Gastric cancer epidemiology

- Gastric cancer remains one of the most common forms of cancer worldwide
- The worldwide incidence of gastric cancer has declined rapidly over the recent few decades, the reasons for which are incompletely understood. However, the rate of decline has been variable in different regions.
- The incidence of gastric cancer varies with different geographic regions. The highest incidence rates are in Eastern Asia, the Andean regions of South America, and Eastern Europe, while the lowest rates are in North America, Northern Europe, and most countries in Africa and South Eastern Asia. There is also substantial difference in the incidence among different ethnic groups within the same region.
- The is also changing histologic pattern of gastric cancer with a decline in the intestinal type compared with the diffuse type.
- There has been a steady decline in gastric cancer mortality worldwide, although the rate of decline differs by region.

Gastric ca Risk factor

- Several risk factors for gastric cancer have been identified, the most important of which are infection with H. pylori and family history
- Gastric cancer developing in patients considered to be at average risk involves an interplay of bacterial, host, and environmental factors. Dietary (nitroso compounds, high-salt diet with few vegetables) and lifestyle factors (smoking and alcohol consumption) probably account for one-third to one-half of all gastric cancers.
- Helicobacter pylori infection, especially certain genotypes (vacAs1, vacAm1, and cagA positive, remains an important risk factor. The risk is increased further in hosts who possess specific types of cytokine polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C).

Gastric ca Risk factor

- Although most gastric cancers are sporadic, aggregation within families occurs in approximately 10 percent of cases.
- Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC),
- gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC). The risk of developing gastric cancer is high in these families, but only HDGC is genetically explained (germline mutations in the CDH1 gene encoding E-cadherin in up to 50 percent of HDGC patients).
- Gastric cancer has also been described in association with certain other inherited cancer syndromes, including Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, juvenile polyposis, hereditary breast and ovarian cancer syndrome, and possibly, phosphatase and tensin homolog (PTEN) hamartoma tumor (Cowden) syndrome, but these are all fairly rare causes of gastric cancer.
- Nevertheless, guidelines for management of individuals affected by these syndromes generally recommend screening for gastric cancer.

Gastric cancer ***SCREENING STRATEGIES***

- Although screening for gastric cancer may be cost-effective in high-risk subgroups, whether screening improves clinical outcomes (ie, gastric cancer-related mortality) is unclear.
- While some observational studies suggest that the screening has contributed to detection of cancer in early stages and an overall decline in gastric cancer mortality, there are no data from large controlled trials.
- Recommendations for screening differ based on the endemic incidence of gastric cancer. Universal or population-based screening for gastric cancer has been implemented in some countries with a high incidence of gastric cancer (eg, Japan, Korea, Venezuela, and Chile).
- In areas of low gastric cancer incidence, screening for gastric cancer with upper endoscopy should be reserved for specific high-risk subgroups. Individuals at increased risk for gastric cancer include those with gastric adenomas, pernicious anemia, gastric intestinal metaplasia, familial adenomatous polyposis, and Lynch syndrome. There may be a future role for screening selected asymptomatic individuals for *H. pylori* (eg, individuals who are both first-generation immigrants from areas of high gastric cancer incidence and have a first-degree relative with gastric cancer).

Early gastric cancer (EGC)

- Early gastric cancer (EGC) is defined as adenocarcinoma limited to the gastric mucosa or submucosa, regardless of involvement of the regional lymph nodes (T1, any N).
- Patients may be asymptomatic or they may present with dyspepsia, mild epigastric pain, nausea, or anorexia
- White light endoscopy in combination with an image-enhanced endoscopic technique such as magnification chromoendoscopy or narrow band imaging is performed with a gastric mucosal biopsy protocol to make the diagnosis of EGC.
- Staging of EGC may be accomplished using a combination of endoscopic resection with endoscopic submucosal dissection (ESD) and endoscopic ultrasound (EUS).
- Factors associated with lymph node metastases include larger tumor size, ulceration, diffuse (undifferentiated) or mixed (intestinal/undifferentiated) type histology, depth of invasion, and submucosal or lymphovascular invasion.

