Locally Advanced Esophageal and Gastric Cancer

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Trends in Esophagogastric Cancer:

Esophageal Cancer
What are the treatment modalities for locally advanced esophageal cancer?

• Surgery
  • Ivor-Lewis
  • 3-hole
  • Transhiatal
  • Minimally invasive
  • Robotic

• Radiation Therapy
  • External Beam Radiation Therapy
    • Conventional
    • IMRT
    • Protons

• Chemotherapy

• Immunotherapy
  • Checkmate 577 – nivolumab vs placebo
Surgery
What is an Esophagectomy

• The esophagus is the conduit between the mouth and the stomach
• It traverses the chest next to the spine
• It extends 2-4 cm into the abdomen before becoming the stomach
• An esophagectomy is removal of MOST of the esophagus.
• A gastrectomy is removal of the stomach
ESOPHAGECTOMY

• Best approach remains controversial

• Chosen technique depends on multiple factors

• Historically was one of the highest incidences of mortality and morbidity

ESOPHAGECTOMY

As better surgical techniques developed, safer more reliable options came about

• Multiple different approaches
  – Thoracotomy/Laparotomy (Ivor Lewis)
  – 3-Hole (Thoracotomy, Laparotomy, neck)
  – Left Thoracoabdominal
  – Transhiatal
Laparoscopic Steps: Gastric Tubularization, Celiac node dissection, stapling of left gastric vessels
ESOPHAGECTOMY

- Minimally invasive approaches are feasible and safe
- Reduced mortality and morbidity rates
- Less Blood loss
- Less respiratory complications
- Similar oncologic results

Patty et al. World J Gastroenterol 2010
Robotic Esophagectomy
## Postoperative Complications

<table>
<thead>
<tr>
<th></th>
<th>Hybrid (103) (N)</th>
<th>Converted (51) (N)</th>
<th>MIE (200) (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Postoperative Complications</td>
<td>77 (74.8%)</td>
<td>34 (66.7%)</td>
<td>147 (73.5%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>27 (26.2%)</td>
<td>7 (13.7%)</td>
<td>53 (26.5%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>26 (25.2%)</td>
<td>12 (23.5%)</td>
<td>58 (29.0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11 (10.7%)</td>
<td>3 (5.9%)</td>
<td>20 (10.0%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (1.9%)</td>
<td>0 (0.0%)</td>
<td>4 (2.0%)</td>
</tr>
<tr>
<td>Vocal Cord Paralysis/Paresis</td>
<td>17 (16.5%)</td>
<td>5 (9.8%)</td>
<td>9 (4.5%)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>11 (10.7%)</td>
<td>2 (3.9%)</td>
<td>12 (6.0%)</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>9 (8.7%)</td>
<td>9 (17.6%)</td>
<td>29 (14.5%)</td>
</tr>
<tr>
<td>Anastomotic and Conduit Complications</td>
<td>13 (12.6%)</td>
<td>9 (17.6%)</td>
<td>36 (18.0%)</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>6 (5.8%)</td>
<td>3 (5.9%)</td>
<td>9 (4.5%)</td>
</tr>
<tr>
<td>30 Day Mortality (N)</td>
<td>1 (1.0%)</td>
<td>1 (2.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>90 Day Mortality (N)</td>
<td>6 (5.8%)</td>
<td>3 (5.9%)</td>
<td>5 (2.5%)</td>
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</tbody>
</table>
Radiation Therapy
Start with PET – CT images of Cancer Target
Identify the Clinical Tumor Volume (CTV)
Identify the Normal Structures that Might be Affected

- Spinal Cord
- Lung
- Lung
- Heart
- Liver
- Kidney
- Kidney
- Spinal Cord

Radiation
Chemotherapy
Fluorouracil

Oxaliplatin

Cisplatin

Irinotecan

Paclitaxel

Epirubicin
Alkylating agents keep the cell from reproducing by damaging its DNA. These drugs work in all phases of the cell cycle and are used to treat many different cancers.

Anthracyclines: Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in copying DNA during the cell cycle. (Enzymes are proteins that start, help, or speed up the rate of chemical reactions in cells.)

Antimetabolites interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA. These agents damage cells during the phase when the cell’s chromosomes are being copied.

These drugs interfere with enzymes called topoisomerases, which help separate the strands of DNA so they can be copied.

Mitotic inhibitors are compounds derived from natural products, such as plants. They work by stopping cells from dividing to form new cells.
Does (Neo)Adjuvant Chemotherapy Improve Surgical Outcomes?
Neoadjuvant Chemotherapy Compared with Surgery Alone for Localized Esophageal Cancer

Localized Esophageal Cancer

Does Neoadjuvant Chemoradiation Therapy Improve Surgery Outcomes?
All-Cause Mortality Estimates for Neoadjuvant C/RT Compared with Surgery Alone

**Chemoradiotherapy regimen:**
- Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
- Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy

**Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)**

CROSS Study: Overall survival

No residual cancer after Chemo+RT: 29%.

Median Survival was doubled with Chemo+ RT over surgery alone.

Median Survival was nearly quadrupled for patients with squamous cell carcinoma.

Median Survival was improved by 66% in adenocarcinoma patients.

