Surgery for Gastric and GE Junction Cancer, Primary, Palliative: When & Where

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Outline for today

- Principles of surgical treatment of gastric cancer (GC)
- Cancer of Gastroesophageal junction
- Current research of GC in Singapore
- Conclusion remarks
Incidence of Gastric Cancer in Asian Countries

GLOBOCAN 2002
Gastric Cancer in Singapore

Singapore Cancer Registry 2010

~2.5% decrease/yr
## Cancer of Gastric Cardia: Trend

<table>
<thead>
<tr>
<th>Year</th>
<th>Time interval (year)</th>
<th>All gastric cancers</th>
<th>Cardia tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968–1982</td>
<td>15</td>
<td>5376</td>
<td>339 (6.3)</td>
</tr>
<tr>
<td>1983–1992</td>
<td>10</td>
<td>4292</td>
<td>326 (7.6)</td>
</tr>
<tr>
<td>1993–1997</td>
<td>5</td>
<td>2362</td>
<td>198 (8.4)</td>
</tr>
<tr>
<td>1998–2002</td>
<td>5</td>
<td>2384</td>
<td>216 (9.1)</td>
</tr>
<tr>
<td>2003–2007</td>
<td>5</td>
<td>2260</td>
<td>365 (16.2)</td>
</tr>
<tr>
<td>2000–2005a</td>
<td>5</td>
<td>159</td>
<td>32 (20.1)</td>
</tr>
</tbody>
</table>

*National University Hospital surgical patients only*

Increasing trend

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Treatment strategy for Gastric Cancer

Gastric Cancer → Lymph nodes → Peritoneum

Local disease
- Endoscopic resection
- Laparoscopic surgery

Systemic disease
- Adjuvant chemotherapy
- Surgical treatment: Gastrectomy + LN dissection

Gotoda T, Gastric Cancer 2007
Multidisciplinary tumor (MDT) meeting

NUH UGI Cancer weekly meeting

Surgeons, Medical & Radiation Oncologists, GI, pathologists, radiologists and research nurses
Our weekly MDT patient list - example

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Comorbid</th>
<th>OGD</th>
<th>Biopsy</th>
<th>CT</th>
<th>Surgery</th>
<th>Histology</th>
<th>Board Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBA</td>
<td>64</td>
<td>Gastric CA</td>
<td>DM</td>
<td>Antral ulcer</td>
<td>Poorly diff. adenoCA</td>
<td>Antral lesion No node</td>
<td>LADG 10/7/15</td>
<td>T1bN1M0</td>
<td>Adjuvant therapy</td>
</tr>
<tr>
<td>LW</td>
<td>60</td>
<td>Gastric GIST</td>
<td>Nil</td>
<td>Fundal ulcer</td>
<td>GIST</td>
<td>No distant mets</td>
<td>Surgery first</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBH</td>
<td>51</td>
<td>Esophageal CA</td>
<td>HT</td>
<td>Tumor at 38cm-42 cm</td>
<td>adenoCA</td>
<td>Peri-esophageal nodes</td>
<td>Neoadjuvant therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgical Strategies - "Tailor Approach"

EMR/ESD  Laparoscopic  Open
Endoscopic Submucosal Dissection

【Concept】

Simple.

‘Inject, Cut & Dissect,’ ‘Remove tumor in one piece.’

For T1 mucosal cancer, differentiated type

Ono et al., Gut 2001
Laparoscopic Gastrectomy

- First described by Prof P Goh (S’pore) in 1992.

1 Surg Laparosc Endosc 1992
Laparoscopic gastrectomy
Trend at NUH: 2005-2013

30% were laparoscopic gastrectomy in 2014

Current Indication for LAG: stage 1 GC
Operative Technique
D2 lymph node dissection

- D2 is recommended for stage 2 or above GC by NCCN, BSG, etc.

