Oncological Aspect of Gastric Cancer

Dr. Lay Aung
Senior Consultant Radiation Oncologist
Radiotherapy Department
Yangon General Hospital

Overview

- Epidemiology
- Aetiology and Risk Factors
- Pathophysiology
- Treatment
- Follow-up

Gastric Cancer

Epidemiology

- Gastric cancer – 5th most frequently diagnosed cancer and 3rd leading cause of cancer-related deaths in the world
- The highest gastric cancer rates occur in Northeast Asia, South and Central America and Eastern Europe.
- Rates are particularly high in Japan and Korea, where gastric cancer is the most commonly diagnosed cancer in males and in China, where gastric cancer is a leading cause of cancer-related mortality

Etiology and Risk Factors

- Average age at diagnosis is 68 years
- Male-to-female ratio is 1.7:1
- African American-to-white ratio is 1.8:1
- Precursor conditions:

1) chronic atrophic gastritis and intestinal metaplasia
2) pernicious anemia (10%-20% incidence)
3) partial gastrectomy for benign disease
4) *Helicobacter pylori* infection (especially childhood exposure—three- to fivefold increase)
5) Ménétrier disease, and
6) gastric adenomatous polyps. These precursor lesions are largely linked to distal (intestinal type) gastric carcinoma

Etiology and Risk Factors

- Family history:

1) first degree (two- to threefold);
2) familial clustering; patients with hereditary nonpolyposis colorectal cancer (Lynch syndrome II) are at increased risk;
3) germline mutations of E-cadherin (*CDH1* gene) have been linked to familial diffuse gastric cancer and associated lobular breast cancer.
4) Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is an autosomal dominant syndrome characterized by fundic gland polyposis and intestinal type adenocarcinoma

- Tobacco use results in a 1.5- to 3-fold increased risk for cancer
- High salt and nitrosamine food content from fermenting and smoking process
- Deficiencies of vitamins A, C, and E; β-carotene; selenium; and fiber
- Blood type A
- Alcohol
- The marked rise in the incidence of gastroesophageal and proximal gastric adenocarcinoma appears to be strongly correlated to the rising incidence of Barrett esophagus

Screening

- In most countries, screening of the general populations is not practical because of a low incidence of gastric cancer.
- However, screening is justified in countries where the incidence of gastric cancer is high.
- Japanese screening guidelines include initial upper endoscopy at the age of 50 years, with follow-up endoscopy for abnormalities.
- Routine screening is not recommended in the United States.

Pathophysiology

Intestinal Type

- most distal cancers
- associated with *H. pylori* infection.
- the interplay of environmental factors leads to glandular atrophy, relative achlorhydria, and increased gastric pH.
- The resulting bacterial overgrowth leads to production of nitrites and nitroso compounds causing further gastric atrophy and intestinal metaplasia, thereby increasing the risk of cancer.
- associated with an increased frequency of overexpression of epidermal growth factor receptor (EGFR) *erbB-2* and *erbB-3.*

Diffuse Type

- proximal stomach, more common in younger patients
- exhibits undifferentiated signet-ring histology
- predilection for diffuse submucosal spread because of lack of cell cohesion, leading to linitis plastica.
- Contiguous spread of the carcinoma to the peritoneum is common.
- Precancerous lesions have not been identified.
- associated with *H. pylori* infection.
- Genetic predispositions, have associations between carcinoma and individuals with type A blood.
- worse prognosis than do distal cancers.

Presentation

Local Disease

- peptic ulcer-like pain
- anaemia
- nausea
- weight loss
- dysphagia
- early satiety
- vomiting

Metastatic Disease

- Ascites
- Jaundice
- Liver mass
- Virchow’s supraclavicular nodes
- Sister Mary Joseph’s nodule
- Irish node (L axillary node)
- bowel obstruction
- Krukenberg tumour
- back pain

Diagnostic and Staging Investigations

Procedure	Purpose
FBC	Assess for IDA
Renal & Liver function	Assess renal & liver function to determine appropriate therapeutic options
Endoscopy & biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER 2 status
CT of Thorax + Abdomen +/- Pelvis	Staging of tumours – to detect local/ distant lymphadenopathy and metastatic disease or ascites
EUS	Accurate assessment of T and N stage in potentially operable tumours Determine the proximal and distal extent of tumour
Laparoscopy + washings	Exclude occult metastatic disease involving peritoneum/ diaphragm
PET (not routinely recommended)	May improve detection of occult metastatic disease in some cases. Often negative in diffuse type gastric cancer
Assessment of nutritional status	May detect relevant dietary and nutritional deficiencies in both localized and advanced disease settings
CEA, CA19-9, CA72-4	Serum levels are associated with tumour stage and patient survival No role in screening but useful for detecting recurrence and distant metastasis
CA125	Often elevated in peritoneal metastasis

