An Overview of the Pathology of Gastric Cancers: pathogenesis, classifications and new understandings.

Dr. Leow Wei Qiang
Associate Consultant
Department of Pathology, Histopathology and Cytology Sections
Gastrointestinal and Hepatopancreatobiliary Service
The complexities of the gastric mucosa

- Non-specialised mucosa (antrum, cardia)
  - Foveolar glands
  - Pyloric glands
  - Endocrine cells
    - G cells (gastrin)
    - EC cells (serotonin)
    - D cells (somatostatin)
The complexities of the gastric mucosa

• Specialised mucosa (fundus, corpus)
  – Foveolar glands
  – Fundic glands
    • parietal cells
    • chief cells
  – Endocrine cells
    • ECL cells (histamine)
Helicobacter pylori

• In 2005, Barry J. Marshall and Robin Warren were awarded the Nobel Prize in Physiology for their discovery of Helicobacter pylori and its role in gastritis and peptic ulcer disease.

• Persistent infection induces a series of phenotypical changes that occur before the development of ‘intestinal type’ adenocarcinoma.

• H.pylori’s potent urease activity releases ammonia, which increases expression of nitrosated compounds, which can induce DNA damage.

• Studies suggest at least 4x increased risk of gastric lesions in patients with H.pylori infection.
Multifactorial etiologies

- Diet rich in salt-preserved or smoked foods, combined with low intakes of fruits and vegetables.
  - Increased intraluminal formation of nitrosated compounds \(\rightarrow\) DNA damage.
  - Protective effect of antioxidants (controversial)

- Bile reflux, particularly after gastric surgery, increases risk of gastric cancers.

- Cigarette smoking, increases risk by 2-3x.

- Helicobacter pylori.

- Polymorphisms of interleukin 1 gene, which plays a role in hypochlorhydria and atrophy, is associated with risk of gastric carcinoma.

- In contrast to intestinal type adenocarcinomas, diffuse type adenocarcinoma shows equal incidence in all geographic areas and occur in younger individuals, suggesting influence by genetic factors over environmental.
Correa cascade of multistep gastric carcinogenesis

- Chronic gastritis → Atrophy → Intestinal metaplasia → Dysplasia → Cancer.

Figure 1. Schematic representation of the main clinical outcomes of *Helicobacter pylori* (*H. pylori*) infection. The right side of the figure shows the sequential steps of the precancerous cascade.
Intestinal metaplasia (IM)

- A phenotypic change from normal gastric epithelium to intestinal type.
- Due to chronic inflammation.
- Attempts to subclassify them into complete and incomplete, but have limited clinical significance.
- Rather than the subtype, the extent and severity of IM is predictive of the cancer risk.
Dysplasia / Intraepithelial neoplasia

- Incidence of gastric dysplasia closely parallels incidence of adenocarcinoma.
  - Represents a direct neoplastic precursor lesion
  - Most dysplastic lesions have an intestinal phenotype (Type 1)

- Dysplasia is also a marker for risk for cancer elsewhere in the stomach.
  - Up to 12.5% cited in a Japanese study

- 57% of gastric cancers found during surveillance of gastric dysplasia are considered early gastric cancers.

- There are interpretive variations in the diagnosis of such lesions.
  - Negative for dysplasia (benign, reactive, metaplastic)
  - Dysplasia (unequivocal features; further classified into low grade and high grade)
  - Indefinite for dysplasia (ambiguous morphological pattern)
### Dysplasia

- Gland size
- Budding, cribriform profiles
- Surface maturation
- Inflammation
- Intraluminal necrotic debris
- Mucin depletion
- Nuclear size
- Nuclear stratification
- Nuclear shape
- Hyperchromasia
- Prominent nucleoli
- Increased / atypical mitoses

#### Table 20.5 Classification of Gastric Dysplasia

<table>
<thead>
<tr>
<th>Western Classification</th>
<th>Japanese Classification</th>
<th>Padova Classification</th>
<th>Vienna Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign reactive</td>
<td>Benign, no atypia (includes intestinal metaplasia, epithelium)</td>
<td>1. Negative 1.0 Normal 1.1 Reactive 1.2 Intestinal metaplasia (IM) 1.2.1 IM, complete type 1.2.2 IM, incomplete type</td>
<td>1. Negative for neoplasia or dysplasia</td>
</tr>
<tr>
<td>Indefinite</td>
<td>Benign, with atypia (frequently associated with active inflammation or found within hyperplastic polyp)</td>
<td>2. Indefinite for dysplasia 2.1 Foveolar hyperproliferation 2.2 Hyperproliferative intestinal metaplasia</td>
<td>2. Indefinite for neoplasia or dysplasia</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>Borderline between benign and malignant (dysplastic lesions with architectural and cytologic atypia)</td>
<td>3. Noninvasive neoplasia 3.1 Low-grade dysplasia 3.2 High-grade dysplasia 3.2.1 Suspect for carcinoma without invasion 3.2.2 Including carcinoma without invasion</td>
<td>3. Noninvasive neoplasia, low grade (low-grade adenoma or dysplasia)</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>Highly suspect for carcinoma (complex architecture)</td>
<td>4. Suspect for invasive carcinoma</td>
<td>4. Noninvasive high grade neoplasia 4.1 High-grade adenoma or dysplasia 4.2 Noninvasive carcinoma (carcinoma in situ) 4.3 Suspicion of invasive carcinoma</td>
</tr>
</tbody>
</table>
Dysplasia: the lows and the highs

