Taipei Veterans General Hospital Practices Guidelines for

Gastric Cancer

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Table of Content

Multidisciplinary Team

- Surgical Oncologist specialized in Gastric Cancer
- Gastroenterologist
- Medical Oncologist
- Radiation Oncologist
- Pathologist
- Diagnostic Radiologist
- Nurses (for specialized)
- Social Workers
- Dietitian (for Nutrition Support)

Taipei VGH Gastric Cancer Panel Members

- **Surgical Oncologist**

  方文良* 黃國宏*

- **Gastroenterologist**

  侯明志* 李重賓* 謝昀蓁* 許劭榮*

  王彥博

- **Medical Oncologist**

  趙毅* 陳明晃* 洪逸平*

- **Radiation Oncologist**

  賴宜君* 吳元宏*

- **Diagnostic Radiologist**

  邱乃祈* 柳建安* 李岡龍*

- **Pathologist**

  李芬瑤*

* 核心成員

Pretreatment work-ups

- **History and physical exam**
- **CBC, platelets, PT/APTT and chemistry profile**
- **Abdominal CT with IV contrast (開單須註明 gastric cancer)**
- **Chest X-rays**
- **Upper GI panendoscopy**
- **Tumor markers: CEA, CA199, CA 72-4**
- **IHC stain: HER2-neu testing if unresectable adenocarcinoma is documented**
- **Optional studies**
  - Whole body bone scan
  - EUS (If early stage disease)
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - PET/CT scan
  - H. pylori test
  - PD-L1 test, EBV test and MSI-H/dMMR testing
  - Tumor Epstein-Barr virus status is emerging as a potential biomarker for personalized treatment strategies for gastric cancer , but is not currently recommended for clinical care
  - Screening of family history

TNM Staging System: UICC/AJCC 2017 8th Edition

- **Primary Tumor (T)**

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ: intraepithelial tumor without invasion of the lamina propria*
T1: Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a: Tumor invades lamina propria or muscularis mucosae
T1b: Tumor invades submucosa
T2: Tumor invades muscularis propria
T3: Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4: Tumor invades serosa (visceral peritoneum) or adjacent structures**,***
T4a: Tumor invades serosa (visceral peritoneum)
T4b: Tumor invades adjacent structures

- **Regional lymph nodes (N)**

NX: Regional lymph node(s) cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in 1 to 2 regional lymph nodes
N2: Metastasis in 3 to 6 regional lymph nodes
N3: Metastasis in 7 or more regional lymph nodes
N3a: Metastasis in 7 to15 regional lymph nodes
N3b: Metastasis in 16 or more regional lymph nodes

- **Distant metastasis (M)**

M0: No distant metastasis
M1: Distant metastasis

General Notes:

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

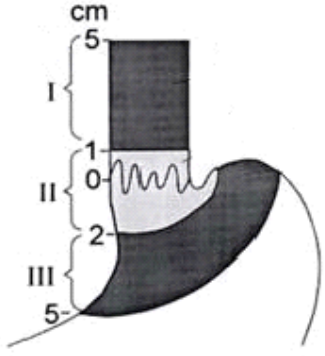
y prefix indicates those cases in which classification is performed during or following initial multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r“ prefix: rTNM.

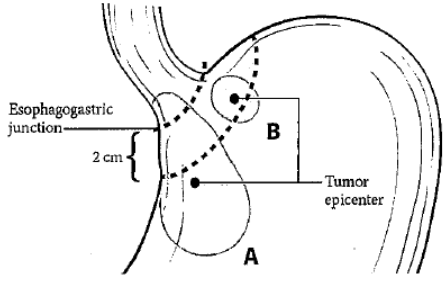
a prefix designates the stage determined at autopsy: aTNM.

TNM Staging System: UICC/AJCC 2017 8th Edition

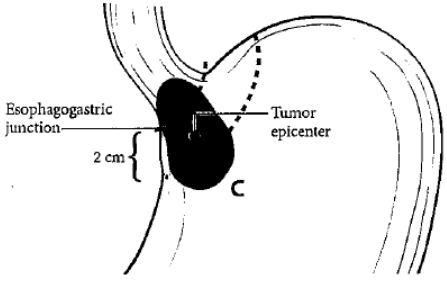
Siewert type



Anatomic boundary between esophagus and stomach: tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancers; EGJ tumors with their epicenter located greater than 2 cm into the proximal stomach are staged as stomach cancers. Cardia cancer not involving the EGJ is staged as stomach cancer.



A tumor that has its epicenter located >2 cm from esophagogastric junction (A) or a tumor located within 2 cm of the esophagogastric junction (B) but does not involve the esophagogastric junction is classified as stomach cancer.



A tumor that has its epicenter located within 2 cm of esophagogastric junction and involves the esophagogatric junction (C) is classified as esophageal cancer.

Type I

Type II (tumor extend into the EGJ)

Esophageal cancer

Type II (tumor not extend into the EGJ)

Type III (tumor extend or not extend into the EGJ)

Stomach cancer

Pathological TNM Staging System: UICC/AJCC 2017 8th Edition

	pN0 0	pN1 1-2	pN2 3-6	pN3a 7-15	pN3b >15
pT1	IA	IB	IIA	IIB	IIIB
pT2	IB	IIA	IIB	IIIA	IIIB
pT3	IIA	IIB	IIIA	IIIB	IIIC
pT4a	IIB	IIIA	IIIA	IIIB	IIIC
pT4b	IIIA	IIIB	IIIB	IIIC	IIIC

Amin MB, Edge S, Greene F, et al. (eds.) AJCC cancer staging manual 8th edition. New York: Springer International Publishing, 2017.

