



MERCOLEDÌ 2 MARZO 2022

DIAGNOSI E TERAPIA DEL CANCRO DELLO STOMACO: COSA FARE NEL 2022

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RESPONSABILE SCIENTIFICO

Prof. Giovanni Dapri
Direttore Chirurgia Mini-Invasiva Generale
e Oncologica, Humanitas Gavazzeni, Bergamo

ore 20:15 **RUOLO DEL GASTROENTEROLOGO**
IMPORTANZA DELLA GASTROSCOPIA NELLA
DIAGNOSI E NELLA STADIAZIONE. IL RUOLO
DELL'ECOENDOSCOPIA. NUOVI APPROCCI
TERAPEUTICI PER I CARCINOMI IN STADIO INIZIALE
Nicola Gaffuri

ore 20:30 **RUOLO DEL PATOLOGO**
ANALISI MORFOLOGICA E MOLECOLARE.
STADIAZIONE TN
Paola Spaggiari

ore 20:45 **RUOLO DEL RADIOLOGO**
STADIAZIONE TAC ADDOMINO-TORACICA
LINFONODALE E A DISTANZA
Alessandro Zanello



Ruolo del patologo

ANALISI MORFOLOGICA E MOLECOLARE

ISTOTIPO

GRADING

entità delle anomalie morfologiche
delle cellule e dell'architettura tissutale

STAGING

l'estensione della malattia nella sede in
cui origina e la sua diffusione
nell'organismo

PARAMETRI PROGNOSTICI MORFOLOGICI

PROFILO GENOTIPICO

anomalie genetiche

PROFILO IMMUNOFENOTIPICO

espressione proteica

**Biopsia endoscopica
della neoplasia**

**Escissione locale
da EMR o ESD**

**Prelievi della neoplasia
da resezione chirurgica**

**Agobiopsie di secondarismi
in organi parenchimali**

**Biopsie peritoneali
di noduli da carcinosi**

Citologico da versamento

PRECURSORI, sec. WHO 2019

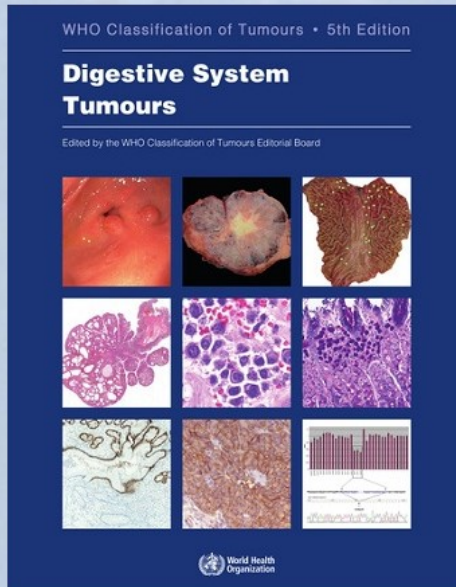
WHO classification of tumours of the stomach

Benign epithelial tumours and precursors

8148/0	<u>Glandular intraepithelial neoplasia, low grade</u>
8148/2	<u>Glandular intraepithelial neoplasia, high grade</u>
8213/0*	Serrated dysplasia, low grade
8213/2*	Serrated dysplasia, high grade
	Intestinal-type dysplasia
	Foveolar-type (gastric-type) dysplasia
	Gastric pit/crypt dysplasia
8144/0*	Intestinal-type adenoma, low grade
8144/2*	Intestinal-type adenoma, high grade
	Sporadic intestinal-type gastric adenoma
	Syndromic intestinal-type gastric adenoma
8210/0*	Adenomatous polyp, low-grade dysplasia
8210/2*	Adenomatous polyp, high-grade dysplasia

Malignant epithelial tumours

8140/3	Adenocarcinoma NOS
8211/3	Tubular adenocarcinoma
8214/3	Parietal cell carcinoma
8255/3	Adenocarcinoma with mixed subtypes
8260/3	Papillary adenocarcinoma NOS
8265/3	Micropapillary carcinoma NOS
8430/3	Mucoepidermoid carcinoma
8480/3	Mucinous adenocarcinoma
8490/3	Signet-ring cell carcinoma
8490/3	Poorly cohesive carcinoma
8512/3	Medullary carcinoma with lymphoid stroma
8576/3	Hepatoid adenocarcinoma
	Paneth cell carcinoma
8070/3	Squamous cell carcinoma NOS
8560/3	Adenosquamous carcinoma
8020/3	Carcinoma, undifferentiated, NOS
8014/3	Large cell carcinoma with rhabdoid phenotype
8022/3	Pleomorphic carcinoma
8033/3	Sarcomatoid carcinoma
8035/3	Carcinoma with osteoclast-like giant cells
8976/1*	Gastroblastoma
8240/3	Neuroendocrine tumour NOS
8240/3	Neuroendocrine tumour, grade 1
8249/3	Neuroendocrine tumour, grade 2
8249/3	Neuroendocrine tumour, grade 3
8153/3	Gastrinoma NOS
8156/3	Somatostatinoma NOS
8241/3	Enterochromaffin-cell carcinoid
8242/3	ECL-cell carcinoid, malignant
8246/3	Neuroendocrine carcinoma NOS
8013/3	Large cell neuroendocrine carcinoma
8041/3	Small cell neuroendocrine carcinoma
8154/3	Mixed neuroendocrine–non-neuroendocrine neoplasm (MlNEN)