Low Grade Dysplasia: nuclear enlargement and elongation, nuclear crowding and pseudostratification

High Grade Dysplasia: in addition, complete loss of nuclear polarity, marked nuclear pleomorphism, complex gland structures
Intramucosal carcinoma
Gastric Carcinoma

- **WHO definition:** Gastric carcinomas are malignant epithelial neoplasms. They represent a biologically and genetically heterogeneous group of tumours with multifactorial etiologies, both environmental and genetic. They are characterised by **broad morphological heterogeneity** with respect to patterns of architecture and growth, cell differentiation and histogenesis.
Gastric CA: new understandings (1)

- Incidence of proximal (cardial) gastric tumours was on the rise since 1980s.
  - Many of these cases can be reclassified as adenocarcinomas of the oesophagogastric junction (OGJ).
  - WHO: if the epicentre of the tumour is within 5cm of the OGJ and extends into the distal oesophagus, the tumour should be staged as an oesophageal CA.
  - WHO: if the epicentre in the stomach is >5cm from the OGJ, or those within 5cm of the OGJ without extension in the oesophagus; are staged as gastric CA.
  - Risk factors for ‘cardial’ cancers parallel lower oesophageal adenocarcinomas and are different from those in distal stomach.
Gastric CA: new understandings (2)

- Incidence of proximal (cardial) gastric tumours has been on the rise since 1980s.
- Detection rates for Early Gastric Cancers (EGC) are on the rise.

(A) Endoscopic classification of early gastric cancer: defined as adenocarcinomas confined to the mucosa or submucosa, regardless of LN mets.
(B) Borrman classification of advanced gastric cancer: defined as tumour that invades beyond the submucosa.
Early Gastric Cancers

• As a result of increased number of upper endoscopies being performed worldwide.
  – 15 - 21% of newly diagnosed cases in Western studies
  – More than 50% in Japan

• Most occurs in males, fifties.

• Symptoms are usually mild.
  – epigastric pain, dyspepsia, asymptomatic

• Tumour size is usually small (2 - 5cm).

• Located on lesser curve.

• Multiple primary sites occur in 3-13%, and is associated with worse prognosis.
Early Gastric Cancers

- Majority of EGCs are well differentiated.
  - *Tubular carcinoma* (52%)
  - *Papillary carcinoma*
  - *Signet ring cell carcinoma*
  - *Poorly differentiated carcinoma*

- With resection, the prognosis is excellent.
  - 5 year survival rates >90%

- Size of tumour and depth of invasion are the two most important prognostic indicators.
Early Gastric Cancers
Early Gastric Cancers
Early Gastric Cancers

Fig 1. Micrograph of few atypical glands lying in the deep mucosa and muscularis mucosae (H&E, original magnification x200).
Inset: Immunohistochemistry for cytokeratins highlights these atypical glands (MNF116, original magnification x200).
Early Gastric Cancers

Fig 2. Micrograph of repeat biopsy showing areas of poorly differentiated areas and deeper lying glandular areas (H&E, original magnification x50).
Inset: Immunohistochemistry for cytokeratins highlights these tumour cells (MNF116, original magnification x50).
Early Gastric Cancers

Fig 2. Micrograph of repeat biopsy showing areas of poorly differentiated areas and deeper lying glandular areas (H&E, original magnification x100). Inset: Immunohistochemistry for cytokeratins highlights these tumour cells (MNF116, original magnification x100).
Gastric CA: new understandings (3)

• Incidence of proximal (cardial) gastric tumours has been on the rise since 1980s.

• Detection rates for Early Gastric Cancers (EGC) are on the rise.

• There is no entirely satisfactory histologic classification of gastric carcinoma.
‘Proliferative Classificationitis’

- The perfect classification scheme should be:
  - Used prevalently in clinical work and research
  - Able to cover all gastric primary lesions
  - High reproducibility and validity
  - Prognostically relevant

![Table 25.1 Gastric Adenocarcinoma Classification Systems](image)
Lauren Classification

- Is still the most commonly used and most studied classification, since established in 1965.

- Divided into:
  - Intestinal
  - Diffuse
  - Indeterminate

- Good reproducibility.

- Prognostic relevance is controversial.