CLINICAL FEATURES

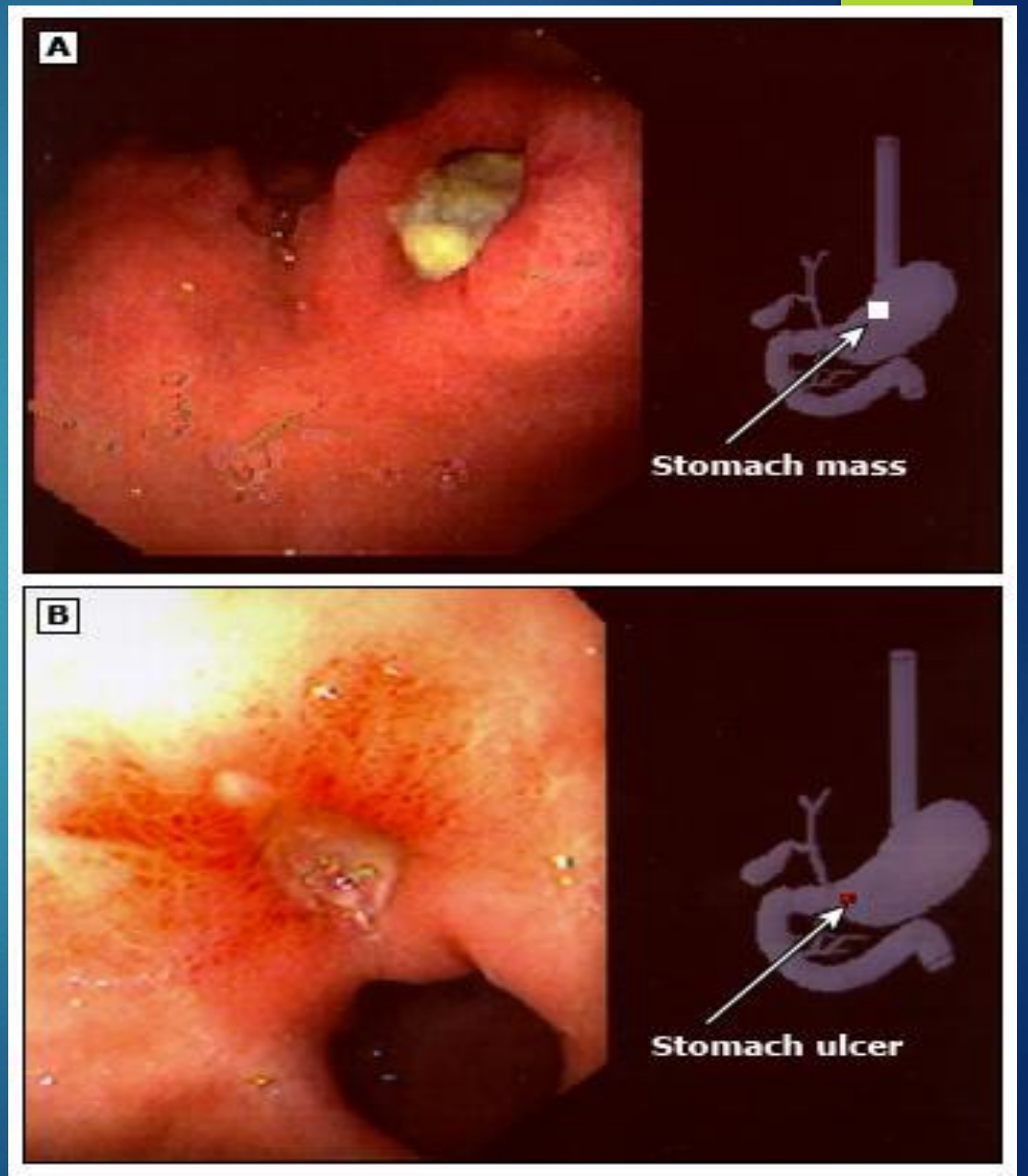
- Weight loss.
- abdominal pain tends to be epigastric, vague, and mild early in the disease but more severe and constant as the disease progresses.
- Dysphagia
- or early satiety.
- Occult gastrointestinal bleeding or overt bleeding
- Patients may also present with signs or symptoms of distant metastatic disease.
- In patients with lymphatic spread
- Peritoneal spread can present with an enlarged ovary (Krukenberg tumor .
- Ascites can also be the first indication of peritoneal carcinomatosis.
- A palpable liver mass can indicate metastases.
- Jaundice or clinical evidence of liver failure
- More rarely, **Paraneoplastic manifestations**

Gastric cancer Clinical

- Most patients with gastric cancer in the United States are symptomatic and already have advanced, incurable disease at the time of presentation.
- Despite advances in medicine, approximately 50 percent have disease that extends beyond locoregional confines at the time of presentation, and only one-half of those who appear to have locoregional tumor involvement can resection. undergo potentially curative
- Surgically curable early gastric cancers are usually asymptomatic and are only infrequently detected outside of screening programs.
- Screening is not widely performed, except in countries that have a very high incidence, such as Japan, Korea, Venezuela, and Chile.

DIAGNOSIS

- Endoscopic appearance
- Biopsy technique



Pathology

- Gastric adenocarcinomas represent a clinically, biologically, genetically, and pathologically heterogeneous group of malignant epithelial tumors resulting from various environmental and genetic causes

Pathology

- *Helicobacter pylori* infection plays an important role in gastric carcinogenesis. Gland-forming adenocarcinomas (ie, those of the tubular, papillary, mucinous, and mixed types) are causally related to *H. pylori* and characterized by a defined series of preneoplastic stages, which are not seen with poorly cohesive-type gastric cancers. Importantly, only a small minority of individuals infected with *H. pylori* develops gastric cancer, and it is thought that modulation of the effects of chronic infection by genetic susceptibility, environmental factors, and *H. pylori*bacterial strain differences all influence the evolution into a neoplastic or nonneoplastic process

Pathology

- Familial aggregation of gastric cancer occurs in around 10 to 20 percent of patients with gastric cancer, fewer than 5 percent of cases result from an inherited predisposition to cancer. One of these syndromes, hereditary diffuse gastric cancer (HDGC), is an autosomal dominant cancer susceptibility syndrome characterized by signet ring cell (diffuse) gastric cancer and lobular breast cancer; it is caused in most cases by a germline defect in the *CDH1* (E-cadherin 1) gene.