precursori

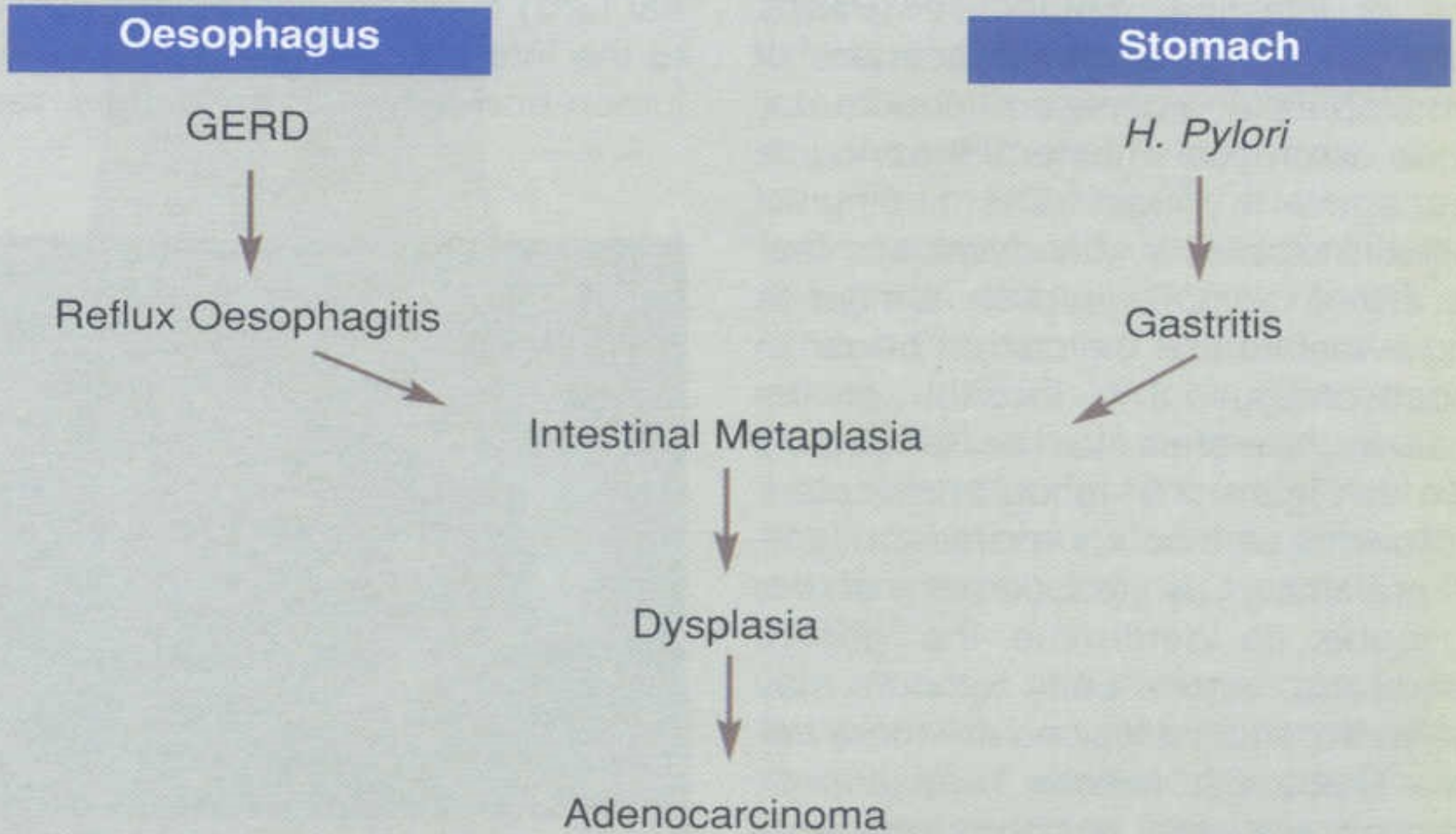


Fig. 2.03 Pathogenetic pathways operative in the evolution of oesophageal and gastric carcinoma. Intestinal metaplasia is a common precursor lesion that may result from gastro-oesophageal reflux disease (GERD) or chronic *H. pylori* infection.

Neoplasia ghiandolare intraepiteliale sec WHO 2019 (displasia)



Basso grado

Atipie citologiche

Alto grado

Atipie citoarchitetturali

Perdita di funzione



'Indefinito per displasia'

**Atipie reattive
vs atipie neoplastiche
in contesto flogistico**

ISTOTIPO, sec. WHO 2019

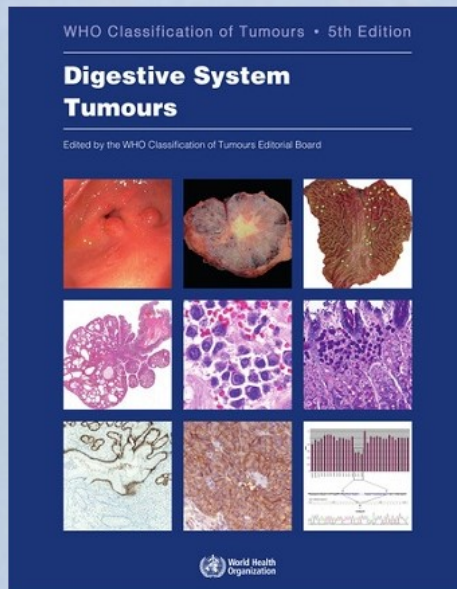
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ISTOTIPO, sec. WHO 2019

Table 3.03 Comparison of the Laurén {1798}, Nakamura {2284}, Japanese Gastric Cancer Association (JGCA) {1430}, and WHO classifications of gastric cancer


Laurén (1965)	Nakamura et al. (1968)	JGCA (2017)	WHO (2019)
Intestinal	Differentiated	Papillary: pap Tubular 1, well-differentiated: tub1 Tubular 2, moderately differentiated: tub2	Papillary <u>Tubular</u> , well-differentiated Tubular, moderately differentiated
Indeterminate	Undifferentiated	Poorly 1 (solid type): por1	Tubular (solid), poorly differentiated
Diffuse	Undifferentiated	Signet-ring cell: sig Poorly 2 (non-solid type): por2	<u>Poorly cohesive, signet-ring cell</u> phenotype Poorly cohesive, other cell types
Intestinal/diffuse/indeterminate	Differentiated/undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (e.g. por2 > sig > tub2)	Mixed
Not defined	Not defined	Special type: Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type	Other histological subtypes: Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid carcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type Micropapillary adenocarcinoma

A histological micrograph showing a dense field of tubular structures, likely glandular or ductal in origin, stained with hematoxylin and eosin (H&E). The tubules are irregular in shape and size, with some showing a clear lumen. The surrounding stroma is composed of a network of connective tissue fibers and scattered cells. The overall appearance is characteristic of a tubular neoplasm or a highly cellular glandular tissue.

tubulare

A histological slide showing a dense population of cells with purple nuclei and pink cytoplasm/extracellular matrix. The cells are arranged in a somewhat disorganized pattern, typical of a tumor. The overall appearance is that of a low-grade neoplasm with low cellularity. The text 'a cellule poco coese' is overlaid on the image, indicating the characteristic of the cells.


a cellule poco coese




**a cellule
ad anello con castone**

A histological micrograph showing a cross-section of a papillary structure. The central part of the image is filled with numerous small, rounded, purple-stained nodules or lobules, which are densely packed and separated by thin, white, fibrous connective tissue septa. These nodules are arranged in a somewhat circular or lobulated pattern. The surrounding tissue is a more uniform, pinkish-purple color, likely representing the underlying stroma or muscle layer. The overall appearance is characteristic of a papillary growth pattern, often seen in certain types of tumors or benign growths.