- A peek into distinct molecular pathways for intestinal and diffuse types.
### WHO classification\(^a\) of tumours of the stomach

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>Neuroendocrine carcinoma (NEC)</th>
<th>8246/3</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Premalignant lesions</em></td>
<td>Large cell NEC</td>
<td>8013/3</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Small cell NEC</td>
<td>8041/3</td>
</tr>
<tr>
<td>Intraepithelial neoplasia (dysplasia), low grade 8148/0*</td>
<td>Mixed adenoneuroendocrine carcinoma</td>
<td>8244/3</td>
</tr>
<tr>
<td>Intraepithelial neoplasia (dysplasia), high grade 8148/2*</td>
<td>EC cell, serotonin-producing NET</td>
<td>8241/3</td>
</tr>
<tr>
<td></td>
<td>Gastrin-producing NET (gastrinoma)</td>
<td>8153/3</td>
</tr>
</tbody>
</table>

#### Carcinoma

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>8140/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary adenocarcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>8211/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Poorly cohesive carcinoma (including signet ring cell carcinoma and other variants) 8490/3*</td>
<td>8811/0*</td>
</tr>
<tr>
<td>Mixed adenocarcinoma</td>
<td>8255/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adenosquamous carcinoma</th>
<th>8560/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma with lymphoid stroma (medullary carcinoma)</td>
<td>8512/3</td>
</tr>
<tr>
<td>Hepatoid adenocarcinoma</td>
<td>8576/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>8020/3</td>
</tr>
</tbody>
</table>

#### Neuroendocrine neoplasms\(^b\)

<table>
<thead>
<tr>
<th>Neuroendocrine tumour (NET)</th>
<th>8240/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET G1 (carcinoid)</td>
<td>8249/3</td>
</tr>
</tbody>
</table>

#### Mesenchymal tumours

<table>
<thead>
<tr>
<th>Glomus tumour</th>
<th>8711/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granular cell tumour</td>
<td>9580/0</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>8890/0</td>
</tr>
<tr>
<td>Plexiform fibromyxoma</td>
<td>8825/1</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>9560/0</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumour</td>
<td>8825/1</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumour</td>
<td>8936/3</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>9140/3</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>8890/3</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>9040/3</td>
</tr>
</tbody>
</table>

#### Lymphomas

#### Secondary tumours

---

\(^a\) The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (904A). 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;  
\(^b\) The classification is modified from the previous WHO histological classification of tumours (891) taking into account changes in our understanding of these lesions. In the case of neuroendocrine neoplasms, the classification has been simplified to be of more practical utility in morphological classification;  
\(^c\) These new codes were approved by the IARC/WHO Committee for ICD-O at its meeting in March 2010.

Figure 1: Tubular adenocarcinoma. Irregular-shaped and fused neoplastic glands with intraluminal mucus and debris.

Figure 2: Papillary adenocarcinoma with papillary projections lined by neoplastic cells.
Figure 2 Mucinous adenocarcinoma. Clusters and scattered tumor cells floating in the abundant extracellular mucin pools

Figure 3 Signet ring cell carcinoma. Signet ring carcinoma cells are predominantly at the superficial lamina propria
Gastric Carcinoma with Lymphoid Stroma

- Also known as medullary carcinoma or lymphoepithelioma-like carcinoma.

- >80% associated with EBV infection.

- Hispanic males.

- Pushing border with irregular syncytial sheets of tumour cells within a rich lymphocytic stroma.

- Prognosis better than other gastric cancers.
Hepatoid / AFP producing Carcinoma

- Hepatoid carcinoma resembles hepatocellular carcinoma with large polygonal cells and prominent eosinophilic cytoplasm.

- AFP producing carcinoma shows well differentiated tubular or papillary architecture with clear cytoplasm.

- Both expresses AFP in immunohistochemistry and patient serum AFP may be raised.

- Aggressive tumour, 5 year survival rate ~ 12%.
Ming Classification

- Based on growth pattern.

- Divided into:
  - Expanding
  - Infiltrative

- Good reproducibility.

- Simple.

- No prognostic significance.
Up to now, no histological classification system could provide additional prognostic information beyond what the TNM system does.

Initial studies suggested that the amount of intra-cellular mucin could be a prognostic factor, but later studies could not confirm this.

Not widely used.
Goseki Classification

Figure 2: Survival after potentially curative resection for gastric cancer according to the Goseki grade of the tumour.
Correlated Classifications

There has been good correlation between all the classification systems.

We routinely report the WHO, Lauren and Ming classification in our reports.

<table>
<thead>
<tr>
<th>Ming</th>
<th>Laurén</th>
<th>WHO</th>
<th>Goseki</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanding</td>
<td>Intestinal type</td>
<td>Papillary adenocarcinoma Tubular adenocarcinoma</td>
<td>Well-differentiated tubules, intracellular mucin poor Well-differentiated tubules, intracellular mucin rich</td>
</tr>
<tr>
<td>Infiltrating</td>
<td>Diffuse type</td>
<td>Poorly cohesive carcinoma Mucinous adenocarcinoma</td>
<td>Poorly differentiated tubules, intracellular mucin poor</td>
</tr>
<tr>
<td>Indeterminate type</td>
<td>Mixed adenocarcinoma Adenosquamous carcinoma Squamous carcinoma Small cell carcinoma Others*</td>
<td>Poorly differentiated tubules, intracellular mucin rich</td>
<td></td>
</tr>
</tbody>
</table>
Gastric CA: new understandings (4)

- Incidence of proximal (cardial) gastric tumours has been on the rise since 1980s.
- Detection rates for Early Gastric Cancers (EGC) are on the rise.
- There is no entirely satisfactory histologic classification of gastric carcinoma.
- The intestinal types and diffuse types arises from distinct tumor development pathways.
Gastric Carcinoma in Young Patients

• 2 - 10% of all gastric carcinomas are diagnosed in young patients (<40 years).