CheckMate 577 study design

• CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial\(^a\)

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<tr>
<th>Key eligibility criteria</th>
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<tr>
<td>Stage II/III EC/GEJC</td>
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<tr>
<td>Adenocarcinoma or squamous cell carcinoma</td>
</tr>
<tr>
<td>Neoadjuvant CRT + surgical resection (R0,(^b) performed within 4-16 weeks prior to randomization)</td>
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<tr>
<td>Residual pathologic disease</td>
</tr>
<tr>
<td>- ≥ ypT1 or ≥ ypN1</td>
</tr>
<tr>
<td>ECOG PS 0–1</td>
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<table>
<thead>
<tr>
<th>Stratification factors</th>
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<tr>
<td>Histology (squamous vs adenocarcinoma)</td>
</tr>
<tr>
<td>Pathologic lymph node status (≥ ypN1 vs ypN0)</td>
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<tr>
<td>Tumor cell PD-L1 expression (≥ 1% vs &lt; 1%)</td>
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N = 794

\[ R \frac{2}{1} \]

n = 532

Nivolumab
240 mg Q2W × 16 weeks then 480 mg Q4W

n = 262

Placebo
Q2W × 16 weeks then Q4W

Primary endpoint:
• DFS\(^e\)

Secondary endpoints:
• OS\(^f\)
• OS rate at 1, 2, and 3 years

Median follow-up was 24.4 months (range, 6.2–44.9)\(^g\)

Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)
Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo.

Per investigator assessment; 6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; The boundary for statistical significance at the pre-specified interim analysis required the P value to be less than 0.036.

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<tr>
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<th>Nivolumab (n = 532)</th>
<th>Placebo (n = 262)</th>
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<tbody>
<tr>
<td>Median DFS, mo</td>
<td>22.4</td>
<td>11.0</td>
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<tr>
<td>(95% CI)</td>
<td>(16.6–34.0)</td>
<td>(8.3–14.3)</td>
</tr>
<tr>
<td>HR (96.4% CI)</td>
<td>0.69 (0.56–0.86)</td>
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<tr>
<td>P value</td>
<td>0.0003c</td>
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Conclusions from these Studies

Localized Esophageal

Pre-operative cisplatin/5-FU chemotherapy offers a small survival advantage in distal esophageal and GE junction cancer.

Neoadjuvant platinum-based chemoradiation (esp. w. carbo/tax) offers a greater survival advantage with better local control but increased surgical morbidity.

Post-operative therapy with nivolumab will likely get FDA approval next year and become standard of care.
Gastric Cancer
The stomach can be divided into 4 regions:
1. Cardia
2. Fundus
3. Body
4. Pylorus
What are the treatment modalities for locally advanced gastric cancer?

• Surgery
  • Subtotal gastrectomy
  • Total gastrectomy
  • Laparoscopic
  • Robotic

• Chemotherapy
Partial gastrectomy

A

Stomach

Pancreas and Ducts

Tumor

Duodenum

Jejunum

Jejunostomy

B

Billroth II Gastro- Jejunostomy

a'

b'
Total gastrectomy

A
- Oesophagus
- Tumor
- Pancreas and Ducts
- Stomach
- Duodenum
- Jejunum

B
- Roux-en-Y Oesophago-Jejunostomy
- Jejuno-Jejunostomy
- Alternative reconstruction

a' b' c' d'
What Is the Ideal Extent of Lymphadenectomy?

D0 - removes less than all relevant N1 nodes

D1 - requires the dissection of the N1 nodes (1 - 6)*

D2 - includes the N1 and N2 nodes (7–11)

D3 – includes the N1, N2, and N3 nodes (12-15)

D4 – includes the N1, N2, N3 and N4 nodes (16)

*nodes 2, 4 remain if distal subtotal gastrectomy
What are Proven Strategies to Enhance Outcomes for Surgical Resection?
ECF q 3 weeks:
- Epirubicin 50/-/s1
- Cisplatin 60/-/d1
- CI 5-FU 200/-/d x 21d

503 Patients:
- 15% Lower Third
- 12% GE Junction

CSC

ECF x 3 q3/52

3-6 weeks

Resection

6-12 weeks

ECF x 3 q3/52

Within 6 weeks

S

Resection

64% started post-op chemo
48% completed 3 cycles

Follow-up

MAGIC: Survival

2-Year Survival: 23% improvement for peri-operative chemotherapy over surgery alone.

5-Year Survival: 57% improvement for peri-operative chemotherapy over surgery alone.

Median Survival: 9 month improvement for MAGIC over surgery alone.
FLOT4 Study Design

Randomized, multicenter, investigator-initiated, phase II/III study

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Presented by: Salah-Eddin Al-Batran
2-Year Survival: 15% improvement for peri-operative FLOT over peri-operative MAGIC.

5-Year Survival: 25% improvement for peri-operative FLOT over peri-operative MAGIC.

Median Survival: 15 month improvement for FLOT over MAGIC
Localized Gastric:

The peri-operative FLOT4 regimen is the current standard of care and should be considered for patients of better performance status.

Perioperative chemotherapy likely has improved survival by 2 years over just surgery alone.
Thank You!