Clinical TNM Staging System: UICC/AJCC 2017 8th Edition

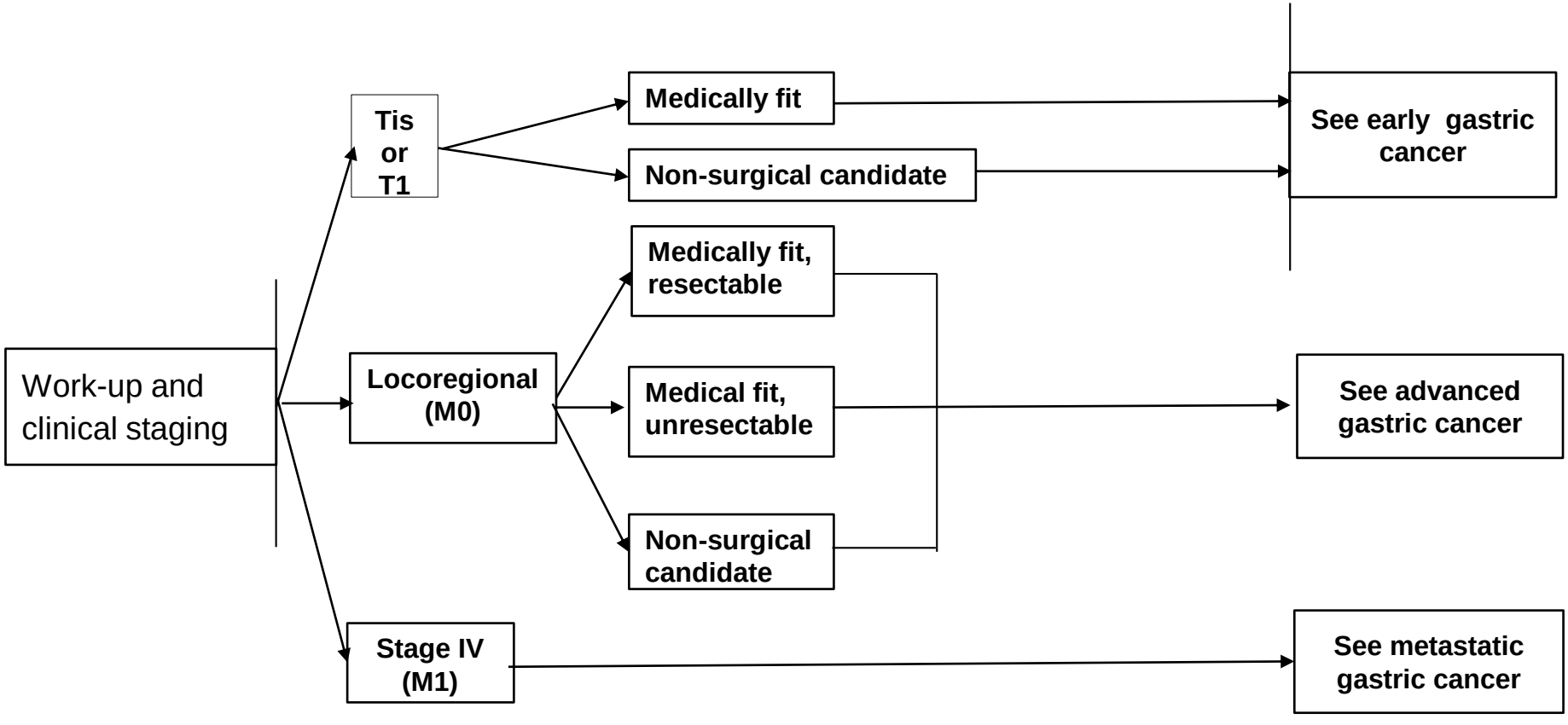
	T1	T2	T3	T4a	T4b
N0	I	I	IIB	IIB	IVA
N+	IIA	IIA	III	III	IVA
M1	IVB	IVB	IVB	IVB	IVB

Amin MB, Edge S, Greene F, et al. (eds.) AJCC cancer staging manual 8th edition. New York: Springer International Publishing, 2017.