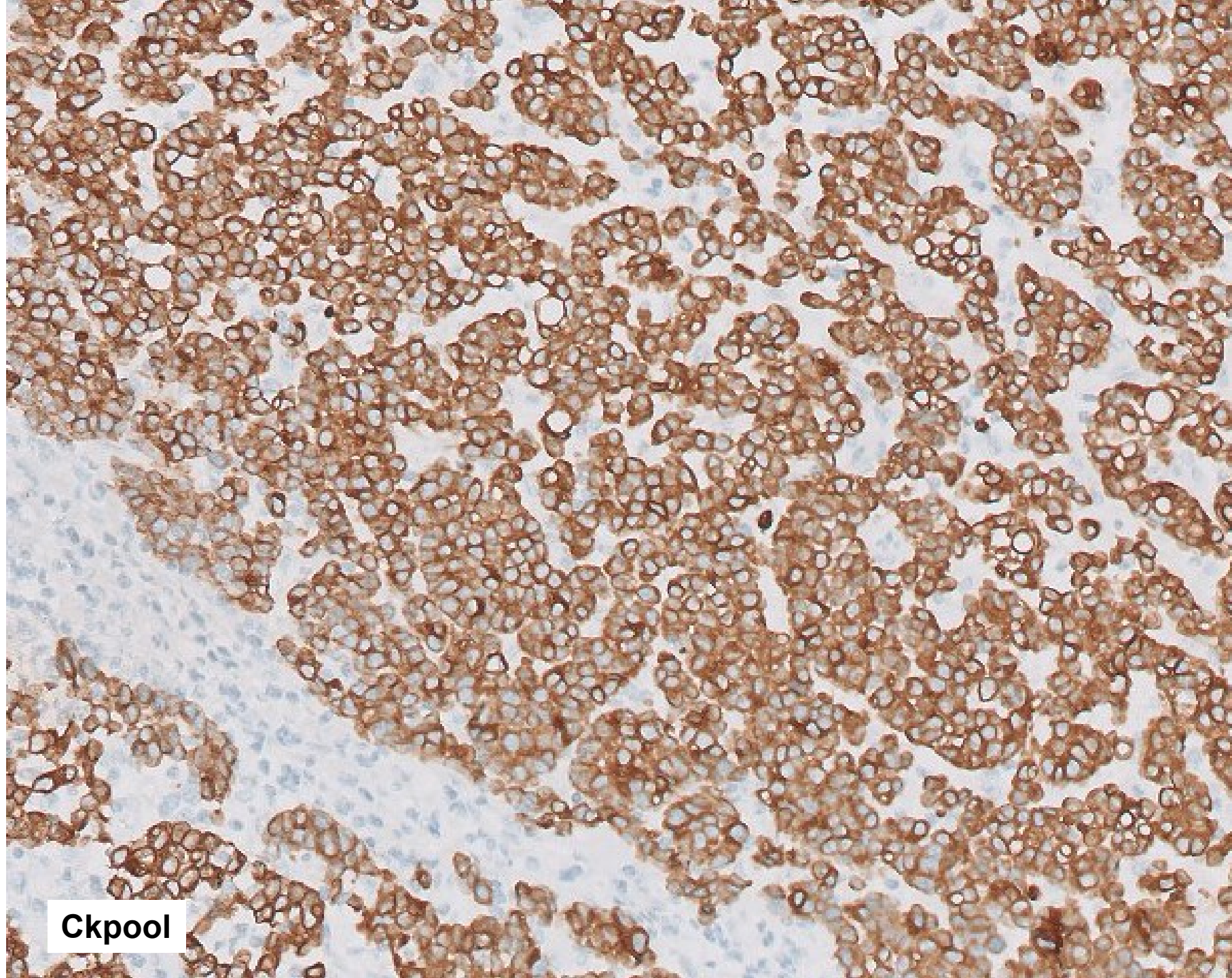
papillare

A histological micrograph showing a cross-section of mucinosa tissue. The image displays a dense population of cells with prominent, dark purple nuclei and a lighter, pinkish cytoplasm and extracellular matrix. The tissue is organized into irregular, glandular-like structures. The overall appearance is characteristic of a mucin-producing epithelium. The word "mucinoso" is overlaid in the center in a bold, black, sans-serif font.

mucinoso

A histological micrograph showing a dense population of small, dark-staining lymphocytes. The tissue is stained with hematoxylin and eosin (H&E), resulting in purple nuclei and pink cytoplasm/extracellular matrix. The overall appearance is that of a lymphoid tissue, possibly a lymph node or spleen, with a prominent medullary region. The text 'midollare con stroma linfoide' is overlaid on the image in a large, bold, black font.

**midollare
con stroma linfoide**



Ckpool



CD3

Classificazione di Lauren

> correlazione clinico-epidemiologica/patologica

INTESTINALE circa 60%

Crescita espansiva

Pattern ghiandolare

Popolazione a rischio

> maschi età medio-avanzata

> sopravvivenza

Gastrite cronica atrofico-
metaplastica Hp relata

Mts epatiche

DIFFUSO circa 30%

Crescita infiltrativa

Cellule isolate non coese

Non popolazione a rischio

> femmine < 50 aa

< sopravvivenza

Atipia colletti ghiandolari

Diffusione peritoneale

MISTI

Genetic and epigenetic changes

High genomic instability for defects of
DNA repair genes

P53 MUTATIONS,
MUTATIONS IN PROTO-ONCOGENES

E-caderin alterations

membrane glycoprotein involved
in cell-cell epithelial adhesion

Due to MUTATION AND
METHYLATION
loss of cell adhesion

Classificazioni molecolari

Classificazione TCGA The Cancer Genome Atlas

Instabilità cromosomica (perlopiu' tubulari)
Stabilità genomica (perlopiu' diffusi)
EBV-relati (midollari)
MSI (MLH1, mutazione/ipermetilazione)

Classificazione ACRG Asina Cancer Reserach Group

Instabilità dei microsatelliti (MSI)

Stabilità dei microsatelliti (MSS)
con transizione epitelio-mesenchimale

Stabilità dei microsatelliti (MSS)
con p53 attiva

Stabilità dei microsatelliti (MSS)
con p53 inattiva

GRADING (G) sec WHO 2019

valutazione complessiva dell'entità delle anomalie morfologiche delle cellule e dell'architettura tissutale

Grading

Grading applies primarily to tubular and papillary carcinomas and not to other GC subtypes. Thus, well-differentiated adenocarcinomas are composed of well-formed glands, whereas poorly differentiated carcinomas have poorly formed glands and may display solid areas or individual cells. Grading is preferably performed using a two-tiered system: low-grade (formerly well or moderately differentiated) versus high-grade (formerly poorly differentiated).

G1 neoplasia ben differenziata

Basso grado

G2 neoplasia moderatamente differenziata

G3 neoplasia scarsamente differenziata

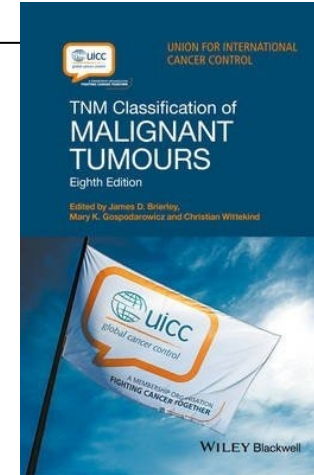
G4 neoplasia indifferenziata (anaplastica)

Alto grado

STAGING sec. TNM versione 8, 2017

T1 mucosa/sottomucosa
 lamina propria/m mucosae (T1a)
 sottomucosa (T1b)
T2 muscolare propria propria
T3 sottosierosa
T4a infiltrante la sierosa
T4b infiltrante strutture adiacenti

T

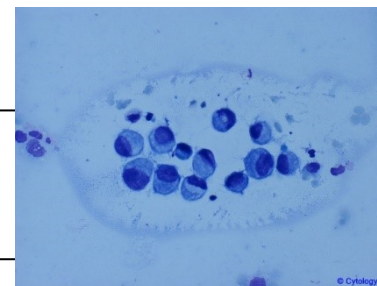


N1 1-2 regionali
N2 3-6 regionali
N3a 7-15 regionali
N3b 16 or piu' regionali

**16 numero minimo
(se < 16 e negativi classificare N0)**

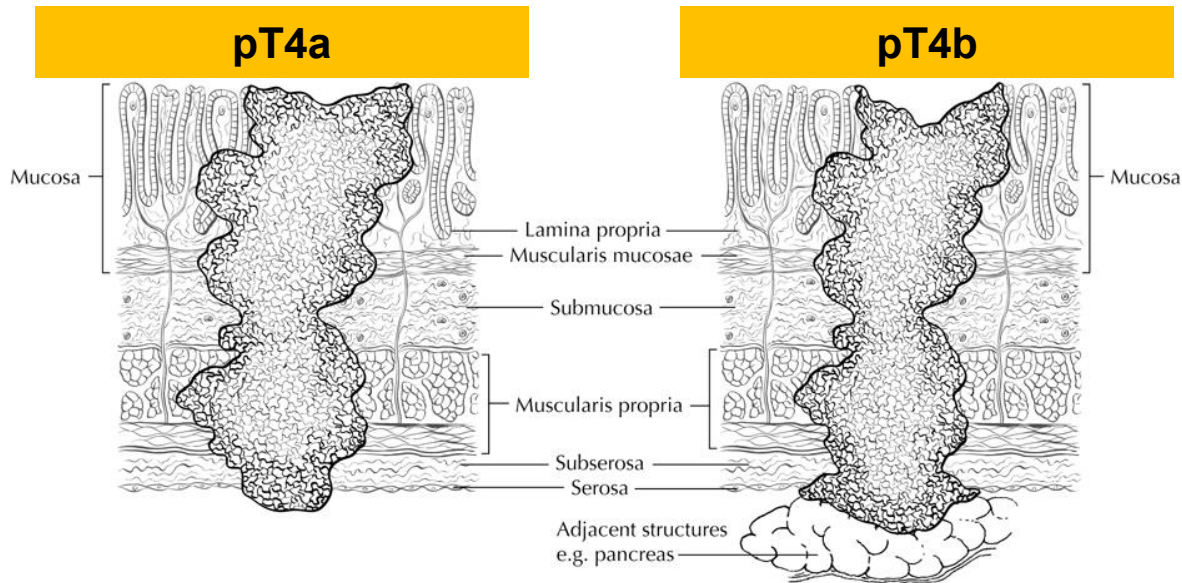
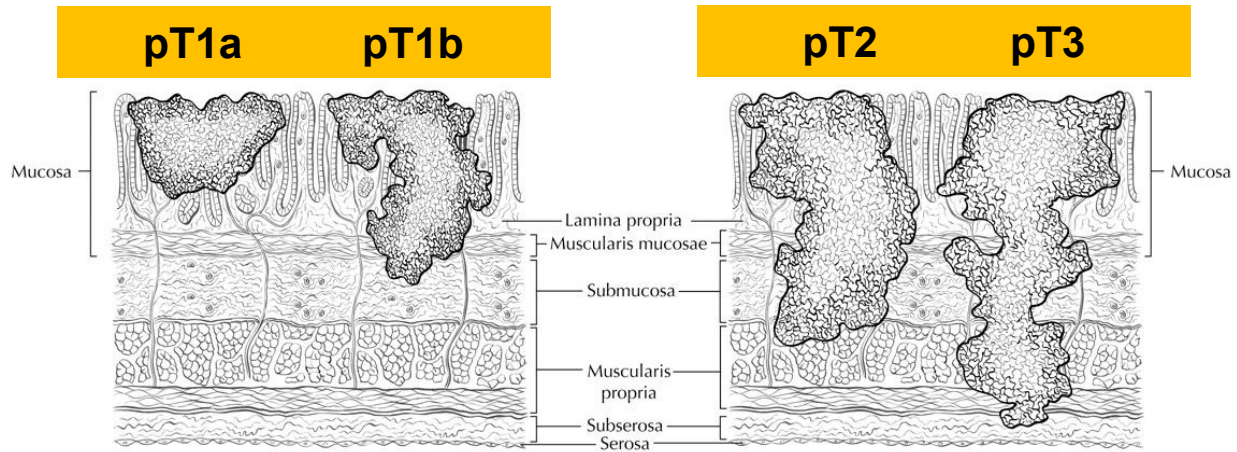
N

