Neoadjuvant and Adjuvant Therapies for Esophageal and Gastric Cancers

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Disclosures

- Speakers' bureau:
- Boehringer Ingelheim (afatinib)
- Seattle Genetics (brentuximab vedotin)
- Merck (pembrolizumab)
- Incyte (ruxolitinib)
- Amgen (denosumab, panitumumab)

Gastroesophageal Cancer: Treatment Overview

- Surgery is primary treatment for medically fit, resectable cases[1]
- For advanced disease, treatment may include perioperative chemotherapy or preoperative chemoradiation
- Postoperative treatment options
  - Chemoradiation (fluoropyrimidine-based or capecitabine)
  - Palliative chemotherapy or best supportive care
- Recurrent or metastatic disease
  - Chemotherapy
  - Palliative chemotherapy, clinical trial, or best supportive care
- Significant need exists for deeper understanding of tumor subtypes, biomarkers for treatment response[2]

1. NCCN. Clinical practice guidelines in oncology: gastric cancer, v2. 2011.
2. Power DG, et al. Cancer Treat Rev. 2010;36:384-392.

NCCN Guidelines Version 2.2018
Esophageal and Esophagogastric Junction Cancers

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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

Category 1 evidence supports the notion that the combined modality therapy is effective for patients with localized esophagogastric cancer.[1,2,3] The NCCN Panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients.

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PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and EGJ adenocarcinoma, SCC of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), comorbidities, and toxicity profile.
- Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising efficacy.[1]
- Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.[2] Perioperative chemotherapy is an alternative option for distal esophagus and EGJ.[3,4]
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.

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PRINCIPLES OF SYSTEMIC THERAPY

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- Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.
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- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.[1]
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Perioperative chemotherapy,[2,3] or postoperative chemotherapy plus chemoradiation[4] is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.[5,6] (See Principles of Surgery [GAST-C])
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

Epidemiology of esophageal cancer in the United States, 2012

	Squamous cell	Adenocarcinoma
Incidence rate, per 100,000 population	1.2	2.8
Male-to-female ratio	2.5:1	6.5:1
White-to-black ratio	1:4	4:1
Most common locations	Middle esophagus	Distal esophagus
Major risk factors	Smoking, alcohol	Barrett's esophagus

Data from: Thrift AP. The epidemic of oesophageal carcinoma: Where are we now? Cancer Epidemiol 2016; 41:88.

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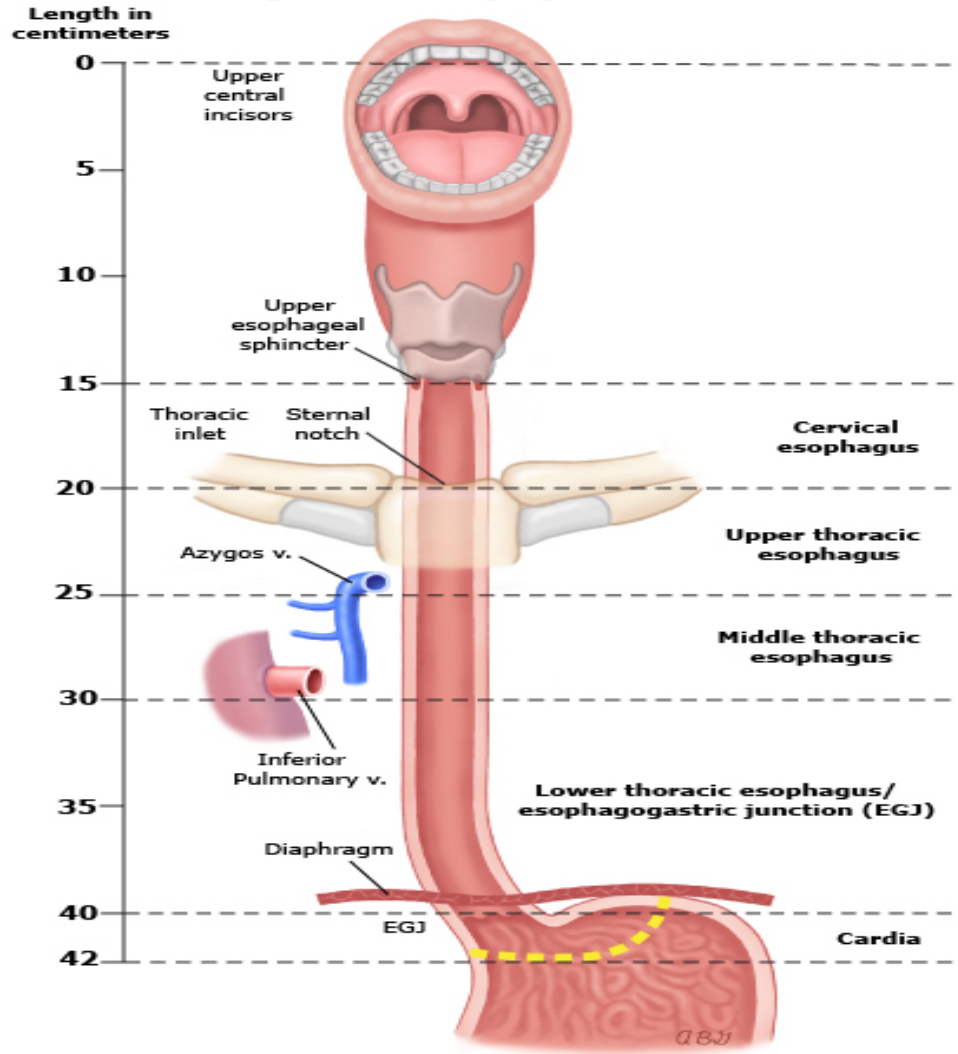
AJCC 8th edition regions of the esophagus



Anatomy of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors. Exact measurements depend on body size and height. For tumors of the EGJ and cardia, location of cancer primary site (ie, esophagus, stomach) is defined by cancer epicenter.