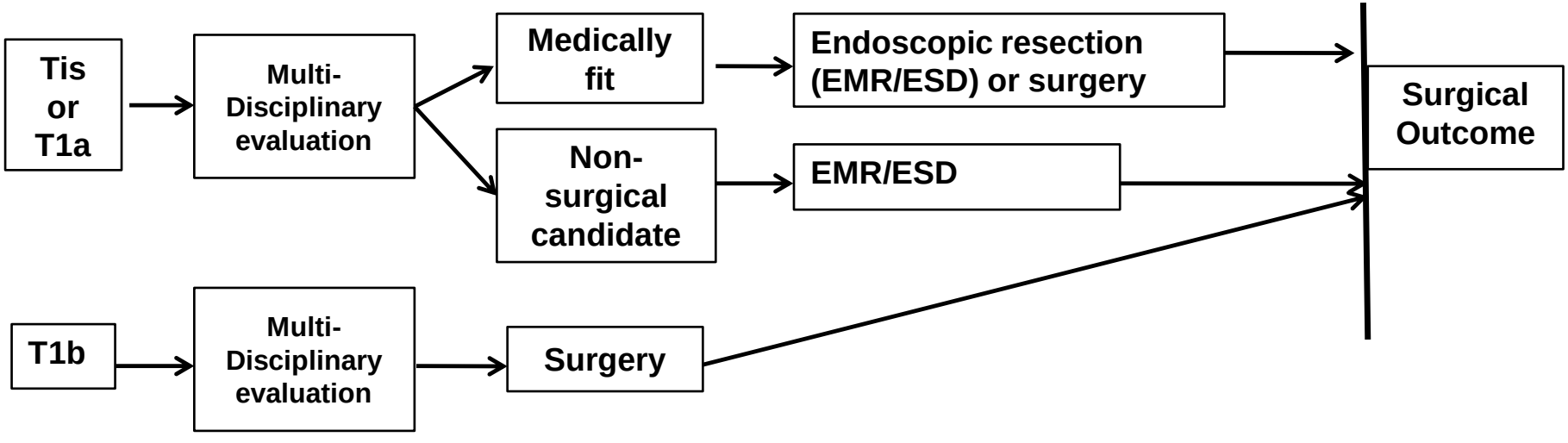
HISTOLOGIC GRADE

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Treatment Stratification

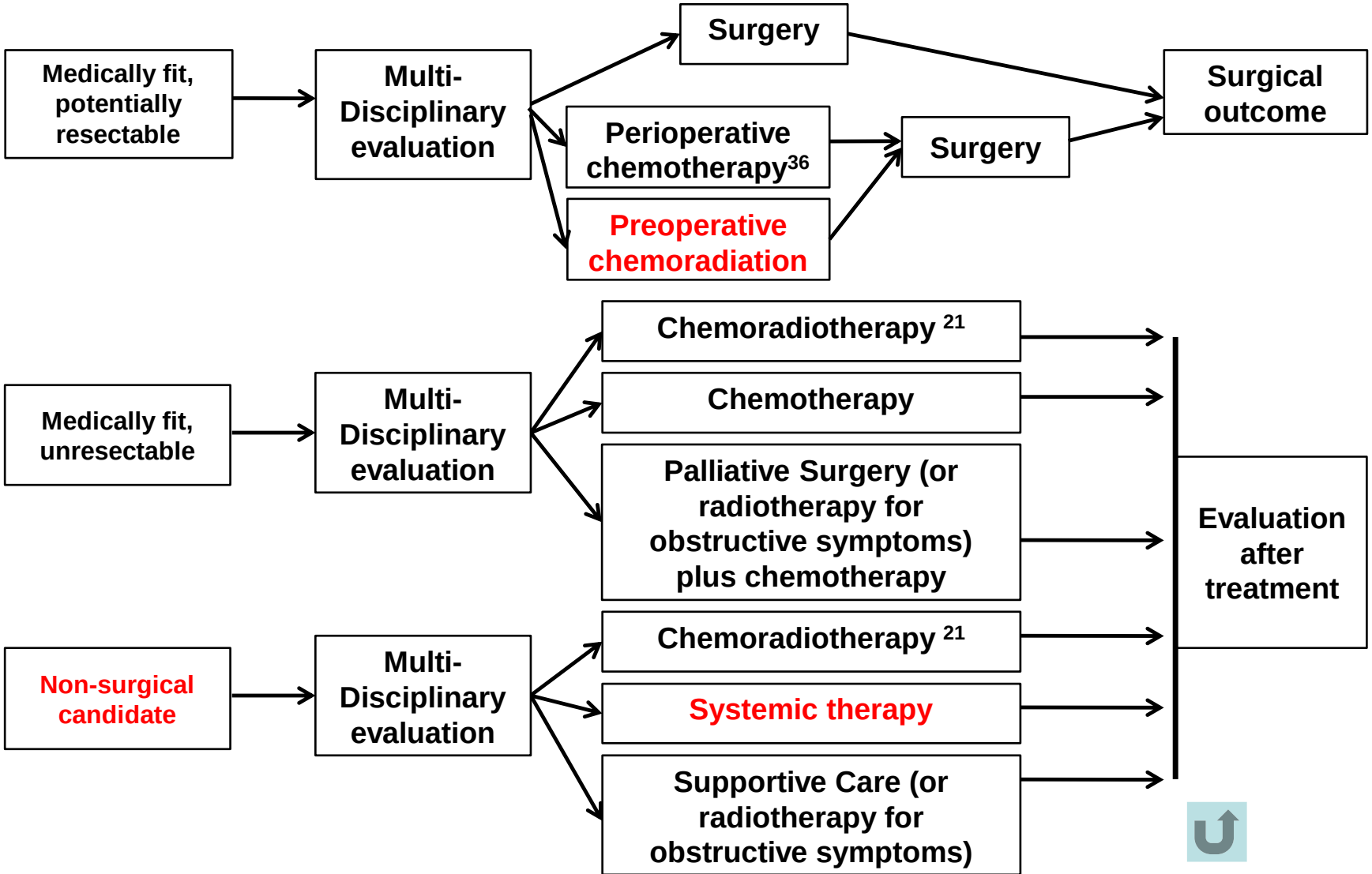


Early gastric cancer (Tis, T1 and N0M0)