Pathology

- Gastric adenocarcinomas have historically been divided into two distinct histomorphologic subtypes
- Intestinal (ie, gland-forming)
- Diffuse (composed of discohesive cells), which have a distinct morphologic appearance, epidemiology, pathogenesis, and genetic profile.
- (WHO) classification of tumors of the digestive tract recognizes several important histologic types of malignant epithelial tumors, which include gland-forming types (tubular, papillary mucinous, mixed) and poorly cohesive types (including the signet ring phenotype)

Pathology

- The morphologic differences are attributable to different genetic and epigenetic alterations, some related to intercellular adhesion molecules, which are preserved in intestinal-type tumors and defective in diffuse carcinomas.
- A lack of adhesion molecules in poorly cohesive carcinomas allows the individual tumor cells to grow and invade neighboring structures without the formation of tubules or glands. Diffuse-type cancers are highly metastatic and characterized by rapid disease progression and a poor prognosis. The main carcinogenic event is loss of expression of *CDH1*, a key cell surface protein for establishing intercellular connections. Biallelic inactivation of the gene encoding E-cadherin (*CDH1*) can occur through germline or somatic mutation, allelic imbalance events (eg, loss of heterozygosity), or epigenetic silencing of gene transcription.
- In direct contrast, the pathogenesis of intestinal-type gastric cancers is less well defined. However, it appears to follow a multistep progression that is usually initiated by *H. pylori* infection.

Pathology

- Although the molecular characterization of gastric cancers as described above has identified gene signatures that are prognostically relevant, they are still inadequate to direct molecularly targeted therapy, with few exceptions.
- To date, there are only three therapeutically relevant, routinely tested molecular biomarkers in gastric carcinoma:
- overexpression of human epidermal growth factor 2 (HER2 [ERBB2]), which permits the selection of patients with advanced disease who might benefit from trastuzumab,
- overexpression of programmed cell death ligand 1 (PD-L1)/deficient mismatch repair (dMMR),
- high levels of tumor mutational burden, all of which may identify patients with advanced disease with the potential to benefit from immune checkpoint inhibitor immunotherapy.

Staging and the staging workup

- Tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal rather than gastric cancers, while EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers, as are all cardia cancers not involving the EGJ.
- CT scan of the chest, abdomen, and pelvis is indicated in all patients to look for metastatic disease (M stage); it should not be relied on for assessing tumor depth (T stage), lymph node involvement (N stage), or the definitive presence of peritoneal metastases. Suspicious visceral lesions, omental masses, or retroperitoneal lymph nodes require biopsy confirmation. Paracentesis should be performed when ascites is detected, and the fluid should be sent for cytology and standard chemical analysis.
- Endoscopic ultrasound (EUS) is better than CT at assessing T stage and perhaps N stage, particularly if fine-needle aspiration (FNA) is also performed. An accurate assessment of T and N stage is important for treatment selection, particularly when selecting patients for neoadjuvant therapy rather than initial surgery.

Staging and the staging workup

- The role of 18-fluorodeoxyglucose (FDG)-PET in the staging evaluation of gastric cancer continues to evolve. Diffuse type tumors are frequently not FDG avid, and for patients with signet ring cell histology, the peritoneum is the most common site of metastatic disease, and this is better assessed by laparoscopy with washings. In general, we reserve PET-CT for those patients with non-diffuse-type tumors who have equivocal findings on CT imaging or in those with clinical suspicion of possible metastatic disease with otherwise negative imaging. As with CT, suspicious lesions warrant biopsy.
- Serum tumor markers (including carcinoembryonic antigen [CEA] and the glycoprotein cancer antigen 125 [CA 125]) are of limited utility, and we do not routinely assay for them, unless a patient is undergoing neoadjuvant therapy on trial.
- We advise preoperative staging laparoscopy for any medically fit patient who appears to have more than a T1a lesion on EUS, no histologic confirmation of stage IV disease, and would not otherwise require palliative gastrectomy.
- For certain patients, such as those with an obstructing or significantly bleeding distal gastric cancer with no evidence of metastases by CT scan, it may be reasonable to directly proceed to surgery without further testing

Genetic issues

- Gastric cancers are sporadic, though familial aggregation occurs in approximately 10 percent of cases. Truly hereditary (familial) gastric cancer accounts for 1 to 3 percent of the global burden of gastric cancer and comprises at least three major syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC).
- Only HDGC has a defined genetic basis
- Referral for genetic counseling and testing for cadherin *1 (CDH1*) mutations and large rearrangements is recommended for individuals with diffuse gastric cancer who meet one or more of the following criteria.
- Family history of two gastric cancers, at any age, with at least one confirmed diffuse gastric cancer.
- Diffuse gastric cancer diagnosed at age <40 years, regardless of family history.
- Personal or family history of diffuse gastric cancer and lobular breast cancer, with at least one diagnosed at <50 years of age.