Staging

TNM	
T1	Lamina propria (T1a), submucosa (T1b)
T2	Muscularis propria
T3	Subserosa
T4a	Perforates serosa
T4b	Adjacent structures
N1	1 - 2 nodes
N2	3 – 6 nodes
N3a	7 – 15 nodes
N3b	> 16 nodes
M1	Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2 T1	N0 N1	M0 M0
Stage IIA	T3 T2 T1	N0 N1 N2	M0 M0 M0
Stage IIB	T4a T3 T2 T1	N0 N1 N2 N3	M0 M0 M0 M0
Stage IIIA	T4a T3 T2	N1 N2 N3	M0 M0 M0
Stage IIIB	T4b T4a T3	N0, N1 N2 N3	M0 M0 M0
Stage IIIC	T4a T4b	N3 N2, N3	M0 M0
Stage IV	Any T	Any N	M1

Prognostic Factors

Prognostic factors	Tumour related	Host related	Environment related
Essential	T category N category M category HER 2 status		Residual disease: R0, R1 or R2
Additional	Tumour site: cardia or distal stomach Histological type Vessel infiltration	Age	Extent of resection
New and promising	Molecular Profile	Race: Asian or Non-Asian	

Treatment of Gastric Cancer According to Stage

Stage 0 Gastric Cancer

- Stage 0 indicates gastric cancer confined to the mucosa.
- Based on the experience in Japan, where stage 0 is diagnosed more frequently, it has been found that more than 90% of patients treated by gastrectomy with lymphadenectomy will survive beyond 5 years.
- An American series has confirmed these findings.
- No additional perioperative therapy is necessary.

Treatment of Gastric Cancer According to Stage

Stage I and II Gastric Cancer

- **Surgery**
- **Postoperative chemoRT** is recommended for patients with at least stage IB disease.
- **Perioperative polychemotherapy** could also be considered for patients who present with at least a T2 lesion preoperatively.

Treatment of Gastric Cancer According to Stage

Stage III Gastric Cancer

- **Radical surgery**: Curative resection procedures are confined to patients who do not have extensive nodal involvement at the time of surgical exploration.
- **Postoperative chemoRT** or **perioperative polychemotherapy** is recommended. The latter should be considered particularly for bulky tumors or with significant nodal burden.

Perioperative (Adjuvant and Neoadjuvant) Therapy

- Treatment of gastric cancer mandates complete surgical resection
- However, even after what is considered a curative gastrectomy, disease recurs in most patients
- Efforts to improve these poor results have focused on developing effective pre- and postoperative systemic and regional therapies

Perioperative (Adjuvant and Neoadjuvant) Therapy

- **Neoadjuvant therapy** refers to treatment before potentially curative surgery and has some advantages:

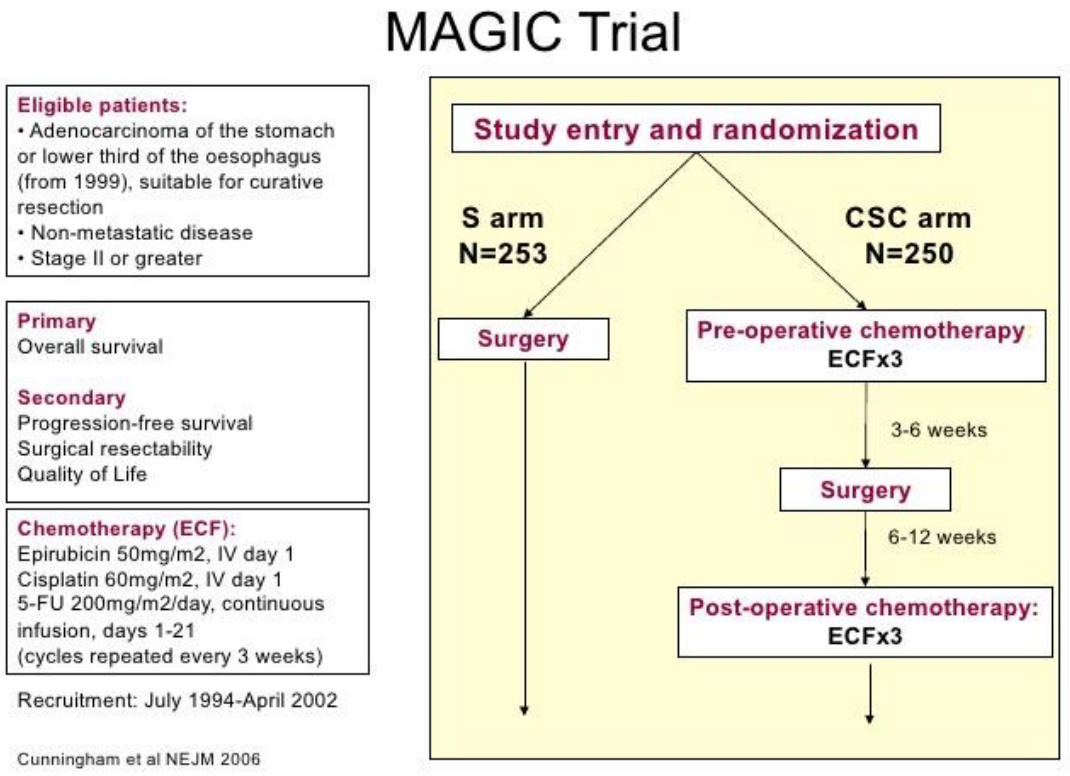
1) higher compliance rates
2) potential downstaging of the tumor, facilitating a higher rate of R0 resections
3) earlier treatment of micro-metastatic disease

