SURGERY FOR GASTRIC AND GE JUNCTION CANCER

Primary, palliative – where and when?

Magnus Nilsson
Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
DISCLOSURE OF INTERESTS

Member of the European Minimal Invasive Oesophagectomy Thinktank, sponsored by Medtronic Inc.
Surgery for gastric and GE junction cancer

Overview of surgical procedure types

Issues of controversy
- The extent of lymph node dissection – limited (D1) or extended (D2) lymphadectomy?
- Open vs laparoscopic surgery

Enhanced recovery after surgery programmes

Palliative surgery for gastric and GE junction cancers
- Procedures and indications
....basics

- **Standard procedures for gastric cancer**
  - **Total gastrectomy**
  - Distal gastrectomy (=subtotal gastrectomy)
  - Proximal gastrectomy
Standard procedures for gastric cancer

- Total gastrectomy
- Distal gastrectomy (=subtotal gastrectomy)
- Proximal gastrectomy
- **Standard procedures for gastric cancer**
  - Total gastrectomy
  - Distal gastrectomy (=subtotal gastrectomy)
  - Proximal gastrectomy

Very rarely used in Western countries due to:
- Only oncogically suitable only for early (T1) cancers
- Leads to severe reflux problems
Gastrectomy reconstruction

Billroth I  Billroth II  Roux-en-Y
basics

- Standard procedures for GE junction cancer
  - Total gastrectomy – Siewert type III
  - Esophagectomy – types I and II
    - Ivor Lewis (intrathoracic anastomosis)
    - Transhiatal esophagectomy (cervical anastomosis)
basics

- Standard procedures for GE junction cancer
  - Total gastrectomy
  - Esophagectomy
    - Ivor Lewis (intrathoracic anastomosis)
    - Transhiatal esophagectomy (cervical anastomosis)
basics

- Standard procedures for GE junction cancer
  - Total gastrectomy
  - Esophagectomy
    - Ivor Lewis (intrathoracic anastomosis)
    - Transhiatal esophagectomy (cervical anastomosis)
      - Mainly used for very frail patients (severe COPD)
Oesophagectomy reconstruction

- Using a **gastric tube** formed by the greater curvature is completely dominating (>95%)

- **Colonic interposition**, using left or right colon, is the second choice
To the issues of controversy:

Gastric and GE junction cancer surgery:

*Lymph node dissection* – limited (D1) or extended (D2) lymphadectomy?
Lymphadenectomy in oncological surgery

**Lord Moynihan in 1908:**

“Surgery of malignant disease is not the surgery of organs; it is the anatomy of the lymphatic system”

Moynihan BGA. *Surg Gynecol Obstet* 1908;6:463–6:
Japanese branch of research in gastric cancer:

Lymphatic Flow from the Stomach

Channels along the greater curve
Channels along the left gastric A.
Channels along the superior mesenteric V.
Channels along the Lt. gastro-epiploic A.
Channels along the posterior gastric A.
Channels along the splenic A.
Channels crossing the pancreatic surface
Since 1970ies
National Cancer Center in Tokyo:
Database on specific lymph node station metastases

- Database variables:
  - Sex, age, location (upper, middle lower third), position (lesser/greater curvature, posterior/anterior, circumferential), Borrmann classification, depth of invasion, max diameter, differentiation grade

- Accurate prediction of the risk of metastasis in each lymph node station
Since 1970ies
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Database on specific lymph node station metastases

- Database variables:
  - **Sex, age, location** (upper, middle lower third), **position** (lesser/greater curvature, posterior/anterior, circumferential), **Borrmann classification**, **depth of invasion**, **max diameter**, **differentiation grade**

- Accurate prediction of the risk of metastasis in each lymph node station
Total gastrectomy:
D1  (low risk T1b)
D1+ (high risk T1b)
D2  (all T2-T4)