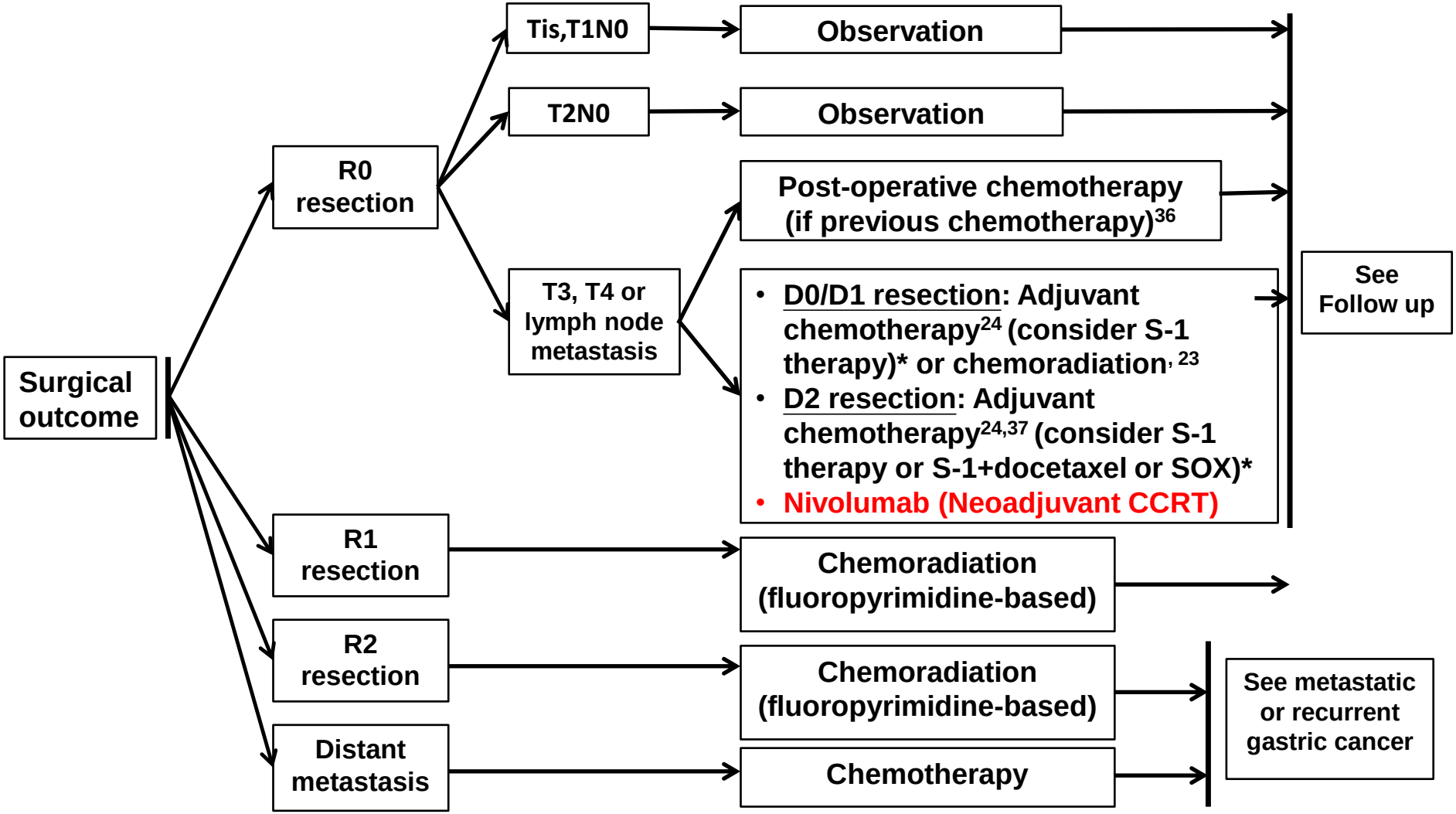


Tis: Carcinoma in situ
T1a:Tumor invades lamina propria
T1b: Tumor invades submucosa
EMR: Endoscopic mucosal resection
ESD: Endoscopic submucosal dissection

Advanced gastric cancer (T2-4N0-3M0)