M1 metastasi a distanza
(inclusa citologia peritoneale positiva)



M

STAGING TNM versione 8, 2017



REPORT ISTOLOGICO COMPLETO

Adenocarcinoma dell'antro/corpo/fondo gastrico

-Tipo istologico: papillare/tubulare/a cellule poco coese/a cellule ad anello con castone (sec. WHO); intestinale/diffuso (sec. Lauren)

-Grado istologico: G1-G2-G3-G4 sec. WHO

-Invasione linfo-vascolare: presente/assente

-Invasione perineurale: presente/assente

-Profondità di invasione

non evidenza di tumore primitivo

neoplasia infiltrante la lamina propria (c.d. 'early gastric cancer') (pT1a)

neoplasia infiltrante la muscularis mucosae (c.d. 'early gastric cancer') (pT1a)

neoplasia infiltrante la tonaca sottomucosa (c.d. 'early gastric cancer') (pT1b)

neoplasia infiltrante la tonaca muscolare propria (pT2)

neoplasia infiltrante il tessuto connettivo sottosieroso (pT3)

neoplasia infiltrante il peritoneo viscerale (pT4a)

neoplasia infiltrante strutture adiacenti (pT4b)

-Metastasi linfonodali:/.... linfonodi periviscerali (N1 1-2; N2 3-6; N3a 7-15; N3b >16)

-Stato dei margini di resezione chirurgica:

margine prossimale indenne da neoplasia infiltrante/sede di neoplasia infiltrante;

margine distale indenne da neoplasia infiltrante/sede di neoplasia infiltrante

-Effetti da trattamento: nessun precedente trattamento neoadiuvante riferito; presenti,

Grado di regressione tumorale (sec. Becker):

1a assenza di neoplasia residua

1b neoplasia residua <10%

2 neoplasia residua 10-50%

3 neoplasia residua >50%

-Metastasi a distanza: presente/assente/non applicabile

-Ulteriori reperti patologici

Gastrite cronica Metaplasia intestinale Displasia

Stadiazione istopatologica (sec. TNM v8):

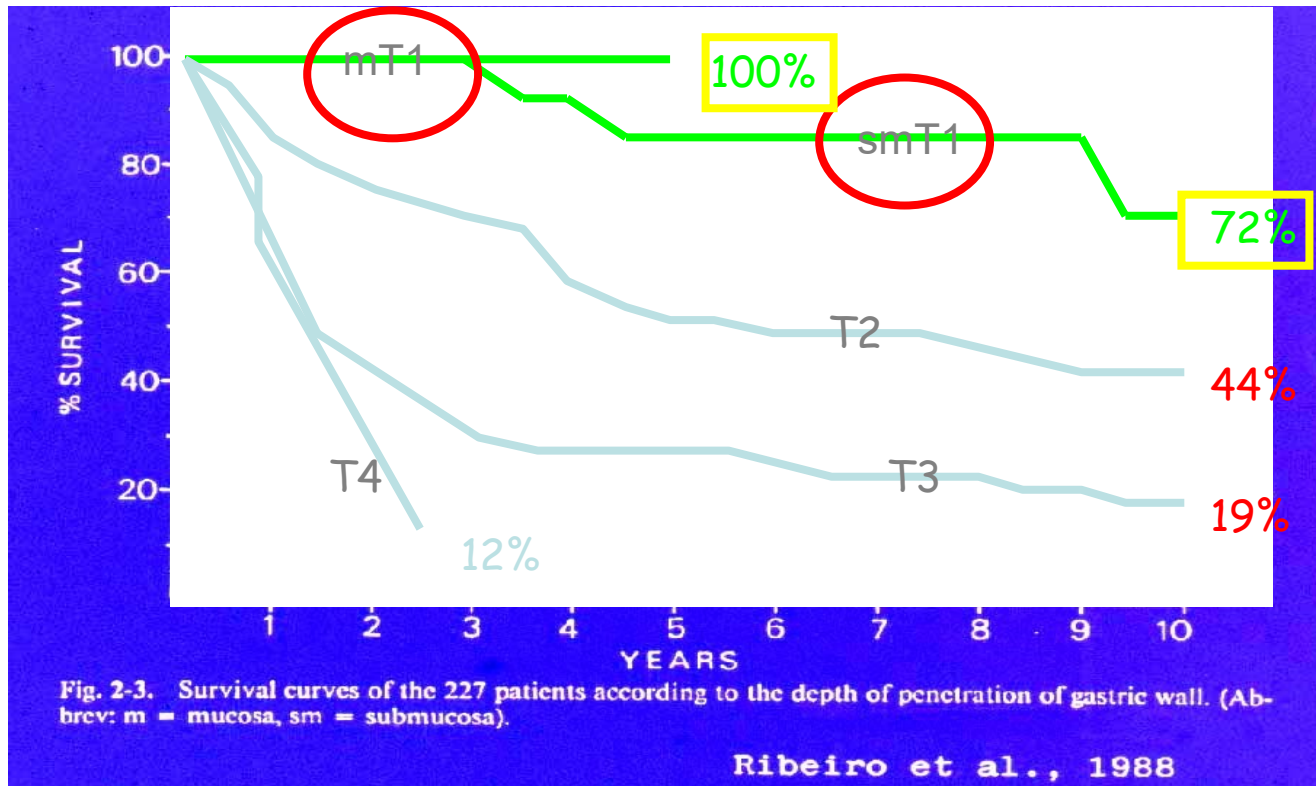
pT N R



EARLY GASTRIC CANCER

Malignant gastric epithelial neoplasm
Limited to MUCOSA or SUBMUCOSA regardless nodal status