Stomach cancer TNM staging AJCC UICC 8th edition

- 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¶Δ
- T4 Tumor invades the serosa (visceral peritoneum) or adjacent structures¶Δ
- T4a Tumor invades the serosa (visceral peritoneum)
- T4b Tumor invades adjacent structures/organs

Stomach cancer TNM staging AJCC UICC 8th edition

- Regional lymph nodes (N)
- N category N criteria
- NX Regional lymph node(s) cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastases in 1 or 2 regional lymph nodes
- N2 Metastases in 3 to 6 regional lymph nodes
- N3 Metastases in 7 or more regional lymph nodes
- N3a Metastases in 7 to 15 regional lymph nodes
- N3b Metastases in 16 or more regional lymph nodes
- Distant metastasis (M)
- M category M criteria
- M0 No distant metastasis
- M1 Distant metastasis

Prognostic stage groups

- Clinical (cTNM)
- When T is... And N is... And M is... Then the stage group is...
- Tis N0 M0 0
- T1 N0 M0 I
- T2 N0 M0 I
- T1 N1, N2, or N3 M0 IIA
- T2 N1, N2, or N3 M0 IIA
- T3 N0 M0 IIB
- T4a N0 M0 IIB
- T3 N1, N2, or N3 M0 III
- T4a N1, N2, or N3 M0 III
- T4b Any N M0 IVA
- Any T Any N M1 IVB

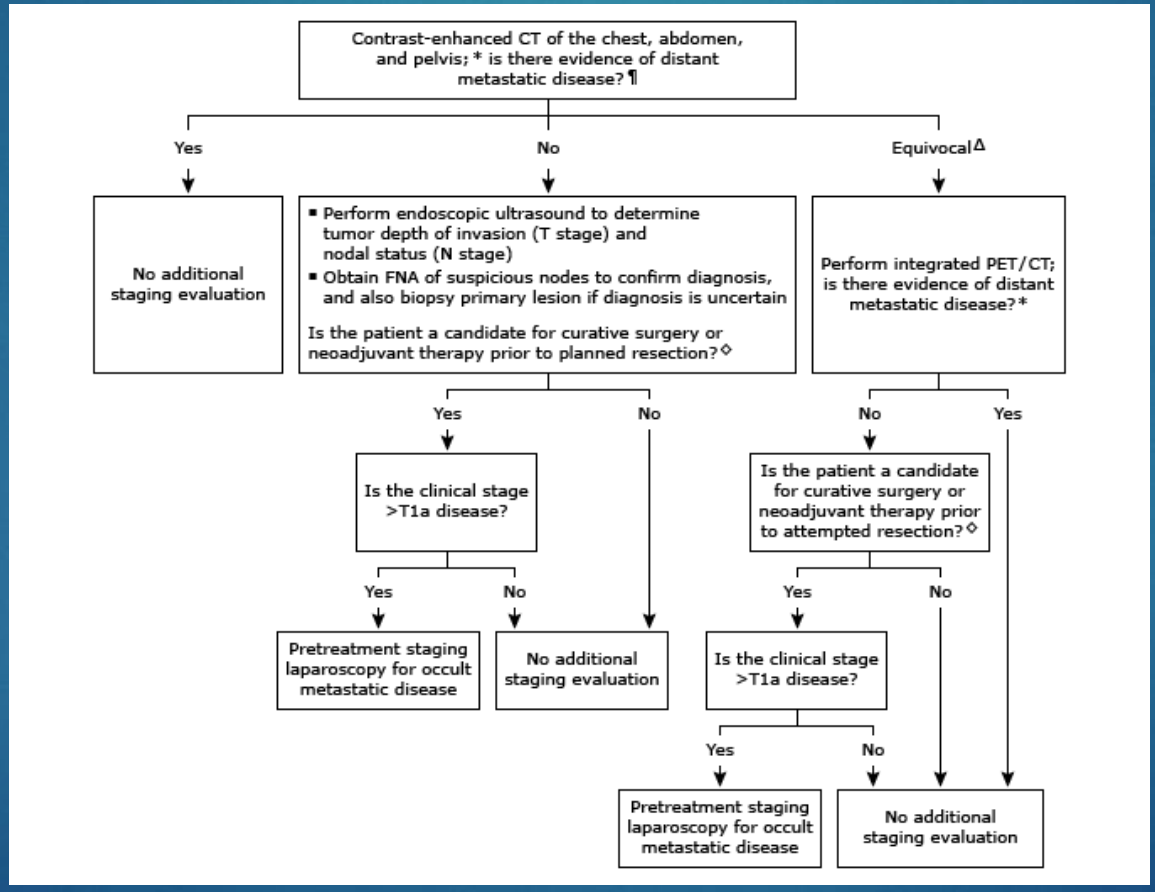
pTNM

Pathological (pTNM)			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T3	N0	M0	IIA
T1	N3a	M0	IIB
T2	N2	M0	IIB
T3	N1	M0	IIB
T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC

Post-neoadjuvant therapy (ypTNM)

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
Any T	Any N	M1	IV

Suggested approach to staging evaluation in patients with gastric cancer



Adjuvant & Neoadjuvant

- For patients with potentially resectable clinical stage T2N0 or higher noncardia gastric cancer, we recommend combined modality therapy over surgery alone.
- The optimal way to integrate combined modality therapy has not been definitively established.
- Multidisciplinary preoperative evaluation is strongly encouraged, as is participation in clinical trials (when possible).
- If protocol treatment is not available or is declined, the following represents our general approach to therapy

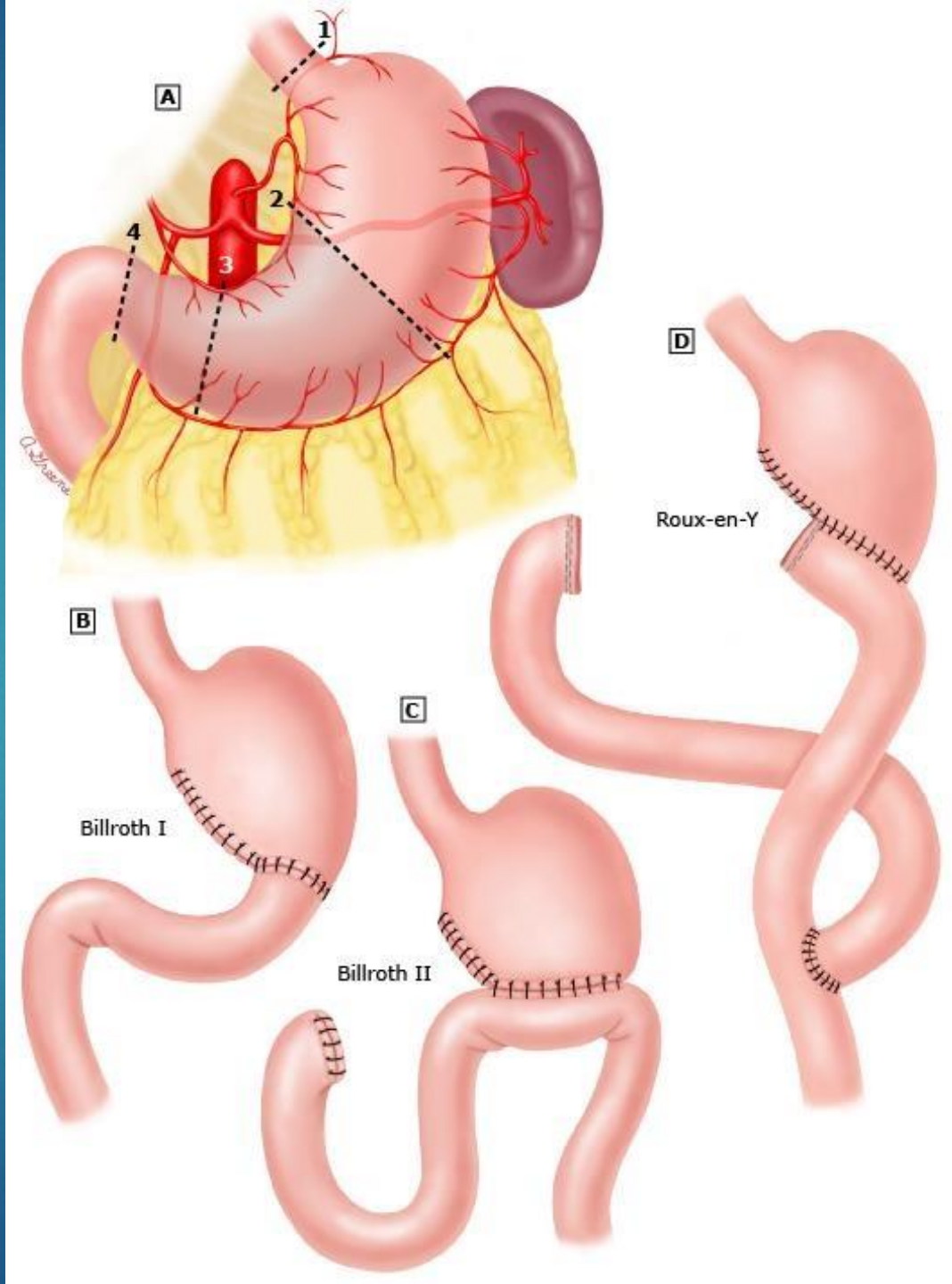
Patients not yet resected

- For most patients with potentially resectable (clinical stage T2 or higher gastric cancer, we suggest neoadjuvant chemotherapy over initial surgery followed by adjuvant therapy .
- However, upfront surgery followed by adjuvant therapy remains an accepted approach, especially for patients with distal, clinically staged, nonbulky T2 tumors with no visible perigastric nodes.
- For most patients with noncardia gastric cancer, we suggest not pursuing preoperative chemoradiotherapy as an alternative to chemotherapy .
- For patients with an excellent performance status without significant comorbidities and able to tolerate intensive chemotherapy, we suggest docetaxel, oxaliplatin, leucovorin(LV), and short-term infusional fluorouracilFU; FLOT, rather than an epirubicin-containing regimen (such as epirubicin, cisplatin, and infusional FU [ECF])
