The new WHO classification of tumours of the digestive tract

Tumours of the upper GI tract

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Porto, Portugal
WHO Classification of Tumours ONLINE

Now available at: tumourclassification.iarc.who.int

Access to the following books:

<table>
<thead>
<tr>
<th>5th edition</th>
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<tr>
<td>Digestive Tumours</td>
<td>Skin Tumours</td>
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<tr>
<td>Breast Tumours</td>
<td>Eye Tumours</td>
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<tr>
<td>Endocrine Tumours</td>
<td>Head and Neck Tumours</td>
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</table>

Special launch rate of 100 Euros

More details from the IARC team – Booth A14, 2nd level, Agora 2 Hall
9am to 5.15pm, from Sunday 8 to Tuesday 10 September
Epithelial Tumours

Tumours of the oesophagus

Tumours of the oesophagus: Introduction

Epithelial tumours

Benign epithelial tumours and precursors

- Oesophageal squamous papilloma
- Barrett dysplasia
- Oesophageal squamous dysplasia

Malignant epithelial tumours

- Adenocarcinoma of the oesophagus and oesophagogastric junction NOS
- Oesophageal adenoid cystic carcinoma
- Oesophageal adenosquamous and mucoepidermoid carcinomas
- Oesophageal squamous cell carcinoma NOS
- Oesophageal undifferentiated carcinoma
- Oesophageal neuroendocrine neoplasms

Tumours of the stomach
Haematolymphoid Tumours

Mesenchymal Tumours
Genetic tumour syndromes of the digestive system

Genetics

Genetic tumour syndromes of the digestive system

Lynch syndrome
Familial adenomatous polyposis 1
GAPPS and other fundic gland polyposes
Other adenomatous polyposes
Serrated polyposis

Hereditary diffuse gastric cancer
Familial pancreatic cancer
Juvenile polyposis syndrome
Peutz-Jeghers syndrome
Cowden syndrome
Other genetic tumour syndromes
Epithelial Tumours

Tumours of the stomach
   Tumours of the stomach: Introduction
   Gastritis and metaplasia: precursors of gastric neoplasms

Epithelial tumours
   Benign epithelial tumours and precursors
      Fundic gland polyps
      Gastric hyperplastic polyps
      Gastric dysplasia
   Intestinal-type gastric adenoma
   Foveolar-type adenoma
   Gastric pyloric gland adenoma
   Oxyntic gland adenoma

Malignant epithelial tumours
   Gastric adenocarcinoma
   Gastric squamous cell carcinoma
   Gastric adenosquamous carcinoma
   Gastric undifferentiated carcinoma
   Gastroblastoma
   Gastric neuroendocrine neoplasms
Unequivocal neoplastic changes in a polypoid lesion consisting of gastric intestinalized glands; no evidence of invasion.

**Intestinal-type gastric adenoma**

*APC, KRAS* mut.

**Pyloric gland adenoma**

Frequent *APC*, *KRAS* mut.

Frequent *APC*, *KRAS* mut., *GNAS* mut.

**Adenomas of the glandular epithelium**

Foveolar-type adenoma

Polypoid growth of dysplastic columnar epithelia with a foveolar-cell phenotype, with a distinctive apical cap of neutral mucins

**Foveolar-type adenoma**

*APC, AXIN1-2*

*OGA–GA–FG (GNAS mut.)*

**Adenomas of the superficial epithelium**

Oxyntic gland adenoma

Intramucosal proliferation of differentiated columnar cells with pale basophilic cytoplasm and mild nuclear atypia, mimicking the oxyntic (fundic) gland.