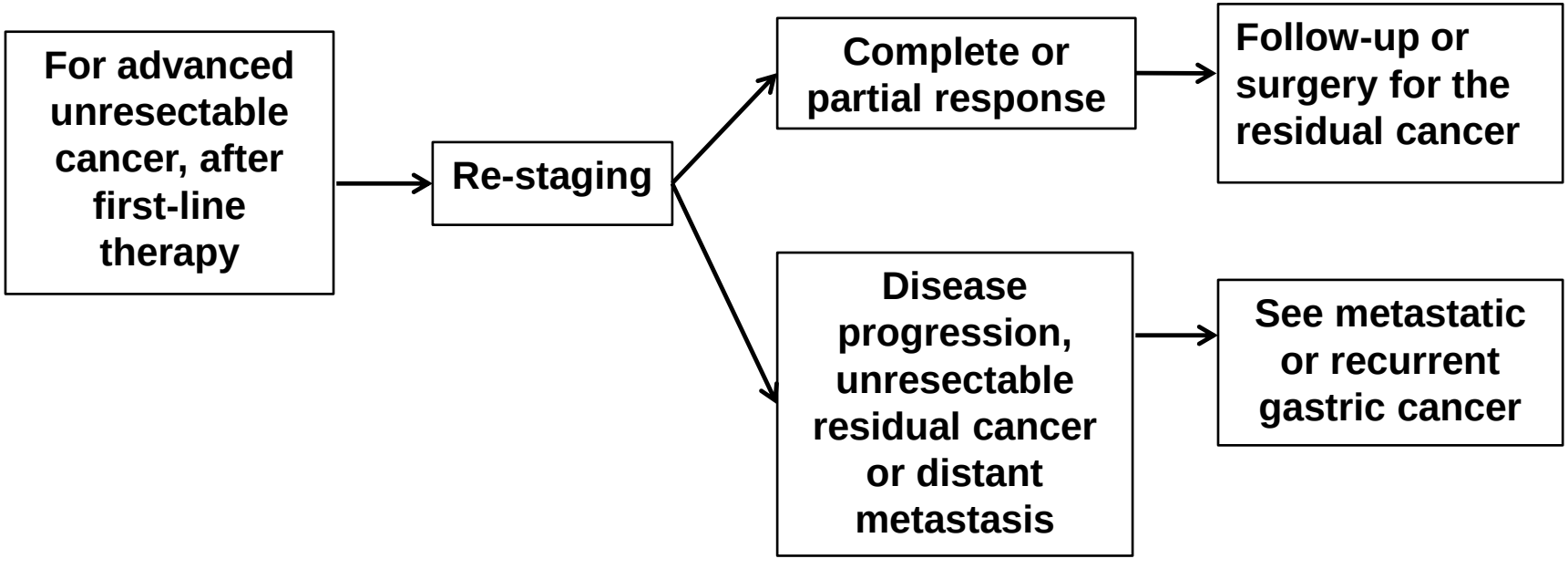


Surgical outcome

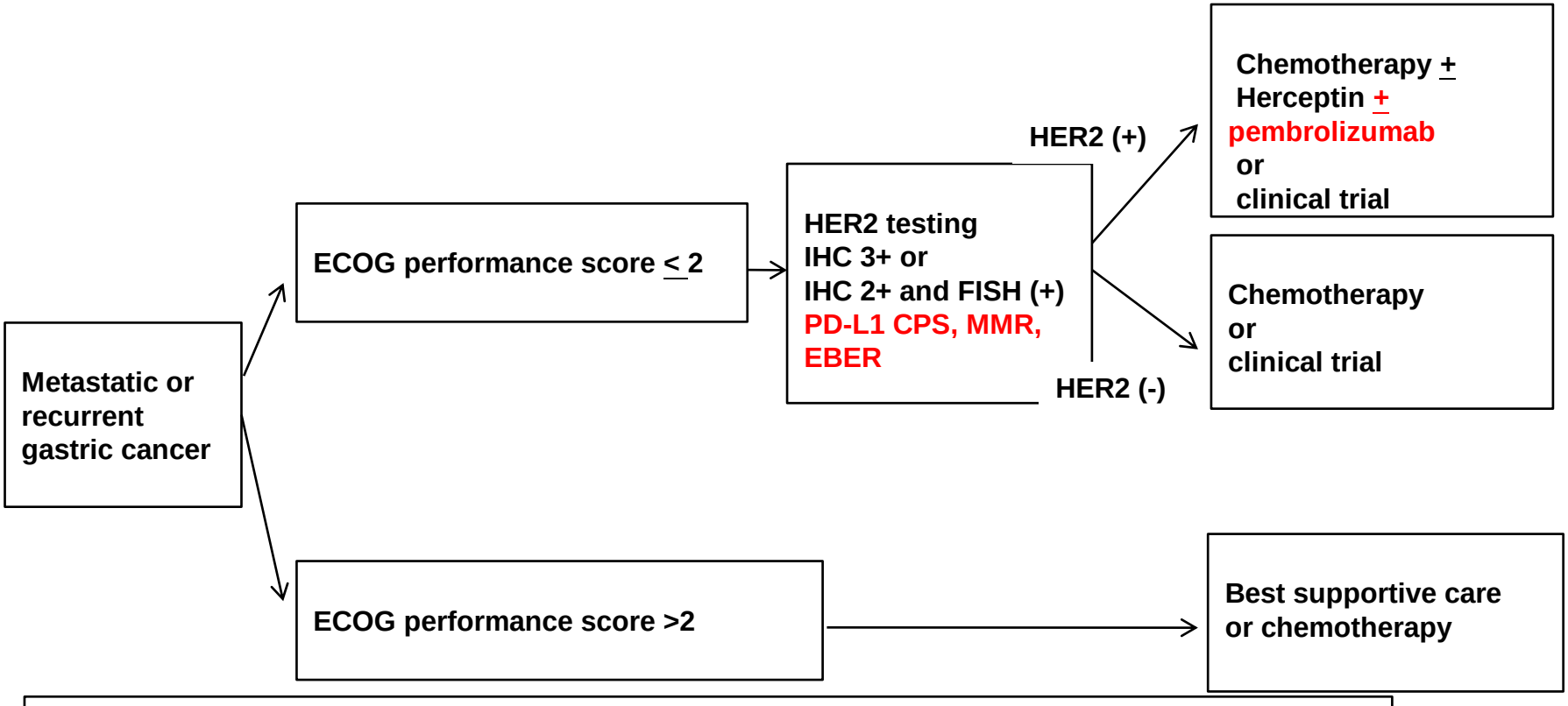


R0 resection：No cancer at resection margin
R1 resection：Microscopic residual cancer
R2 resection：Macroscopic residual cancer
*S1 therapy: After D2 dissection or stage II or IIIA

Evaluation after treatment

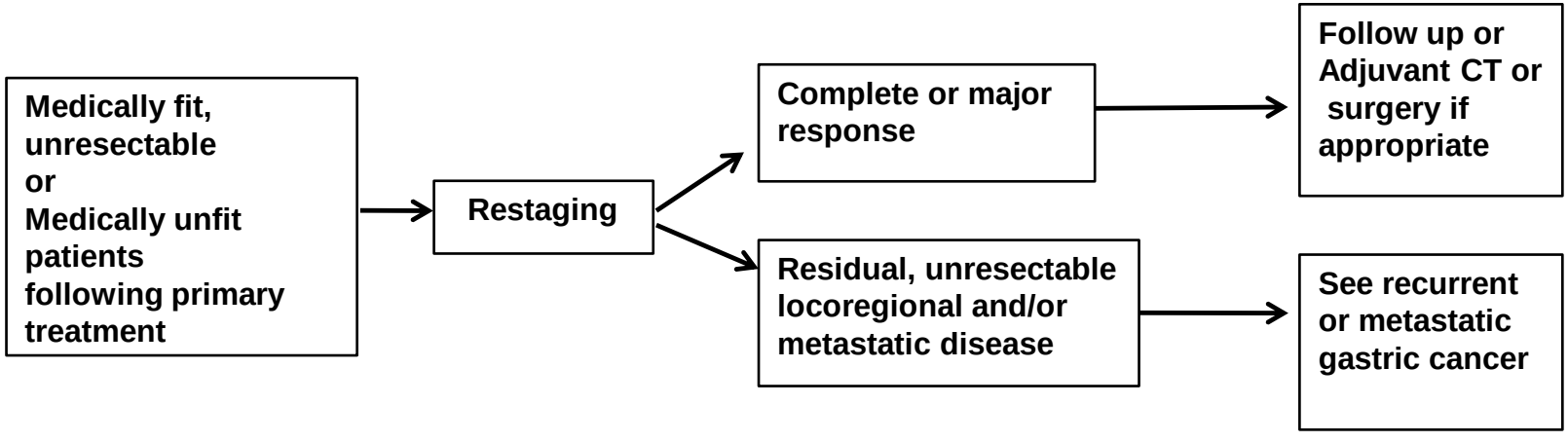


Metastatic or recurrent gastric cancer (M1)



Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Post Treatment Assessment/Adjunctive treatment



Recommended adjuvant regimens of gastric cancer

• Recommended regimens of adjuvant chemotherapy

- **TS-1**[1]

  TS-1 80mg/m2 per day for 4 weeks every 6 weeks for 1 year

- **XELOX**[2]

  Oxaliplatin 135mg/m^2 on D1, Capecitabine 1000mg/m^2 BID for 14 days every 3 weeks for 6 months

  or

  Oxaliplatin 85mg/m^2 on D1, Capecitabine 1000mg/m^2 BID for 10 days every 2 weeks for 6 months

- **High dose PFL**[3]

  Cisplatin 30mg/m^2 IV, folinic acid 500 mg/m^2 IV, 5-fluorouracil (5-FU 2200 mg/m^2 CIVD for 22 h, weekly for 6 months

- **TS-1 + Docetaxel**[37]

  S-1 80-120mg/body for 14 days every 3 weeks, followed by 6 cycles of S-1 combined with docetaxel 40mg/m^2 on day 1 of each cycle, and then 4 further cycles of S-1 at 80-120mg/body on days 1-28 every 42 days

- **SOX**[39]

  S1 40 mg/m^2 twice daily on days 1-14 and oxaliplatin 130 mg/m^2 every 3 weeks for 8 cycles

Recommended adjuvant regimens of gastric cancer (Continue)

• Recommended regimens of adjuvant chemotherapy and concurrent chemoradiotherapy

-CT followed by CCRT (XP/XRT/XP)[31] (SOX/SRT/SOX)[39]

-XP (capecitabine 2,000 mg/m2 per day) on days 1 to 14 and cisplatin 60 mg/m2 on day 1, repeated every 3 weeks
The XP/XRT/XP arm receives two cycles of XP followed by 45-Gy XRT (capecitabine 1,650 mg/m2 per day for 5 weeks) and two cycles of XP.