- Other acceptable alternatives, especially for patients with a lesser performance status or extensive comorbidity, include oxaliplatin plus infusional FU and LV (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) .

SURGICALTREATMENST

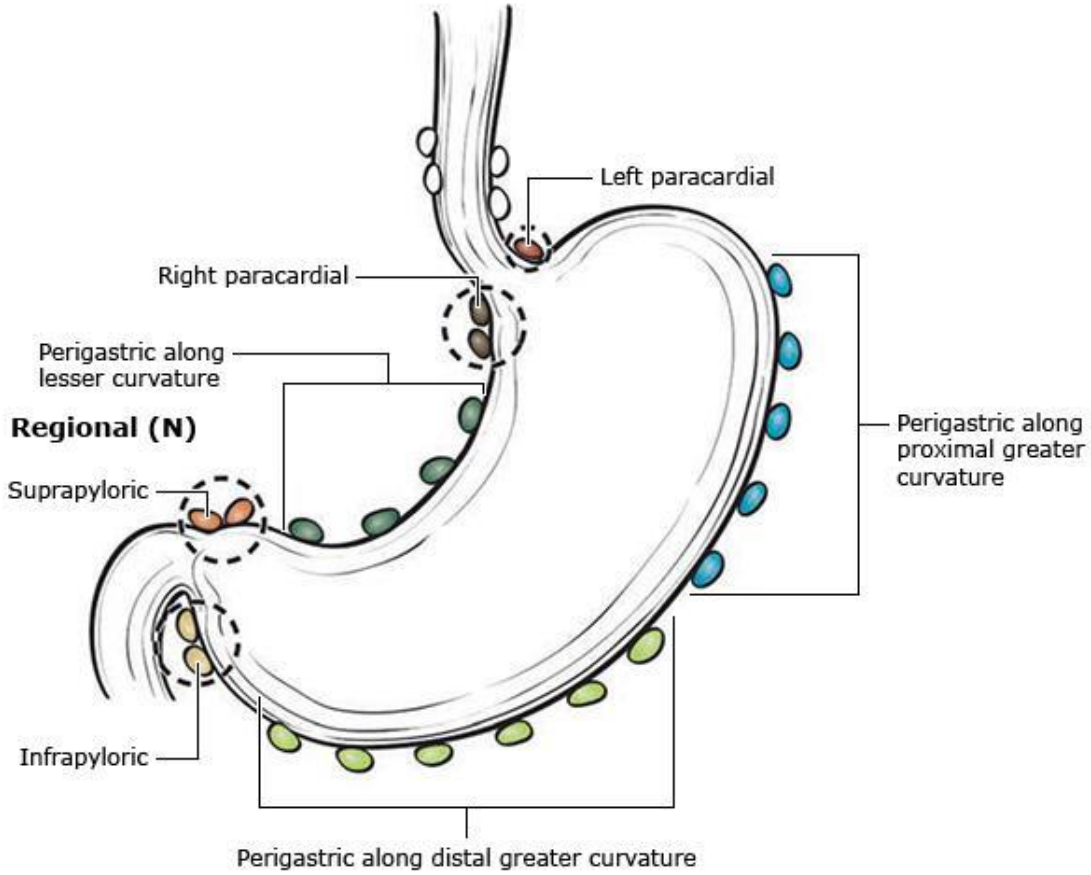
- Complete surgical eradication of a gastric tumor with resection of adjacent lymph nodes represents the best chance for long-term survival.
- Unless there is unequivocal evidence of disseminated disease, there is major vascular invasion, or there are other contraindications to surgery, either abdominal exploration (preferably with an initial laparoscopic approach) with curative-intent resection should be undertaken or a neoadjuvant approach should be considered.
- Total gastrectomy is usually performed for lesions in the proximal (upper third) stomach, while distal gastrectomy (with resection of adjacent lymph nodes) appears to be sufficient for lesions in the distal (lower two-thirds) stomach. Patients with large midgastric lesions or infiltrative disease (eg, linitis plastica) may require total gastrectomy.
- Tumors of the proximal stomach that do not invade the esophagogastric junction (EGJ) can be approached with either total gastrectomy or proximal subtotal gastrectomy. Total gastrectomy is preferred by most surgeons.

