Challenges in the surgical management of gastric cancer

William H. Allum, MD, FRCS
R0 Resection

A surgical procedure in which there is no evidence of macroscopic residual tumour in the tumour bed, lymph nodes and/or distant sites with microscopic negative resection margins.

Any surgeon can cure

Surgeon-dependent

No surgeon can cure

EMR, endoscopic mucosal resection.
T1 Tumours

- Protruding
- Superficial Elevated
- Superficial Flat
- Superficial Ulcerated
- Excavated
Endoscopic Resection - Indications

- well differentiated adenocarcinoma
- no lymphatic or venous invasion
- intramucosal cancer regardless of size without ulceration
- intramucosal cancer <30mm with ulceration
- minute submucosal penetration (sm1) and <30mm
LN Metastasis from EGC

About 10% of EGC

3% of M cancer

20% of SM cancer

5% of SM has N2

Multiple sections of the primary tumour detect SM

Multiple sections of LN detects metastasis
Surgery For Early Gastric Cancer

- T1 m  D1 alpha (Stations 7 & 8)
- T1 sm  D1 beta (D1 alpha + station 9 & 11p)
- Function preserving gastrectomy
Surgery for Early Gastric Cancer

D1

D1+
Locally Advanced Gastric Cancer

- Mass
- Ulcerative
- Infiltrative, ulcerative
- Infiltrative, diffuse
Japanese Rules

End Results of Surgical Resection

Absolute curative
78.7 ± 1.7%; n=2706

Relative curative
39.6 ± 3.7%; n=823

Relative non-curative
16.5 ± 4.8%; n=281

Absolute non-curative
1.4 ± 0.9%; n=923

Medical Research Council

D1 vs D2 Trial

Operative Mortality
D1 13%
D2 6.5%

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>(58)</td>
</tr>
<tr>
<td>D2</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>(68)</td>
</tr>
</tbody>
</table>

Events Total

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>(200)</td>
</tr>
<tr>
<td>D2</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>(200)</td>
</tr>
</tbody>
</table>

Survival

The Royal Marsden

Dutch Gastric Cancer Trial Results

<table>
<thead>
<tr>
<th></th>
<th>D$_1$</th>
<th>D$_2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 711</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity, %</td>
<td>25</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>4</td>
<td>10</td>
<td>0.004</td>
</tr>
<tr>
<td>5-year survival, %</td>
<td>45</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>11-year survival, %</td>
<td>30</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>15-year survival, %</td>
<td>21</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Gastric Cancer Deaths</td>
<td>48</td>
<td>37</td>
<td>0.01</td>
</tr>
</tbody>
</table>

NS not significant.
### Morbidity And Mortality

<table>
<thead>
<tr>
<th>Complication</th>
<th>Oesophagectomy (n = 1220)</th>
<th>(95% CI)</th>
<th>Gastrectomy (n = 747)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>2.9%</td>
<td>1.9 to 3.9</td>
<td>2.2%</td>
<td>1.3 to 3.6</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.7%</td>
<td>1.0 to 2.5</td>
<td>1.1%</td>
<td>0.5 to 2.1</td>
</tr>
<tr>
<td>≥1 complication</td>
<td>29.7%</td>
<td>27.1 to 32.2</td>
<td>14.7%</td>
<td>12.3 to 17.5</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>7.4%</td>
<td>5.9 to 8.9</td>
<td>4.4%</td>
<td>3.1 to 6.1</td>
</tr>
<tr>
<td>Re-operation rate</td>
<td>8.9%</td>
<td>7.2 to 10.5</td>
<td>8.1%</td>
<td>6.2 to 10.5</td>
</tr>
<tr>
<td>Length of stay, days (median; IQR)</td>
<td>13; 10</td>
<td>N/A</td>
<td>11;7</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CI, confidence interval; IQR, interquartile range; N/A, not available.
Italian Gastric Cancer Study Group

