Objectives

To review key aspects of stomach cancer for radiation oncology trainees through a case vignette, contouring example, & epidemiology

1. Recognize the presentation of stomach cancer

2. Peer review a neoadjuvant radiation treatment plan

3. Apply epidemiology, classification systems, & prognosis

4. Justify a management framework
Outline

1. Stomach Cancer Case Presentation
2. Epidemiology
3. Classification Systems
4. Key Trials
5. Clinical Practice Guidelines
6. Treatment Planning

*denotes epidemiology relevant to our case throughout this deck
Case

59yo male presents w/3-month h/o progressive heartburn. Also trouble swallowing, anorexia, & early satiety w/a 30lb weight loss.

**ROS:** independent of daily activities & active most of the day. No melena/hematochezia. Regular bowel movements

**PMHx:** treated for H. Pylori, GERD, & IDA. No upper scopes.

**SocHx:** ex-smoker (>20 pack-years).

**Meds:** ranitidine & Fe supplements.

**FMHx:** no h/o of gastric, breast, or ovary ca. No FAP/HNPCC.

**Physical Exam:** ++epigastric tenderness. No rebound or guarding. Abdomen tympanic. No jaundice, clinically palpable nodes, or hepatomegaly. Unremarkable DRE.

IDA = Iron Deficiency Anemia; FAP/HNPCC = Familial Adenomatous Polyposis/Hereditary Nonpolyposis Colorectal Cancer
**Case**

**EGD:** circumferential tumor at the EGJ ~ 30% of the lumen. Epicenter 4cm below the EGJ extending 7cm below. Diffuse linitis plastica appearance of stomach. Bx showed poorly differentiated adenocarcinoma, HER2-negative.

**CT CAP/PET:** thickened distal esophagus & gastric wall. Uptake in the primary (mSUV 8) & ~3 x enlarged right cardio-esophageal/lesser curve LNs (6.4cm, mSUV 6). No distant mets.

**Bloodwork:** within normal limits

**Laparoscopy & washings:** No peritoneal or diaphragmatic mets. Few atypical cells.

=>Stage IIA cT1/2 cN2 M0

*Fig 1. Linitis plastica. Source: Dr. Wiley Chung*

*Fig 2. Intense PET uptake at the EGJ.*

*Fig 3. G3 Adenocarcinoma on H&E. Source: CORUS13*
Clinical Presentations

Weight loss (62%)*
Abdo pain (52%)*
Nausea (34%)
Anorexia (32%)*
Dysphagia – proximal (26%)*
Melena or Hematochezia (20%)
Early satiety (18%)

Paraneoplastic states include diffuse seborrheic keratoses (Leser-Trélat), acanthosis nigricans, microangiopathic hemolytic anemia, membranous nephropathies, & hypercoaguable states incl pulmonary emboli

Risk Factors

Stronger
Abdominal radiation
Familial, polymorphisms (IL-1B, vacAs1)
EBV, H. Pylori, adenomas (high-grade dysplasia),
Chronic gastritis
Pernicious anemia, male,
Obesity, low fruits/veggies, high salt or
pickled/smoked meats (nitrites)
Smoking, partial gastrectomy
Late menarche/early menopause
Ranitidine (Zantac)¹

Weaker
Feculent emesis, irregular stool
Palpable nodes
Jaundice/hepatomegaly
Palpable abdominal mass
Bowel obstruction

Perez & Brady, 2019; Wanebo, 1993; ¹Appendix
Stomach Cancer

- 27,510 cases & 11,140 deaths (USA)
- Median age 68
- Males 2:1 Females
- 3rd most common cause of death in males worldwide (13th in the USA)
- 95% adenocarcinoma (others: lymphoma, GIST, carcinoid, & SCC)
- ~80% present w/advanced disease
- Overall incidence is declining, but increasing for cardia tumors in men*
- All-comer 5-year OS 32% (USA)