- **Adjuvant therapy** refers to administration of treatment following a potential curative resection

Perioperative Chemotherapy

The first evidence for a survival benefit of perioperative chemotherapy - " **MAGIC study**"

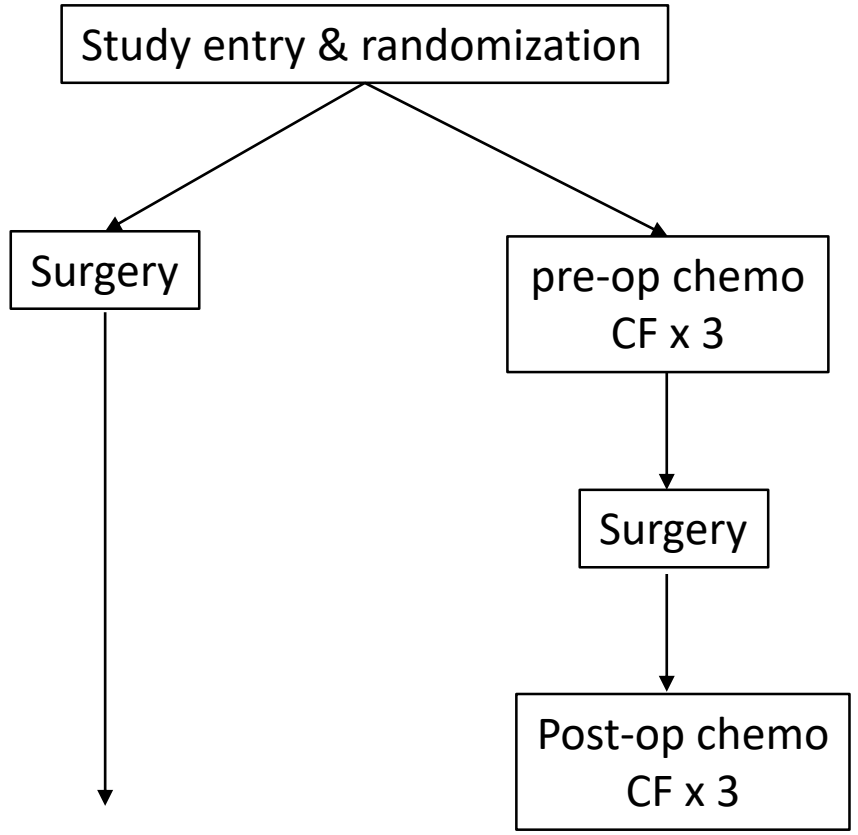
- The addition of peri-op chemo did not result in an increase in surgical morbidity or mortality
- Downstaging and an improved R0 resection rate were seen in patients receiving peri-op chemo
- 5-year OS: those receiving peri-op chemo (36%) vs Surgery alone (23%) [HR, 0.75, P = 0.009]