5 YRS SURVIVAL AFTER RADICAL SURGERY



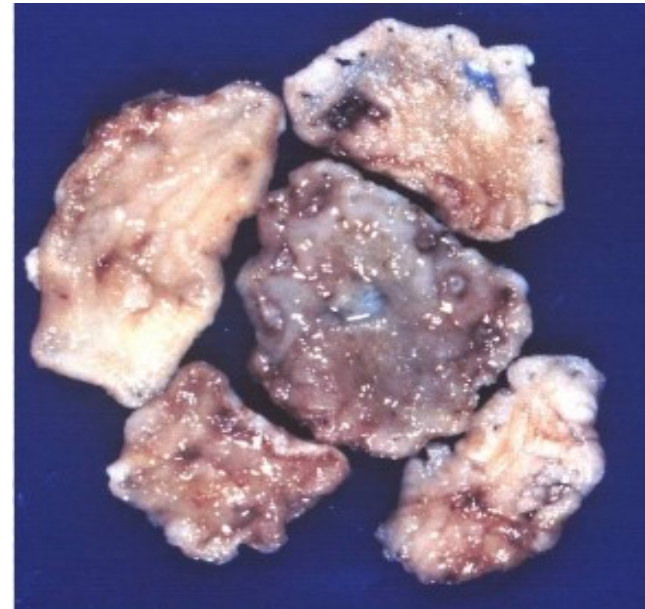
Endoscopic submucosal dissection

ESD

vs

Endoscopic mucosal resection

EMR



92% en bloc
82% R0
<1% recurrence
4% perforation

48% Piecemeal
42% R0
6% recurrence
<1% perforation

A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer

Jingjing Lian, MD,¹ Shiyao Chen, MD, PhD,¹ Ying Zhang, MD,² Feng Qiu, MD³

Shanghai, China

Curative resections (standard criteria)

En bloc resection of lesion
 Tumor size $< \phi = 2$ cm
 Differentiated type
 Intramucosal carcinoma (m1-m3)
 Negative resection margins
 No lymphovascular invasion
 No ulcer or ulcer scar

Depth \ Histology	Mucosal cancer				Submucosal cancer	
	UL(-)		UL(+)		SM1	SM2
	≤ 20 mm	>20 mm	≤ 30 mm	>30 mm	≤ 30 mm	any size
Differentiated	Absolute criteria for EMR	Expanded criteria for ESD	Expanded criteria for ESD	Surgery	Expanded criteria for ESD	Surgery
Undifferentiated	Absolute criteria for EMR	Surgery	Surgery	Surgery	Surgery	Surgery

Absolute criteria for EMR
 Expanded criteria for ESD

Surgery
 Consider surgery

Curative resections (expanded criteria)

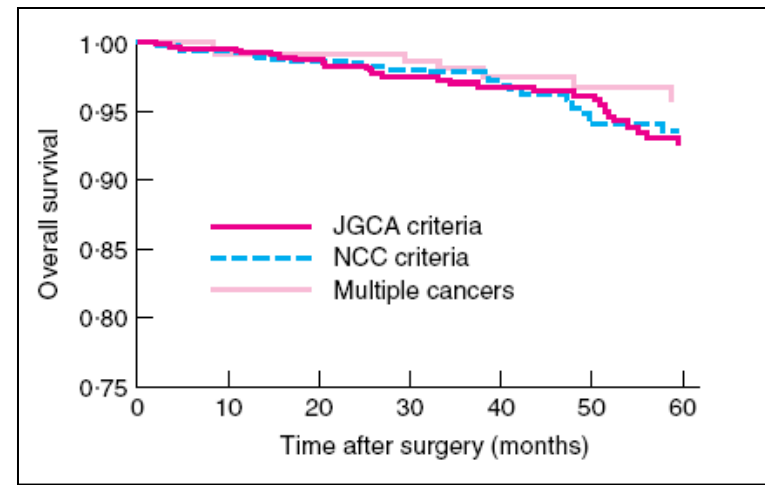
en bloc resection
negative margins
no lymphovascular invasion

- Tumor < o = 2 cm, undifferentiated, pT1a, UL (-)
- Tumor > 2 cm, differentiated, pT1a, UL (-)
- Tumor < o = 3 cm, differentiated, pT1a, UL (+)
- Tumor < o = 3 cm, differentiated, pT1b (SM1, < 500 micron)

Depth \ Histology	Mucosal cancer				Submucosal cancer	
	UL(-)		UL(+)		SM1	SM2
	≤ 20mm	>20mm	≤ 30mm	>30mm	≤ 30mm	any size
Differentiated	Green	Yellow	Yellow	Red	Yellow	Red
Undifferentiated	Green	Red	Red	Red	Red	Red

■ Absolute criteria for EMR
■ Expanded criteria for ESD

■ Surgery
■ Consider surgery





Proper pathologic preparation and assessment of endoscopic mucosal resection and endoscopic submucosal dissection specimens

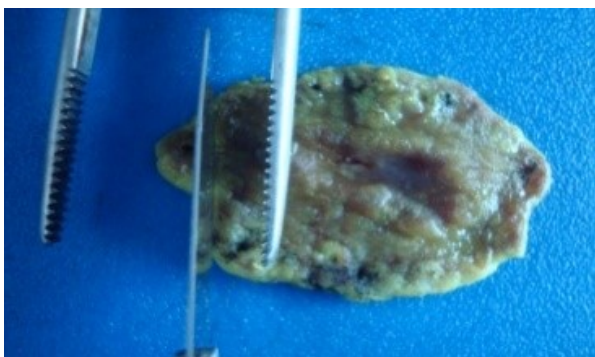
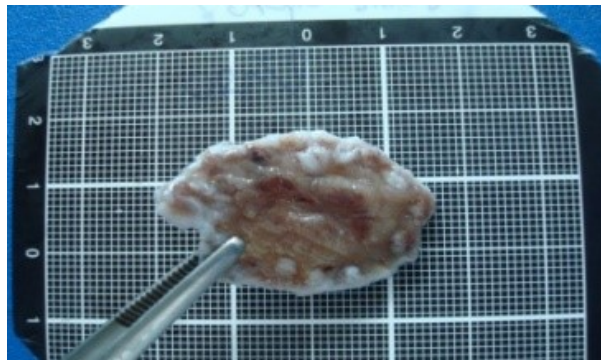
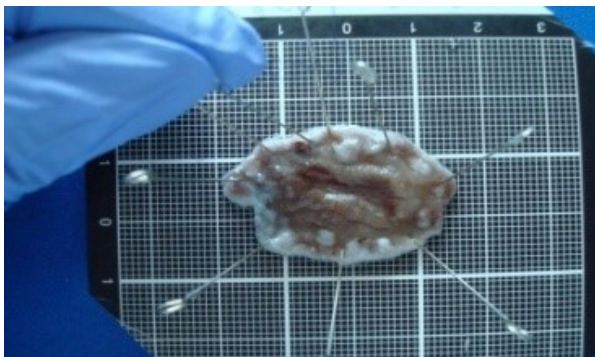
Amirkaveh Mojtahed, MD,^a Tadakazu Shimoda, MD, PhD^b