\[GLOBOCAN, \, 2019; \, SEER, \, 2017\]
Disparities & Interventions

Canada: 5.2
First Nations: 7.6
Inuit: 13

USA: 5.6
American Indian: 9.4
Alaskan Inuit, Yupik, Inupiat: 30.8

Chile: 26.9
Mapuche: 47.2

Sweden: 4.2
Sami: 18.0

Russia: 20.4
Indigenous Siberian: 47.4

Japan: 40.7
Screening ≥ 50y UGIS q1y or scope q2-3y. NNS ~ 1323-6303²

South Korea: 57.8
Screening 40-75y q2y scope. Mortality ↓ 47%.¹

USA: 5.6
American Indian: 9.4
Alaskan Inuit, Yupik, Inupiat: 30.8

Chile: 26.9
Mapuche: 47.2

Incidence
ASR (World) per 100,000

Canada: 5.2
First Nations: 7.6
Inuit: 13

USA: 5.6
American Indian: 9.4
Alaskan Inuit, Yupik, Inupiat: 30.8

Chile: 26.9
Mapuche: 47.2

Sweden: 4.2
Sami: 18.0

Russia: 20.4
Indigenous Siberian: 47.4

Japan: 40.7
Screening ≥ 50y UGIS q1y or scope q2-3y. NNS ~ 1323-6303²

South Korea: 57.8
Screening 40-75y q2y scope. Mortality ↓ 47%.¹

USA: 5.6
American Indian: 9.4
Alaskan Inuit, Yupik, Inupiat: 30.8

Chile: 26.9
Mapuche: 47.2

Incidence
ASR (World) per 100,000

Australia: 6.5
Indigenous: 18.0
Maori: 26.5

Arnold 2014, Jun 2017¹, Hamashima 2018², GLOBCAN 2019

Gastric Cancer

Association of Residents in Radiation Oncology (ARRO)
Stomach Adenocarcinoma Initial Diagnostic Workup

**Multidisciplinary Tumor Board**

*Resectability; Need for EUS;*

*Neoadjuvant, Adjuvant or Clinical Trial Eligibility*

**Other Investigations: CBC, Renal/Liver Function**

- Anemia -> Fe supplementation or Transfusion
- Kidney/Liver Disease -> Optimize prior to chemotherapy decision-making

**EGD** = Upper GI endoscopy; **Bx** = Biopsy; **CAP (C+)** = Chest, Abdomen, & Pelvis w/Contrast; **PC** = Peritoneal Carcinomatosis; **CHT** = chemotherapy; **RT** = radiation treatment

*There are differences on the extent of workup for T1b*

---

**H&P**

- **EGD + Bx**
  - Siewert I & II → Treat as a distal esophageal cancer
  - Siewert III → Treat as a gastric cancer

**CT CAP (C+) (Gross Staging)**

- T1a: Endoscopic Resection

**EUS (T-stage) +/- Bx of suspicious nodes**

- T1b: Surgery

**PET-CT**

- T2+: 20-30% will have PC
- PET: ~50% sensitivity for PC

- T2+ N+:*
  - Periop FLOT
  - Neoadj CRT(Cat 2b/On trial)

**Laparoscopy + Washings (Peritoneal Carcinomatosis)**

- Unresectable
  - Systemics or Chemoradiation then reassess

---

NCCN 2020; ESMO 2016, UptoDate 2020
Siewert & AJCC

**Used to guide therapeutic decision-making.**

**Siewert Class:**
For esophagogastric junction (EGJ) tumors based on the tumor epicentre.

**AJCC 8\textsuperscript{th} Ed:**
Esophagus: Siewert 1 o2

Stomach*: Siewert 3 involving the EGJ OR if tumor epicenter within 2cm of the EGJ without crossing it

**Mainly for Clinical Trials.**

**Lauren Classification:**

- **Diffuse** (32%): signet-cell, ↓ risk areas, young ♀, peritoneal mets w/small body primary, & ↓ prognosis
- **Intestinal** (54%): H.Pylori, LVI, scattered lesions & antrum, ↑ risk areas, elderly ♂, & ↑ prognosis

**WHO (2010):**
22 AdenoCa subtypes

*AJCC 8\textsuperscript{th} ed changed stomach cancer staging to include Siewert 3
### AJCC 8th ed

<table>
<thead>
<tr>
<th>T1</th>
<th>a Lamina propria or muscularis mucosae</th>
<th>cN0</th>
<th>cN1</th>
<th>cN2</th>
<th>cN3a</th>
<th>cN3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>b Submucosa</td>
<td></td>
<td></td>
<td></td>
<td>IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Muscularis propria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Subserosal connective tissue</td>
<td>IIB</td>
<td></td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>a Serosa (visceral peritoneum)</td>
<td>IIIB</td>
<td></td>
<td></td>
<td>IVA</td>
<td></td>
</tr>
<tr>
<td>b Adjacent organs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IVB</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

cN1 1-2 regional LNs; cN2 3-5 regional LNs; cN3a 7-15 regional LNs; cN3b is ≥ 16 regional LNs.

**Good Prognostic Factors:**
- ECOG 0-2
- Early-Stage
- N0 > N+
- R0 > R1 > R2
- Intestinal > Diffuse Type

**Regional LNs**
- Perigastric & 2\(^{nd}\) tier

**Rate of LN Mets:**
- 80% present w/nodal mets
  - T1: 10-20%;* T2: 50%;*
  - T3: 65%; T4a: 75%; T4b: 80%

**Distant LNs:** include mediastinal, pancreatic, mesenteric, para-aortic

---

*Ward 2018, AJCC 8th ed 2017, TOPGEAR 2017*
Stage at Presentation & Outcomes

Presentation

- Localized: 28%
- Regional (N+)*: 36%
- Distant (M1): 26%
- Unknown: 5%

NCDB Outcomes

- 10y OS by Nodes:
  - N0: 92%
  - N1: 82%
  - N2: 73%
  - N3: 27%

5-Year OS

- Localized: 69.5%
- Regional: 32.0%
- Distant: 5.5%
- Unknown: 23.4%
Treatment Planning