Perioperative Chemotherapy

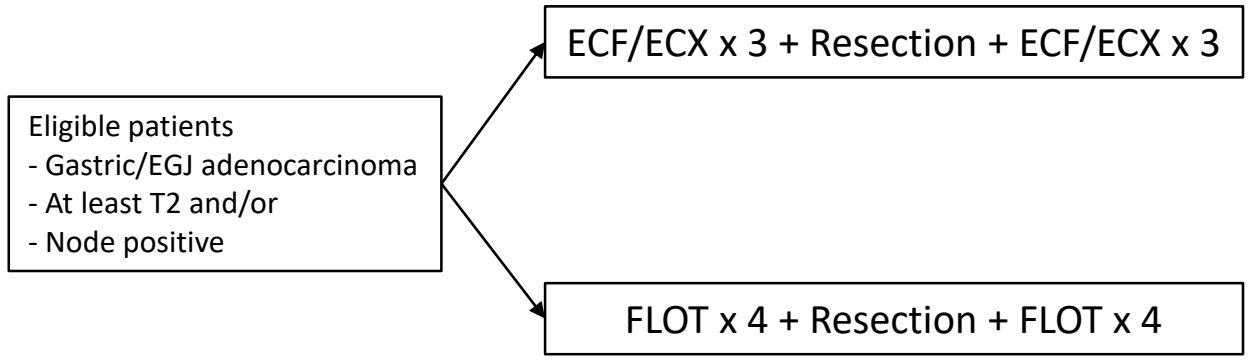
The ACCORD 07-FFCD 9703 study

- perioperative CF (cisplatin plus 5-FU) vs Surgery
- adenocarcinoma of the lower esophagus/EGJ (75%) , and purely gastric cancer (25%)
- 5-year OS : 24% for surgery alone versus 38% for those who received perioperative chemo (HR, 0.69, *P* = 0.02)
- The results of the ACCORD 07 study suggest that a doublet chemotherapy may suffice



Perioperative Chemotherapy

The FLOT 4 Study

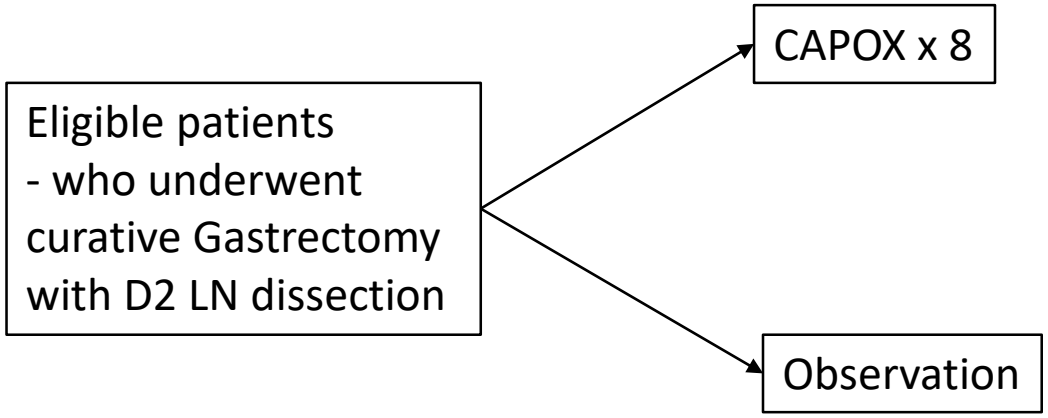


	FLOT	ECF/ECX3
Median DFS (P = 0.0036)	30 months	18 months
Median OS (HR, 0.77, P = 0.012)	50 months	35 months
3 yrs OS	57%	48%
Complete Pre-op Tx	90%	91%
Complete Post-op Tx	50%	37%

FLOT is considered SoC in perioperative therapy for locally advanced gastric and EGJ adenocarcinoma

Adjuvant Chemotherapy

The CLASSIC study



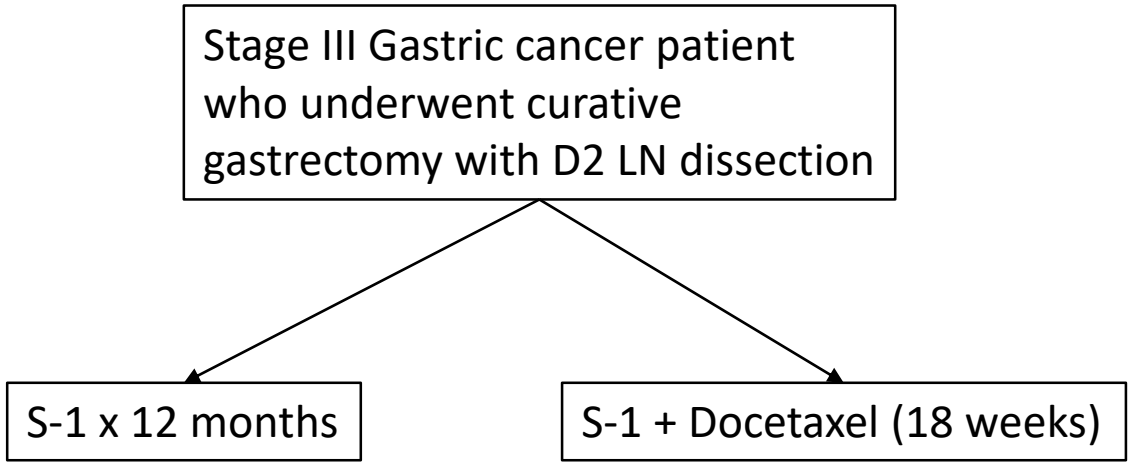
- Estimated 5-year OS was 78% in the adjuvant CAPOX group vs 69% in the observation group, with reduced risk of death (HR, 0.66; *P* = 0.0015)