• An equal gender distribution is reported.

• Most are of the diffuse type and are not associated with gastric atrophy and intestinal metaplasia.

• 10 - 25% of these young patients have a positive family history, suggesting genetic aetiologic factors.

• Different genomic profile between younger and older patients with gastric carcinoma.
Intrinsic Subtypes of Gastric Cancer, Based on Gene Expression Pattern, Predict Survival and Respond Differently to Chemotherapy

Iain Beehuat Tan¹,²,³, Tatiana Ivanova⁴, Kiat Hon Lim⁵, Chee Wee Ong⁶, Niantao Deng³, Julian Lee⁴, Sze Huey Tan¹⁹, Jeanie Wu⁴, Ming Hui Lee⁴, Chia Huey Ooi³, Sun Young Rha⁸, Wai Keong Wong⁹, Alex Boussioutas¹⁰, Khay Guan Yeoh¹¹, Jimmy So¹², Wei Peng Yong⁶, Akira Tsuburaya¹³, Heike Grabsch¹⁴, Han Chong Toh¹, Steven Rozen³, Jae Ho Cheong¹⁵, Sung Hoon Noh¹⁵, Wei Kiat Wan⁵, Jaffer A. Ajani¹⁶, Ju-Seog Lee¹⁷, Manuel Salto Tellez⁶,¹⁸, and Patrick Tan³,⁴,⁶,¹⁹
3 major molecular mechanisms:

1. Chromosomal instability.
   - Intestinal type: 8q, 17q, 20q gains and 3p, 5q losses
   - Diffuse type: 12q, 13q gains and 4q, 15q, 16q, 17p losses
   - Contributes to focal gene amplifications – HER2, MET.

2. Microsatellite instability.
   - Associated with intestinal subtype.
   - EGFR-MAPK, PI3K pathways are reported in relation.

3. Epigenetic alterations.
   - DNA hypermethylation
   - CIMP (CpG island methylator phenotype) – EBV associated

“When interpreting the data, it is useful to consider gastric cancer not as one disease, but rather as at least two major subtypes with unique features.”
Asian and Non-Asian gastric cancers may exhibit distinct gene signatures related to inflammation and immunity, with T-cell pathways preferentially associated with non-Asian gastric cancers.
## Common genetic alterations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>“Intestinal” carcinoma</th>
<th>“Diffuse” carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>LOH, mutation</td>
<td>30–40%</td>
<td>&lt; 2%</td>
</tr>
<tr>
<td>BCL2</td>
<td>Overexpression</td>
<td>—</td>
<td>10–30%</td>
</tr>
<tr>
<td>CDH1</td>
<td>Mutation, hypermethylation, LOH</td>
<td>—</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>CDKN1B</td>
<td>Reduced expression</td>
<td>—</td>
<td>40–50%</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>Mutation</td>
<td>17–27%</td>
<td></td>
</tr>
<tr>
<td>Cyclin E</td>
<td>Overexpression</td>
<td>15–20%</td>
<td></td>
</tr>
<tr>
<td>DCC</td>
<td>LOH</td>
<td>60%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>10–15%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Amplification</td>
<td>—</td>
<td>35%</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>1–28%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification</td>
<td>20–40%</td>
<td></td>
</tr>
<tr>
<td>MYC</td>
<td>Overexpression</td>
<td>40–45%</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>LOH, mutation</td>
<td>20–30%</td>
<td></td>
</tr>
<tr>
<td>RB1</td>
<td>Reduced expression</td>
<td>—</td>
<td>30%</td>
</tr>
<tr>
<td>TP53</td>
<td>Mutation, LOH</td>
<td>25–40%</td>
<td>0–21%</td>
</tr>
</tbody>
</table>
Hereditary Tumour Syndromes

- Familial Diffuse Gastric Carcinoma
  - CDH1 (E-cadherin) gene

- Hereditary Non-polyposis Colorectal Cancer Syndrome
  - MSI phenotype

- Familial Adenomatous Polyposis Coli
  - APC

- Li-Fraumeni Syndrome
  - TP53

- Peutz-Jeghers Syndrome
  - STK11
Familial Diffuse Gastric Carcinoma

- Autosomal dominant germline mutation in E-cadherin gene.
- Increased risk of diffuse gastric carcinoma and lobular breast carcinoma.
- Average age at diagnosis: 37 years old.
- Lifetime risk of gastric carcinoma: 67%-83%.
• Epidermal growth factor gene.
• Preferentially expressed in the intestinal type gastric cancers.
• HER2 amplification described after its discovery in breast cancers.
• Identification of cases with HER2 amplification presents a therapeutic target for Herceptin therapy.

