Gastric cancer: Exploring the differences between Asian and Western patients

Andrew H. Ko, MD
Professor of Medicine, Division of Hematology/Oncology

Oct 8, 2016
Refresher: Gastric anatomy
Lauren classification of gastric cancer

**Intestinal** type: ~50%; more common in distal stomach

**Diffuse** type (infiltrative, linitus plastica): ~35%; more common in young patients, females, and a/w hereditary forms
### Incidence and mortality associated with gastric cancer, 2016

<table>
<thead>
<tr>
<th></th>
<th>Estimated new cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Gastric</td>
<td>16,480</td>
<td>9,890</td>
</tr>
</tbody>
</table>

Temporal trends in the United states

- Leading cause of cancer deaths in the U.S. until late 1930s
- Decline in incidence and mortality related to improvements in diet, food storage, and effective treatment for *H. pylori*
- However, significant increase in one particular type/location: **GE junction cancers**
Gastric cancer is most common in the United States amongst **Asian-Americans**.
Gastric cancer: geographic trends

- Worldwide 2\textsuperscript{nd} leading cause of cancer mortality (1 million/year)
- E. Asia > Europe/S America > United States/Australia/Africa
  - ½ of world total from Eastern Asia (esp China)
  - Mortality rates in E. Asia: 28.1 per 100,000 in men, 13.0 per 100,000 in women
  - Mortality rates in Northern America: 2.8 per 100,000 in men, 1.5 per 100,000 in women

Estimated Gastric Cancer Incidence Worldwide in 2008*

- China: 41.3 per 100,000
- Japan: 46.8 per 100,000
- United States: 5.7 per 100,000

*Data are for males only

GLOBOCAN 2008, International Agency for Research on Cancer

*Data are for males only
Temporal trends by geographic region

**Age-standardized incidence rate per 100,000 men**

- USA
- Canada
- Australia
- Republic of Korea
- Japan
- India

**Age-standardized mortality rate per 100,000 men**

- USA
- Canada
- Australia
- Republic of Korea
- Japan
- Russian Federation

GLOBOCAN 2008, International Agency for Research on Cancer
SO WHY IS GASTRIC CANCER MORE COMMON IN ASIANS?

• Genetic vs. environmental factors

• Evidence from migrant studies:
  • Subsequent generations of Japanese born in the United States show declining incidence and mortality rates from gastric cancer – however, still remain higher than U.S. whites
  • Groups with older immigration histories (Japanese, Filipinos) have cancer burdens more similar to those commonly observed in Westernized countries than groups with more recent immigration histories (Vietnamese, Korean)
why is gastric cancer more common in asians?:

risk factors

- Consumption of salty foods, N-nitroso compounds; low fruit/vegetable consumption
- *H. pylori* infection (esp. cagA strain)
  - Increases risk for *distally* located, but NOT proximal, gastric cancers
- Tobacco
- Obesity/GERD/Barrett’s
- Genetics: E-cadherin (**CDH1**) mutation
  - Associated with diffuse histology, autosomal dominant pattern, **high** penetrance rate (>70%), early-age onset
  - Also increased incidence of breast (lobular), colorectal, prostate ca
  - Appropriate candidates to consider prophylactic gastrectomy
JAPANESE PUBLIC HEALTH CENTER (STUDY COHORT I), 1990-2001: SALT INTAKE AND GASTRIC CANCER RISK ACCORDING TO GENDER

Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies
(D’elia et al, *Clin Nutrition* 2012, 31:489)

<table>
<thead>
<tr>
<th>High vs. low intake of:</th>
<th>RELATIVE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALT</td>
<td>1.68 (95% CI, 1.17-2.41)</td>
</tr>
</tbody>
</table>
H. pylori and gastric cancer risk

36 pts (23 intestinal, 13 diffuse)


- Large inter-country variation in incidence of gastric cancer and H. pylori seroprevalence among Asian countries
- Strong link between the two in some countries (Japan); weak link in others (India/ Bangladesh)

Synergistic interaction between salt intake and H. Pylori infection to promote the development of gastric cancer?