Enrolled onto TOP GEAR & Randomized to Neoadj CRT

Neoadjuvant FLOT x 3 Cycles: no issues

CT Simulation: With IV contrast. Immobilized with arms above his head, an arm board, & neck/knee rest. Directions given for similar stomach filling daily (following a light meal at a similar time each day or NPO 3 hours prior). Scanned from the whole thorax to the inferior kidneys w/2mm slices. Fused w/PET-CT & Diagnostic CT (w/small bowel contrast)

Technique/Rx: FLOT x 3 -> Neoadjuvant RT 45 Gy in 25 daily# to the PTV concurrent with systemic therapy (5-FU or Capecitabine per TOPGEAR) w/IMRT\(^1\) (3DCRT & 4DCT are other options)

Imaging: Daily Cone Beam CT (bony match) & treatment verification at least weekly.

\(^1\)IMRT may spare dose to kidneys & other OARs.

Wieland et al. IMRT for postoperative treatment of gastric cancer: covering large target volumes in the upper abdomen. IJROBP 2004. PMID:15234061
## Treatment Planning

<table>
<thead>
<tr>
<th>TOP GEAR*1</th>
<th>EORTC-ROG²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GTV</strong></td>
<td>GTVtumor = Primary; GTVnodal = Involved Regional Nodes$^5$</td>
</tr>
<tr>
<td>Primary + Involved Regional Nodes$^5$</td>
<td></td>
</tr>
<tr>
<td><strong>CTVstomach</strong></td>
<td>Proximal 1/3: GS excluding pylorus/antrum</td>
</tr>
<tr>
<td>T1/2: Gastric Silhouette (GS)*</td>
<td>Middle 1/3: GS (cardia to pylorus)</td>
</tr>
<tr>
<td>T3: GS + GTV + 0.5cm</td>
<td>Distal 1/3: GS excluding cardia &amp; fundus; if involving fundus then use a 3cm distal margin</td>
</tr>
<tr>
<td>T4: GS + GTV + 1cm</td>
<td></td>
</tr>
<tr>
<td>Superior margin is 1cm of proximal esophagus or 4cm if the tumor involves the cardia/GEJ/distal esophagus*</td>
<td>CTVtumor = GTVtumor + 1.5cm</td>
</tr>
<tr>
<td>+1cm of the proximal duodenum; 4cm if tumor involves the pylorus</td>
<td>CTVnodal = GTVnodal + 0.5cm</td>
</tr>
<tr>
<td><strong>CTV</strong></td>
<td>CTVgastric + CTVtumor + CTVnodal + CTVelective†</td>
</tr>
<tr>
<td>CTVstomach + Regional Lymphatics†</td>
<td></td>
</tr>
<tr>
<td>(not specified)</td>
<td>Siewert III: CTV + 1cm radial, 1.5cm distal, &amp;1cm proximal</td>
</tr>
<tr>
<td><strong>ITV</strong></td>
<td>Gastric: CTV + 1.5cm</td>
</tr>
<tr>
<td>CTV + 1cm</td>
<td>ITV + 5mm</td>
</tr>
<tr>
<td><strong>PTV</strong></td>
<td></td>
</tr>
<tr>
<td>CTV + 1cm</td>
<td></td>
</tr>
</tbody>
</table>

$^5$Based on EGD, EUS, imaging, laparoscopy +/- discussion w/radiology & surgery

†Regional Lymphatics include JRSGC 1-16, excluding 15 for Siewert III/Gastric Tumors (See Appendix)

‡CTVelective for Siewert III tumors includes JRSGC 1-4,7,9-11, 19,20, 110,111; a 5mm margin around vessels; & a superior border 3cm above the tumor or the esophageal hiatus (whichever is higher)

†For Proximal 1/3 tumors: JRSGC 1-4,7,9-11,19

†For Middle 1/3 tumors: JRSGC 1-5,7-11,18,19

†For Distal 1/3 tumors: JRSGC 3-9,11-13,17,18

---

1 Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol. 2017;24(8):2252-2258. PMID: 28337660


3. Wo et al. Gastric lymph node contouring atlas. PRO. 2013. PMID: 24674268
Contours & Dose
Dose Volume Histograms

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BilatLung GTV</td>
<td>2987.8</td>
<td>45.3</td>
<td>4727.5</td>
<td>830.7</td>
</tr>
<tr>
<td>Heart</td>
<td>1003.4</td>
<td>217.8</td>
<td>4781.6</td>
<td>1680.8</td>
</tr>
<tr>
<td>Kidney_L</td>
<td>270.7</td>
<td>153.0</td>
<td>4766.7</td>
<td>1935.8</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>230.2</td>
<td>137.9</td>
<td>4249.5</td>
<td>1232.4</td>
</tr>
<tr>
<td>Liver</td>
<td>1917.9</td>
<td>787.9</td>
<td>4763.8</td>
<td>2574.3</td>
</tr>
<tr>
<td>PTV</td>
<td>2158.9</td>
<td>4254.7</td>
<td>4793.1</td>
<td>4575.9</td>
</tr>
<tr>
<td>SpCord</td>
<td>64.2</td>
<td>15.6</td>
<td>2360.7</td>
<td>1253.1</td>
</tr>
</tbody>
</table>