AJCC: American Joint Committee on Cancer; v: vein.

Modified from: Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th Ed, Amin MB (ed), Springer Science+Business Media, LLC, New York, 2017.

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Esophagus and Esophagogastric Junction (8th ed., 2017)
Squamous Cell Carcinoma and Adenocarcinoma

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Definition of Histologic Grade (G)

G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Squamous Cell Carcinoma

Definition of Location (L)

Location Category	Location Criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction
Note: Location is defined by the position of the epicenter of the tumor in the esophagus.	

Continued

***Table 1* (continued)**

AJCC PROGNOSTIC STAGE GROUPS (Squamous Cell Carcinoma)

Clinical Staging (cTNM)

	cT	c N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0–1	M0
Stage II	T2	N0–1	M0
	T3	N0	M0
Stage III	T3	N1	M0
	T1-3	N2	M0
Stage IVA	T4	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	pT	pN	M	G	Location
Stage 0	Tis	N0	M0	N/A	Any
Stage IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
Stage IB	T1a	N0	M0	G2-3	Any
	T1b	N0	M0	G1-3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
Stage IIA	T2	N0	M0	G2-3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
Stage IIB	T3	N0	M0	G2-3	Upper/middle
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	Location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any T	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Postneoadjuvant Therapy (ypTNM)

	yp T	yp N	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

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***Table 1* (continued)**

AJCC PROGNOSTIC STAGE GROUPS (Adenocarcinoma)

Clinical Staging (cTNM)

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3	N0-1	M0
	T4a	N0-1	M0
Stage IVA	T1-4a	N2	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	any T	Any N	M1

Pathological (pTNM)

	pT	pN	M	G
Stage 0	Tis	N0	M0	N/A
Stage IA	T1a	N0	M0	G1
	T1a	N0	M0	GX
Stage IB	T1a	N0	M0	G2
	T1b	N0	M0	G1-2
	T1b	N0	M0	GX
Stage IC	T1	N0	M0	G3
	T2	N0	M0	G1-2
Stage IIA	T2	N0	M0	G3
	T2	N0	M0	GX
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any T	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Postneoadjuvant Therapy (ypTNM)

	yp T	yp N	M
Stage I	T0	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

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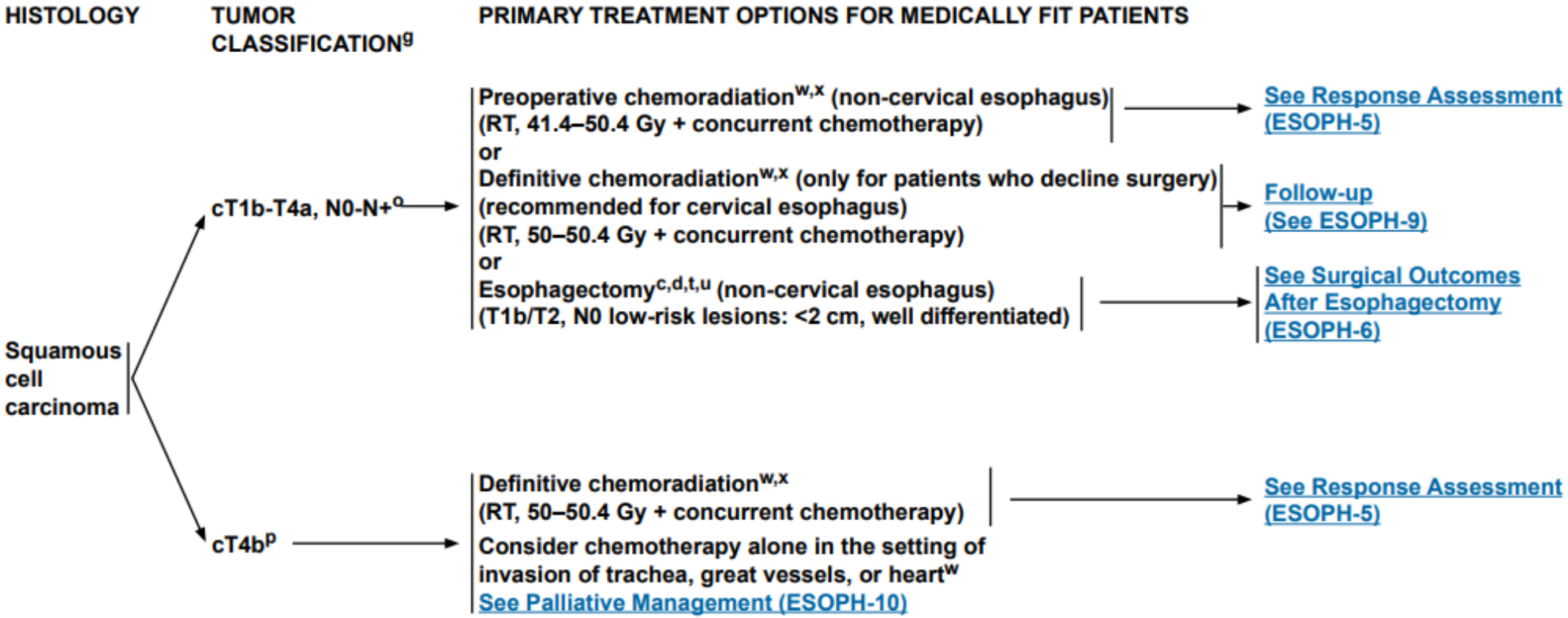


Esophageal Cancer

- Squamous vs. AdenoCA?
- Semin Radiat Oncol. 2007;17(1):38.
- The localization of AC is in 94% below the tracheal bifurcation, whereas SCC has contact to the tracheal bronchial tree in 75%.
- SCC shows an earlier lymphatic spread and a worse prognosis compared to AC.
- This has led some authors to suggest AC does not require radiation in induction, but there is no clear data to support this.
- A major area where data are lacking is nonsurgical management for adenocarcinomas.