Adjuvant Chemotherapy

The ACTS-GC study (Japan)

- Randomized patients who underwent curative surgery to either S-1, an oral fluoropyrimidine given for 12 months, or placebo
- 5-year OS: adjuvant S-1 (71.7%) vs surgery alone (61.1%) [HR, 0.68 (*P* = 0.003)]

JACCRO GC-07 study (Japan)



Three-year relapse-free survival (RFS) and OS were better with S-1+ docetaxel

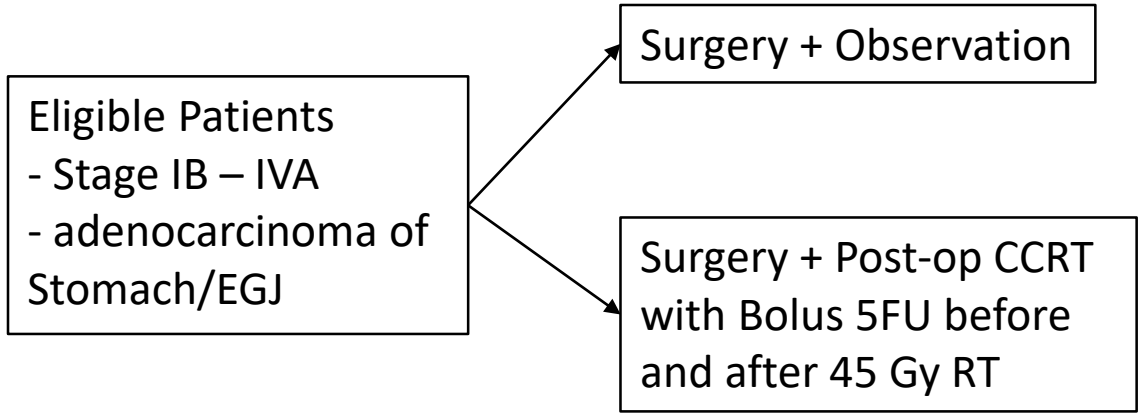
RFS: S-1 + Docetaxel (68%) vs S-1 (57%) [HR, 0.715]

OS: S-1 + Docetaxel (78%) vs S-1 (71%) [HR, 0.742]

Adjuvant Chemoradiation

The Intergroup (INT) 0116 study

- With more than 10 years of median follow-up, the survival advantage was maintained, the HR for OS was 1.32 ($P = 0.0046$), and the HR for RFS was 1.51 ($P < 0.001$)
- There was significant criticism of this trial due to the limited number of patients who underwent adequate lymph node dissection. This suboptimal nodal dissection made it difficult to interpret the study results.
- Current guidelines limit the use of postoperative chemoradiation to patients who underwent a less than D2 dissection or those with an R1/R2 resection
- The regimen used in this trial was associated with high rates of GI and hematologic toxicities and therefore, infusional 5-FU has been replaced with oral capecitabine, which is better tolerated



	Surgery + Observation	Surgery + CCRT with 5FU
3 yr PFS ($P = 0.001$)	31%	48%
Median OS	27 months	36 months
Local recurrence	29%	19%