Spinal Cord
- Dmax ≤ 45Gy
- V1/3 ≤ 50Gy; V2/3 ≤ 35Gy; Mean Liver Dose ≤ 30Gy
- < 0.2% Myelopathy

Liver
- V1/3 ≤ 50Gy; V2/3 ≤ 35Gy; Mean Liver Dose ≤ 30Gy
- TD < 5/5
- < 5% Radiation Induced Liver Damage
- D95 > 42.8Gy
- Mean & Median 44.5 to 45.9Gy
- Dmin > 40.5 Gy
- Dmax < 48.2 Gy

Kidneys
- V1/3 (Single) ≤ 35Gy; V2/3 ≤ 20Gy; Mean Kidney Dose ≤ 23Gy
- TD < 5/5
- < 2% Symptomatic Radiation Nephropathy

Heart
- V40Gy ≤ 30%
- Any pericarditis/pericardial effusion

Lungs
- V20Gy ≤ 30%, Mean Lung Dose ≤ 18 Gy
- < 20% Symptomatic Pnuemonitis
- Mean Lung Dose ≤ 20Gy
- Heart V30 ≤ 30% (20% preferred); Mean Heart Dose < 30Gy
- Bowels V45Gy < 195cc
- Liver V30Gy ≤ 33%, Mean Liver Dose < 25Gy

Follow-Up & Surveillance

• Neoadjuvant CRT: no any issues*
• Restaging CT ~3wks prior to surgery – no mets*
• Surgery: Unfortunately lost to follow-up...*  
• Scheduled Perioperative Adjuvant FLOT:
  – FLOT q2w x 4 cycles
  – H&P, weight, PS, & bloodwork including tumor markers (CEA, CA19-9, CA125), lytes, creatinine, liver function tests, post-sx ax, & chemo/radiation toxicity ax prior to each cycle
• Scheduled Surveillance:
  – Y1: months 1,3,6,9,12 – Basics (H&P, wt, PS, sx/toxicity ax, and patient reported outcome ax), tumor markers, & CT CAP (months 6 & 12),
  – Y2: q3months x 1y – Basics & CT CAP (Y2 only)
  – Y3-5: q6months x 3y Basics