Versus RT alone?

- **RTOG 85-01** – RT alone versus concurrent chemoradiotherapy (two cycles of infusional FU [1000 mg/m^2 per day, days 1 to 4, weeks 1 and 5] plus cisplatin [75 mg/m^2 day 1 of weeks 1 and 5] and RT [50 Gy in 25 fractions over five weeks]). Surgery was not part of the treatment schema.
- Analysis showed a significant survival advantage for chemoradiotherapy (five-year survival 27 versus 0 percent) However, despite this benefit, 46 percent of patients in the chemoradiotherapy group had locally recurrent or persistent disease in the esophagus at 12 months.
- As a result of this trial, definitive chemoradiotherapy became the standard of care for patients with inoperable disease

Versus surgery alone?

- **CALGB 9781** – CDDP+FU+ RT versus surgery. Five-year survival was 39 versus 16 percent in favor of trimodality therapy, although the difference was not statistically significant.
- ●**NEOCRTEC5010 trial** –RT concurrent with vinorelbine plus cisplatin or surgery alone. At surgery, the pCR rate was 43 percent in those receiving chemoradiotherapy. Compared with surgery alone, patients receiving neoadjuvant chemoradiotherapy had a higher R0 resection rate (98 versus 91 percent), better overall median survival (100 versus 66.5 months), better three-year overall survival (69 versus 59 percent), and longer median disease-free survival. The incidence of postoperative complications was similar between the two groups.
- **CROSS trial** –Preoperative chemoradiotherapy using weekly paclitaxel 50 mg/m^2 plus carboplatin [AUC] of 2) plus concurrent RT or surgery alone. The microscopically complete (R0) resection rate was higher with chemoradiotherapy (92 versus 69 percent), and 29 percent of those treated with chemoradiotherapy had a pathologic complete response (pCR). At a median follow-up of 32 months, median overall survival was significantly better with preoperative chemoradiotherapy (HR for death 0.657, 95% CI 0.495-0.871, three-year survival rate 58 versus 44 percent). The survival benefit persisted with longer (median 84-month) follow-up (five-year survival 47 versus 33 percent, HR for death 0.67, 95% CI 0.51-0.87).

Is Surgery needed?

- A Cochrane analysis concluded:
- ●There was high-quality evidence that the addition of esophagectomy had no significant impact on survival (HR 0.99, 95% CI 0.79-1.24).
- ●There was moderate-quality evidence that the addition of esophagectomy improved freedom from locoregional relapse (HR 0.55, 95% CI 0.39-0.76)
- ●Given that 93 percent of the patients enrolled in these trials had SCC, it cannot be determined whether these results can be applied to the treatment of adenocarcinomas or to individuals with a poor response to chemoradiotherapy.

Is RT needed?

- In contrast to the data on concurrent chemoradiotherapy, at least three trials comparing sequentially administered chemotherapy and RT followed by surgery with surgery alone have failed to show any survival advantage to combined modality therapy

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
(3 cycles preoperative and 3 cycle postoperative)

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[b]
- Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Preoperative Chemotherapy (2 cycles)
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

Definitive Chemoradiation
Infusional fluorouracil can be replaced with capecitabine

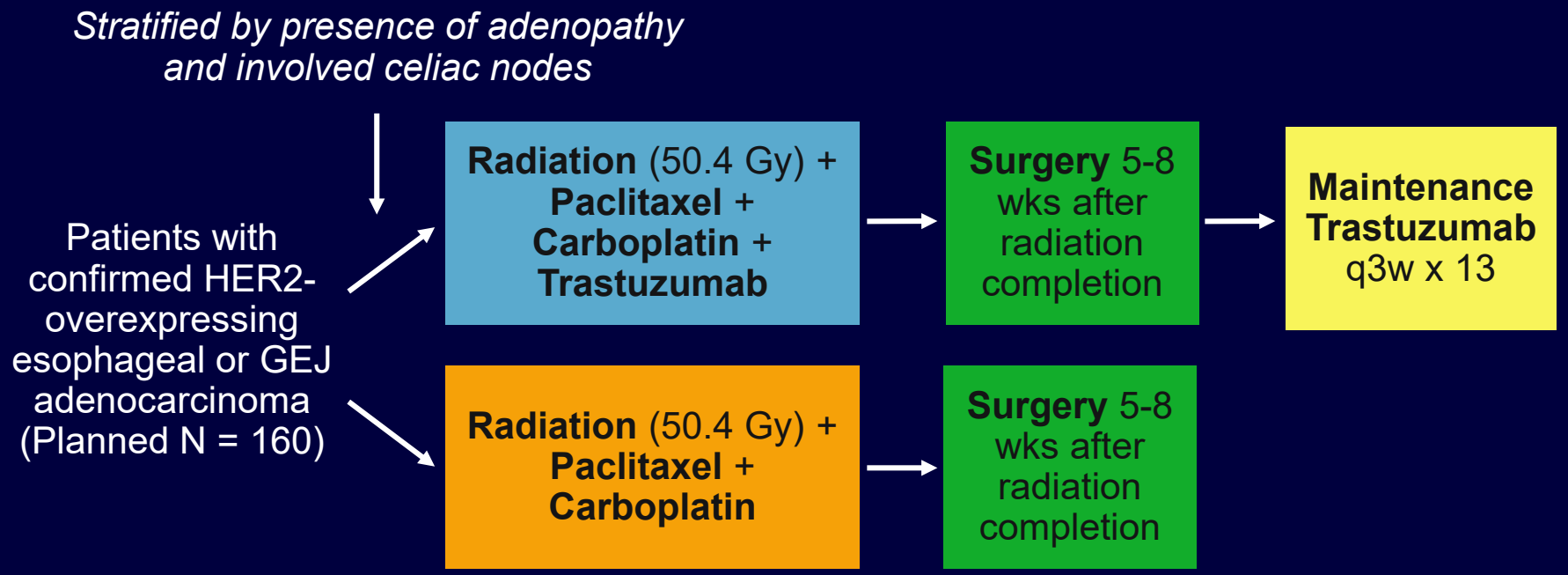
Preferred Regimens
- Fluorouracil and cisplatin (category 1)[11]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]
- Paclitaxel and carboplatin[1]