In the old classification distal pancreatectomy and splenectomy were also required.
Distal gastrectomy:
D1  (low risk T1b)
D1+ (high risk T1b)
D2  (all T2-T4)
### Randomised trials addressing lymphadenectomy for gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Author, year</th>
<th>No. Pts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch</td>
<td>Bonenkamp, 1999</td>
<td>711</td>
<td>No survival benefit of D2. High mortality.</td>
</tr>
<tr>
<td>British MRC</td>
<td>Cuschieri, 1999</td>
<td>400</td>
<td>No survival benefit of D2. High mortality.</td>
</tr>
<tr>
<td>Chile</td>
<td>Csendes, 2002</td>
<td>187</td>
<td>Splenectomy is not necessary.</td>
</tr>
<tr>
<td>Taegu</td>
<td>Yu, 2006</td>
<td>207</td>
<td>Prophylactic splenectomy is not justified.</td>
</tr>
<tr>
<td>Taipei</td>
<td>Wu, 2006</td>
<td>221</td>
<td>D3 (actually more like D2) &gt; D1</td>
</tr>
<tr>
<td>JCOG 9501</td>
<td>Sasako, 2008</td>
<td>523</td>
<td>Prophylactic D3 should not be done.</td>
</tr>
<tr>
<td>Italian D1-D2</td>
<td>Deguili, 2014</td>
<td>267</td>
<td>Low morbidity and mortality, no overall survival difference, subgroup differences (N+ patients)</td>
</tr>
</tbody>
</table>
Dutch D1/D2 Trial

Accrual and publication history:

- 1989-1993 996 randomized; 711 curative
- 1995 Morbidity/mortality (Lancet)
- 2004 “Final” results (J Clin Oncol)
- 2010 15-yr follow-up (Lancet Oncol)
- 2015 Lymph node dissection per protocol data (BJS)
Dutch D1/D2 Trial

Survival curves after D1 or D2 gastrectomy
n=711

Bonenkamp et al NEJM 1999
## Inhospital Mortality

### Dutch D1/D2 trial

<table>
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<tr>
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Mortality largely attributed to splenectomy and distal pancreatectomy

Bonenkamp et al NEJM 1999
# Inhospital Mortality

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Mortality largely attributed to splenectomy and distal pancreatectomy

Bonenkamp et al NEJM 1999
Dutch D1 vs. D2

Overall survival

Years since surgery

Survival (%)

D1 - female
D1 - male
D2 - female
D2 - male

Overall survival
Dutch D1 vs. D2

Overall survival

Survival (%) over years since surgery for D1 and D2, separated by gender.
Dutch trial per protocol (quality assured pathology)

Treatment delivery problems in D1-D2 trials:

- **Non-compliance** = less Igll dissection than required for D2
- **Contamination** = more Igll dissection than required for D1

![Graph showing cumulative survival over time after surgery](image)

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Non-compliance:

- At most D1
- At least D2

Contamination:

- At least D2

**Fig. 3** Survival curves for D2 compliant + contaminated (139 patients) and D1 without contamination (282) subgroups. 

$P = 0.041$ (log rank test)
Taipei D1 vs extended lymphadenectomy trial

- Single institutional RCT
- N=221
- No adjunct therapy

Significantly better overall survival after extended lymphadenectomy

Wu et al. Lancet Oncology 2006
Extent of lymphadenectomy in gastric cancer surgery

Take home message:

Extended lymphadectomy (D2) improves the oncological outcome in gastric cancer
Under the condition that postoperative mortality is kept low (SURGERY IS STANDARDIZED = High volume centers)

ESMO guidelines 2016:

Consensus opinion is that, in Western countries, medically fit patients should undergo D2 dissection that is carried out in specialised, high-volume centres with appropriate surgical expertise and postoperative care [I, B] [25–27]. As a result, perioperative
Next issue of controversy:

Gastric and GE junction cancer surgery:

Laparoscopic /minimal invasive or open surgery?
Minimal invasive or open surgery
What’s the actual difference?

• Entry wound trauma

• Vision
Minmal invasive oesophagectomy (MIO) for GE junction cancer: Less entry wound trauma

Open vs MIO

True both for abdominal and thoracic parts of the operation
Vision in open oesophagectomy
Vision in MIO

- Enhanced vision in MIO ➔ More precise dissection ➔
  - Less bleeding
  - Potential for better lymph node dissection and radicality
  - Less unintentional tissue damage
First port placement
Laparoscopic or open gastrectomy?