Operative Mortality
D1  3%
D2  2.2%
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Gastric Resection</th>
<th>Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGN</td>
<td>R0 (proximal, distal circumferential margins)</td>
<td>D2 ≥ 25 lymph nodes</td>
</tr>
<tr>
<td></td>
<td>R0 (proximal, distal circumferential margins)</td>
<td>D2 &gt; 25 lymph nodes</td>
</tr>
<tr>
<td>German S3</td>
<td>5cm intestinal 8cm diffuse</td>
<td>&gt; 16 nodes for TNM</td>
</tr>
<tr>
<td></td>
<td>R0</td>
<td>No pancreatectomy/splenectomy</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td>D2 for stage II &amp; III – if fit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 15 nodes for TNM</td>
</tr>
<tr>
<td>St Gallen</td>
<td>cT1 diffuse – resect</td>
<td>D2 – without pancreatectomy or splenectomy</td>
</tr>
<tr>
<td></td>
<td>R0</td>
<td></td>
</tr>
</tbody>
</table>

SIGN, Scottish Intercollegiate Guidelines Network; TNM, tumour node metastases.
Indication and Division Lines for Distal Subtotal and Total Gastrectomy

**Distal subtotal gastrectomy**
- >2cm from cardia: Early cancer or well-circumscribed advanced cancer
- >5cm from cardia: Infiltrative advanced cancer

**Total gastrectomy**
- <5cm: When the proximal distance from the cardia is less than the required length, total gastrectomy is indicated
- 3cm: Total gastrectomy is always indicated in diffuse carcinoma (Borrmann type 4) regardless of its size
Lymphadenectomy by Extent of Resection

- D1
- D1+
- D2
JCOG 9502

Randomized trial in Siewert type II and III cancers

Left thoraco-abdominal approach versus abdominal transhiatal approach

JCOG, Japan Clinical Oncology Group.
**JCOG 9502 Scheme**

Gastric carcinoma, oesophageal invasion (≤3 cm)
T2-4, N0-2, M0

Preoperative randomisation of institution, macroscopic type, clinical T

**Abdominal (AT)**
Total gastrectomy, D2 + left upper paraaortic dissection

**Thoraco-abdominal (LT)**
Total gastrectomy, D2 + left upper paraaortic + mediastinal dissection

Observation if curative resection

AT, abdominal transhiatal; LT, left thoraco-abdominal.
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JCOG 9502

Overall Survival

Years After Randomization

AT: Abdominal (n=82)

LT: Thoraco-abdominal (n=85)

D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer

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**JCOG 9501**

*Scheme*

- **Endpoints**
  1. Overall survival
  2. Recurrence-free survival, morbidity/mortality

- **Adenocarcinoma**
  T2b/T3/T4, N0/N1/N2, Curative operation, Lavage cytology (-)

- **Intraoperative Randomisation**

- **Group A (standard)**
  D2

- **Group B (Extended)**
  D2 + PAND

- **Observation**

- 523 patients enrolled between July 1995 and April 2001
- 24 Institutions
- Survival analysis performed April 2006

PAND, para-aortic nodal dissection.
**JCOG 9501**

*Overall Survival*

<table>
<thead>
<tr>
<th>Years</th>
<th>D2 (n=263) Survival</th>
<th>D2 + PAND (n=259*) Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>76.4%</td>
<td>76.4%</td>
</tr>
<tr>
<td>5-year</td>
<td>69.2%</td>
<td>70.3%</td>
</tr>
</tbody>
</table>

HR=1.03 (0.77-1.37)

one-sided $P=0.57$

HR, hazard ratio.

*One case was ineligible because of changed histologic diagnosis.

Overall Survival in pN(+) 

- **D2 (n=184)**: 3-year Survival 71.7%, 5-year Survival 65.2%
- **D2 + PAND (n=164)**: 3-year Survival 63.4%, 5-year Survival 54.9%

HR = 1.38 (1.01-1.88), one-sided $P=0.979$

pN(+), node-positive.
Overall Survival in pN(-)

Proportion Surviving

<table>
<thead>
<tr>
<th></th>
<th>3-year Survival</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2 (n=79)</td>
<td>87.3%</td>
<td>78.4%</td>
</tr>
<tr>
<td>D2 + PAND (n=95)</td>
<td>98.9%</td>
<td>96.8%</td>
</tr>
</tbody>
</table>

pN(-), node-negative.
Conclusion of JCOG 9501

PAND can be safely performed in fit patients by specialist surgeons

PAND should not be used for prophylactic lymph node dissection for curable advanced gastric cancer