Other Recomended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation[15]

Postoperative Chemotherapy
- Capecitabine and oxaliplatin[d,16]

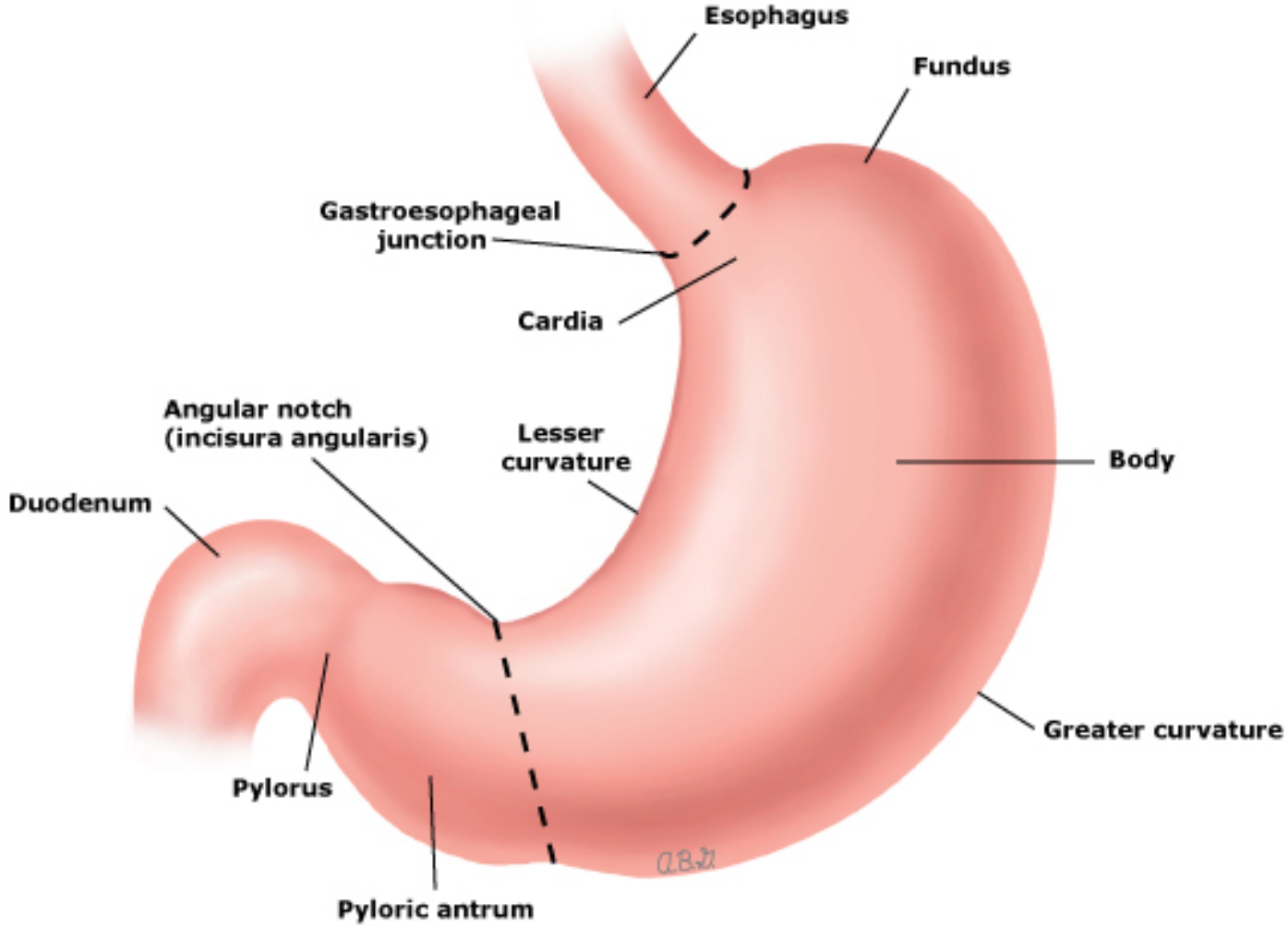
RTOG 1010: Neoadjuvant Phase III Trial in Esophageal/GEJ Adenocarcinoma



- Primary endpoint: DFS (15 → 27 mos; HR: 0.56)

Principal investigator: H. Safran, Providence, RI. ClinicalTrials.gov. NCT01196390.

Parts of the stomach



This drawing shows the parts of the anterior surface of the stomach. The body of the stomach is separated from the pyloric part by an oblique line that extends from the angular notch (incisura angularis) on the lesser curvature to the greater curvature.

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Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Stomach (8th ed., 2017)

Definition of Primary Tumor (T)

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

*A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classifi ed as T4.
**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
***Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classifi ed using the depth of the greatest invasion in any of these sites.