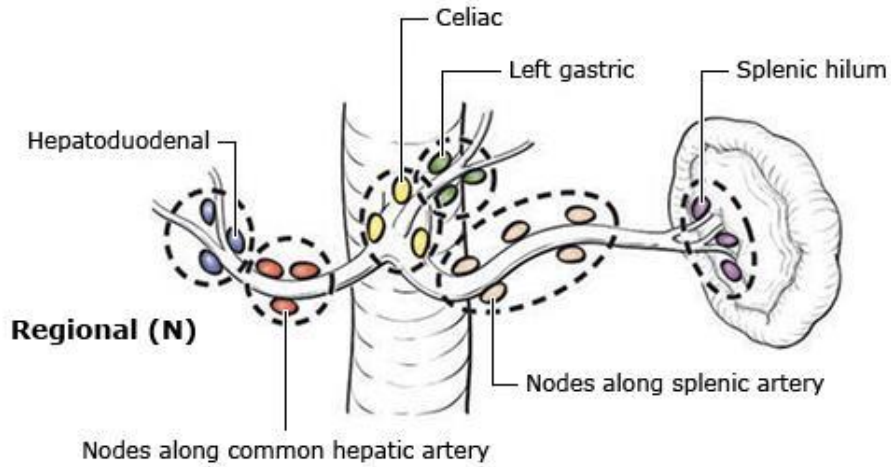
Billroth 1&2



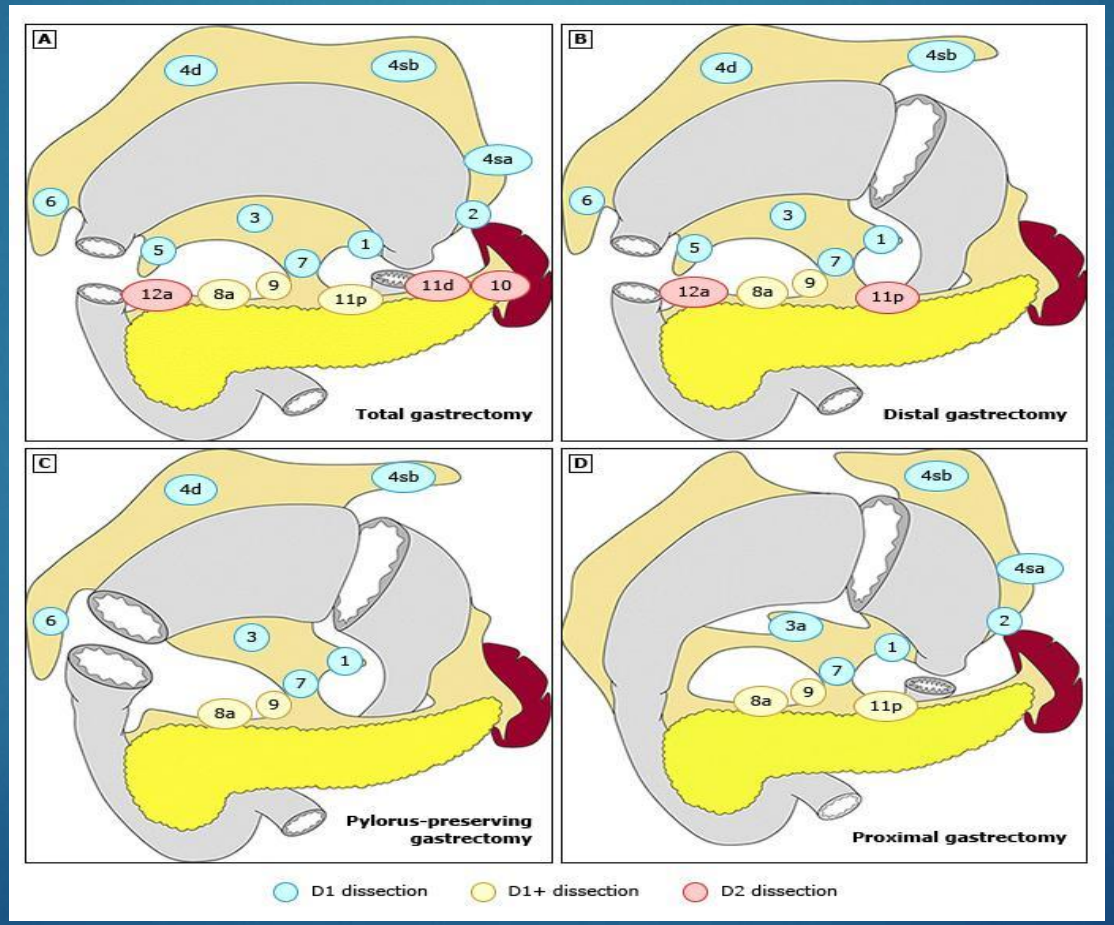
SURGICAL TREATMENST

- The optimal extent of lymphadenectomy is debated. While several randomized trials have failed to show an overall survival benefit from a D2 compared with a D1 resection, excess morbidity and mortality were clearly associated with the use of splenectomy and distal pancreatectomy to achieve complete node dissection.
- The most recent report of the Dutch trial and a 2015 Cochrane meta-analysis suggest that cancer-specific mortality rates are significantly lower in patients who undergo a D2 rather than a D1 lymphadenectomy.


