Histological tumour type (Core and Non-core)

Several classification schemes have been used for subtyping gastric carcinomas histologically, including the Laurén,[1] Nakamura,[2] Japanese Gastric Cancer Association (JGCA),[3] World Health Organization (WHO)[4] (Table 1) and Ming[5] classifications. For consistency in reporting, the WHO Classification of Tumours of the Digestive System, 5th edition, is recommended (Tables 2 and 3).[4] However, if a carcinoma does not fit into a category of the WHO Classification for gastric carcinomas, a descriptive diagnosis should be given. The Laurén Classification is widely used for gastric adenocarcinomas. In the Laurén Classification, gastric adenocarcinomas are divided into two histological subtypes - intestinal type and diffuse type.[1] Gastric carcinomas that do not fit into one of the two are placed into the mixed or indeterminate categories. The Laurén Classification provides a simplified categorisation of common types of gastric carcinoma and facilitates a general understanding of pathogenesis of most gastric carcinomas .[6] However, unlike the WHO Classification, the Laurén Classification is difficult to apply to all histologic gastric cancer subtypes and is therefore a non-core element.[1,7]

Table 1: Comparison of the Laurén, Nakamura, Japanese Gastric Cancer Association (JGCA) and World Health Organization (WHO) Classification 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 Tubular, 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	Poorly cohesive, signet-ring cell phenotype Poorly cohesive, other cell types
Intestinal/ diffuse/ indeterminate	Differentiated/ undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (e.g., por2>sign>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 adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type Micropapillary adenocarcinoma

Reproduced with permission from Frayling I et al (2016). Association for Clinical Genomic Science (ACGS) Best practice guidelines for genetic testing and diagnosis of Lynch syndrome. https://www.acgs.uk.com/quality/best-practice-guidelines/, derived from van Lier et al etc.; and from World Health Organization (WHO) Classification of Tumours Editorial Board. *WHO Classification of Digestive System Tumours, 5th Edition,* IARC Press, Lyon.[4]

Table 2: World Health Organization histological classification of gastric carcinomas.[8]

Tumour type	Histologic features
Adenocarcinoma, main histologic types	
Tubular adenocarcinoma	Most common subtype; composed of dilated or slit-like branching tubules of variable diameter or acinar structures
Papillary adenocarcinoma	Exophytic growth pattern and most commonly well differentiated; composed of elongated finger-like processes lined by columnar or cuboidal cells supported by fibrovascular cores
Poorly cohesive carcinoma, including signet ring cell carcinoma and other subtypes	Accounting for 20-54% of gastric cancers; composed of neoplastic cells that are isolated or arranged in small aggregates without well-formed glands; either signet-ring cell type (composed predominantly or exclusively of signet-ring cells) or non-signet ring cell type with marked desmoplasia
Mucinous adenocarcinoma	Composed of malignant epithelium and extracellular mucin pools (mucin pools >50% of the tumour area)
Mixed adenocarcinoma	Composed of signet ring cell/poorly cohesive component and one or more other distinct histological components such as tubular/papillary carcinoma
Adenocarcinoma, other histological subtypes	
Gastric (adeno)carcinoma with lymphoid stroma	Characterised by irregular sheets, trabeculae, ill-defined tubules or syncytia of polygonal cells embedded within a prominent lymphocytic infiltrate, with intraepithelial lymphocytes; frequently associated with Epstein-Barr virus infection; less commonly associated with microsatellite instability or DNA mismatch repair deficiency
Hepatoid adenocarcinoma and related entities	Composed of large polygonal eosinophilic hepatocyte-like neoplastic cells with alpha fetoprotein (AFP) expression; other AFP-producing carcinomas including well differentiated papillary/tubular-type adenocarcinoma with clear cytoplasm, adenocarcinoma with enteroblastic differentiation and yolk-sac tumour-like carcinoma
Micropapillary adenocarcinoma	Composed of micropapillary component (10-90% of the tumour area) and tubular/papillary adenocarcinoma
Gastric adenocarcinoma of fundic-gland type	Likely develop from oxyntic gland adenoma with oxyntic gland differentiation; include chief-cell predominant (most common), parietal cell-predominant, and mixed phenotype
Rare histological subtypes	Mucoepidermoid carcinoma, paneth cell carcinoma, and parietal cell carcinoma
Gastric squamous cell carcinoma	Only composed of squamous cell carcinoma with no other histological component after thorough sampling
Gastric adenosquamous cell carcinoma	Admixture of adenocarcinoma and squamous cell carcinoma with the squamous cell component ≥25%
Gastric undifferentiated (anaplastic) carcinoma	Composed of diffuse sheets of anaplastic, large to medium size polygonal cells, with frequent pleomorphic tumour giant cells; other morphologies that may be seen include rhabdoid cell, sarcomatoid pleomorphic pattern, undifferentiated carcinoma with osteoclast-like giant cells, carcinoma with lymphoepithelioma-like feature, and a glandular component
Gastroblastoma	Composed of uniform spindle cells and uniform epithelial cells arranged in nests