* c.t. NCCN Gastric Cancer v1.2020:
  H&P q3-6mos x 1-2y; q6-12mos x 3-5y; then annually
  CT CAP q 6-12mos x 2y than annually x 3y
  BW & EGD prn; monitor for nutrititional deficiency
<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Dates</th>
<th>Trial Type</th>
<th>n</th>
<th>Criteria</th>
<th>Population</th>
<th>%EGJ</th>
<th>Arms</th>
<th>Outcomes</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUTCH D1D2</td>
<td>1989-1993 Bonenkampf, 2006</td>
<td>Sx</td>
<td>1078</td>
<td>Stomach, &lt;85</td>
<td>Dutch</td>
<td>10% upper 1/3 stomach</td>
<td>D1 vs D2 Surgery</td>
<td>15yOS 21% D1 v 29% D2; cancer-related death 48% v 37%; LR 22% v 12%; higher mortality in D2 13 v 19%.</td>
<td>D2 resection improved survival &amp; local recurrence at the expense of higher operative mortality</td>
</tr>
<tr>
<td>INT0116</td>
<td>1991-1998 Macdonald 2001 Smalley, 2012</td>
<td>Adj CRT</td>
<td>556</td>
<td>Stomach or EGJ, T3+ or N+</td>
<td>USA</td>
<td>7% Cardia, 8% body</td>
<td>Sx -&gt; observation vs. CRT (45Gy + FL)</td>
<td>5-year OS 22% vs 42%, mOS 27 vs. 36mos (P=0.005); 10% D2</td>
<td>Adjuvant CRT improves OS, but a limited resection</td>
</tr>
<tr>
<td>MAGIC</td>
<td>1994-2002 Cunningham, 2006</td>
<td>Periop CHT</td>
<td>503</td>
<td>Resectable T2+NxM0 esophagogastric</td>
<td>UK</td>
<td>74% gastric including Siewert III</td>
<td>Sx alone vs. Periop ECF</td>
<td>5yOS 23 vs 36% (P=0.008); 42% D2</td>
<td>ECF decreases tumor size and improves survival, but a limited resection</td>
</tr>
<tr>
<td>FFCD</td>
<td>1995-2003 Ychou, 2011</td>
<td>Periop CHT</td>
<td>224</td>
<td>Esophagogastric</td>
<td>France</td>
<td>11% Siewert I &amp; 64% Siewert 2 or 3</td>
<td>Sx alone vs. Periop CF</td>
<td>Closed early due to low accrual.</td>
<td>Periop CF improves OS.</td>
</tr>
<tr>
<td>POET</td>
<td>2000-2005 Stahl, 2017</td>
<td>Neoadj CRT</td>
<td>119</td>
<td>EGJ Siewert 1-3, T3+NxM0</td>
<td>Germany</td>
<td>0% Siewert 3</td>
<td>Neoadj Cx (PLF) vs. Induction PLF + Neoadj CRT (30Gy + CE)</td>
<td>7yOS 73 vs 75%; Trend for DFS in N+ or intestinal-type subsets</td>
<td>Trends towards improved survival w/neoadjuvant CRT, but no gastric patients</td>
</tr>
<tr>
<td>ARTIST</td>
<td>2004-2008 Park, 2015</td>
<td>Adj CRT</td>
<td>458</td>
<td>Gastric, IB-IVA, D2 resection</td>
<td>East Asia, majority stage I/II</td>
<td>4.8% proximal stomach</td>
<td>Adj XP vs. Adj CRT (45G + XP)</td>
<td>7yOS 73 v 75%; Trend for DFS in N+ or intestinal-type subsets</td>
<td>In pts receiving a D2 resection, a subset may have benefit.</td>
</tr>
<tr>
<td>CROSS</td>
<td>Hagen, 2012</td>
<td>Neoadj CRT</td>
<td>364</td>
<td>Esophageal/EGJ (I/II), T2+ or N+ M0</td>
<td>Dutch</td>
<td>24% Siewert II, 75% adenoCa</td>
<td>Sx Alone vs. Neoadj CRT (Carbo/Paclitaxel + 41.4Gy )</td>
<td>5yOS 34 vs. 37% p=0.003, but less for adenoCa and N+ subgroups.</td>
<td>For esophageal cancer (incl Siewert II), CROSS is standard of care. Unclear how much Siewert III actually in the study.</td>
</tr>
<tr>
<td>CRITICS</td>
<td>2007-2015 Cats, 2018</td>
<td>Adj CRT</td>
<td>788</td>
<td>Stage IB-IVA, resectable, gastric or EGJ, At least D1+</td>
<td>Dutch</td>
<td>17% Siewert 2 or 3, 80% D1 &amp; 14% D2</td>
<td>Periop CHT (ECX or EOX) vs. Periop CHT + Postop CRT (45Gy+ XP)</td>
<td>mOS 43 vs. 37mos (p=0.9), surgical compliance 43 vs. 39% (p=0.3); adjuvant compliance 59 vs. 62%.</td>
<td>No survival benefit for adj CRT, but poor surgical and adjuvant compliance in both arms.</td>
</tr>
<tr>
<td>FLOT4</td>
<td>2010-2015 Al-Batran, 2019</td>
<td>Periop CHT</td>
<td>716</td>
<td>&gt;=T2 or N+, EGJ/gastric, D2 resection</td>
<td>56% EGJ, 80% N+, Germany</td>
<td>32% Siewert 2 or 3</td>
<td>Periop CHT (ECF/ECX) vs. Periop CHT (FLOT)</td>
<td>5y OS 36% vs. 45%, mOS 35 v s. 50mos, similar complication rates (50 vs. 51%)</td>
<td>Periop FLOT improved OS w/similar tox.</td>
</tr>
<tr>
<td>ARTIST-2</td>
<td>2013-2018</td>
<td>Adj SOX, SOXRT</td>
<td>538</td>
<td>Stage II/III N+, D2 resection</td>
<td>East Asia</td>
<td>Unknown</td>
<td>Adj S1 vs. SOX vs. SOXRT (SOX -&gt; S-1 + 45Gy -&gt; SOX)</td>
<td>DFS S1/SOX vs. SOXRT HR 0.86 p=0.40</td>
<td>Stopped early due to futility of S1 alone. Interim analysis suggested no difference in DFS for SOX vs. SOXRT.</td>
</tr>
</tbody>
</table>

**CRT** = chemoradiation; **CHT** = chemotherapy; **F= 5-FU**, **C = Cisplatin**, **PLF = Cis + Leucovorin + 5-FU**, **CE = Cis + Etoposide**, **XP = Capecitabine + Cisplatin**, **FLOT = 5-FU + leucovorin + oxaliplatin + docetaxel**, **SOX = S-1 + Oxaplatin**. For the full chemotherapy regimens please see the appendix.
### Summaries from East & West

**West (North America, EU, & AUS/NZ)**
- Stage II/III (T2+ or N+ M0)
  - Periop CHT (FLOT)
  - FLOT4-AIO
  - Neoadj CRT (on trial)
    - TOPGEAR (Canada, EU, AUS/NZ)
    - ESOPEC/NEO-AEGIS (EU)
    - RACE? (USA)