- SOX (S1 40 mg/m^2 twice daily on days 1-14 and oxaliplatin 130 mg/m^2 every 3 weeks), SRT (S1 40mg/m^2 +45Gy for 5 weeks RT)
SOX x 2 cycles, followed by SRT and followed by 4 cycles SOX[39]

•Recommended regimens of peri-operative chemotherapy

- Perioperative CT (FLOT4)[36]

- Docetaxel 50 mg/m2, oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 2600 mg/m² as 24-hour infusion, all d1

Recommended adjuvant regimens of gastric cancer (Continue)

- **Recommended regimens of adjuvant therapy after preoperative CCRT**
  - Nivolumab 240mg Q2W x16 weeks, then 480mg Q4W

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Recommended regimens of recurrent or metastatic gastric cancer**
- **First line therapy**
- **- Preferred regimens: Fluorouracil/leucovorin plus platinum based C/T**
  - **High dose PFL (cisplatin/fluorouracil/leucovorin, *prefer regimen*)**
    Cisplatin 30mg/m^2 IV, folinic acid 500 mg/m^2 IV, 5-fluorouracil (5-FU) 2200 mg/m^2 CIVD for 22 h, weekly
  - **Xelox (capecitabine/oxaliplatin, *prefer regimen*)**[4,5,6]
    Oxaliplatin 135mg/m^2 on D1, Capecitabine 1000mg/m^2 BID for 14 days every 3 weeks
    or Oxaliplatin 85mg/m^2 on D1, Capecitabine 1000mg/m^2 BID for 10 days every 2 weeks
  - **TS-1 + cisplatin**[7]
    TS-1:40-60 mg/m^2 BID for 21 days every 5 weeks, Cisplatin 60mg/m^2 on D8
  - **XP(Capecitabine/cisplatin)**[8]
    Cisplatin 80mg/m^2 IV on D1, Capecitabine 1000mg/m^2 BID for 14 days every 3 weeks
  - **FOLFOX**[9]
    Oxaliplatin 85mg/m^2 IV, Leucovorin 400 mg/m^2 IV, 5-fluorouracil 400 mg/m^2 IV on D1 and 5-fluorouracil 1200 mg/m^2 CIVD on D1, D2, every 2 weeks
  - **Weekly OFL**[10]
    Oxaliplatin 65mg/m^2 IV, Leucovorin 300 mg/m^2 IV, 5-fluorouracil 2600 mg/m^2 CIVD for 24 hours, weekly

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Recommended regimens of recurrent or metastatic gastric cancer**
- **First line therapy (continued)**
- **- Preferred regimens: Fluorouracil/leucovorin plus platinum based C/T and immune checkpoint inhibitor (PD-L1 CPS ≥ 5)**
  - Nivolumab 360mg + XELOX Q3W (ATTRACTION-4)
  - Nivolumab 240mg + FOLFOX Q2W (CHECKMATE-649)

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Preferred targeted therapy**
  - Trastuzumab + standard chemotherapy in HER-2 (+)[11]
  - Trastuzumab+ Pembrolizumab+ standard chemotherapy in HER-2 (+)[43]
- **Alternative regimens**
  - **Taxane based**

    DCF regimen[12]

    Docetaxel 75mg/m^2 IV and Cisplatin 75mg/m^2 IV on D1

    5-FU 750mg/m2 CIVD on D1-5, every 3 weeks

    Modified TCF[13]

    Paclitaxel 100 mg/m^2 and Cisplatin 30 mg/m^2 IV on D1 and 8

    UFT 300 mg/m^2 plus LV 90 mg per day on D1-14, every 3 weeks
  - **Irinotecan based[14]**

    Irinotecan 80 mg/m^2 IV, folinic acid 500 mg/m^2 IV, 5-fluorouracil (5-FU) 2000 mg/m^2 CIVD for 22 h, for 6 weeks every 7 weeks

    - Folfiri[32]

- Irinotecan 180 mg/m^2 IV on D1, folinic acid 400 mg/m^2 IV on D1,
- 5-fluorouracil 400mg/m^2 IV bolus then 5-fluorouracil 2400mg/m^2 IV every 2 weeks.

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Second line therapy**
  - **Ramucirumab[15]**
    Ramucirumab 8 mg/kg IV on Day 1
    Cycled every 14 days
  - **Ramucirumab + paclitaxel[16]**
    Ramucirumab 8 mg/kg IV on Days 1 and 15
    Paclitaxel 80 mg/m2 on Days 1, 8, and 15
    Cycled every 28 days
  - **Docetaxel[17]**
    Docetaxel 75–100 mg/m2 IV on Day 1
    Cycled every 21 days
  - **Paclitaxel[18]**
    - Paclitaxel 135–250 mg/m2 IV on Day 1 Cycled every 21 days
    - Paclitaxel 80 mg/m2 IV on Day 1 weekly Cycled every 28 days
    - Paclitaxel 80 mg/m2 IV on Days 1, 8, and 15 Cycled every 28 days

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Second line therapy**
  - **Irinotecan[18]**
    - Irinotecan 250–350 mg/m2 IV on Day 1
      Cycled every 21 days
    - Irinotecan 150–180 mg/m2 IV on Day 1
      Cycled every 14 days
    - Irinotecan 125 mg/m2 IV on Days 1 and 8
      Cycled every 21 days
  - **Immunotherapy (Anti-PD1/Anti-PDL1 therapy, only MSI-H/DMMR or CPS>10)[40]**
    - Nivolumab 3 mg/kg IV on D1[34]
      Cycle every 14 days
    - Pembrolizumab 2 mg/kg on D1 in Patients with PD-L1 positive[35]
      Cycle every 21 days

Recommended regimens of recurrent or metastatic gastric cancer (Continue)

- **Third line therapy**
  - **Immunotherapy (Anti-PD1/Anti-PDL1 therapy)**

    •Nivolumab 3 mg/kg IV on D1[34]

