MOLECULAR CLASSIFICATION OF GASTRIC CANCER IN THE CLINICS

New Approaches

Rodrigo Dienstmann

Vall d’Hebron Institute of Oncology
Gastrointestinal cancer molecular biology

Advisory role: Roche
Boehringer-Ingelheim
Astra Zeneca

Speaker’s fee: Roche
Symphogen
IPSEN
Amgen
Servier
Sanofi
MSD

Research support: Merck
Gastrointestinal cancer molecular biology
### Pathological classification of gastric adenocarcinoma

#### Lauren (1965) ¹ | WHO (2010) ²
---|---
**Intestinal** |  
Adenocarcinoma papilar  
Adenocarcinoma tubular  
Adenocarcinoma mucinous  
**Diffuse** |  
Carcinoma with signet ring cells  
Other undifferentiated carcinomas  
**Indeterminate** | Carcinoma mixed

#### Intestinal type
- Well-differentiated
- Related to gastritis, gastric atrophy, intestinal metaplasia
- More common in older men, East Asia, Eastern Europe, Central and South America
- Decreasing incidence

#### Diffuse type – Poorly cohesive carcinoma
- Undifferentiated
- Related to pangastritis
- More common in younger patients, male = female
- Increasing incidence
- “Worse prognosis”

---

¹ Lauren Classification 1965, ² AJCC TNM 2010, 7th Edition
Molecular classification of gastric adenocarcinoma

TCGA — unsupervised

TCGA Nature 2014
Molecular classification of gastric adenocarcinoma

TCGA – unsupervised

TCGA Nature 2014
Molecular classification of gastric adenocarcinoma

TCGA, Nature 2017
Molecular classification of gastric adenocarcinoma

Prognosis in early-stage gastric cancer

- **EBV**
- **MSI**
- **GS**
- **CIN**

Probability

- **RFS (months)**
- **OS (months)**

$P = 0.04$

$P = 0.03$
Molecular classification of gastric adenocarcinoma

**Asia – semi supervised**

**ACRG gastric tumors**

- MSI 68 tumors (22%)
- MSS 232 tumors (15%)
- MSS/EMT 46 tumors (26%)
- MSS/epithelial 186 tumors (37%)

Nat Med 2015
Molecular classification of gastric adenocarcinoma

Prognosis in early-stage gastric cancer

Nat Med 2015
# Molecular classification of gastric adenocarcinoma

<table>
<thead>
<tr>
<th>GC</th>
<th>Lauren</th>
<th>Diffuse type</th>
<th>Intestinal type</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCGA</td>
<td>GS</td>
<td>EBV</td>
<td>MSI</td>
</tr>
<tr>
<td>CDH1 and RHOA mutations</td>
<td>DNA hypermethylation</td>
<td>Hypermethylation</td>
<td>RTK–RAS activation (ERBB2, EGFR, MET, VEGFA and KRAS or NRAS)</td>
</tr>
<tr>
<td>CLDN18–ARHGAP26 fusion</td>
<td>PIK3CA mutation</td>
<td>MLH1 silencing</td>
<td>TP53 mutation</td>
</tr>
<tr>
<td>Cell adhesion pathways</td>
<td>PDL1 and PDL2 overexpression</td>
<td>KRAS or NRAS activation</td>
<td>Amplifications of cell cycle mediators (CCNE1, CCND1 and CDK6), GATA4 and GATA6</td>
</tr>
<tr>
<td>Younger patients</td>
<td>Recurrent JAK2 and ERBB2 amplification</td>
<td>RASA1 and PTEN inactivation</td>
<td>Common in GOJ and cardia cancer</td>
</tr>
<tr>
<td></td>
<td>CDKN2A silencing</td>
<td>Mitotic pathways</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune cell signalling</td>
<td>Older patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less A&gt;C transversion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACRG</th>
<th>MSS/EMT</th>
<th>MSS/TP53−</th>
<th>MSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1 silencing</td>
<td>Intact TP53</td>
<td>Common in the antrum</td>
<td>TP53 mutation</td>
</tr>
<tr>
<td>Younger patients</td>
<td>MDM2 amplification</td>
<td>Best prognosis</td>
<td>Genomic instability</td>
</tr>
<tr>
<td>Worst prognosis</td>
<td>EBV infection</td>
<td>Hypermutation</td>
<td>Recurrent amplification (ERBB2, EGFR, GATA6, MYC, CCNE1 and CCND1)</td>
</tr>
<tr>
<td></td>
<td>Enrichment with PIK3CA or ARID1A mutation and</td>
<td>MLH1 silencing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cytokine signature in EBV+ tumour</td>
<td>Frequent mutations in KRAS, M2TOR, PTEN, PIK3CA, ASL and ARID1A</td>
<td></td>
</tr>
</tbody>
</table>