**Oxyntic gland adenoma**

*APC, AXIN1*–*2*
Tumours of the stomach

- Tumours of the stomach: Introduction
- Gastritis and metaplasia: precursors of gastric neoplasms

Epithelial tumours

- Benign epithelial tumours and precursors
  - Fundic gland polyps
  - Gastric hyperplastic polyps
  - Gastric dysplasia
  - Intestinal-type gastric adenoma
  - Foveolar-type adenoma
  - Gastric pyloric gland adenoma
  - Oxyntic gland adenoma

- Malignant epithelial tumours
  - **Gastric adenocarcinoma**
  - Gastric squamous cell carcinoma
  - Gastric adenosquamous carcinoma
  - Gastric undifferentiated carcinoma
  - Gastroblastoma
  - Gastric neuroendocrine neoplasms
WHO Classification of Tumours of the Digestive System, 4th edition, 2010
ICD-O Code

Adenocarcinoma 8140/3
Papillary adenocarcinoma 8260/3
Tubular adenocarcinoma 8211/3
Mucinous adenocarcinoma 8480/3
Poorly cohesive carcinoma 8490/3
(Signet-ring cell carcinoma and variants)
Mixed carcinoma 8255/3
The same frame for the classification of major types of gastric cancer was kept.
Tumours of the stomach

Tumours of the stomach: Introduction
Gastritis and metaplasia: precursors of gastric neoplasms

Epithelial tumours

Benign epithelial tumours and precursors
  - Fundic gland polyps
  - Gastric hyperplastic polyps
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  - Intestinal-type gastric adenoma
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Malignant epithelial tumours
  - Gastric adenocarcinoma
  - Gastric squamous cell carcinoma
  - Gastric adenosquamous carcinoma
  - Gastric undifferentiated carcinoma
  - Gastroblastoma
  - Gastric neuroendocrine neoplasms
Tubular adenocarcinoma. The tumour is composed of dilated tubules invading the muscle layer.

Papillary carcinoma. The tumour consists of elongated finger-like processes with fibrovascular connective tissue cores, lined by columnar cells.
Poorly cohesive carcinoma, signet-ring cell type
The tumour is composed predominantly of signet-ring cells; the neoplastic cells are larger at the superficial part of the mucosa.

Poorly cohesive carcinoma NOS
The tumour consists of poorly cohesive cells of non–signet-ring cell type that invade the gastric wall widely, with marked desmoplasia.
Mixed carcinoma

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**Histological variants:**
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Carcinoma with lymphoid stroma
- Hepatoid adenocarcinoma
- Adenocarcinoma with enteroblastic differentiation
- Adenocarcinoma of fundic gland type

*JGCA, Japanese Gastric Cancer Association {978-4-307-20375-3}. **Table prepared in collaboration with Prof. Ryoji Kushima, Japan
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<td>Papillary&lt;br&gt;Tubular, well-differentiated&lt;br&gt;Tubular, moderately-differentiated</td>
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<td></td>
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<td>Micropapillary adenocarcinoma</td>
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</tbody>
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Poorly cohesive carcinoma, **SRC**

Poorly cohesive carcinoma, **NOS**
Heterogeneity of poorly cohesive carcinoma

PCC-NOS: TP53, BRAF, PI3CA, SMAD4, and RHOA
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*JGCA, Japanese Gastric Cancer Association*

**Histological variants:**

- Adenosquamous carcinoma (separate chapter)
- Squamous cell carcinoma (separate chapter)
- Undifferentiated carcinoma (separate chapter)
  - Carcinoma with lymphoid stroma
  - Hepatoid carcinoma
  - Adenocarcinoma with enteroblastic differentiation
  - Adenocarcinoma of fundic gland type
  - Micropapillary adenocarcinoma

**WHO, 5th edition**

- Classification of Tumours of the Digestive System, 5th edition, 2019
Invasive micropapillary adenocarcinoma
The tumour clusters display the characteristic inside-out growth pattern, with the luminal pole of the cells present on the outer surface of the cluster

Adenocarcinoma with enteroblastic differentiation
The glands consist of the columnar neoplastic cells characterized by glycogen-rich clear cytoplasm, reminiscent of fetal gut epithelium (variant of hepatoid carcinoma)
Gastric carcinoma with lymphoid stroma (EBV-positive gastric cancer)

Cancer cells form small nests or fused glands, accompanied by abundant lymphocyte infiltration. Nuclei of carcinoma cells are positive by in situ hybridization targeting EBV-encoded small RNA (EBER). Nuclei of infiltrating lymphocytes are negative.
Gastric adenocarcinoma of fundic-gland type
Submucosal invasion in the central portion of the tumor
Neoplastic cells of immature fundic-gland type