Lower Incidence (<10)
- No Screening
- D2 largely in fit patients
- 5yOS ~10-15%

**East (Japan, South Korea, Taiwan, China)**
- Stage II/III (T2+ or N+ M0)
  - Sx -> Adj CHT
    - ACTS-GC (S-1)\(^1\): +10% 5yOS vs. Sx alone
    - CLASSIC (Cape+Oxali)\(^2\): +9% 5yOS vs. Sx alone
    - JACCRO GC-07 (S1+Docetaxel)\(^3\): +16% 3yOS vs. S1

Higher Incidence (>20)
- National Gastric Cancer Screening Programs (Taiwan, S. Korea, Japan)
  - Diagnosed earlier (T1a) -> more endoscopic resection
  - Routine D2 dissection
  - 5yOS ~45-50%

---

**ARTIST**

- Intestinal Diffuse LN
  - Negative Positive
    - 1.359
    - 0.700
  - 0.477 to 3.876
    - 0.493 to 0.994

- Favor XPRT vs. XP
  - 0.442
  - 0.826
  - 0.231 to 0.845
  - 0.643 to 1.765

- 130 death events occurred
  - Hazard ratio 1.130 (95% CI, 0.775 to 1.647)
  - \(P = .5272\)

**References**
- Sakuramoto 2007\(^1\)
- Bang 2012\(^2\)
- Yoshida 2019\(^3\)
# Open Trials – Locally Advanced EGJ/Gastric

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Type</th>
<th>Criteria</th>
<th>Population</th>
<th>Arms</th>
<th>Endpoints</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPGEAR*</td>
<td>Neoadj CRT</td>
<td>IV-III, Siewert 2 &amp; 3, 17% EGJ</td>
<td>Periop CHT (ECF or FLOT) vs. Periop CHT + Preop CRT (45Gy + F or X)</td>
<td>OS. Interim results - similar proportion of pts proceeding to surgery (90 vs 85%), but less completion of postop CHT (65 vs. 53%)</td>
<td>High compliance w/preop regimens, but lower compliance w/postop CRT arm. Est Completion: Dec 2020 NCT01924819</td>
<td></td>
</tr>
<tr>
<td>ESOPEC</td>
<td>Neoadj CRT</td>
<td>cT2+ or N+ M0 Esophageal/EGJ (I-III)</td>
<td>Periop FLOT vs. CROSS (Neoadj CRT Carbo/Pac + 41.4Gy)</td>
<td>OS</td>
<td>Est Completion: Jun 2024 NCT02509286</td>
<td></td>
</tr>
<tr>
<td>NEO-AEGIS</td>
<td>Neoadj CRT</td>
<td>cT2+NxM0 Esophageal/EGJ</td>
<td>Periop FLOT or ECF vs. CROSS (Neoadj CRT)</td>
<td>OS</td>
<td>Est Completion: Jan 2024 NCT01726452</td>
<td></td>
</tr>
<tr>
<td>CRITICS-2</td>
<td>Neoadj CRT, no Adj</td>
<td>NeoAdj CHT (DOC x 4) vs. NeoAdj CHT (DOC x 2) -&gt; CRT (45Gy + carbo/pac) vs. Neoadj CRTalone</td>
<td>Event-free survival</td>
<td>Event-free survival</td>
<td>Est Completion: Oct 2022</td>
<td></td>
</tr>
<tr>
<td>Swing &amp; Berens</td>
<td>Phase II Neoadj CRT</td>
<td>cT3+ or N+ adeno Esophagus or EGJ</td>
<td>Periop FLOT + Neoadj CROSS</td>
<td>pCR</td>
<td>Est Completion: April 2025 NCT04028167</td>
<td></td>
</tr>
</tbody>
</table>

**CRT** = chemoradiation; **CHT** = chemotherapy; **F** = 5-FU, **C** = Cisplatin, **PLF** = Cis + Leucovirin + 5-FU; **CE** = Cis + Etoposide; **XP** = Capecitabine + Cisplatin; **FLOT** = 5-FU + leucovorin + oxaliplatin + docetaxel; **SOX** = 5-FU + Oxaloplatin. **X** = Capecitabine. For the full chemotherapy regimens please see the appendix.
Conclusion