JGCA guidelines 2011
Dutch D2 Trial- 15 year follow-up results

Lancet 2010
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GE Junction Cancer: Siewart Classification

Tumor epicenter within 5cm above or below GEJ
Differences in pathological features

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1,002)</th>
<th>Type I Tumors (n = 361)</th>
<th>Type II Tumors (n = 271)</th>
<th>Type III Tumors (n = 370)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (years, mean ± SD)</td>
<td>61.0 ± 11.3</td>
<td>60.1 ± 10.5</td>
<td>60.4 ± 11.3</td>
<td>62.6 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>3.9:1</td>
<td>9.0:1</td>
<td>5.4:1</td>
<td>2.1:1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Prevalence of associated intestinal metaplasia in the distal esophagus (Barrett esophagus)</td>
<td>31.0%</td>
<td>76.9%</td>
<td>9.8%</td>
<td>2.0%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Prevalence of G3/G4 (undifferentiated) tumors</td>
<td>60.2%</td>
<td>51.0%</td>
<td>55.4%</td>
<td>71.6%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Prevalence of tumors with intestinal growth pattern</td>
<td>53.7%</td>
<td>78.9%</td>
<td>41.3%</td>
<td>38.1%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Siewart et al., Ann Surg 2000
Treatment approach

- **Type 1**: Treat as esophageal cancer
  - Esophagectomy

- **Type 3**: Treat as gastric cancer
  - Total gastrectomy

**Type 2**: controversial
- Total gastrectomy + distal esophagectomy
- Esophagectomy + proximal gastrectomy
Lymph nodes spread in Type II tumors

Siewart et al., Ann Surg 2000
Survival for Type 2 Cardia cancer

Siewart et al., Ann Surg 2000
NUH experience on GEJ adenocarcinoma  
$n=85$ (2001-2015)

- Male = 82%
- Mean age = 62
- Siewart classification
  - Type I = 10 (12%)
  - Type II = 30 (35%)
  - Type III = 45 (53%)
- Surgical approach:
  - Transabdominal 70 (82%)
  - Transthoracic 13 (15%)
- Pathological stage (AJCC 7th ed.)
  - Stage 1-2 = 46%
  - Stage 3-4 = 54%
Overall survival

5YSR 39%
Gastric Cancer Research in Singapore
Singapore Gastric Cancer Consortium

a national effort in translating science to benefit patient care

1st Translational and Clinical Research (TCR) Flagship Grant awarded in 2007
1st TCR grant renewal awarded in 2013

RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER

Strongly Facilitated by

NMRC National Medical Research Council
## 3 Themes

1. **Early Detection**
   - Screening strategy based on identifying high risk groups + biomarker

2. **Improve Treatment**
   - Genomic profiling to guide chemotherapy

3. **Biology of Gastric Ca**
   - Model of gastric carcinogenesis, critical events, gatekeeper gene, biomarkers.

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**Aims & Target**

**RE-DEFINING THE MANAGEMENT OF GASTRIC CANCER**

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**Singapore Gastric Cancer Consortium**
International Collaborators


Loss of Runx3 is a key event in inducing precancerous state of the stomach. *Gastroenterology 2011*; 140(5):1536-1546.
Peritoneal Carcinomatosis

- Peritoneum is the most common site of metastasis from DGC
- The prognosis is very poor
- Most difficult to treat medically

- Complications include
  - Intestinal obstruction
  - Hydronephrosis
  - Ascites
Current treatment for peritoneal metastasis

- Systemic chemotherapy
- Hyperthermic intraperitoneal chemotherapy with peritonectomy
- Intraperitoneal normothermic chemotherapy with Paclitaxel
Paclitaxel as Intraperitoneal chemotherapy

1. Large size molecule
   - less absorption into circulation
2. Antiproliferative
   - Less adhesion
   - Allows repeated use

Advantages:
Our Study Design (Phase 2)

<table>
<thead>
<tr>
<th></th>
<th>Each Cycle (3 weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PO Capecitabine</strong></td>
<td>Week 1</td>
</tr>
<tr>
<td><strong>IV Oxaliplatin</strong></td>
<td>Day 1 only</td>
</tr>
<tr>
<td><strong>IP paclitaxel</strong></td>
<td>Day 1</td>
</tr>
</tbody>
</table>