    Cycle every 14 days

    •Pembrolizumab 2 mg/kg on D1 in Patients with PD-L1 positive (CPS>1) [35]

    Cycle every 21 days

  - Lonserf (TAS102; Trifluridine and tipiracil)[38]

  Lonserf (35 mg/m^2 twice daily on days 1-5 and days 8-12 every 28 days)

Principle of surgery-1

- **Staging**

  Determine extent of disease with CT scan ± EUS

  Laparoscopy may be useful in selected patients in detecting radiographically occult metastatic disease

- **Criteria of unresectability for cure**

  - Locoregionally advanced
  - Level 3 or 4 lymph node highly suspicious on imaging or confirmed by biopsy
  - Invasion or encasement of major vascular structures
  - Distant metastasis or peritoneal seeding (including positive peritoneal cytology)

Principle of surgery-2

- **Resectable tumors[13,14]**
- Tis or T1 tumors limited to mucosa (T1a) may be candidates for endoscopic mucosal resection
- T1b-T3 : Adequate gastric resection to achieve negative microscopic margins (typically 4 cm from gross tumor).
- Distal/Subtotal/ total gastrectomy
- T4 tumors require en bloc resection of involved structures
- Gastric resection should include the regional lymphatics-- perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining 15 or greater lymph nodes
- Routine or prophylactic splenectomy is not required. Splenectomy is acceptable when the spleen or the hilum is involved.

Principle of surgery-3

- **Unresectable tumors (palliative procedures)** [13,14,15]
- Palliative gastric resection could be performed in symptomatic patients.
- Lymph node dissection not required
- Gastric bypass with gastrojejunostomy to the proximal stomach may be useful in palliating obstructive symptoms in symptomatic patients
- Venting gastrostomy and/or jejunostomy tube may be considered
- Stent implantation for pyloric obstruction may be considered

Principles of radiation therapy-1

General Guidelines

- Prior to simulation, pertinent radiographs, procedure notes and pathology reports should be reviewed by a multidisciplinary team including surgical, radiation, medical oncologists, gastroenterologists, radiologists and pathologists. This will allow an informed determination of treatment volume and field borders prior to simulation.
- In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal cancers. Depending on the clinical situation, Siewert III tumors, may be more appropriately managed with radiation therapy guidelines applicable to either esophageal or gastric cancers. These recommendations may be modified depending on where the bulk of the tumor is located.

Principles of radiation therapy-2

Simulation and Treatment Planning

- Use of CT simulation and 3D or IMRT treatment planning is strongly encouraged.
- The patient should be instructed to avoid intake of a heavy meal for 3 hours before simulation and treatment. When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily set-up.
- All patients should be simulated and treated in the supine position.

Principles of radiation therapy-3

Target Volume (General Guidelines)

- **Definitive or Preoperative[19]**
  - Pre-treatment diagnostic studies (EUS, UGI, EGD, and CT scans) should be used to identify the tumor and pertinent nodal groups.[20,21]
  - The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.
- **Postoperative[22]**
  - Pre-treatment diagnostic studies (EUS, UGI, EGD, and CT scans) and clip placement should be used to identify the tumor/gastric bed, the anastomosis or stumps, and pertinent nodal groups. [20,21]
  - Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach.
  - The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.[23] Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.

Principles of radiation therapy-4

- **Proximal one-third/Cardia/Esophagogastric Junction Primaries**
  - With proximal gastric lesions or lesions at the EG junction, a 3- to 5-cm margin of distal esophagus, medial left hemidiaphragm and adjacent pancreatic body should be included. Nodal areas at risk include: adjacent paraesophageal, perigastric, suprapancreatic, and celiac lymph nodes.
- **Middle one-third/Body Primaries**
  - Nodal areas at risk include: perigastric, suprapancreatic, celiac, splenic hilar, porta hepatic, and pancreaticoduodenal lymph nodes.
- **Distal one-third/Antrum/Pylorus Primaries**
  - A 3- to 5-cm margin of duodenal stump should be included if the gross lesion extended to the gastroduodenal junction.
  - Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.

Dose

- 45-50.4 Gy (1.8 Gy/day)
  - **Higher doses may be used for positive surgical margin in selected cases**

Follow up

Physical examination and radiologic imaging:

- Every 3-6 mo for 1-3 y, every 6 mo for 3-5 y, then annually
- CXR every 3-6 months for high risk patients (including Old age, male gender, previous anti-TB treatment, and gastrectomy)[29]

CBC and chemistry profile:

As indicated

Tumor marker:

CEA, CA199

Endoscopy:

As clinically indicated

Supplement of vitamin B12 and iron (optional):

In patients receiving total gastrectomy and patients receiving subtotal gastrectomy with anemia

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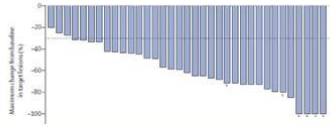
Background

- Standard first-line therapy for HER2-positive metastatic gastric or gastroesophageal junction (G/GEJ) cancer is trastuzumab (anti–HER2) with a fluoropyrimidine and a platinum
- Phase 2 data suggested antitumor activity and manageable safety for adding pembrolizumab (anti–PD-1) to trastuzumab and chemotherapy
  - MSKCC study (N = 37): 91% ORR, 100% DCR, 70% 6-mo PFS, 80% 12-mo OS



Janjigian YY et al. *Lancet Oncol* 2020;21:821-31.
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  - PANTHERA (N = 43): 77% ORR, 98% DCR, 77% 6-mo PFS, 77% 12-mo OS

Rha SY et al. *J Clin Oncol* 2020;38:Abstr 3081.