Left paracardial
Right paracardial
Perigastric along lesser curvature
Regional (N)
Suprapyloric
Perigastric along proximal greater curvature
Infrapyloric
Perigastric along distal greater curvature


Celiac
Left gastric
Splenic hilum
Hepatoduodenal
Regional (N)
Nodes along splenic artery
Nodes along common hepatic artery

The numbers correspond to the lymph node station as defined in the Japanese Classification of Gastric Carcinoma.[1]
(A) The extent of lymphadenectomy after total gastrectomy.
(B) The extent of lymphadenectomy after distal gastrectomy.
(C) The extent of lymphadenectomy after pylorus-preserving gastrectomy.
(D) The extent of lymphadenectomy after proximal gastrectomy.



SURGICALTREATMENST

- However, more extensive nodal dissection should only be performed in selected centers where surgeons have demonstrated acceptably low operative morbidity and mortality rates. Perioperative mortality rates under 2 percent should be expected at centers with higher patient volume.
- By contrast, there is no evidence that a D3 resection (paraaortic lymphadenectomy) confers a survival benefit over a D2 dissection, and it is associated with greater perioperative mortality. We recommend that a D3 dissection **not** be considered for surgical treatment of gastric cancer
- While open gastrectomy remains the standard surgical treatment for gastric cancer worldwide, laparoscopic gastrectomy is performed with increasing frequency in high-volume centers with the requisite expertise (ie, primarily Asian countries). Laparoscopic gastric cancer surgery is most commonly performed for early gastric cancers that are not amenable to endoscopic resection. Laparoscopic gastrectomy for more advanced gastric cancers has been shown to be feasible in Asia, but further validation as to its long-term outcomes compared with open surgery is needed in Western populations before it can be considered a standard approach.

SURGICALTREATMENT

- Data from several uncontrolled series suggest the **unresectable** disease may respond to chemotherapy or chemoradiotherapy sufficiently that they are able to undergo potentially curative surgeryat some patients with initially locally advanced . However, this approach should ideally be considered in the context of a clinical trial.
- Surgical intervention may provide effective palliation of symptoms such as pain, nausea, bleeding, or obstruction. The criteria for selection of patients who may benefit from palliative gastrectomy as compared with other palliative procedures (including radiation therapy, endoscopic intervention, and surgical bypass) are not firmly established.
- Hepatic metastasectomy for isolated lesions is not associated with long-term survival. Pulmonary metastasectomy for isolated lesions can potentially result in long-term survival in rare, highly selected patients.
- Cytoreductive surgery and heated intraperitoneal chemotherapy for patients with gastric cancer and peritoneal metastases or positive peritoneal cytology in the absence of overt metastatic disease should only be considered in the context of a clinical trial.
- There are no randomized trials to inform the optimal frequency or components of post-treatment surveillance.

Palliative treatments for advanced gastric cancer

- The majority of patients with gastric cancer will require palliative treatment at some point in the course of their disease.
- Cytotoxic chemotherapies the most effective treatment modality for metastatic disease but may be inadequate for palliation of local symptoms, such as nausea, pain, obstruction, perforation, or bleeding from a locally advanced or locally recurrent primary tumor. Many patients require multidisciplinary management using endoscopic, surgical, radiotherapeutic, or other approaches.
- For patients with obstructive symptoms, we recommend external beam radiation therapy (RT) or endoscopic placement of a stent rather than palliative surgery For most patients, we prefer RT, particularly in instances where there needs to be control of tumor bleeding, because it provides longer term tumor control. For more immediate relief in a patient where chemotherapy cannot be given concurrently with RT, we prefer placement of an endoscopic stent over RT. Besides a shorter duration of tumor control, stents also can cause increased heartburn and require dietary modifications to avoid stent displacement, which can be difficult for patients.
- RT can control pain, bleeding, and obstruction in patients with localized but unresectable gastric cancer, but responses may be delayed. Furthermore, while control of bleeding may be possible with low RT doses that are not associated with significant side effects, doses above 40 Gy are often required for palliation of obstruction.

Palliative treatments for advanced gastric cancer

- Another option to palliate dysphagia due to obstruction in patients with esophageal or gastric cardia tumors is endoscopic laser ablation.
- Given the lack of a survival benefit and the worse chemotherapy-related toxicity, we recommend against palliative gastrectomy for most patients with advanced gastric cancer who are receiving systemic therapy. Palliative resection should be reserved for extreme, highly symptomatic cases where less invasive methods cannot be used.
- In current practice, palliative gastrojejunostomy for patients with metastatic gastric cancer is reserved for cases where less invasive methods, such as palliative RT with or without chemotherapy, and endoscopic procedures, such as ablation, stenting, or J-tube placement to establish a route for enteral nutrition, cannot be used.