---

**Table 2 Human epidermal growth factor receptor 2 (HER2) scoring criteria for gastric cancer**

<table>
<thead>
<tr>
<th>Score</th>
<th>Surgical specimen-staining pattern</th>
<th>Biopsy specimen-staining pattern</th>
<th>HER2 overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt;10% of tumor cells</td>
<td>No reactivity or no membranous reactivity in any tumor cell</td>
<td>Negative</td>
</tr>
<tr>
<td>1+</td>
<td>Faint/barely perceptible membranous reactivity in &gt;10% of tumor cells; cells are reactive only in part of their membrane</td>
<td>Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Negative</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral, or lateral membranous reactivity in &gt;10% of tumor cells</td>
<td>Tumor cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Equivocal</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral, or lateral membranous reactivity in &gt;10% of tumor cells</td>
<td>Tumor cell cluster with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Positive</td>
</tr>
</tbody>
</table>
ERBB2 / HER2 protooncogene amplification

- 20 nuclei are enumerated.
- $\text{Her2/Chr17 ratio} \geq 2.0 = \text{Amplified}$
- $\text{Her2/Chr17 ratio} < 2.0 = \text{Non-amplified}$
- If HER2/Chr17 ratio falls between 1.8 – 2.2 on first count, 20 additional nuclei should be enumerated.
Other tumours of the stomach

• Neuroendocrine neoplasms

• Gastrointestinal stromal tumours (GISTs)

• Gastrointestinal Lymphomas
# Neuroendocrine neoplasms

## TABLE 3. Systems of Nomenclature for Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lung and Thymus (WHO)(^\text{34})</th>
<th>GEP-NETs (ENETS)(^{28,29})</th>
<th>GEP-NETs (WHO 2010)(^3)</th>
<th>Lung and Thymus (Moran et al)(^23)</th>
<th>Pancreas (Hochwald et al)(^14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>Carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 1 (G1)</td>
<td>Neuroendocrine neoplasm, grade 1</td>
<td>Neuroendocrine carcinoma, grade 1</td>
<td>Well-differentiated pancreatic endocrine neoplasm, low grade</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>Atypical carcinoid tumor</td>
<td>Neuroendocrine tumor, grade 2 (G2)</td>
<td>Neuroendocrine neoplasm, grade 2</td>
<td>Neuroendocrine carcinoma, grade 2</td>
<td>Well-differentiated pancreatic endocrine neoplasm, intermediate grade</td>
</tr>
<tr>
<td>High grade</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma</td>
<td>Poorly differentiated pancreatic endocrine carcinoma, large cell neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

The grade of the tumor MUST be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as *neuroendocrine tumor* or *neuroendocrine carcinoma* without reference to grade do not provide adequate pathology information.
Neuroendocrine neoplasms grading

<table>
<thead>
<tr>
<th>Neuroendocrine Tumor Grade</th>
<th>Mitoses (per 10 HPFs)</th>
<th>Ki67 Proliferation Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>
# Neuroendocrine proliferations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria for Increased Endocrine Cells</th>
<th>Common Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple or diffuse hyperplasia</td>
<td>&gt;2 × standard deviations (age and gender matched)</td>
<td>ZES, primary gastrin cell hyperplasia</td>
</tr>
<tr>
<td>Linear hyperplasia</td>
<td>Linear groups of 5 or more cells inside the glandular BM</td>
<td>ZES, pernicious anemia</td>
</tr>
<tr>
<td>Micronodular hyperplasia</td>
<td>Clusters of 5 or more cells within epithelium measuring &lt;150 μm in diameter</td>
<td>Autoimmune atrophic gastritis</td>
</tr>
<tr>
<td>Adenomatoid hyperplasia</td>
<td>Aggregates of 5 or more micronodules in lamina propria</td>
<td>Autoimmune atrophic gastritis, MEN-ZES</td>
</tr>
<tr>
<td>Dysplasias</td>
<td></td>
<td>Autoimmune atrophic gastritis, MEN-ZES</td>
</tr>
<tr>
<td>Enlarged micronodules</td>
<td>&gt;150 μm</td>
<td></td>
</tr>
<tr>
<td>Adenomatous micronodules</td>
<td>Collections of at least 5 closely adherent micronodules, intervening BM only</td>
<td></td>
</tr>
<tr>
<td>Fused micronodules</td>
<td>Adenomatous micronodules with no intervening BM</td>
<td></td>
</tr>
<tr>
<td>Microinfiltrative lesions</td>
<td>Infiltration of the lamina propria</td>
<td></td>
</tr>
<tr>
<td>Carcinoids</td>
<td></td>
<td>Autoimmune atrophic gastritis, MEN-ZES</td>
</tr>
<tr>
<td>Intramucosal</td>
<td>Expansile or infiltrative nodules &gt; 0.5 mm</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>Any size tumor within submucosa</td>
<td></td>
</tr>
</tbody>
</table>
Neuroendocrine neoplasms
### Gastric NETs: clinical subtypes