Nat Rev Cancer 2016
Immune markers across molecular subtypes

IFN-Gamma Score in gastric cancer
Molecular classification of gastric adenocarcinoma

ESMO 2019

HER2, MSI, EBV testing

(-)  (+)

MSI +

EBV +

CIN HER2 ampl

CIN TP53 mut

no-CIN TP53 wt
CDH1 alt

Early-stage
Metastatic

22%  7%

8%   4%

20%  18%

15%  41%

35%  30%
Molecular classification of gastric adenocarcinoma

VHIO cohort (metastatic)

Diffuse (n=26):
- n=17 (65%)
- n=6 (23%)
- n=2 (8%)
- n=1 (4%)

Intestinal (n=11):
- n=4 (36%)
- n=2 (18%)
- n=1 (9%)
- n=4 (36%)

Legend:
- TP53 mut CIN
- HER2 ampl CIN
- MSI
- EBV
- TP53 wt (GS or no-CIN)

ESMO 2019
Poor outcome of MSI in advanced disease

VHIO cohort (metastatic)

Overall survival by molecular subtype (N=95)

Median OS (months; 95% CI)
- CIN HER2 negative = 29.7m (24.0-92.9)
- CIN HER2 positive = 30.0m (21.0-36.9)
- EBV = 18.4m (18.4-NA)
- MSI positive = 9.8m (7.0-NA)
- No CIN = 24.0m (19.8-43.9)

ASCO 2018
Poor outcome of MSI in advanced disease
Poor outcome of MSI with chemo in early-stage

![Survival curve](chart)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Chemotherapy and surgery, MSI-negative patients</th>
<th>Chemotherapy and surgery, MSI-positive patients</th>
<th>Surgery, MSI-negative patients</th>
<th>Surgery, MSI-positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>129</td>
<td>9</td>
<td>151</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>3</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>1</td>
<td>58</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td></td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td></td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td></td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Predictive markers for immune-checkpoint inhibitors

Nat Med 2018
Predictive markers for immune-checkpoint inhibitors
Predictive markers for immune-checkpoint inhibitors
Immune markers across molecular subtypes

VHIO cohort (metastatic)
DNA damage repair alterations in advanced disease

VHIO cohort (metastatic)

Metastatic Overall survival by DDR status

HR = 0.51 (0.3-1.0)  
\( p = 0.06 \)
Predictive markers for immune-checkpoint inhibitors

TMB (MSI), PDL1 expression and hot immune microenvironment (IFN Gamma) explain 80% of responses to immunotherapy across solid tumors
Spatial and temporal molecular heterogeneity

Significant discrepancies
- Within the primary tumor
- Between the primary tumor and metastasis

PANGEA Trial (28 pts)
- 32% discordance between primary tumor and metastasis
- 85% concordance within metastatic lesions and cfDNA

Potential use of cfDNA as a biomarker

Cancer Discov 2017
Spatial and temporal molecular heterogeneity
Spatial and temporal molecular heterogeneity

Results from Biomarker study

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>IHC</th>
<th>FISH</th>
<th>HER2 status</th>
<th>IHC</th>
<th>FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>3</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Definition of HER2 positive: IHC3+ or IHC2+ with FISH positive
Spatial and temporal molecular heterogeneity

HER2 positive gastric cancer
Conclusions

• Substantial inter-tumor molecular heterogeneity of gastric cancer
• **EBV** positive tumors *excellent prognosis* with standard therapy early-stage disease
• **MSI** tumors *worse prognosis with standard therapy* advanced disease
• **EBV** positive and **MSI** tumors are *highly responsive to checkpoint inhibitors*
• Other tumors may also respond to anti-PD1/L1
  (highly enriched for TMB high, PDL1 positive and/or IFNG positive signature)
• Predictive value of **CIN vs. GS (Mesenchymal)** tumors remains to be studied
• Intra-tumor molecular heterogeneity of gastric cancer may have therapeutic implications (*HER2 amplification may be lost after trastuzumab*)
Acknowledgements

Josep Tabernero
Andres Cervantes
Fatima Carneiro

Maria Alsina