Further research is needed to understand the paradoxical observation that patients with less advanced tumours seem to benefit from PAND

Extended Lymphadenectomy

T3/4 cancers

Mixed or diffuse histology

Upper third of the stomach

JCOG 0110 “Splenectomy or Not”

Endpoints
1. Overall survival
2. Morbidity, operation time, blood loss

Adenocarcinoma in upper 1/3
T2/T3/T4, N0/N1/N2, Not greater curve,
Curative operation, Lavage cytology (-)

Intraoperative randomisation

Group A (Splenectomy)
Total gastrectomy, D2

Group B (Spleen preserve)
Total gastrectomy, D2

Observation
(S-1 adjuvant for Stage II/III)

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JCOG 0110 “Splenectomy or Not”

- 505 patients
- Similar operative mortality with or without splenectomy
- Greater postoperative morbidity with splenectomy
- Greater intraoperative blood loss with splenectomy

Minimally Invasive Surgery

- Shorter inpatient stay
- Less blood loss
- Quicker return to GI function
- ? Anastomotic leak rates
- Intraluminal bleeding
<table>
<thead>
<tr>
<th>Variables</th>
<th>Extent of LND</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1 + β (n=103)</td>
<td></td>
</tr>
<tr>
<td>Operating time, mean, min ± SD</td>
<td>277 ± 86</td>
<td>0.001</td>
</tr>
<tr>
<td>EBL, mean, mL ± SD</td>
<td>231 ± 190</td>
<td>0.019</td>
</tr>
<tr>
<td>Harvested lymph nodes, mean, n ± SD</td>
<td>42 ± 16</td>
<td>0.484</td>
</tr>
<tr>
<td>Morbidity, n %</td>
<td>19 (18.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality, n %</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay, mean, d ± SD</td>
<td>10.8 ± 9.1</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Minimally Invasive Surgery

Early gastric cancer
Distal Gastrectomy

KLASS Trial
Comparison of laparoscopic vs open gastrectomy for gastric cancer: a prospective randomized trial

JCOG 0912
Phase III study of laparoscopy-assisted vs open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer: a multicenter study

ADVANCED DISEASE
Palliative Resection

Dutch D1 vs D2 trial

295 / 996 (29%) incurable

- \( T^+ \) macroscopically irresectable
- \( H^+ \) liver metastasis
- \( P^+ \) peritoneal metastasis
- \( N4^+ \) distant lymph nodes

**Fig. 2** Survival following resection and no resection in patients aged 70 years or less and with two or more positive signs of incurability. $P = 0.07$ (log rank test)
Patient Selection

Natural history
Comorbidity and its assessment
Quality of life
Patient wishes
1. **Initial assessment**
   - Assessment of underlying cancer
   - Pre-operative health & risk assessment
   - Dietetic assessment
   - Patient information & expectations
   - Stratification of risk

2. **Pre-surgery assessment**
   - Detailed discussions of
   - Surgical procedure
   - Physio assessment
   - Dietetic assessment
   - Patient information & expectations
   - Immunonutrition

3. **Formal Pre-assessment**
   - Anaesthetic review
   - CPEX
   - Physiotherapy instruction
   - Dietetic advice to optimise nutritional status

4. **Admission day before surgery**
   - Immunonutrition (Oral Impact®)
   - Carbohydrate loading

5. **Intraoperative (Intra-op)**
   - Optimise fluid management
   - Epidural
   - JEJ

6. **Clinical daily assessment**
   - to determine progress along the pathway according to the protocol

7. **Outpatient 2 weeks**
   - Surgical review
   - Dietitian review
   - Dietary advice
   - JEJ removed if not used

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CPEX, cardiopulmonary exercise testing; ERAS, enhanced recovery after surgery; JEJ, jejunostomy; MDT, multidisciplinary team.
Conclusions

- Role of surgical specialisation
- Standard approaches for gastric resection and lymphadenectomy
- Minimally invasive surgery is investigational
- Importance of patient selection and perioperative care
Thank you for your attention