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in seven to 15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Definitions of Histologic Grade (G)

G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Continued

***Table 1* (continued)**

AJCC PROGNOSTIC STAGE GROUPS

Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T1	N1, N2, or N3	M0
	T2	N1, N2, or N3	M0
Stage IIB	T3	N0	M0
	T4a	N0	M0
Stage III	T3	N1, N2, or N3	M0
	T4a	N1, N2, or N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	pT	pN	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1 or N2	M0
	T4b	N0	M0
Stage IIIB	T1	N3b	M0
	T2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1 or N2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1

Post–Neoadjuvant Therapy (ypTNM)

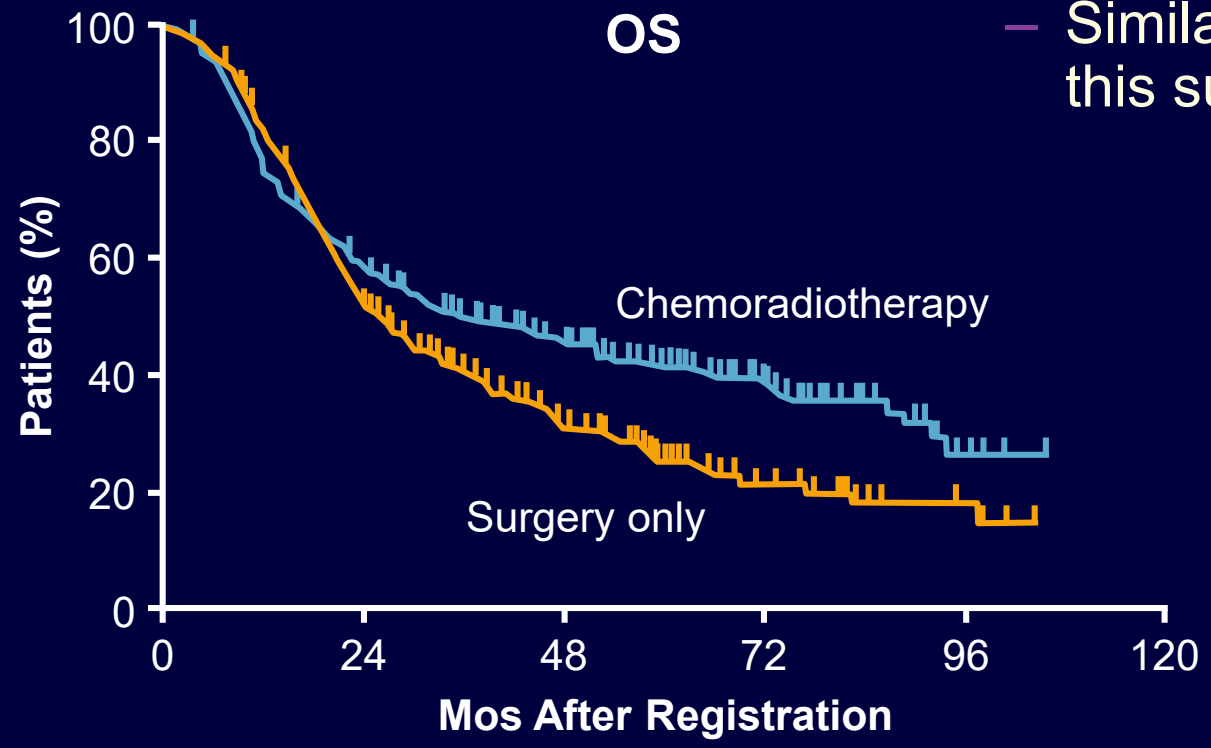
	yp T	yp N	M
Stage I	T1	N0	M0
	T2	N0	M0
	T1	N1	M0
Stage II	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage III	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

Gastric Cancer

- Surgical cure rates are high with lesions limited to the mucosa or submucosa (ie, T1)
- However, for patients with stage II or higher, 5-yr survival remains poor
- Patients increasingly presenting with T1 N0 disease, but proportion remains low
- 40% to 50% of patients will present with unresectable disease
- Overall 5-yr survival remains low
- This is a bad disease
  - After surgery, chances of long-term survival for most patients remains < 50%. Can we do better??