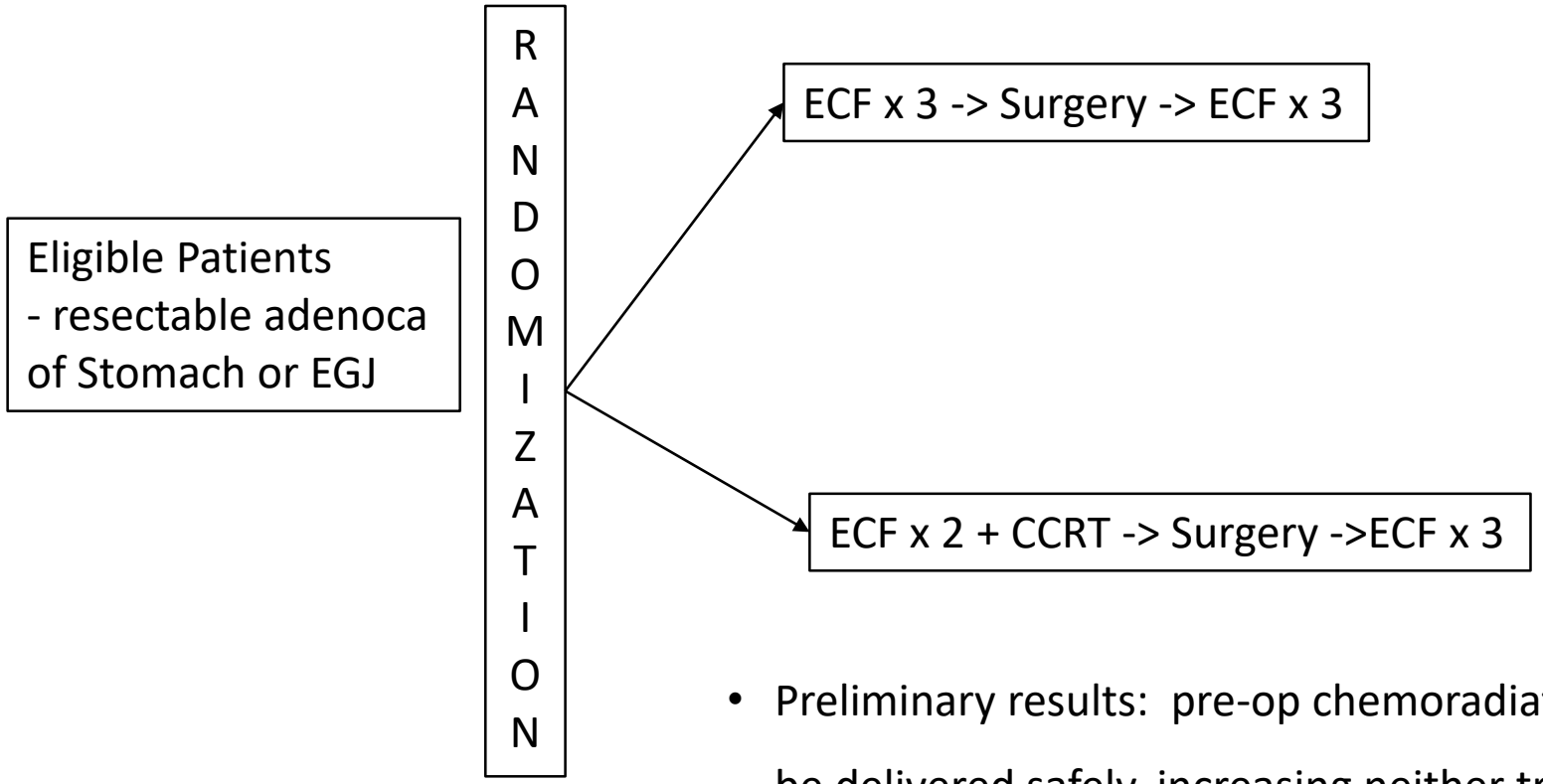
Post hoc subset analyses showed only a minimal nonsignificant treatment effect on OS in diffuse-type tumors

Adjuvant Chemoradiation following R1/R2 Resection

- A positive resection margin is an independent predictor of worse survival
- Several retrospective studies have suggested that postoperative chemoradiation improves prognosis

Preoperative Chemoradiation

TOPGEAR Intergroup Study (Ongoing)



- Preliminary results: pre-op chemoradiation can be delivered safely, increasing neither treatment-related toxicity nor surgical morbidity

Adjuvant Immunotherapy

- The role of immunotherapy in the adjuvant setting of gastric cancer is yet to be determined and is being investigated in the ongoing KEYNOTE-585 (NCT03221426), ATTRACTION-05 (NCT03006705), IMAG- INE (NCT04062656), and DANTE (NCT03421288) studies

HER 2 Targeted and Other Drugs in Perioperative Treatments

- The role of HER2 inhibitors, trastuzumab alone or the combination with pertuzumab, in the neo/adjuvant setting of gastric cancer is being investigated in the ongoing INNOVATION (NCT02205047), PETRARCA (NCT02581462), and JCOG1301 studies
- Other targeted agents are also investigated in the perioperative setting
- For example, ramucirumab added to perioperative FLOT is evaluated in the RAMSES (NCT02661971) study

Adjuvant Intraperitoneal Chemotherapy

- Peritoneal recurrence is a common pattern of failure for patients with gastric cancer, even after curative resection
- Modes of administering IP chemotherapy:

1) hyperthermic intraperitoneal chemotherapy (HIPEC),
2) pressurized intraperitoneal aerosol chemotherapy (PIPAC)
3) normothermic intraperitoneal chemotherapy (NIC) given at the conclusion of the operation
4) early postoperative intraperitoneal (normothermic) chemotherapy (EPIC), or
5) delayed postoperative intraperitoneal (normothermic) chemotherapy

- Most trials used 5-FU, mitomycin C, or cisplatin for IP chemotherapy

Intraoperative Radiation Therapy

- Intraoperative radiation therapy (IORT) technique facilitates the delivery of a single large fraction (10 Gy to 20 Gy) of radiation to the tumor or tumor bed while excluding surrounding normal tissue
- IORT is most appropriate in the treatment of suspected positive margins, with individualized decisions being made in the operating theater.
- The widespread use of IORT in gastric cancer remains investigational.