- This was repeated for 8 cycles
- After 8 cycles, oxaliplatin is discontinued, IP paclitaxel may continue with or without capecitabine
Methods - Surgical Technique
Preliminary Result (n=13; total=22)

Conversion gastrectomy
- N=4 (30%)
- (3 R0, 1 R1)

1 year overall survival- 70%

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESCIST guideline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>53.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4</td>
<td>30.8</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>Peritoneal cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turned negative</td>
<td>9</td>
<td>69.2</td>
</tr>
</tbody>
</table>
Patients with Conversion Gastrectomy (n=4, 40%)

<table>
<thead>
<tr>
<th></th>
<th>Initial staging</th>
<th>No. of IP cycles</th>
<th>Operation</th>
<th>Final histology</th>
<th>Cytology</th>
<th>Post-op complications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/ F</td>
<td>P1</td>
<td>5</td>
<td>D2 Distal gastrectomy</td>
<td>T4aN0</td>
<td>Negative</td>
<td>UTI and pneumonia</td>
<td>Alive at 23 months</td>
</tr>
<tr>
<td>60/ F</td>
<td>P3</td>
<td>2</td>
<td>D2 Total gastrectomy</td>
<td>T2N3</td>
<td>Negative</td>
<td>nil</td>
<td>Disease progression Demised 18months after diagnosis</td>
</tr>
<tr>
<td>49/ F</td>
<td>P2</td>
<td>8</td>
<td>D2 Total gastrectomy</td>
<td>T4aN2</td>
<td>Atypical cells No definitive malignant cells seen</td>
<td>nil</td>
<td>Alive at 16 months</td>
</tr>
<tr>
<td>54/ F</td>
<td>P2</td>
<td>6</td>
<td>D2 Total gastrectomy</td>
<td>T3N2</td>
<td>Negative</td>
<td>nil</td>
<td>Alive at 10 months</td>
</tr>
</tbody>
</table>
Extensive Intraoperative Peritoneal Lavage as a Standard Prophylactic Strategy for Peritoneal Recurrence in Patients with Gastric Carcinoma

Masafumi Kuramoto, MD, PhD,* Shinya Shimada, MD, PhD,* Satoshi Ikeshima, MD,* Akinobu Matsuo, MD, PhD,* Yasushi Yagi, MD, PhD,† Masakazu Matsuda, MD, PhD,† Yutaka Yonemura, MD, PhD,† and Hideo Baba, MD, PhD§

Annals of Surgery 2009
Extensive peritoneal lavage
Kuramoto et al.
Extensive peritoneal lavage: Principle

Limiting dilution method

FIGURE 1. Schema of ‘limiting dilution method.’ This method is expected to lead to a logarithmic reduction of numerous cancer cells to zero.
Extensive Peritoneal Lavage after Curative Gastrectomy for Gastric Cancer: A Randomized Trial
Clinical T3/4, any N, M0 Gastric Cancer

**Trial Design**

N=600 (300 per arm)

- **Primary endpoints**
  - Overall survival
- **Secondary endpoints**
  - Disease free survival
  - Peritoneal recurrence rate

- **Trial Design**
  - **Primary registration & consent**
  - **Curative Gastrectomy***
  - **Randomization (after resection)**
  - **Standard†**
  - **Follow upΨ**

- **Primary endpoints**
  - **Extensive Intraoperative Peritoneal Lavage (EIPL)††**

* D2 (JGCA 2010 ed.); open or laparoscopic
** stratified by centers
† ≤2 litres of warm normal saline
‡‡ 10 litres of warm normal saline
Ψ adjuvant therapy according to individual center
1 Including Siewart Type 3 junctional cancer

Clintrial registration number: NCT02140024
2nd EXPEL investigator meeting, KINGCA 2015
(6 countries, 14 sites)
EXPEL Cumulative Accrual

Planned total accrual (600)
Visit us at www.sgcc.sg
Summary

- Epidemiology of GC is changing
- Surgical treatment is tailored according to stage
- Siewart classification is widely accepted for management of cancer of gastric cardia
- Multi-modality treatment is essential for advanced GC
Thank You