Gastric INT 116: Postoperative Chemoradiotherapy vs Surgery Alone

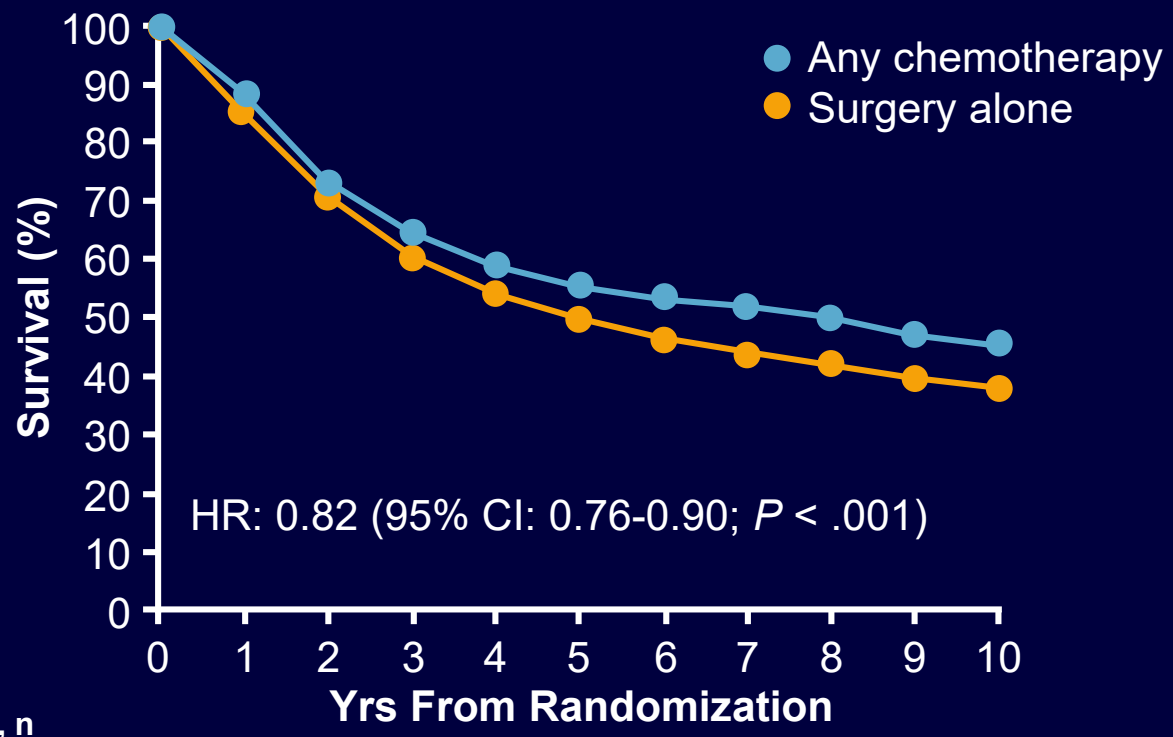
- 20% were GEJ tumors
  - Similar survival benefit in this subset



Macdonald JS, et al. N Engl J Med. 2001;345:725-730.

Meta-analysis: Surgery vs Surgery + Any Adj CT in Resectable GC

- Survival benefit for addition of chemotherapy



Pts at Risk, n											
Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery along	1857	1568	1300	1092	952	782	583	407	267	172	138

GASTRIC Group, et al. JAMA. 2010;303:1729-1737.

Chemotherapy in Resectable Gastric Cancer

- Addition of pre/peri/postsurgery chemotherapy consistently demonstrates benefit vs surgery alone

Study	Regimens	Primary Endpoint	Primary Endpoint Results	*P* Value
CLASSIC[1]	Surgery vs surgery + adjuvant capecitabine/oxaliplatin	3-yr DFS	59% vs 74%	< .0001
MAGIC[2]	Surgery vs surgery + periop ECF	5-yr OS	23% vs 36%	.009
Sakuramoto et al[3]	Surgery vs surgery + adjuvant S-1	3-yr OS	70% vs 80%	.003

1. Bang YJ, et al. Lancet. 2012;379:315-321. 2. Cunningham D, et al. N Engl J Med. 2006;355:11-20.
3. Sakuramoto S, et al. N Engl J Med. 2007;357:1810-1820.

Chemotherapy in Resectable Gastric Cancer

- However, resounding lack of progress in improving patient outcomes with any specific CT/CRT regimen vs any other chemotherapy regimen

Study	Regimens	Primary Endpoint	Primary Endpoint Results	*P* Value
CALGB 80101[1]	Postop 5-FU/LV CRT vs ECF CRT	OS	37 vs 38 mos	.80
ARTIST[2]	Postop CT vs CRT (capecitabine/cisplatin)	3-yr DFS	74% vs 78%	.086

1. Fuchs CS, et al. ASCO 2011. Abstract 4003. 2. Lee J, et al. J Clin Oncol. 2012;30:268-273.

RT yes or no?

- ●**ARTIST trial** – In one of the largest trials, the Adjuvant Chemoradiation Therapy in Stomach Cancer trial: six courses of postoperative capecitabine plus cisplatin or two courses of postoperative capecitabine plus cisplatin followed by chemoradiotherapy (45 Gy RT with concurrent capecitabine [825 mg/m^2 twice daily]) and two additional courses of capecitabine plus cisplatin .
- Aa median follow-up of 84 months, three-year DFS was not significantly better in patients who received combined modality therapy (HR 0.74), although an unplanned subset analysis did indicate a significantly better DFS with chemoradiotherapy in those with node-positive disease (three-year DFS 76 versus 72 percent, p = 0.004) Overall survival was not significantly different (HR 1.13).
- ●**Dutch CRITICS trial** –induction chemotherapy (three courses of epirubicin, cisplatin/oxaliplatin, and capecitabine) followed by surgery and randomization to postoperative chemotherapy (three cycles of the same regimen) or chemoradiotherapy (45 Gy in 25 fractions with weekly cisplatin and daily capecitabine). At a median follow-up of 61 months, there were no significant differences in five-year overall survival or progression-free survival; local recurrence rates were 15 versus 11 percent. (NOTE all patients received chemotherapy)
- ●The only trial to show a significant survival benefit for the addition of RT randomly assigned 68 patients undergoing complete resection with a D1 or D2 lymph node dissection for previously untreated gastric cancer to chemoradiotherapy (administered according to the INT 0116 trial but using intensity-modulated RT) or chemotherapy alone (five cycles of FU 425 mg/m^2 per day and LV calcium 25 mg/m^2 per day, given five days in a row once monthly). The three-year DFS rate was significantly higher in the chemoradiotherapy group (56 versus 29 percent), as was overall survival (68 versus 44 percent).
- However, the chemotherapy in this study may have been suboptimal.