Gastric neuroendocrine carcinoma (NEC)	
Small cell NEC	Resemble its lung counterpart; frequent necrosis
Large cell NEC	Resemble its lung counterpart; frequent necrosis
Mixed neuroendocrine-non-neuroendocrine neoplasm	
Mixed adenocarcinoma-NEC	Composed of both adenocarcinoma and NEC with each component ≥30%
Mixed adenocarcinoma-neuroendocrine tumour	Composed of both adenocarcinoma and neuroendocrine tumour with each component ≥30%

Results on the prognostic value of histological types in gastric cancer are conflicting. While many studies have reported that diffuse, signet ring or anaplastic carcinomas confer an unfavourable prognosis, some multivariate studies showed no relationship between histological tumour types, and prognosis when stage was included in the model, which might be explained by inconsistent histology typing by pathologists.[9,10]

A high incidence of intragastric recurrence is observed in certain histological subtypes, including undifferentiated carcinoma and mixed adenocarcinoma with both signet ring cell carcinoma and poorly differentiated adenocarcinoma.[11]

Table 3: World Health Organization Classification of tumours of the stomach.[8]

Descriptor	ICD-O codes[a]
Benign epithelial tumours and precursors	
Glandular intraepithelial neoplasia, low grade	8148/0
Glandular intraepithelial neoplasia, high grade	8148/2
Serrated dysplasia, low grade	8213/0*
Serrated dysplasia, high grade	8213/2*
Intestinal-type dysplasia	
Foveolar-type (gastric-type) dysplasia	
Gastric pit/crypt dysplasia	
Intestinal-type adenoma, low grade	8144/0*
Intestinal-type adenoma, high grade	8144/2*
Sporadic intestinal-type gastric adenoma	
Syndromic intestinal-type gastric adenoma	
Adenomatous polyp, low-grade dysplasia	8210/0*
Adenomatous polyp, high-grade dysplasia	8210/2*
Malignant epithelial tumours	
Adenocarcinoma NOS	8140/3
Tubular adenocarcinoma	8211/3
Parietal cell carcinoma	8214/3
Adenocarcinoma with mixed subtypes	8255/3
Papillary adenocarcinoma NOS	8260/3
Micropapillary carcinoma NOS	8265/3
Mucoepidermoid carcinoma	8430/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Poorly cohesive carcinoma	8490/3

Descriptor	ICD-O codes[a]
Medullary carcinoma with lymphoid stroma	8512/3
Hepatoid adenocarcinoma	8576/3
Paneth cell carcinoma	
Squamous cell carcinoma NOS	8070/3
Adenosquamous carcinoma	8560/3
Carcinoma, undifferentiated, NOS	8020/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Pleomorphic carcinoma	8022/3
Sarcomatoid carcinoma	8033/3
Carcinoma with osteoclast-like giant cells	8035/3
Gastroblastoma	8976/3*
Neuroendocrine tumour NOS	8240/3
Neuroendocrine tumour, grade 1	8240/3
Neuroendocrine tumour, grade 2	8249/3
Neuroendocrine tumour, grade 3	8249/3
Gastrinoma NOS	8153/3
Somatostatinoma NOS	8156/3
Enterochromaffin-cell carcinoid	8241/3
ECL-cell carcinoid, malignant	8242/3
Neuroendocrine carcinoma NOS	8246/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)	8154/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).[12] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Subtype labels are indented. Incorporates all relevant changes from the 5th edition Corrigenda, January 2022.[13]
* Codes marked with an asterisk were approved by the International Agency for Research on Cancer /World Health Organization Committee for ICD-O at its meeting in April 2019.

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