Major randomized trials comparing open to laparoscopic gastrectomy for gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Primary outcome</th>
<th>Sample size</th>
<th>Status</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG0703</td>
<td>Stage I, DG only</td>
<td>Morbidity</td>
<td>176</td>
<td>Published</td>
<td>Equal</td>
</tr>
<tr>
<td>Cai et al.</td>
<td>Stage II-III</td>
<td>R0, Lgll count, morbidity, recovery</td>
<td>123</td>
<td>Published</td>
<td>Equal R0, Lgll yield, lap less pulmonary morbidity</td>
</tr>
<tr>
<td>Cui et al.</td>
<td>Stage II-III</td>
<td>R0, Lgll count + recovery</td>
<td>296</td>
<td>Published</td>
<td>Equal R0/Lgll, lap faster recovery</td>
</tr>
<tr>
<td>KLASS-01</td>
<td>Stage I, DG only</td>
<td>Overall survival</td>
<td>1416</td>
<td>Published</td>
<td>Non-inferiority for OS, Lap less morbidity</td>
</tr>
<tr>
<td>JCOG 0912</td>
<td>Stage I, DG only</td>
<td>Overall survival</td>
<td>920</td>
<td>Published</td>
<td>Non-inferiority regarding OS, less blood loss, less wound complications</td>
</tr>
<tr>
<td>KLASS02</td>
<td>Stage II-III, DG only</td>
<td>Relapse-free survival, complications</td>
<td>1050</td>
<td>Preliminary results</td>
<td>Non-inferiority for relapse free survival, less w.c.</td>
</tr>
<tr>
<td>JLSSG0901</td>
<td>Stage II-III, DG only</td>
<td>Relapse-free survival, complications</td>
<td>507</td>
<td>Preliminary, early results</td>
<td>No difference in morbidity, less blood loss and analgetics in lap</td>
</tr>
<tr>
<td>LOGICA</td>
<td>Stage II-III, DG only</td>
<td>Postop stay</td>
<td>210</td>
<td>Preliminary results</td>
<td>No difference</td>
</tr>
<tr>
<td>STOMACH</td>
<td>Stage II-III, TG only</td>
<td>Lymph node yield</td>
<td>168</td>
<td>Preliminary results</td>
<td>No difference</td>
</tr>
</tbody>
</table>

- Non-inferiority for lap in survival
- Lap: minor reduction in:
  - Blood loss
  - Analgetic use
  - Morbidity
Minimally invasive or open oesophagectomy?

Three randomised trials comparing open to minimal invasive oesophagectomy for oesophageal or GE junction cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Primary outcome</th>
<th>Sample size</th>
<th>Status</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIME trial, open vs MIO</strong></td>
<td>Esophageal and GE types I and II</td>
<td>Pulmonary complications</td>
<td>N=115</td>
<td>Published 2012</td>
<td>MIO: less pulmonary complications, quicker recovery, better QoL</td>
</tr>
<tr>
<td><strong>Robot trial, open vs robotic MIO</strong></td>
<td>Esophageal and GE types I and II</td>
<td>All complications</td>
<td>N=112</td>
<td>Published 2018</td>
<td>RMIO: less overall complications, quicker funct recovery better QoL</td>
</tr>
<tr>
<td><strong>MIRO trial, Open vs hybrid</strong></td>
<td>Esophageal and GE types I and II</td>
<td>All complications</td>
<td>N=207</td>
<td>Published 2019</td>
<td>HMIO: less overall complications, better OS (P=0.06)</td>
</tr>
</tbody>
</table>

**MIO:**
- Less complications
- Quicker functional recovery
- Better quality of life (up to 1 year after)
- No signs of oncological disadvantages

Biere et al. Lancet 2012
Van der Sluis et al. Ann Surg 2018
Mariette et al. NEJM 2019
Enhanced recovery programmes
(standardized clinical pathways)
Enhanced recovery programmes in oesophagogastric surgery

Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer

S. R. Preston¹, S. R. Markar², C. R. Baker¹, Y. Soon¹, S. Singh¹ and D. E. Low²

¹Oesophago-Gastric Unit, Royal Surrey County Hospital, Guildford, UK and ²Department of Thoracic Surgery, Virginia Mason Medical Center, Seattle, Washington, USA

Correspondence to: Dr D. E. Low, Department of Thoracic Surgery, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, Washington 98111, USA (e-mail: Donald.low@vmmc.org)

Key components:

• Standardisation of perioperative clinical pathway
• "Aggressive" mobilisation

Preston et al. BJS 2011
Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer

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Key components:
- Standardisation of perioperative clinical pathway
- "Aggressive" mobilisation
Clinical care pathway from Royal Surrey County Hospital 2011, adopted at Karolinska in 2013

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<tr>
<th>Postoperative day</th>
<th>Aim or goal</th>
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<tr>
<td><strong>Evening of day of surgery</strong></td>
<td>Goal-directed fluid therapy with LIDCO™ Rapid* for 6 h to maximize fluid status</td>
</tr>
<tr>
<td></td>
<td>Epidural analgesia ± additional intravenous analgesia</td>
</tr>
<tr>
<td></td>
<td>Sits up in bed for 4 h</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td>Mobilizes twice in the day as far as the patient is able</td>
</tr>
<tr>
<td></td>
<td>Sits up in chair/bed for 4 h</td>
</tr>
<tr>
<td></td>
<td>Start jejunal feeding (30 ml/h)</td>
</tr>
<tr>
<td></td>
<td>Start 30 ml/h water orally</td>
</tr>
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<td></td>
<td>Commence prophylactic anticoagulation</td>
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<tr>
<td><strong>Day 2</strong></td>
<td>Mobilizes three times in the day</td>
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<tr>
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<td>Increase jejunal feeding to 50 ml/h continuously</td>
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<td></td>
<td>Remove nasogastric aspirate if &lt; 300 ml per 24 h</td>
</tr>
<tr>
<td></td>
<td>Transfer to surgical HDU</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td>Mobilizes four times in the day</td>
</tr>
<tr>
<td></td>
<td>Basal chest drain may be removed if serous output &lt; 250 ml per 24 h</td>
</tr>
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<td><strong>Day 4</strong></td>
<td>Mobilizes five times in the day</td>
</tr>
<tr>
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<td>When flatus passed, increased jejunal feeds to 80 ml/h, and oral intake to 50 ml/h including cups of tea/coffee</td>
</tr>
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<td><strong>Day 5</strong></td>
<td>Mobilizes six times in the day, increasing distance of walks</td>
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<tr>
<td></td>
<td>Consider discontinuation of epidural following pain team review</td>
</tr>
<tr>
<td></td>
<td>Central line removal</td>
</tr>
<tr>
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<td>If bowel opens, discontinue urinary catheter</td>
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<td>Convert intravenous proton pump inhibitor to oral formulation</td>
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<td><strong>Day 6</strong></td>
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<td>Remove apical chest drain if clear fluid is draining</td>
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<td>Receive pump training for jejunostomy</td>
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<td><strong>Day 7</strong></td>
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<td>Dietitian education on postoperative diet and enteral feeding regimen</td>
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<td>Planned discharge, following physiotherapy assessment and instructions</td>
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## Clinical care pathway from Royal Surrey County Hospital 2011, adopted at Karolinska in 2013

**Table 2** Clinical care pathway at Royal Surrey County Hospital, 2011

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Two hours post oesophagectomy

Photo shown after patient’s permission
First walk postop day 1

Photo shown after patient’s permission
A worn down track in the floor by now
Leaving the hospital at postop day 10

Total game changer for us:

- Major reduction in all types of complications (incidence and severity)
- ICU-time most reduced (unplanned ICU admittance 20% → <5%)

Photo shown after patient’s permission
Annual ICU costs after oesophagectomy 2012-2015 (millions of SEK)
Palliative surgery
for gastric and GE junction cancer
Palliative surgery for gastric and GE junction cancer

What types of palliative surgery may be indicated?