Summary of Perioperative Treatment

- The most established treatment options for stage II–III gastric cancer are either peri-op chemotherapy or adjuvant chemotherapy after surgery with D2 dissection
- Whether to give systemic therapy first followed by operation or to proceed directly to operation followed by systemic treatment is yet to be determined
- Postoperative radiation use is limited to R1/R2 resection or in patients who underwent inadequate lymphadenectomy

Treatment of Gastric Cancer According to Stage

Stage IV Gastric Cancer

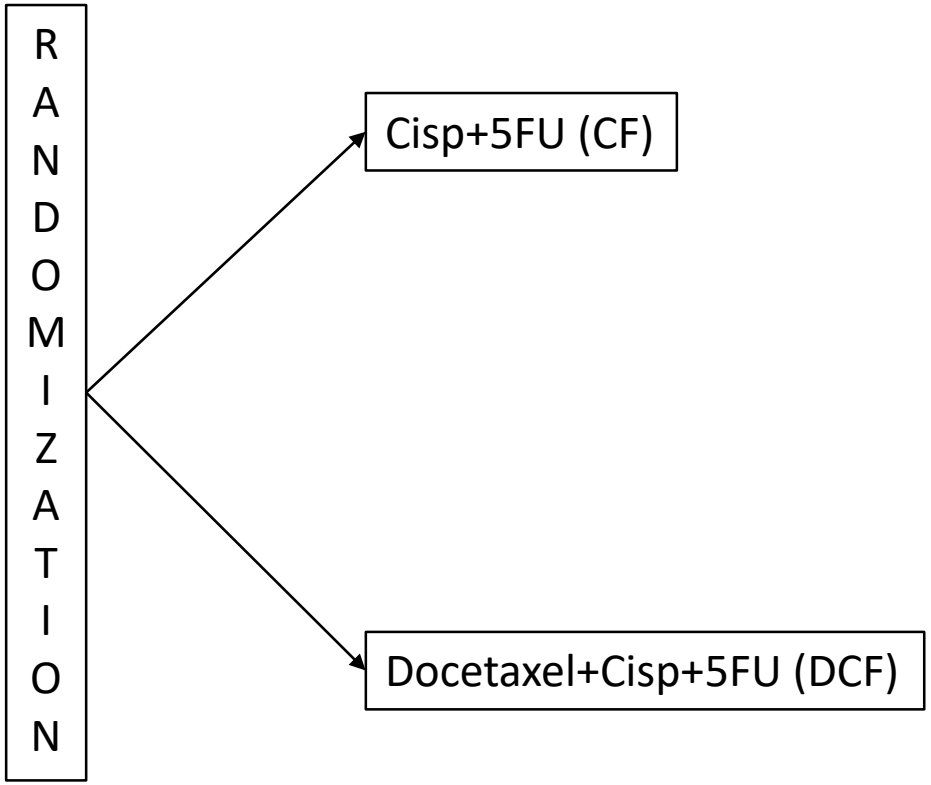
Chemotherapy VS Best supportive care (BSC)

- A Cochrane meta-analysis comparing systemic chemotherapy with BSC concluded that systemic therapy extends OS by approximately 6.7 months over BSC, from a median of 4.3 months to approximately 11 months (HR, 0.37).

First Line Systemic Treatment

Three Drug Combinations

The TAX325 study



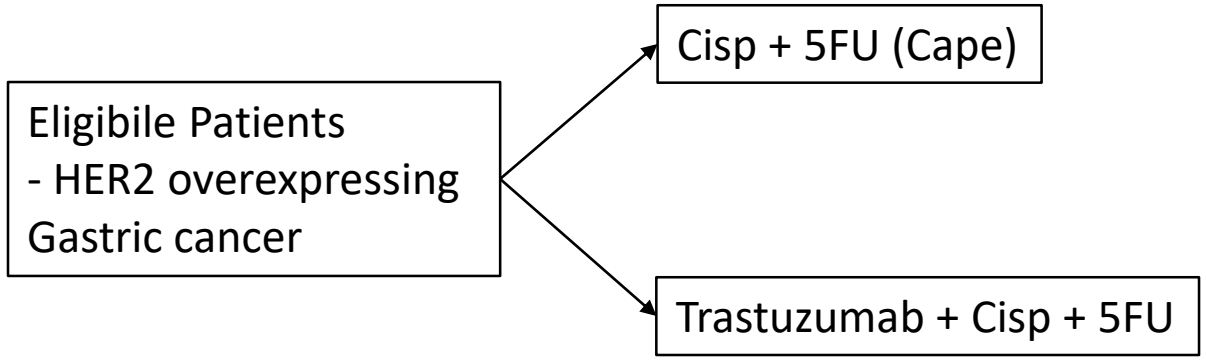
	CF	DCF
Median TTP (HR, 1.47; *P* < 0.001)	3.7 months	5.6 months
ORR	25%	37%
Median OS (*P* = 0.02)	8.6 months	9.2 months
2 year survival rate	9%	18%
Grade 3-4 toxicities	59%	69%
Febrile neutropenia	12%	29%

To summarize, based on efficacy and toxicity, the use of mainly oxaliplatin-based doublet regimens is preferred over triplet regimens as well as cisplatin-containing doublets.