- For locally advanced cancer, outcomes are limited.
- Not discussed, for patients who did not have neoadjuvant treatment, indications for adjuvant treatment include N+ pathology (→ adj CHT) or R1/2 resection (→ adj CRT).
- Eastern patient populations have a lower incidence of advanced gastric cancers, perhaps due to established screening programs.
- Perioperative (West – FLOT) or adjuvant (East – S-1 +/- Docetaxel) is an established standard of care. This may be driven both by more advanced presentation in the West to facilitate surgery, and more aggressive surgery (D2) in the East.
- The role of radiation is still unclear. It has shown a survival benefit in the setting of limited surgery (MAGIC, INT0116). It has not shown benefit in the adjuvant setting with older chemo (non-FLOT: CRITICS, ARTIST-2). However, in subsets of pts (ARTIST, POET) it has suggested promising trends in the neoadjuvant setting.
- Studies are currently underway to address the question of whether neoadjuvant CRT will have benefit in the Western societies (ESOPEC, CRITICS-2), with TOPGEAR results eagerly anticipated soon.
- However, with the recent shift of esophagogastric junction (EGJ) adenocarcinomas in AJCC 8th ed to Siewert I-II being classified as esophageal and Siewert III as gastric, and their limited inclusion in trials to date, it is unclear if this increasing Western disease will have the attention it requires, for now.
- Other areas of investigation include biomarkers including liquid biopsies, reducing toxicity or improving coverage with improved treatment techniques including QA/QI for radiation and surgery, and addressing disparities such as our neglected populations (under-represented minorities, the frail, and our elderly).
ARROCase
Stomach Cancer

References & Appendices
References


References

doi:10.1093/jjco/hyy077
What Makes a Good Resection?

The Dutch D1D2

D1 = N1

D2 = N1 + N2

---

What’s Needed After a Limited Resection?

**SWOG/INT 0116**

<table>
<thead>
<tr>
<th></th>
<th>FU + leucovorin + RT</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>282</td>
<td>277</td>
</tr>
<tr>
<td>Events (months)</td>
<td>209</td>
<td>229</td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
<td>27</td>
</tr>
</tbody>
</table>

**HR for OS 1.32 (95% CI, 1.10 to 1.60)**

**10yOS ~25 vs 15%**

Could not require specific surgical procedures. The operating surgeon completed a form defining the extent of lymphadenectomy. Of 552 patients whose surgical records were reviewed for completeness of resection, only 54 (10 percent) had undergone a formal D2 dissection. A D1 dissection (removal of all invaded [N1] lymph nodes) had been performed in 199 patients (36 percent), but most patients (54 percent) had undergone a D0 dissection, which is less than a complete dissection of the N1 nodes.

Is there an art to chemoradiation?

Improved pCR

POET

Overall Survival

Induction PLF + Neoadj CRT (30Gy + CE)

Neoadj Cx (PLF)

Table 3. Pathohistologic Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arm A</th>
<th></th>
<th>Arm B</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with resection</td>
<td>49</td>
<td>100.0</td>
<td>45</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>pT0 N0 M0</td>
<td>1</td>
<td>2.0</td>
<td>7</td>
<td>15.6</td>
<td>.03*</td>
</tr>
<tr>
<td>pT1-4 N0 M0</td>
<td>17</td>
<td>34.7</td>
<td>22</td>
<td>48.9</td>
<td></td>
</tr>
<tr>
<td>pT0-4 N0 M0†</td>
<td>18</td>
<td>36.7</td>
<td>29</td>
<td>64.4</td>
<td>.01*</td>
</tr>
<tr>
<td>pT0-4 N0 M0</td>
<td>18</td>
<td>36.7</td>
<td>29</td>
<td>64.4</td>
<td>.01*</td>
</tr>
<tr>
<td>pTall N+ M0</td>
<td>27</td>
<td>55.1</td>
<td>14</td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td>pTall N+ M1</td>
<td>4</td>
<td>8.2</td>
<td>2</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

TOP GEAR
(AUS/NZ, Canada, EU)
EGJ (II-III)/Gastric
Ib - IVa

R
FLOT x 3
FLOT x 3
FLOT x 3

eCRT
(45Gy+C or X)
D2 Resection
D2 Resection
FLOT x 4

+FLOT was a protocol addition from ECF (after FLOT4-AIO)

ESOPEC
(Germany)
Esophageal/EGJ (I-III)
AdenoCa
cT2+ or N+

R
FLOT
CROSS
D2 Resection
D2 Resection

FLOT x 4
Appendix

1. Guides to defining CTV
2. CTV Contouring Atlas Glossary
3. CTV Contouring Atlas
4. Surgeries for Stomach Cancer
5. Follow-up Guidelines & Tumour Markers
6. Ranitidine- A Risk Factor for Esophageal and Stomach Cancer
Chemotherapy Regimens

**FL:** Fluorouracil and Leucovorin
- start 1 month prior to RT, 2 cycles FL given 1 month after RT
- Fluorouracil given concurrently with RT

**ECF:** Epirubicin, Cisplatin, Fluorouracil
- 3 cycles pre-op & 3 cycles post op

**ECX:** Epirubicin, Cisplatin, Capecitabine (X)
- 3 cycles pre-op & 3 cycles post op.
- in CRT: Cisplatin and Capecitabine concurrent with RT

**EOX:** Epirubicin, Oxaliplatin, Capecitabine (X)
- 3 cycles pre-op & 3 cycles post op.
- in CRT: Cisplatin and Capecitabine concurrent with RT

**FLOT:** Fluorouracil (2600mg/m² IV 24h infusion day 1, Leucovorin 200mg/m2 IV D1, Oxaliplatin 85mg/m2 IV D1, & Docetaxel 50mg/m2 IV day 1)