- Distal gastrectomy
  - For severe bleeding

- Gastro-jejunostomy bypass
  - For gastric outlet obstruction

- Palliative gastrectomy in general for reduction of tumour burden
Does resection of primary tumour improve survival in metastatic gastric cancer?

Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial

Kazumasa Fujitani*, Han-Kwang Yang*, Junki Mizueawa, Young-Woo Kim, Masanori Terashima, Sang-Uk Han, Yoshiaki Iwaseki, Woo Jin Hyung, Akinori Takegane, Da-Joong Park, Takaki Yoshikawa, Seokyung Hahn, Kenichi Nakamura, Cho Hyun Park, Yukinori Kurakawa, Yong-Jue Bang, Byung-Joo Park, Mitsuaki Sasako, Toshimasa Tsubinaka, for the REGATTA study investigators

- RCT palliative chemo vs palliative chemo + distal gastrectomy for metastatic disease in one organ
- N=175
- Trend towards worse OS

[Graph showing overall survival with Kaplan-Meier curves]

HR 1.09 (95% CI 0.78–1.52); one-sided stratified log-rank p=0.70
How should the gastro-jejunostomy bypass for gastric outlet obstruction be performed?

- Conventional vs
- "Modified Devine procedure" = bypass with partial stomach partioning
How should the gastro-jejunostomy bypass for gastric outlet obstruction be performed

A systematic review and meta-analysis comparing partial stomach partitioning gastrojejunostomy versus conventional gastrojejunostomy for malignant gastroduodenal obstruction

Koshi Kumagai¹ • Ioannis Rouvelas¹ • Annika Ernberg¹ •Saga Persson¹ • Apostolos Anagnostov² • Daniela Mariona³ • Mats Lindblad¹ • Magnus Nilsson¹ • Weimin Ye¹ • Lars Lundell¹ • Joe A. Tsai¹

Modified Devine procedure

<table>
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<tr>
<th>Study</th>
<th>Events, Partial Partitioning</th>
<th>Events, Conventional</th>
</tr>
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<tbody>
<tr>
<td>Kanazawa 1997</td>
<td>0.16 (0.03, 1.17)</td>
<td>1/8</td>
</tr>
<tr>
<td>Kato 2001</td>
<td>0.36 (0.04, 2.84)</td>
<td>1/7</td>
</tr>
<tr>
<td>Yamagishi 2004</td>
<td>0.20 (0.02, 3.62)</td>
<td>0/6</td>
</tr>
<tr>
<td>Oida 2009</td>
<td>0.14 (0.04, 0.57)</td>
<td>2/20</td>
</tr>
<tr>
<td>Ushiba 2011</td>
<td>0.56 (0.24, 1.34)</td>
<td>6/26</td>
</tr>
<tr>
<td>Ernberg 2015</td>
<td>0.12 (0.01, 1.88)</td>
<td>0/8</td>
</tr>
<tr>
<td>Overall</td>
<td>0.32 (0.17, 0.60)</td>
<td>10/82</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Modified Devine:
- Better gastric emptying
- Shorter length of stay

Kumagai et al. Langenbeck Archives of Surgery 2016
Take home message:

- **Extended (D2) lymphadenectomy is recommended** in curative intent surgery for locally advanced gastric cancer (ESMO)

- **Laparoscopic gastrectomy and minimal invasive oesophagectomy are safe and oncologically non-inferior** in curative intent surgery for gastric and GE junction cancer

- **Palliative gastrectomy is not recommended**, except for palliation of specific symptoms such as severe bleeding

- Gastro-jejunostomy bypass with partial stomach partitioning (modified Devine) is the most recommendable palliative procedure for malignant gastric outlet obstruction
Thank you
Surgery for gastric and GE junction cancer

The dilemma of oncological surgery

High level of radicality → Increased risk of morbidity

Low level of radicality → Increased risk of cancer recurrence
Dutch D1/D2 trial: 15-yr results
Post hoc analyses

Cumulative risk of death

Death due to gastric cancer

Death due to other causes