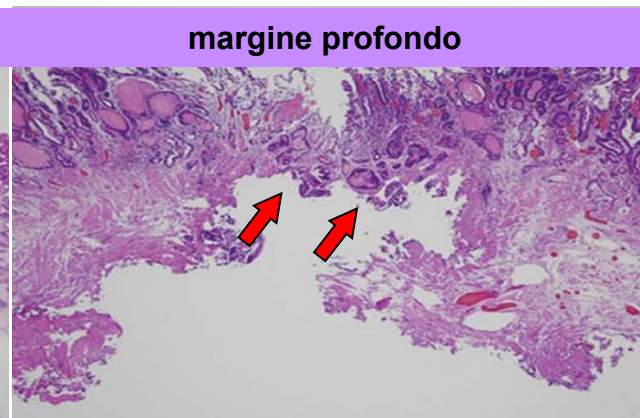
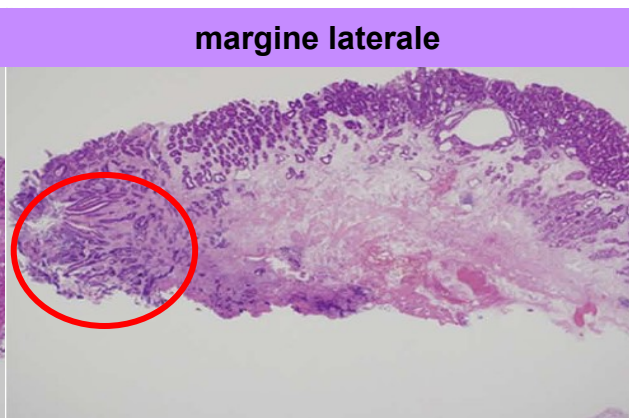
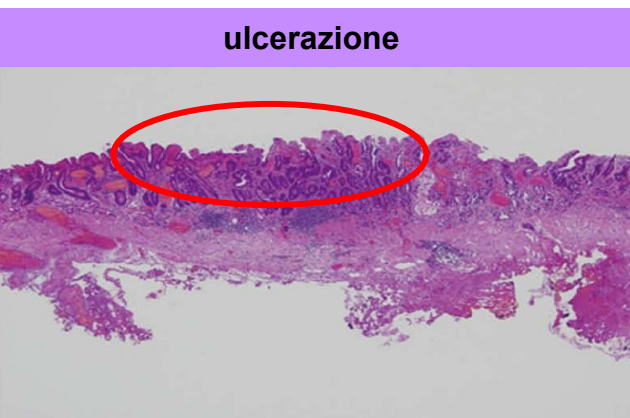
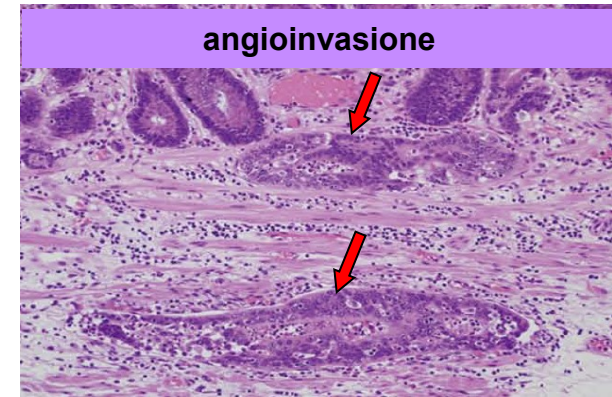
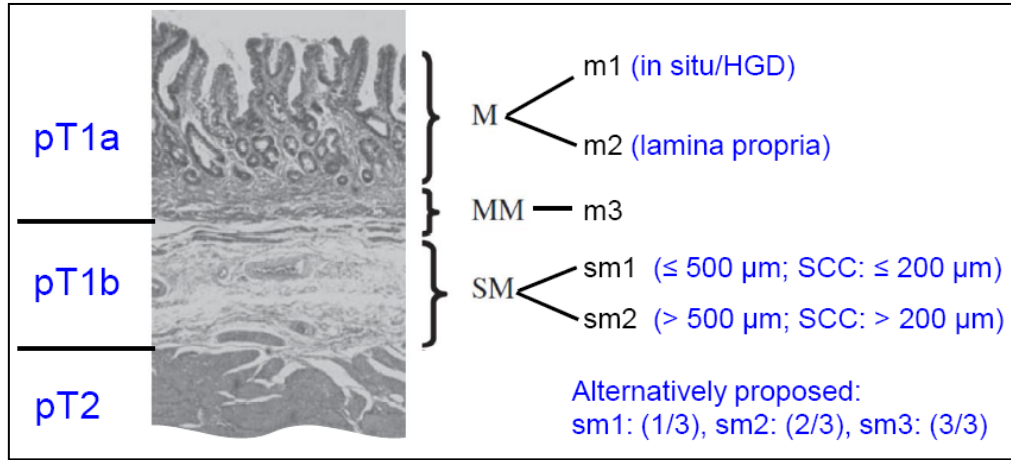
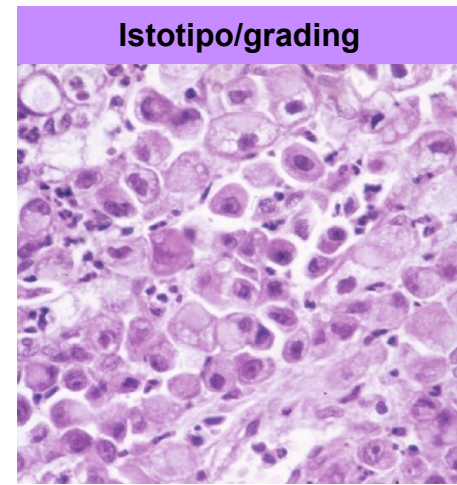
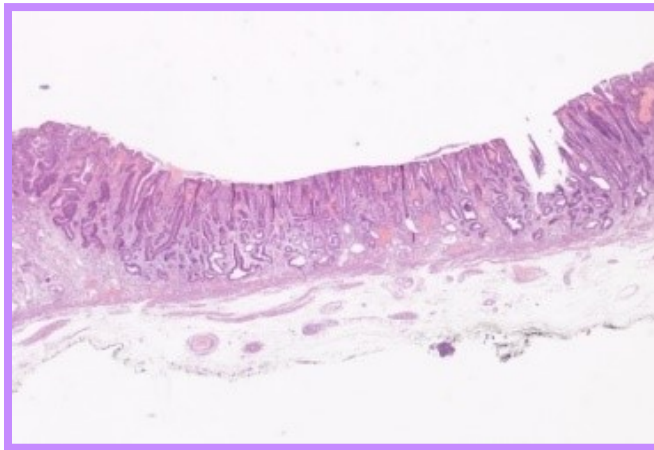
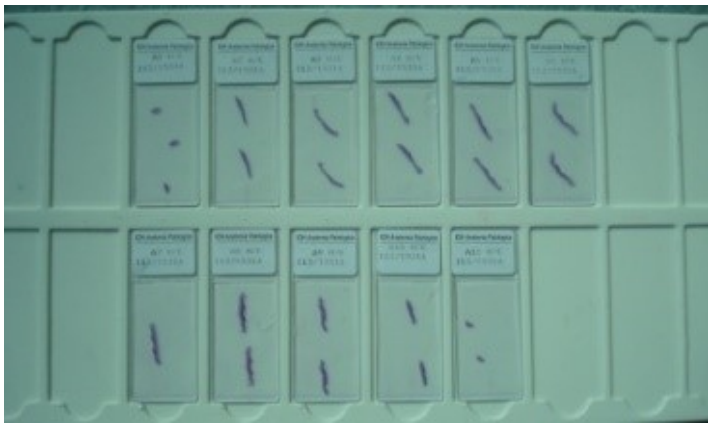
^aDepartment of Pathology, Veterans Affairs Palo Alto, Stanford University Medical Center, Stanford, California.
^bCancer for Control and Information Services, National Cancer Center, Tokyo, Japan.