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Protocol-Specified First Interim Analysis (IA1)

Key Points

- Timing: to occur when first 260 participants enrolled had ≥8.5 mo of follow-up
- Objective: to assess whether adding pembrolizumab to trastuzumab and chemotherapy significantly improves ORR
- Superiority boundary: $P = 0.002$ (one-sided)
- Data cutoff date: June 17, 2020
  - 434 participants enrolled

Efficacy Population

- First 264 participants enrolled
- Follow-up duration[a]
  - Median: 12.0 mo
  - Range: 8.5-19.4 mo
- Continuing any study treatment
  - Pembro arm: 40.6%
  - Placebo arm: 28.5%

Safety Population

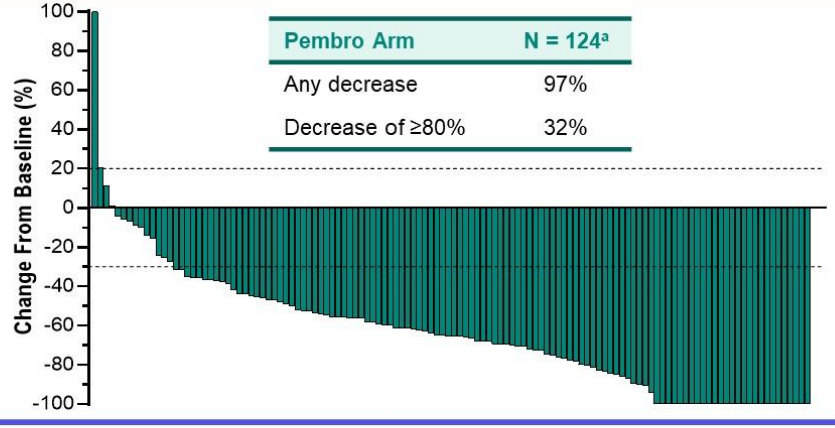
- 433 participants who received ≥1 dose of study medication
- Follow-up duration[a]
  - Median: 9.9 mo
  - Range: 0.1-19.4 mo
- Continuing any study treatment
  - Pembro arm: 58.5%
  - Placebo arm: 48.1%

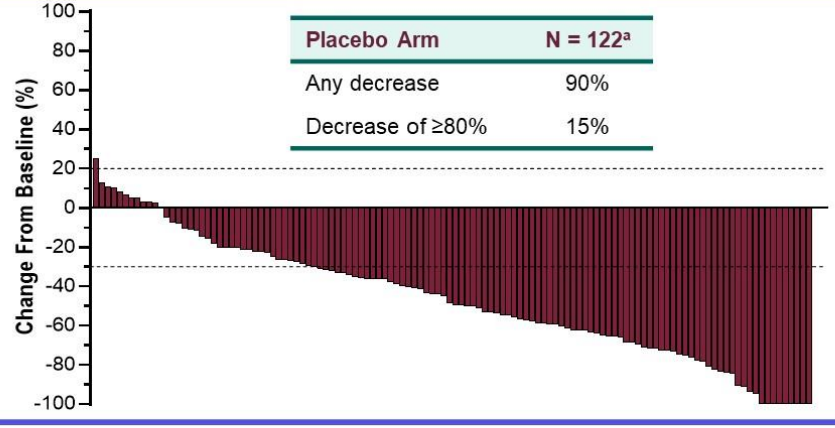
Baseline Characteristics – Efficacy Population

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
Age, median (range)	62 y (19-84)	61 y (32-83)
Male sex	84%	79%
Region of enrollment		
Aus/EU/Isr/NAm	31%	34%
Asia	30%	30%
ROW	39%	37%
ECOG PS 1	51%	55%
Primary location of stomach	72%	68%
Histologic subtype		
Diffuse	21%	20%
Intestinal	61%	48%
Indeterminate	18%	32%
PD-L1 CPS ≥1	88%	85%
HER2 status		
IHC 2+, ISH positive	18%	21%
IHC 3+	82%	79%
Choice of chemotherapy		
CAPOX	86%	88%
FP	14%	12%

[a]Follow-up duration was defined as the time from randomization to the data cutoff date.
Aus, Australia; EU, Europe; Isr, Israel; NAm, North America; ROW, rest of world.
The treatment regimen in both arms included trastuzumab and chemotherapy.

Confirmed Response at IA1





ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Adverse Events at IA1

All-Cause AEs

	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	97%		98%	
Grade 3-5	57%		57%	
Serious	31%		38%	
Led to death	3%		5%	
Led to discon, any drug	24%		26%	
Incidence >20%	**Any**	**Gr 3-5**	**Any**	**Gr 3-5**
Diarrhea	53%	7%	44%	8%
Nausea	49%	5%	44%	6%
Anemia	41%	9%	44%	9%
↓ Appetite	31%	2%	32%	4%
Vomiting	31%	5%	27%	2%
↓ Platelet count	24%	8%	28%	7%
Fatigue	24%	4%	20%	3%
↓ Neutrophil count	24%	7%	25%	7%
Peripheral sensory neuropathy	23%	3%	19%	1%
↑ AST	21%	<1%	13%	<1%

Immune-Mediated AEs and Infusion Reactions[a]

	Pembro Arm (N = 217)		Placebo Arm (N = 216)	
Summary				
Any grade	34%		21%	
Grade 3-5	10%		3%	
Serious	9%		3%	
Led to death	1%		<1%	
Led to discon, any drug	6%		2%	
Incidence ≥2 Participants	**Any**	**Gr 3-5**	**Any**	**Gr 3-5**
Infusion reactions	18%	3%	13%	1%
Pneumonitis	5%	1%	1%	0
Colitis	5%	3%	2%	2%
Hypothyroidism	5%	0	3%	0
Hyperthyroidism	4%	0	3%	0
Hypophysitis	1%	<1%	0	0
Hepatitis	1%	1%	1%	0
Severe skin reactions	1%	1%	0	0

[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Participants in both arms received trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Summary of KEYNOTE-811 IA1

- Pembrolizumab plus trastuzumab and chemotherapy provided a 74.4% ORR that resulted in a statistically significant, clinically meaningful 22.7% improvement in ORR compared with placebo plus trastuzumab and chemotherapy
- Responses to pembrolizumab plus trastuzumab and chemotherapy were deeper and more durable
- AE incidence was similar between arms, and the observed AEs were as expected with no new safety concerns identified
- Study is continuing as planned, and analyses of OS and PFS will be performed in the future in accordance with the analysis plan

Key Takeaway

- Pembrolizumab plus trastuzumab and chemotherapy is a potential new treatment option for previously untreated, unresectable or metastatic, HER2-positive gastric or gastroesophageal junction cancer

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For Questions or Comments, Contact Yelena Y. Janjigian

Email: janjigiy@mskcc.org **Twitter**: @YJanjigianMD

Poster

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