First Line Systemic Treatment

Anti-HER2 Targeted Therapy

ToGa study (landmark phase III)



	CF	Tras+CF
Median OS (HR, 0.74; *P* = 0.0046)	11.1 months	13.8 months
RR	35%	47%

First Line Systemic Treatment

Immunotherapy

- There is emerging evidence for the role of immunotherapy in gastric cancer treatment.
- Immune checkpoint inhibitors have demonstrated activity in multiple solid tumor types.
- Nivolumab is currently approved in combination with fluoropyrimidine and platinum-containing chemotherapy for first line treatment of advanced or metastatic gastric cancer, EGJ and esophageal adenocarcinoma, for patients with CPS ≥5
- Pembrolizumab in combination with trastuzumab and either CF or CAPOX in Patients with HER2-positive advanced gastric or EGJ adenocarcinoma who had not previously received systemic therapy for metastatic disease

First Line Systemic Treatment

Other Targeted Therapy

- **Ramucirumab**
- **Bevacizumab**
- antibodies against EGFR (cetuximab and panitumumab)
- Tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib, and apatinib

Second and Subsequent Lines of Treatment

Chemotherapy

- Second-line chemotherapy vs BSC has been demonstrated to improve OS in randomized studies.
- However, patients with gastric cancer often have numerous comorbidities and complications (i.e., cachexia, malnutrition, peritoneal carcinomatosis with limited bowel function or obstruction) that preclude administration of second-line therapy.
- **Single agent chemotherapy**: Irinotecan, Docetaxel , Paclitaxel, etc…..
- **Combination chemotherapy**: FOLFIRI
- There is a role of second-line treatment for patients with metastatic gastric and preserved performance status.
- A recent systemic review and meta-analysis evaluated third-line treatment in gastric cancer compared with BSC. Therapy improved median OS from 3.2 months to 4.8 months compared with BSC.

Second and Subsequent Lines of Treatment

- **Immunotheapy**: Pembrolizumab, Nivolumab
- **Immunotherapy in tumours with Mismatch Repair Defect** (dMMR): Pembrolizumab
- **Anti-HER 2 Targeted Therapy:** Trastuzumab deruxtecan (The FDA approved trastuzumab deruxtecan for patients with advanced or metastatic gastric or EGJ adenocarcinoma who have received a prior trastuzumab-based regimen)
- Ramucirumab
- **Neurotrophic tyrosine receptor kinase (NTRK) inhibitors:** Larotrectinib and entrectinib
- **Tyrosine Kinase Inhibitors:** Apatinib, Regorafenib

Summary of Systemic Therapy for Advanced, Recurrent or Metastatic Disease

- In patients with advanced gastric cancer, systemic therapy can provide palliation of symptoms and improved survival and QOL.
- HER2, MMR/MSI and PD-L1 testing should be done to guide treatment decisions.
- Treatment choice should integrate patient comorbidities, prior treatments and related toxicity, and performance status in the decision to offer systemic treatment or best supportive care.
- Benefit of intensive systemic treatment should be carefully weighed against toxicity and treatment tolerance.

Palliative Measures for Advanced Disease

Surgery

- Palliative gastrectomy in advanced-stage gastric cancer is not included as an option in current consensus guidelines

Radiation

- Principal palliative indications for radiotherapy are gastric bleeding, pain, and dysphagia/obstruction, obstructive jaundice

Gastrojejunostomy

- Palliative gastrojejunostomy for gastric outlet obstruction can improve oral intake

Endoscopic Stent

- Endoscopic stent placement may provide palliation of obstructive symptoms

Surgery of Peritoneal Metastasis

Follow-up

After curative endoscopic resection for T1a tumours:

- Annual endoscopy for local recurrence or new lesions
- Abdominal US or CT for regional recurrence

After R0 surgery for Stage I disease:

- Annual abdominal US or CT and tumour markers
- Biennial endoscopy of the remnant stomach

After R0 surgery for Stage II/III disease:

- Biannual abdominal US or CT and tumour markers
- Biennial endoscopy of the remnant stomach

Thank you!