Shigetaka Yoshinaga, MD, PhD, Series Editor

Pathological evaluation of gastrointestinal endoscopic submucosal dissection materials based on Japanese guidelines

Koji Nagata, Michio Shimizu







Pathology report (EMR/ESD) minimum items

- **Number of specimens (en bloc vs piece meal)**
- **Size of the specimen, size of the lesion (macro/micro)**
- **Macroscopic tumor type (Paris Classification)**
- **Histological tumor type (differentiated vs undifferentiated)**
- **Depth of invasion ('extended' TNM)**
- **Presence of intratumoral ulcer**
- **Presence of lymphovascular invasion**
- **Resection margin status (HM,VM)**

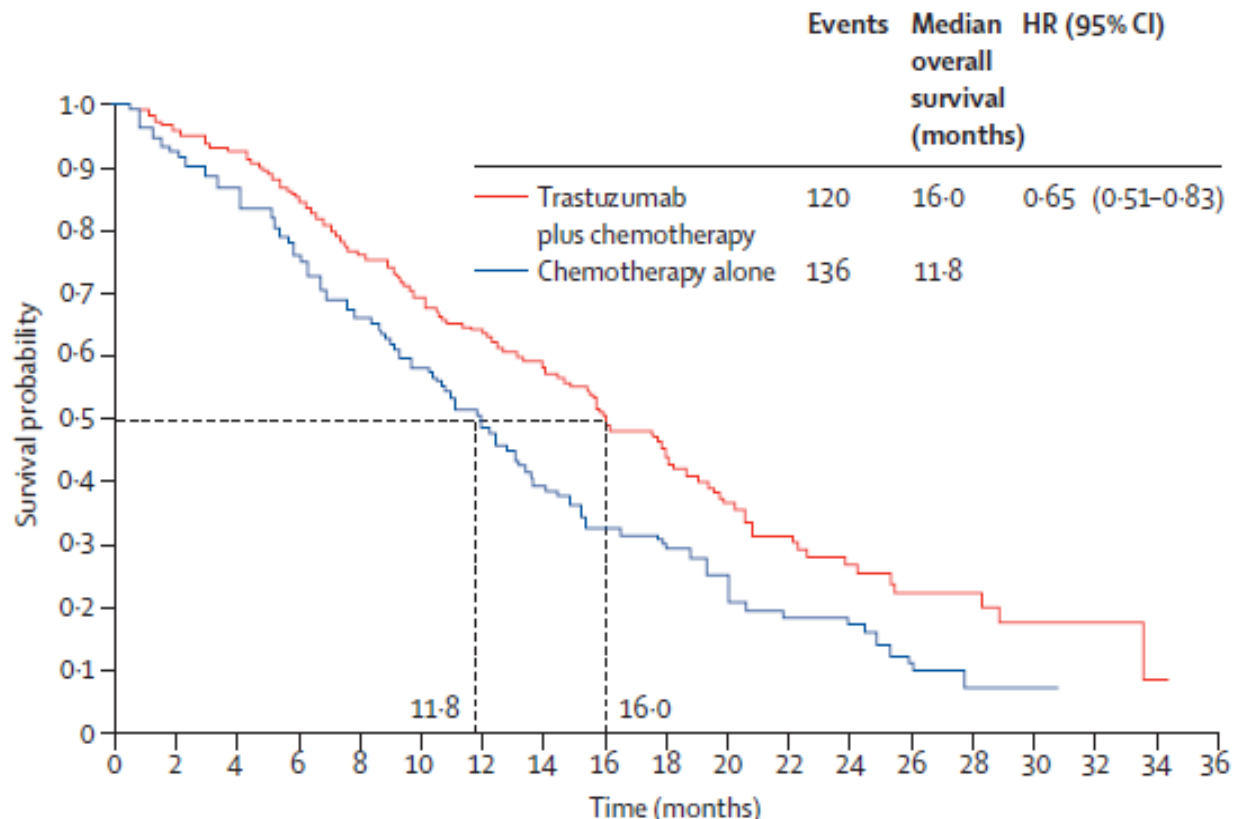
- **Curative resection (yes/no)**



ANALISI MOLECOLARE

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang,* Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†
Lancet 2010; 376: 687–97



HER2 positivity rates

gastric cancer: 10-30%
gastro-esophageal junction cancer: 20-25%

HER2 and histotype

HER2 expression is mainly restricted to intestinal-type, gland-forming cancer

HETEROGENEITY

staining is more heterogeneous
and incomplete membrane immunoreactivity is more frequent

IMMUNOHISTOCHEMISTRY

Easier to perform and relatively inexpensive.
However, the sensitivity and specificity of the assay vary significantly depending on commercial antibody used.

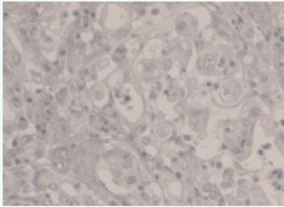
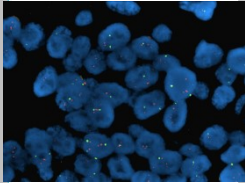
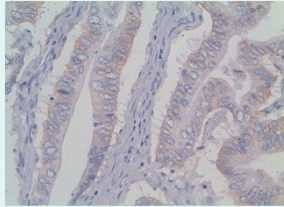
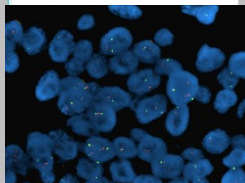
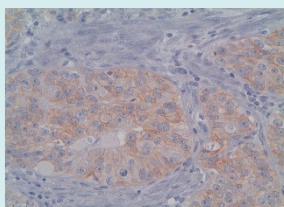
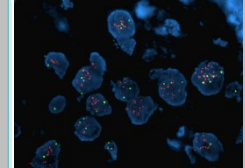
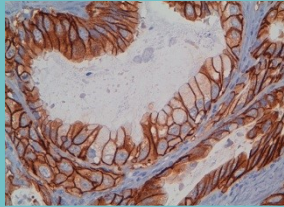
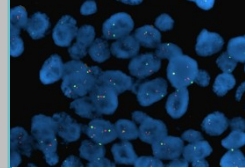
Use of FDA approved antibodies is recommended:
HercepTest – 4B5

MOLECULAR BIOLOGY

FISH method is more standardized and less variable and has, therefore, emerged as a “gold standard” for assessment of HER2

Chromogenic In Situ Hybridization – CISH
Silver-enhanced In Situ Hybridization – SISH

IMMUNOHISTOCHEMISTRY SCORING SYSTEM

		BIOPSY	SURGICAL SPECIMEN	FISH
	0	no reactivity in any tumor cell	no reactivity or membranous reactivity in less than 10% of cells	 NEGATIVE
	1+	faint/barely perceptible membranous reactivity in at least a cluster of ≥ 5 cells	faint/barely perceptible membranous reactivity in $\geq 10\%$ of cells	 NEGATIVE
	2+	weak to moderate complete or basolateral membranous reactivity in at least a cluster of ≥ 5 cells	weak to moderate complete or basolateral membranous reactivity in $\geq 10\%$ of tumor cells	 EQUIVOCAL
	3+	strong complete or basolateral membranous reactivity in at least a cluster of ≥ 5 cells	strong complete or basolateral membranous reactivity in $\geq 10\%$ of tumor cells	 POSITIVE

Hoffmann F. *Histopathology* 2008, 52:797-805

Bang YJ. *Lancet* 2010; 46:31-37

Rúshoff J. *Virchows Arch* 2010;457:299-307

Reliability of HER2 evaluation in endoscopic biopsies

- ✓ In the western world, half of GC and GEJC are diagnosed at an unresectable stage
- ✓ The only material available are endoscopic biopsies
- ✓ Intra-tumour heterogeneous HER2 expression in about 50% IHC2+/3+ cases
- ✓ 60% of biopsies taken for cancer diagnosis are effectively composed of invasive neoplasia

The hypothesis that HER2 status on biopsy may not be truly representative should be considered

- ✓ predictive value of HER2 assessment by IHC in biopsies is on the whole high
- ✓ it may be increased if FISH is applied on both 1+ and 2+ cases
- ✓ approximately 10% of cases will not be accurately predicted by IHC evaluation on biopsy alone.