**TABLE 29.3 Clinical Features of Gastric Neuroendocrine Tumors**

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Course</th>
<th>Genetics</th>
<th>Clinical Features</th>
<th>Serum Gastrin Levels</th>
<th>Pathogenetic Mechanism</th>
<th>Number of Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Regress spontaneously, endoscopic removal often adequate</td>
<td>May have <em>MEN1</em> mutation</td>
<td>Mucosa-covered polyps, superficial, rarely invasive</td>
<td>Secondary hypergastrinemia (resulting from achlorhydria)</td>
<td>Autoimmune gastritis</td>
<td>Multifocal</td>
</tr>
<tr>
<td>2</td>
<td>Somatostatin analogues effective</td>
<td>Associated with <em>MEN1</em> mutation</td>
<td>Mucosa-covered polyps, superficial, rarely invasive</td>
<td>Primary hypergastrinemia (resulting from ectopic gastrin secretion)</td>
<td>ZES, MEN 1</td>
<td>Multifocal</td>
</tr>
<tr>
<td>3</td>
<td>Aggressive behavior</td>
<td>Sporadic</td>
<td>Deep, advanced lesions, metastatic</td>
<td>No hypergastrinemia</td>
<td>Undetermined</td>
<td>Unifocal</td>
</tr>
</tbody>
</table>

*MEN 1*, Multiple endocrine neoplasia syndrome, type 1; *ZES*, Zollinger-Ellison syndrome.
Mixed adenoneuroendocrine carcinomas (MANECs)

• MANECs are mixed carcinomas with a NET component of at least 30%.

• Rare in the stomach.

• NET component usually high grade, large cell type.
Gastrointestinal Stromal Tumours (GISTs)

• Arises from interstitial cells of Cajal (pacemaker cells).

• May arise anywhere in the GI tract but stomach is most common (60%).

• Sporadic or occur in connection with tumour syndromes.
Gastrointestinal Stromal Tumours (GISTs)
Gastrointestinal Stromal Tumours (GISTs)

- Behaviour of GIST ranges from benign to malignant.
  - Anatomic site
  - Tumour size
  - Mitotic activity

- If metastatic, usually within abdomen or liver.

- Nodal metastases are uncommon.

Table 30.4: Risk Stratification of Primary GIST by Mitotic Index, Size, and Anatomic Site.

Data from references 23, 38, 43, 45, and 46.

<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk of Progressive Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic Index</td>
<td>Gastric</td>
</tr>
<tr>
<td>≤5 per 5 mm²</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>&gt;2 to ≤5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td>&gt;5 to ≤10 cm</td>
<td>Low (3.6%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td>&gt;5 per 5 mm²</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None¹</td>
</tr>
<tr>
<td>&gt;2 to ≤5 cm</td>
<td>Moderate (16%)</td>
</tr>
<tr>
<td>&gt;5 to ≤10 cm</td>
<td>High (55%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>High (86%)</td>
</tr>
</tbody>
</table>

GIST, Gastrointestinal stromal tumor; HPF, high-power field.

Note:¹ Insufficient data.
Gastrointestinal Lymphomas

- 55-75% of GI lymphomas arises from the stomach.

- Most common types are:
  - Extranodal marginal zone lymphoma
  - Diffuse large B cell lymphoma

- Uncommon types include:
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Burkitt lymphoma
  - Peripheral T cell lymphoma
Extranodal marginal zone lymphoma, MALT type (MZL)

- Usually has H. pylori infection and may respond with antibiotic therapy.
- Monotonous monocytoid cells mixed with immunoblasts and plasmacytoid cells.
- Lymphoepithelial lesions.
- Immunophenotype:
  - $\text{CD}20(+)$
  - $\text{CD}5(-)$
  - $\text{CD}10(-)$
  - $\text{BCL}-2 (+)$
  - $\text{CD}43(+)$
- $t(11;18)$ rearrangement indicates poor response to antibiotic therapy and chemotherapy.
Diffuse Large B-cell Lymphoma (DLBCL)

- May be de novo or arise due to large cell transformation from MZL.

- Aggressive.

- Diffuse infiltrative large lymphoid cells with high grade cytomorphology.

- Immunophenotype:
  - CD20(+)
  - Ki-67 >40%
  - Variable expression of CD10, BCL-6, BCL-2 and MUM-1

- May be EBV-associated in immunocompromised patients.
The molecular age will bring answers