**S1:** S-1 | **SOX:** S-1, Oxaliplatin | **SOX-RT:** S1, Oxaliplatin, RT

**DOC:** Docetaxel, Oxaliplatin, Capecitabine

**PLF** = Cisplatin + Leucovirin + 5-FU

**CROSS:** 41.4Gy/23 concurrently with Caroaplatin and Paclitaxel

**TOPGEAR Arm-CRT:** Periop ECF x 2 (previously) or Periop FLOT x 3 & CRT - 45Gy/25# w/continuous 5-FU infusion (200 mg/m2/day, 7 days per week, throughout the entire period of RT) or capecitabine (825mg/m2, bid, days 1 to 5 each week of RT)
Gastric Lymph Node Stations JRSGC 2010

CTV_{nodes} = Regional Lymphatics (Perigastrics & 2\textsuperscript{nd} Tier Nodes)

Based on Japanese Research Society for Gastric Cancer surgical data. Identifying landmarks including the esophagus, stomach, proximal duodenum, hepatogastric ligament, porta hepatis, splenic hilum, pancreas, celiac axis, SMA, fusion of diagnostic imaging, scopes, & discussions with surgery/radiology help with contouring target volumes.

1. e-Contour Gastric Case (pending)
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAW</td>
<td>Anterior abdominal wall</td>
</tr>
<tr>
<td>Adr</td>
<td>adrenal</td>
</tr>
<tr>
<td>Aor</td>
<td>Aorta</td>
</tr>
<tr>
<td>CeA</td>
<td>Celiac artery</td>
</tr>
<tr>
<td>Col</td>
<td>Colon</td>
</tr>
<tr>
<td>Duo</td>
<td>Duodenum</td>
</tr>
<tr>
<td>Duo-3</td>
<td>Third part of duodenum</td>
</tr>
<tr>
<td>Eso</td>
<td>Esophagus</td>
</tr>
<tr>
<td>GaB</td>
<td>Gall bladder</td>
</tr>
<tr>
<td>Hea</td>
<td>Heart</td>
</tr>
<tr>
<td>HeA</td>
<td>Hepatic Artery</td>
</tr>
<tr>
<td>HGL</td>
<td>Hepatogastric ligament</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior Vena Cava</td>
</tr>
<tr>
<td>Jej</td>
<td>Jejunum</td>
</tr>
<tr>
<td>Kid</td>
<td>Kidney</td>
</tr>
<tr>
<td>LGA</td>
<td>Left Gastric Artery</td>
</tr>
<tr>
<td>Live</td>
<td>Liver</td>
</tr>
<tr>
<td>Pan</td>
<td>Pancreas</td>
</tr>
<tr>
<td>PoV</td>
<td>Portal vein</td>
</tr>
<tr>
<td>ReA</td>
<td>Renal artery</td>
</tr>
<tr>
<td>ReV</td>
<td>Renal vein</td>
</tr>
<tr>
<td>SMA</td>
<td>Superior mesenteric artery</td>
</tr>
<tr>
<td>SMV</td>
<td>Superior mesenteric vein</td>
</tr>
<tr>
<td>SpA</td>
<td>Splenic artery</td>
</tr>
<tr>
<td>SpC</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>SpF</td>
<td>Splenic flexure</td>
</tr>
<tr>
<td>SpH</td>
<td>Splenic Hilum</td>
</tr>
<tr>
<td>Spl</td>
<td>Spleen</td>
</tr>
<tr>
<td>SpV</td>
<td>Splenic Vein</td>
</tr>
<tr>
<td>Sto</td>
<td>Stomach</td>
</tr>
<tr>
<td>Sto-A</td>
<td>Stomach antrum</td>
</tr>
<tr>
<td>Sto-F</td>
<td>Stomach fundus</td>
</tr>
<tr>
<td>Sto-P</td>
<td>Stomach pyloris</td>
</tr>
</tbody>
</table>

*Images reproduced from TOPGEAR protocol with approval of Dr. Trevor Leong*
CTV Contouring for Pre-operative Radiotherapy for Stomach Cancer
Celiac Axis (CeA): First branch arising from the front of the abdominal aorta, around T12
Ranitidine – A Risk Factor

- N-Nitrosodimethylamine (NDMA) is a probable carcinogen (EPA B2) especially for esophageal & gastric cancers
- Last year it was found in ranitidine
- Investigations showed that it was present in formulations from multiple manufacturers, increased over time, & increased when stored at higher temperatures resulting in unacceptable levels
- FDA, Health Canada, & other regulators worldwide have recalled the drug

*If patients are on Ranitidine, switch to another H2 blocker or consider a PPI*

**FDA News Release**

**FDA Requests Removal of All Ranitidine Products (Zantac) from the Market**

*FDA Advises Consumers, Patients and Health Care Professionals After New FDA Studies Show Risk to Public Health*

For Immediate Release: April 01, 2020
Thank you.