious: a lifelong endoscopic surveillance

Barrett's Esophagus

Defining BE by pathologic confirmation of intestinal metaplasia (goblet cells) is somewhat problematic

This definition is based primarily on the fact that intestinal-type epithelium is at highest risk for neoplastic progression

Rare cancer may also develop in goblet cell–poor or even nongoblet epithelium

The background nongoblet columnar epithelium shows physiologic properties of "intestinal" differentiation, such as expression of CDX2, HepPar-1, Villin, DAS-1, and MUC3

PATHOGENESIS: a multistep process

1. Squamous epithelium converts initially to a *multilayered epithelium* with a high capacity for cell proliferation and differentiation
2. Development of a columnar epithelium morphologically similar to the gastric
3. With ongoing injury and chronic inflammation, mucinous columnar epithelium converts to an intestinal phenotype by a secondary metaplastic reaction
4. Bile acids (specifically deoxycholic acid) upregulate both the intestinal differentiation factor, CDX2, and the goblet cell–specific gene, *MUC2*
5. Cell of origin of BE probably resides in the esophagus, rather than in the proximal stomach.

NEOPLASTIC COMPLICATIONS IN BE

Adenocarcinoma develops in patients with BE through a sequence of molecular and phenotypic changes that begin with intestinal metaplasia and progress through various grades of dysplasia to adenocarcinoma

Risk Factors

Hiatus hernia
Longer lengths of BE
GERD and obesity
Dietary fat and tobacco
Dietary fruits, vegetables, and fiber decreases the risk

Metaplasia-dysplasia-carcinoma sequence

Accumulation of multiple genetic and epigenetic alterations, many of which occur prior to the onset of morphologic dysplasia

Inactivation of the p16 tumor suppressor gene

Loss or mutations of p53 tumor-suppressive gene

Proliferative abnormalities: increased S-phase fraction and Ki67

DNA instability (most often aneuploidy) predict progression to carcinoma

NATURAL HISTORY AND RISK OF MALIGNANCY

The overall cancer risk without dysplasia is 2%.

The risk of having/developing cancer in HGD is 16% - 59% (22%.)

"Prevalent" dysplasia: detected at initial screening or during the first 12 months

"Incident" dysplasia: detected during the course of endoscopic surveillance (? less advanced)

59% vs 31%
progression "prevalent" vs "incident" HGD to carcinoma in 5 yrs

NATURAL HISTORY AND RISK OF MALIGNANCY

The natural history of low-grade dysplasia in BE is more controversial

45% of BE patients with LGD, confirmed by three GI pathologists, showed progression to cancer within 5 years

Factors Affecting Treatment Decisions for HGD

Patient age

Comorbidities

Institution esophagectomy mortality rate

Status of surveillance program

Extent of dysplasia

Location of dysplasia

Growth pattern (flat, nodule, ulcer)

Length of Barrett's esophagus

DNA content data

Premalignant lesions of the digestive tract

(Pre)occupied pathologists-clinicians for a long time (pain in the gut)

1. Some of them are morphologically close to invasive cancer.

2. Some of them are morphologically closer to normal mucosa.

3. Some are so ambiguous because in the context of active inflammation and repair with regenerative epithelial changes that mimick premalignant neoplasia.

The new WHO classification of premalignant lesions of the digestive tract - 2010

1. Adoption of Intraepithelial Neoplasia (avoidance of the term dysplasia)

2. A 6 tier scheme provides risk stratification to guide patient management

3. In addition to Intraepithelial Neoplasia, Intramucosal and Superficial Invasive Neoplasia, also amenable to endoscopic therapy, are defined

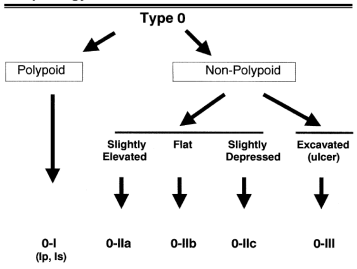
(New) WHO classification	
No intra-epithelial neoplasia	Benign,inflammatory or reactive processes or normal mucosa.
Indefinite for intra-epithelial neoplasia	Not a final diagnosis but a pragmatic solution to an ambiguous morphological pattern (reactive atypia vs dysplasia) Follow up endoscopy, repeated biopsies, chromoendoscopy are recommended.
Low grade intra-epithelial neoplasia (LG adenoma; LG dysplasia)	
High grade intra-epithelial neoplasia (HG adenoma; HG, non-invasive intramucosal carcinoma)	
Intramucosal invasive neoplasia (syn. intramucosal carcinoma)	Carcinoma limited to the lamina propria. Increased risk of lymphatic invasion and lymph node metastasis. Resection is necessary. Novel endoscopic techniques may allow to adequately treat the patient without open surgery.
Invasive neoplasia (syn. invasive carcinoma)	Carcinomas invading the beyond the lamina propria. Depending of the organ, the phenotype and depth of invasions, IN is associated with varying risk of nodal and distant metastasis. Surgical resection, sometimes associated by neo-adjuvant therapy is recommended.

Paris Classification superficial neoplastic lesions of esophagus, stomach and colon

Type 0: superficial carcinoma

Type 1-4:Borrmann's classification for advanced carcinoma

Table 2. Neoplastic lesions with "superficial" morphology



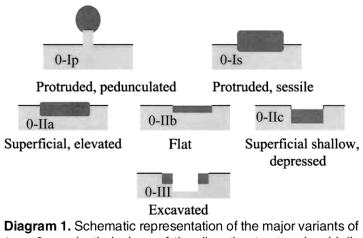


Diagram 1. Schematic representation of the major variants of *type 0* neoplastic lesions of the digestive tract: polypoid *(Ip and Is)*, non-polypoid *(IIa, IIb, and II c)*, non-polypoid and excavated *(III)*. Terminology as proposed in a consensus macroscopic description of superficial neoplastic lesions.[15]

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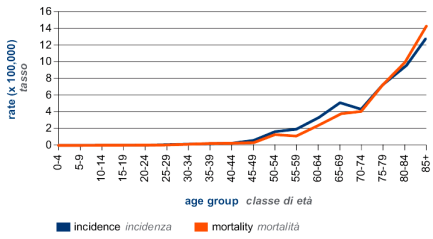

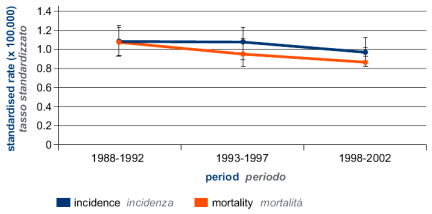

Basis of diagnosis *Modalità di diagnosi*	n. cases	%
histology *istologica*	492	81%
cytology *citologica*	4	1%
clinical *clinica*	92	15%
DCO *solo certificato di morte*	18	3%
	606	

More frequent morphologies among histologically verified cases
Morfologie più frequenti tra i casi con conferma istologica

8070	Squamous cell carcinoma *Carcinoma a cellule squamose*	305	62%
8140	Adenocarcinoma *Adenocarcinoma*	76	15%
8010	Carcinoma, NOS *Carcinoma, NAS*	38	8%
8000	Tumour, malignant NOS *Tumore maligno, NAS*	25	5%
8071	Squamous cell carcinoma keratinizing, NOS *Carcinoma spinocellulare cheratinizzante, NAS*	22	4%