Fig. 1. Applications of molecular profiling in diagnosis and treatment of GC. The applications of gene expression profiling in GC include diagnosis, subgroup, TNM staging, treatment, and prognosis evaluation. EGC: early gastric cancer; CUP: cancer of unknown primary site.
Comprehensive molecular characterization of gastric adenocarcinoma
Thank you for your kind attention.
Additional Slides
Goseki’s 4 subtypes
| 1. Features of ≥pT1b carcinoma(s) | Growth pattern (diffuse infiltration vs localised tumour)  
|                                 | Anatomic location (cardia, fundus, body, transitional zone, antrum)  
|                                 | Measurements  
|                                 | Histological type according to WHO\textsuperscript{89} and Laurén’s\textsuperscript{90} classifications  
|                                 | Lymphatic, venous and neural invasion (present or absent)  
|                                 | Tumour, node, metastases stage  
| 2. Features of intramucosal precursor lesions and pT1a SRCC | Number of lesions  
|                                 | Anatomic location (cardia, fundus, body, transitional zone, antrum)  
|                                 | Measurements  
|                                 | Aggressive features: pleomorphism, loss of mucin, spindle cells, small cells, mitoses  
|                                 | Stromal reaction related to lesions: desmoplasia; lymphocytic, eosinophilic or granulomatous inflammatory reaction  
|                                 | Surgical margin status (proximal oesophageal, distal duodenal mucosa, including donuts), to confirm there is no residual gastric mucosa and no tumour at margins  
|                                 | Lymph node status  
| 3. Non-neoplastic mucosa: changes more commonly seen in this condition | Tufting/hyperplastic mucosal changes  
|                                 | Surface epithelial vacuolisation  
|                                 | Globoid change  
| 4. Other findings in surrounding mucosa | Inflammation (acute, chronic, erosion, ulceration)  
|                                 | \textit{Helicobacter pylori}  
|                                 | Intraepithelial lymphocytes  
|                                 | Lymphoid infiltrates  
|                                 | Glandular atrophy  
|                                 | Intestinal metaplasia  
|                                 | Adenomatous dysplasia  

SRCC, signet ring cell carcinoma.
## Tumour Regression Grade (AJCC)

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumor Regression Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells</td>
<td>0 (Complete response)</td>
</tr>
<tr>
<td>Single cells or small groups of cancer cells</td>
<td>1 (Moderate response)</td>
</tr>
<tr>
<td>Residual cancer outgrown by fibrosis</td>
<td>2 (Minimal response)</td>
</tr>
<tr>
<td>Minimal or no tumor kill; extensive residual cancer</td>
<td>3 (Poor response)</td>
</tr>
</tbody>
</table>

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

This protocol does not preclude the use of other systems for assessment of tumor response, such as the schemes reported by Memorial Sloan-Kettering Cancer Center investigators and others.¹⁴,¹⁵
Molecular targets in OGJ cancers

Figure 1. Receptor tyrosine kinases and their targeted therapies in gastroesophageal cancers: EGFR, VEGFR and MET. The EGFR family of receptor tyrosine kinases (RTKs) includes four distinct receptors: the EGFR (also known as ErbB-1/HER1), ErbB-2 (neu, HER2), ErbB-3 (HER3) and ErbB-4 (HER4). All proteins of this family have an extracellular ligand-binding domain, a single hydrophobic transmembrane domain and a cytoplasmic tyrosine kinase-containing domain. The intracellular tyrosine kinase domain of EGFR receptors is highly conserved, although HER3 lacks kinase activity. HER2 functions as a ligand-less receptor and induces hetero-dimerization with other EGFR family receptors upon ligand binding, whereas EGFR and HER4 undergo homo-dimerization. The subsequent activation of the intrinsic tyrosine kinase domain activates phosphorylation cascades, and the downstream effectors include RAF, PI3K and PLC. VEGF and its receptor VEGFR promote angiogenesis. The overexpression of VEGF is significantly associated with poor prognosis in gastrointestinal cancers. The HGF/MET pathway activates complex signaling events that depend on the cellular context and produces a variety of cellular responses such as proliferation, motility, angiogenesis and invasion. The MET pathway is upregulated in a wide range of human tumors, and this finding often signals a poor prognosis.
In-vitro chemosensitivity of cell lines to 5-FU, oxaliplatin and cisplatin

Figure 4. In vitro chemosensitivity of G-INT and G-DIF cell lines
GI-50 values of 11 G-INT and 17 G-DIF cell lines upon treatment with 5-FU, oxaliplatin and cisplatin. GI-50s refer to the drug concentration at which 50% growth inhibition is achieved. (y-axis: GI-50 enumerated in negative log$_{10}$). The horizontal grey lines represent the therapeutic concentration patients are exposed to based on pharmacokinetic data$^{25–27}$. Mean GI-50 concentrations for G-INT and G-DIF cell lines respectively: 5FU: 5.20 μM, 23.22 μM; Cisplatin: 38.61 μM, 13.35 μM; Oxaliplatin: 1.33 μM, 5.49 μM.
A comprehensive survey of genomic alterations in gastric cancer reveals systemic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets

Niantao Deng, Liang Kee Goh, Hannah Wang, Kakoli Das, Jiong Tao, Iain Beehuat Tan, Shenli Zhang, Minghui Lee, Jeannie Wu, Kiat Hon Lim, Zhengdeng Lei, Glenn Goh, Qing Yan Lim, Angie Lay-Keng Tan, Dianne Yu Sin Poh, Sudep Riahi, Sandra Bell, Michael M Shi, Ronald Linnartz, Feng Zhu, Khay Guan Yeoh, Han Chong Toh, Wei Peng Yong, Hyun Cheol Cheong, Sun Young Rha, Alex Boussioutas, Heike Grabsch, Steve Rozen, and Patrick Tan

Significance of this study

What is already known about this subject?