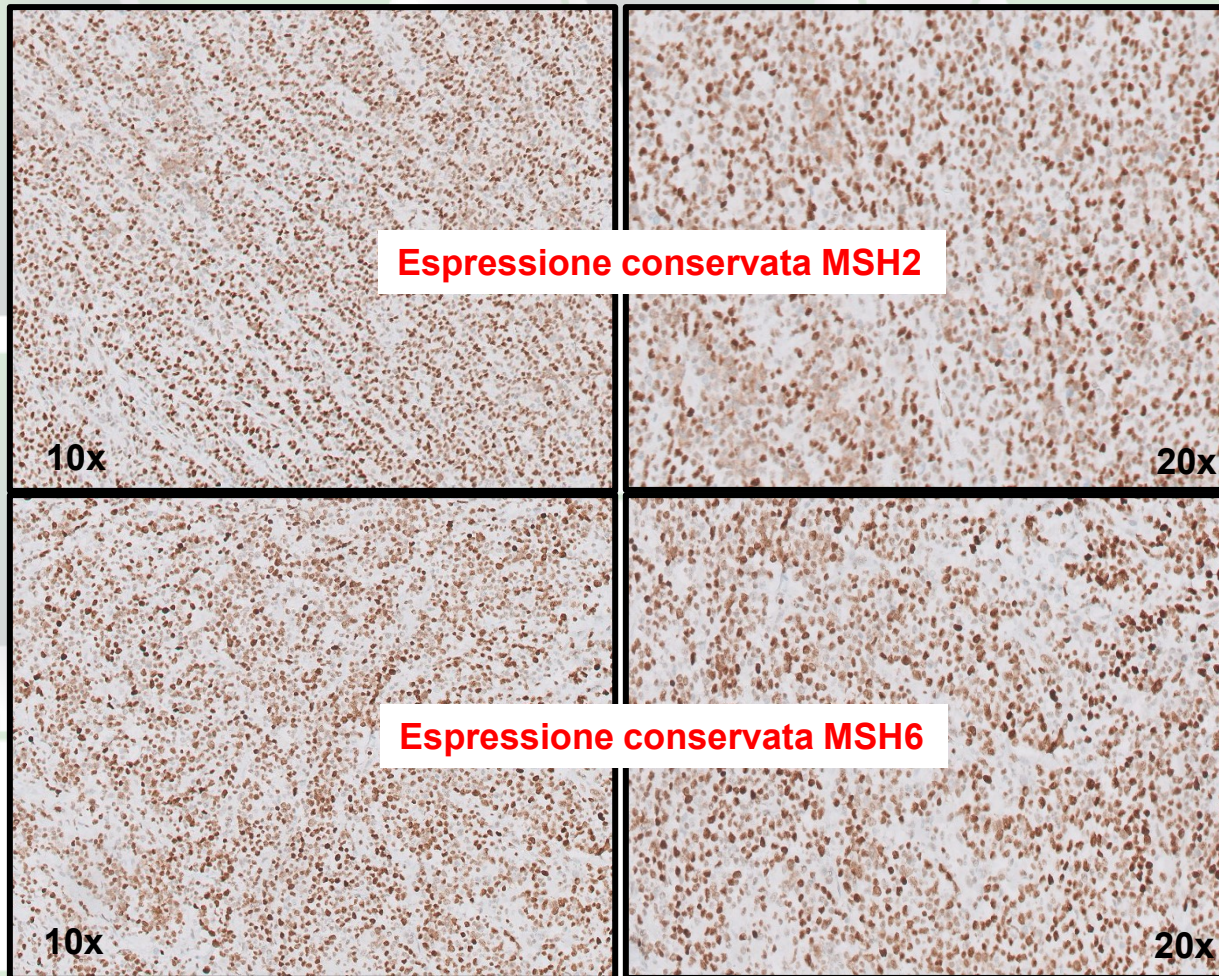
The reliability of endoscopic biopsies in assessing HER2 status in gastric and gastro-esophageal junction cancer: a study comparing biopsies with surgical samples

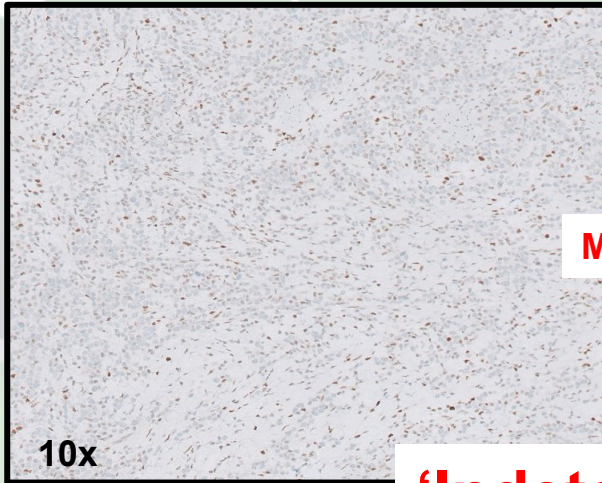
Federica Grillo^{1*}, Matteo Fassan^{2-3*}, Chiara Ceccaroli¹, Cinzia Giacometti², Monica Curto¹, Vittorina Zagonel⁴, Paola Ceppa¹, Donato Nitti⁵, Carlo Castoro⁴, Roberto Fiocca¹, Massimo Rugge^{2,4}, Luca Mastracci¹

Translational Oncology, 2013

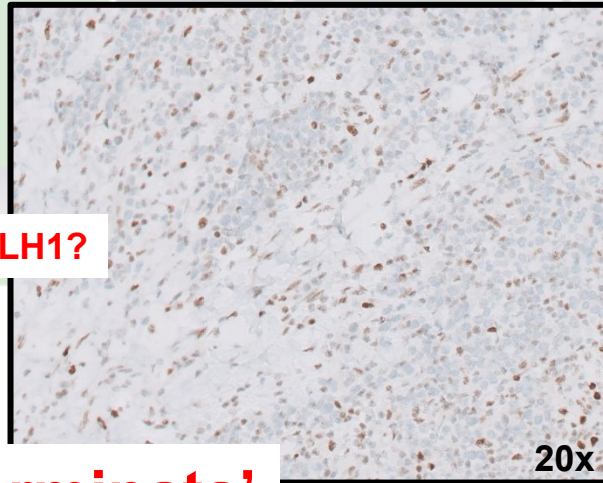


Grazie per l'attenzione



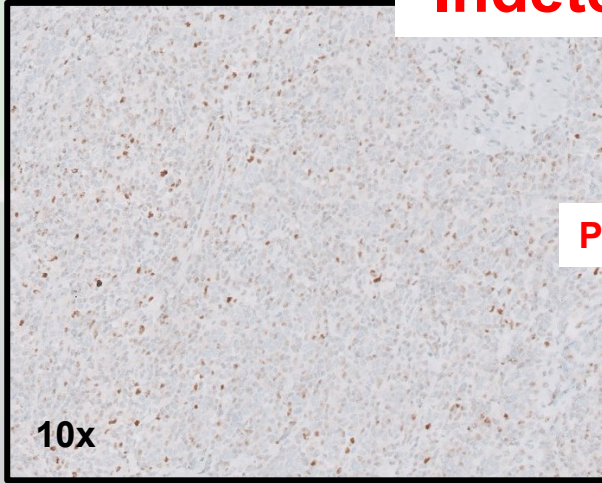


MLH1?

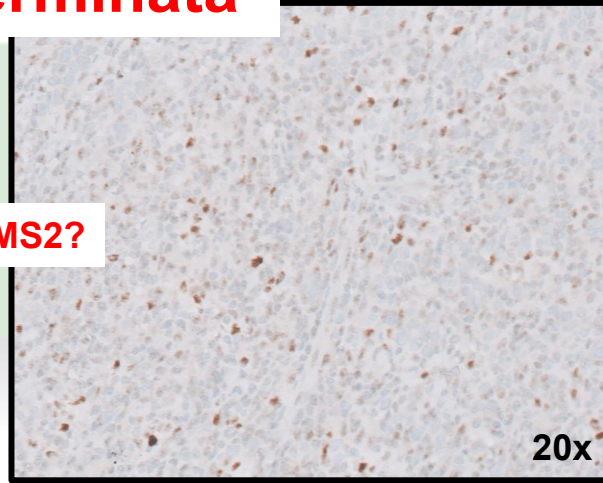


20x

'Indeterminata'



PMS2?



20x

**Reazione immunoistochimica
Esuberanza di controllo interno**

**pattern
biologicamente plausibile**

**conferma
molecolare
MSI**