Protective factors for development of gastric cancer

• Aspirin, NSAID use
  – Effects may be more specific for non-cardia tumors and in Caucasians

SCREENING FOR GASTRIC CANCER

• Western countries: no population-wide screening approach

• Mass screening advocated in Asian countries (Japan, Korea)
  – May entail either double contrast barium x-ray/upper GI series or upper endoscopy
  – Screening intervals? (Every 2-5 years)
  – Age to begin screening? (40 or 50 y.o.)
HOW DOES GASTRIC CANCER DIFFER IN ASIANS VS NON-ASIANS?
Gastric cancer in Asian patients

- Younger age at diagnosis
- More localized disease at presentation (53% in Japan vs 27% in U.S.)
- More common in distal (lower) portion of stomach
- Greater proportion of signet ring histology

- National Cancer Center, Japan (Ohtsu, Gastrointest Cancer Res 2007, suppl 1:S10-15)
- British Columbia Cancer Agency (Gill et al, J Clin Oncol 2003, 21:2070)
- California Cancer Registries (Theuer et al, Cancer 2000, 89:1883)
impact of ethnicity on prognosis in gastric cancer: results from the national cancer database (Al-Refaie, *Cancer* 2008;113:461-9)
How to explain differences in outcomes between asians and non-asians?

• Tumor biology and disease behavior?
  • Japanese patients’ stage-stratified survival: Tokyo > Honolulu (Hundahl et al, Arch Surg 1996, 131:170-5)

• Practice patterns and treatment differences between East and West
  – Surgical approaches
  – Exposure and responsiveness to chemotherapy
Example #1: differences in surgical approaches
Which lymph nodes need to be removed during a gastric cancer operation?

- D0 (suboptimal)
- D1 (standard)
- D2 (extended)
- D3 (super-extended)

Early Japanese data supported more extensive lymph node dissection

Cumulative Survival Rate (%)

0 1 2 3 4 5

Year

D2/D3 dissection
63.8% n=5051

D1 dissection
41.2% n=1232

D0 dissection
20.3% n=254


<table>
<thead>
<tr>
<th></th>
<th>15-year survival rate</th>
<th>Gastric cancer-related death rate</th>
<th>Locoregional 5-year recurrence survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D1</strong></td>
<td>25%</td>
<td>4%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>D2</strong></td>
<td>43%</td>
<td>10%</td>
<td>47%</td>
</tr>
</tbody>
</table>

![Graph showing survival and risk of relapse](image-url)
Why does the extent of Lymph node resection matter?

U.S. INTERGROUP 0116 STUDY

RESECTABLE GASTRIC CANCER (n=556)

OBSERVATION

ADJUVANT CHEMORADIATION (5-FU/LV → 5-FU/RT → 5-FU/LV)

Results of int-0116 led to **chemo + Radiation** becoming standard of care in the U.S. for post-op adjuvant therapy.

Relapse-free survival
19 vs. 30 months
(p < 0.001)

Overall survival
36 vs. 27 mos.
(p < 0.001)
So Why didn’t Asians accept these data?

- Surgery Q/A performed
- Types of lymph node dissection performed on study patients:
  - 10% D2
  - 36% D1
  - 54% D0 (!!)

Therefore, with better surgery, is chemoXRT necessary??
surgical outcomes between western vs. asian patients in adjuvant trials: differences attributable to tumor biology… or adequacy of operation?

<table>
<thead>
<tr>
<th>Country</th>
<th>Median age</th>
<th>D2 dissection (or greater)</th>
<th>3-year overall survival</th>
<th>3-year relapse-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>59 yrs</td>
<td>10%</td>
<td>41%</td>
<td>31%</td>
</tr>
<tr>
<td>Japan</td>
<td>63 yrs</td>
<td>100%</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>Korea/Taiwan/China</td>
<td>55.8 yrs</td>
<td>100%</td>
<td>78%</td>
<td>59%</td>
</tr>
</tbody>
</table>
endoscopic mucosal resection (EMR) is also a more common approach in Asia for early-stage disease.