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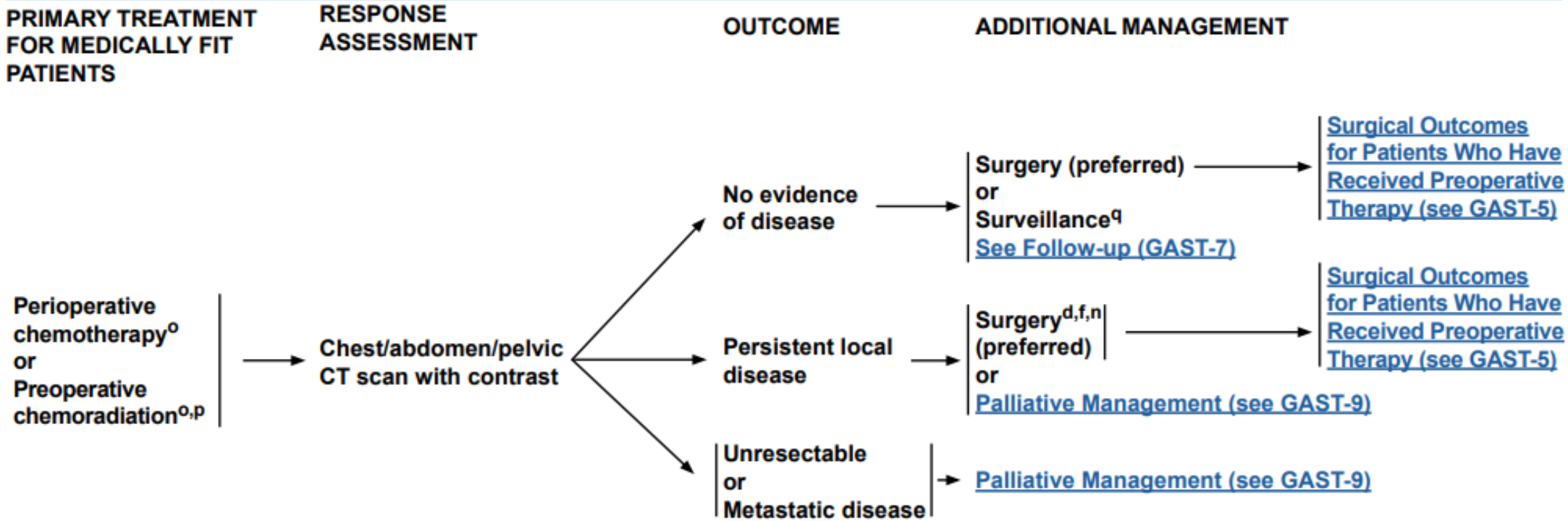
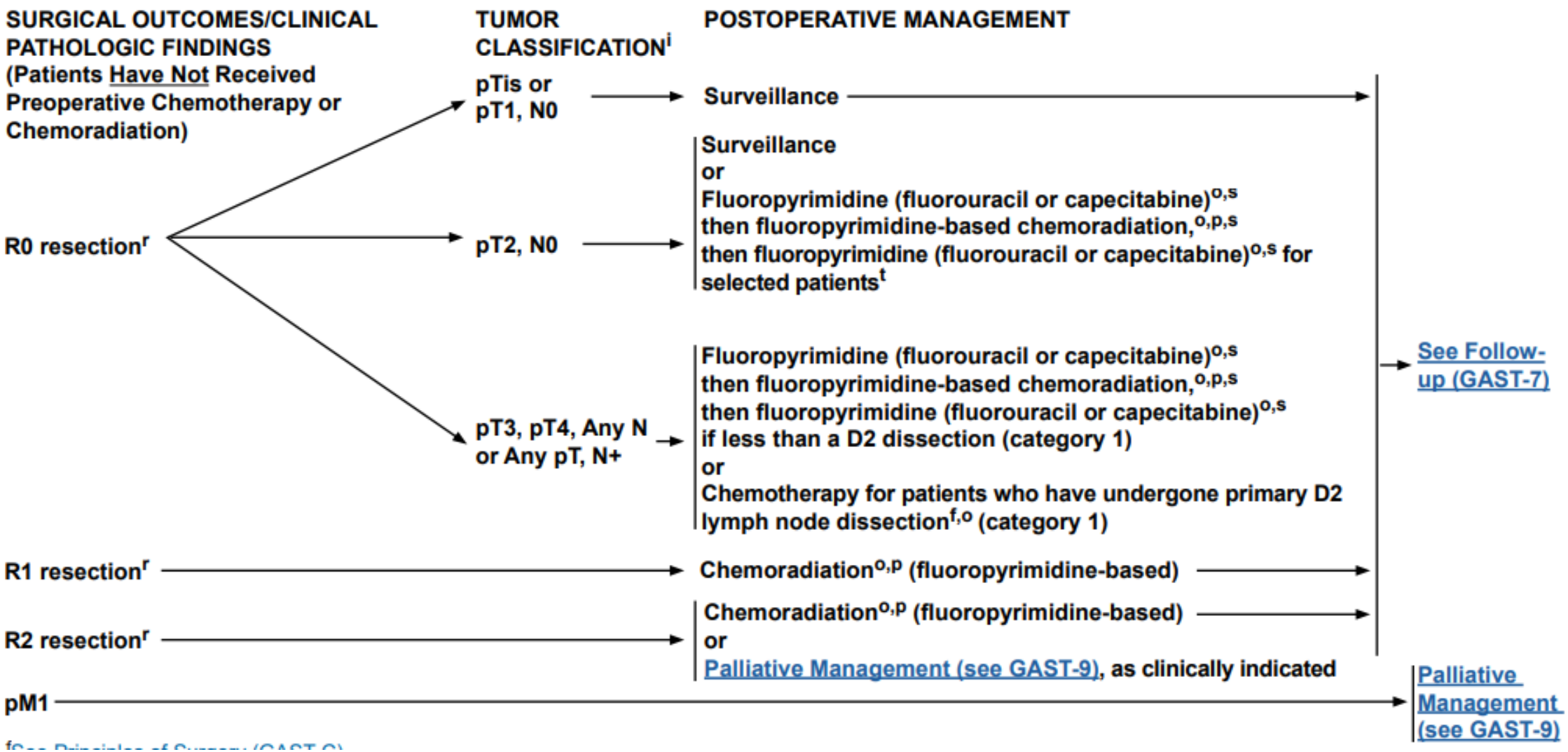
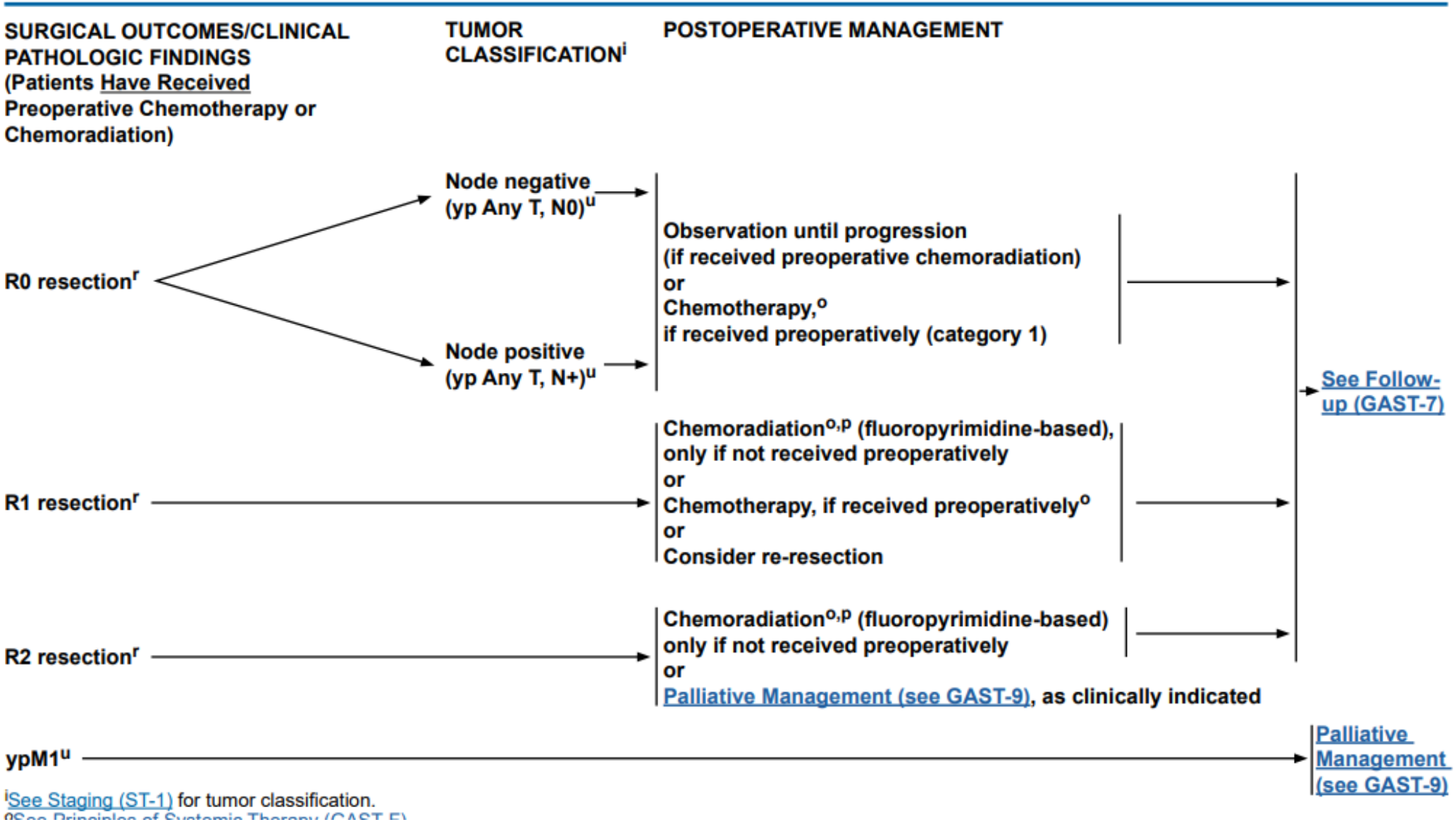