- Gastric cancer patients with ERBB2-amplified tumours can clinically benefit from ERBB2-targeted therapies. Similar to ERBB2, several other molecularly targeted therapies are currently being evaluated in gastric cancer.
- Little is known regarding which molecular targets are concurrently expressed in the same gastric tumours, or independently in different tumours.
- Unlike other cancer types, activating mutations in KRAS are also rarely observed in gastric cancer.

What are the new findings?

- This study identified 22 recurrent genomic alterations in gastric cancer, comprising both known gastric cancer targets (FGFR2, ERBB2) and genes not previously reported to be amplified in gastric cancer (KLF5, GATA16).
- Genes related to RTK/RAS signalling, in particular FGFR2, KRAS, ERBB2, EGFR and MET are frequently amplified in gastric cancer in a mutually exclusive manner.
- FGFR2-amplified gastric cancers exhibited sensitivity to dovitinib, an orally bioavailable targeted therapy.
- KRAS amplifications, frequently observed in gastric cancer, are significantly associated with adverse prognosis.

How might it impact on clinical practice in the foreseeable future?

- Dovitinib may represent a subtype-specific therapy for FGFR2-amplified gastric cancers.
- KRAS genomic amplification status should be assessed in clinical trials involving therapies targeting upstream RTK.
- Genomic amplifications in RTK/RAS components define five distinct gastric cancer molecular subgroups, to which differing therapies can be allocated. In total, 37% of the gastric cancer population may be treatable by RTK/RAS targeting agents.
Molecular subtypes: mesenchymal, proliferative and metabolic

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Histological features</th>
<th>Associated genes</th>
<th>Drug sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenchymal</td>
<td>Diffuse subtype</td>
<td>EMT pathways, CSC pathways, TGFβ, mTOR signalling, Genomic instability, TP53 mutations, Cell cycle, DNA replication, Mitosis, Copy number alterations (ERBB2/HER2 and KRAS)</td>
<td>Sensitive to PI3K/AKT/mTOR inhibitors</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Intestinal subtype</td>
<td></td>
<td>Unresponsive to 5-FU</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Gastric phenotype</td>
<td>Metabolic processes, Digestion, Secretion, SPEM</td>
<td>Increased sensitivity to 5-FU</td>
</tr>
</tbody>
</table>

CSC, cancer stem cell; EMT, epithelial mesenchymal transition; 5-FU, 5-fluorouracil; mTOR, mammalian target of rapamycin; SPEM, spasmylytic polypeptide-expressing metaplasia; TGFβ, transforming growth factor beta.
Fig. 1. The Yasui/Tahara multistep model of molecular pathogenesis of gastric cancer (reproduced with permission from [94]).
Figure 1. Schematic representation of the main clinical outcomes of Helicobacter pylori (H. pylori) infection. The right side of the figure shows the sequential steps of the precancerous cascade.

Figure 1. Cause and pathogenesis of intestinal-type GC. A summary of current knowledge of the cause and pathogenesis of intestinal type GC is shown, including host and environmental factors as well as acquired molecular events. [2,13-14] GC, gastric cancer.
PD-1 / PDL-1 (Programmed Death Ligand)

Figure 1 Immune checkpoint blockade in central and peripheral immune compartments. (A) Expression of CTLA-4 is upregulated on T cells in lymphoid tissues following activation via MHC/TCR and M7/CD28-mediated signaling. Once activated, CTLA-4 inhibits T cell function leading to immune tolerance. In the presence of blocking antibodies this tolerance can be broken, allowing for enhanced antitumor response; (B) PD-1, also expressed on T lymphocytes, inhibits the action of T lymphocytes upon binding to its ligand PD-L1/2; this process likely occurs in the tumor microenvironment, between PD-L1/2 expressing tumor cells and PD-1 expressing T lymphocytes; (A,B) blocking antibodies to either PD-1 or its ligands allows for T cell activation, enhancing anti-tumor effects peripherally. CTLA-4, cytotoxic T-lymophocyte antigen 4; PD-1, programmed death 1; PD-L1, programmed death ligand 1; APC, antigen presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor.

Results
A total of 3107 patients with solid tumors from 28 published studies were included in the meta-analysis. The median percentage of solid tumors with PD-L1 overexpression was 52.5%. PD-L1 overexpression was associated with worse OS at both 3 years (OR = 2.43, 95% confidence interval (CI) = 1.60 to 3.70, P < 0.0001) and 5 years (OR = 2.23, 95% CI = 1.40 to 3.55, P = 0.0008) of solid tumors. Among the tumor types, PD-L1 was associated with worse 3-year OS of esophageal cancer, gastric cancer, hepatocellular carcinoma, and urothelial cancer, and 5-year OS of esophageal cancer, gastric cancer and colorectal cancer.

PD-L1 and Survival in Solid Tumors: A Meta-Analysis
Pin Wu1,2, Dang Wu3,4, Lijun Li5, Ying Cha1 6, Jian Huang3,4