- Should only be used for early gastric cancers (confined to mucosal layer).
- Contraindications: > 2 cm in size, LN metastases, lymphovascular invasion, or poor differentiation.
Example #2: Ethnic differences in sensitivity to anti-cancer drugs

3,807 patients tested for HER2

22.1% (+)

HER2-positive advanced gastric cancer (IHC 3+ and/or FISH+)

N = 594

96% metastatic
18% GEJ
22% prior gastrectomy
55% Asian

Cisplatin +
Fluoropyrimidine*
q 3 weekly x 6

Cisplatin + fluoropyrimidine PLUS
Trastuzumab (HERCEPTIN)
q 3 weekly until disease progression

* Capecitabine or 5-FU

ToGA trial in advanced gastric cancer: efficacy results

<table>
<thead>
<tr>
<th></th>
<th>Chemo alone</th>
<th>Chemo + trastuzumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>34.5%</td>
<td>47.3%</td>
<td>P=0.0017</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.5 months</td>
<td>6.7 months</td>
<td>P=0.0002, HR 0.71</td>
</tr>
<tr>
<td>Median survival</td>
<td>11.1 months</td>
<td>13.5 months</td>
<td>P=0.0048, HR 0.74</td>
</tr>
</tbody>
</table>

No major increase in treatment-related toxicities; decrease in LVEF in < 5% of patients

Led to first targeted therapy being approved for gastric cancer!
DID TRASTUZUMAB BENEFIT ASIAN AND NON-ASIAN PATIENTS EQUALLY?
Ramucirumab: a new treatment option for advanced gastroesophageal cancer

Medscape.org
Ramucirumab: anti-VEGFR antibody

Courtesy of Genentech.
Phase III RAINBOW trial

<table>
<thead>
<tr>
<th></th>
<th>RAM+PTX</th>
<th>PLACEBO+PTX</th>
<th>Signif?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS</strong></td>
<td>9.63 months</td>
<td>7.36 months</td>
<td>P=0.017 (HR 0.81)</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>4.40 months</td>
<td>2.86 months</td>
<td>P&lt;0.0001 (HR 0.64)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>28%</td>
<td>16%</td>
<td>P=0.0001</td>
</tr>
</tbody>
</table>
### Differences in ORR and PFS, Japanese vs Western patients

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>West</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAM + PTX N = 68</td>
<td>PL + PTX N = 72</td>
</tr>
<tr>
<td>ORR, %</td>
<td>41</td>
<td>19</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0035</td>
<td>0.0004</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.6 mos</td>
<td>2.8 mos</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0002 (HR 0.503)</td>
<td>&lt;0.0001 (HR 0.631)</td>
</tr>
<tr>
<td>Median OS</td>
<td>11.4 mos</td>
<td>11.5 mos</td>
</tr>
<tr>
<td>p-value</td>
<td>0.51 (HR 0.880)</td>
<td>0.005 (HR 0.726)</td>
</tr>
</tbody>
</table>

Probably because many more Japanese patients received post-progression therapy! (75% vs. 37%)
What to make of these data?

• Do clinical trials of new (cancer) therapies need to be validated in different ethnic groups given potential for differential responses and toxicity?
  • *Do pivotal studies conducted in Asia need to be duplicated in the U.S. (and vice-versa)?*

• Should clinical trials at least be stratified by ethnicity/race/nationality?

• How practical/feasible/ethical is this?
Finally, A GLIMPSE INTO THE FUTURE...
The immunotherapy revolution in cancer

Immunotherapeutic approaches have transformed the way we treat many cancer patients, including:

- Melanoma
- Lung cancer
- Bladder and renal cell cancer
- Head and neck cancer
Does immunotherapy work in gastric cancer?

Pembrolizumab in Gastric Ca: Maximum Percentage Change From Baseline in Tumor Size, N=32

53.1% decrease in target lesions
Overall RR 22%

*Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 post-baseline tumor assessment were included (n=32). Analysis cut-off date: March 23, 2015.

Bang, J Clin Oncol 33, 2015 (suppl, abstr 4001)
Clues from the Cancer Genome Atlas: Gastric cancer can be categorized into four molecular subtypes

4 distinct molecular subtypes of gastric cancer

Particularly sensitive to immunotherapeutic approaches?

CONCLUSIONS

• The burden of gastric cancer is declining both in the United States and worldwide -- but remains 2\textsuperscript{nd} leading cause of cancer mortality throughout the world.

• Gastric cancer represents an ideal disease to demonstrate the differences between Asian and Western patients in terms of:
  – Incidence
  – Prognosis/clinical outcomes
  – Therapeutic approaches

• Need for greater understanding of the biologic/genetic differences in gastric cancer arising from different ethnicities.

• Exciting new ways of categorizing and treating patients with gastric cancer are in the horizon!
THANK YOU