WHO Classification of Tumours of the Digestive System, 5th edition, 2019

Very good prognosis
MOLECULAR CLASSIFICATION OF GASTRIC CANCER (TCGA)

The Cancer Genome Atlas (TCGA) project; Nature 2014
MOLECULAR CLASSIFICATION OF GASTRIC CANCER (ACRG)

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<td>Relative frequency</td>
<td>9%</td>
<td>22%</td>
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<td>CIMP</td>
<td>CIMP</td>
<td>Rare</td>
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<td>Rare</td>
<td>Rare</td>
<td>Frequent</td>
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<td>CD274 (PD-L1) and PDCD1LG2 (PD-L2) amplification</td>
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<td>Rare</td>
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A PROTEIN AND MRNA EXPRESSION-BASED CLASSIFICATION OF GASTRIC CANCER

Gastric Cancer

EBV GC
- Gp1 (5%)
  - strong association with PD-L1
  - better survival

MSI-H GC
- Gp2 (10%)
  - associated with a lower frequency of nodal metastasis
  - better survival

Gp 3 (21%)
- recognition of an aberrant pattern of E-cadherin staining
- associated with Lauren Diffuse type GC

Gp 4 (51%)
- associated with higher Lymph node stage >N0
- associated with Lauren Intestinal type GC

GC WITH ABERRANT E-CADHERIN

GC WITH NORMAL P53

REMAINING


Prognostic and predictive biomarkers

Molecular profile:
The recently identified molecular profiles are not only important to improve our understanding of driver alterations involved in gastric carcinogenesis, but may also help identify clinically relevant biomarkers and new potential therapeutic targets in the future.

Established predictive biomarkers:
ERBB2 (HER2): Anti-ERBB2 therapy benefits patients with unresectable or metastatic/recurrent ERBB2-positive GC, and ERBB2 testing is used to predict potential therapy response. ERBB2 status is assessed primarily by immunohistochemistry; if the findings are equivocal, ERBB2 in situ hybridization is recommended. The prognostic value of ERBB2 overexpression / ERBB2 amplification has been demonstrated in some studies but not in others.
HER2 IN GASTRIC CARCINOMA: PROGNOSTIC AND/OR PREDICTIVE FACTOR

Prognostic factor?

- YES (56%)
- NO (44%)

HER2 amplification in intestinal-type gastric carcinoma

Blood born metastases
Poor prognosis

Predictive factor

ToGA Trial
HER-2 overexpression in 22% of advanced gastric cancers; improved survival in patients treated with trastuzumab

David L et al; Mod Pathol 5:384, 1992
Barros-Silva J et al; Br J Cancer 100: 487, 2009

ASCO 2009 (LBA 4509)
EVALUATION OF HER2 STATUS

Immunohistochemistry

In situ hybridization
Predictive biomarkers partly established and/or under development:

**RTK: POOR PROGNOSIS**

*EGFR* amplification has been suggested to be an independent prognostic factor in stage II/III GC. Similarly, c-MET status has been suggested to be an independent prognostic factor for unresectable or recurrent GC in patients who received standard chemotherapy.

**MSI and EBV: GOOD PROGNOSIS**

Histological recognition of GC with lymphoid stroma, EBV detection by EBER testing, and detection of hypermethylation of *MLH1* are biomarkers of good prognosis.

**Cancer immunotherapy, biomarkers of response:**

| Tumour mutation load | MSI GC |
| Density of intratumoural CD8+ T-cell infiltrates | EBV+ GC |
| PDL1 expression | EBV+ GC | Potential candidates for immunotherapy |

WHO Classification of Tumours of the Digestive System, 5th edition, 2019
1) Established predictive biomarkers: HER2 (anti-HER2 therapy in patients with unresectable or metastatic/recurrent HER2-positive GC)

2) Biomarkers partly established and/or under development:
   a. MSI status and conventional chemotherapy;
   b. Biomarkers for cancer immunotherapy (targeting of the PD-L1/PD-1 axis)
      • MSI-high and EBV +
      • PD-L1 expression
      • Tumour mutational load
Thanks for your attention