[f]See Principles of Surgery (GAST-C)

Resectable Tumors

- Tis or T1[7] tumors limited to mucosa (T1a) may be candidates for EMR (in experienced centers).[8]
- T1b-T3[9]: Adequate gastric resection to achieve negative microscopic margins (typically ≥4 cm from gross tumor).
  - Distal gastrectomy
  - Subtotal gastrectomy
  - 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 at least 15 or greater lymph nodes.[10-12]
  - Definition of D1 and D2 lymph node dissections
    - D1 dissection entails gastrectomy and the resection of both the greater and lesser omenta (which would include the lymph nodes along right and left cardiac, lesser and greater curvature, suprapyloric along the right gastric artery, and infrapyloric area);
    - D2 dissection is a D1 plus all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery.



[i] See Staging (ST-1) for tumor classification.

[o] See Principles of Systemic Therapy (GAST-F)

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy
(3 cycles preoperative and 3 cycle postoperative)

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[a]
- Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[b] (category 1)[1]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[2]

Preoperative Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[3]
- Fluorouracil[c] and oxaliplatin (category 1)[4,5]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[6,7]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[8]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[c] or capecitabine) before and after fluoropyrimidine-based chemoradiation[9]

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection (See Principles of Surgery [GAST-C])
- Capecitabine and oxaliplatin[d] (category 1)[10]

Questions?

Thank you for your attention!!