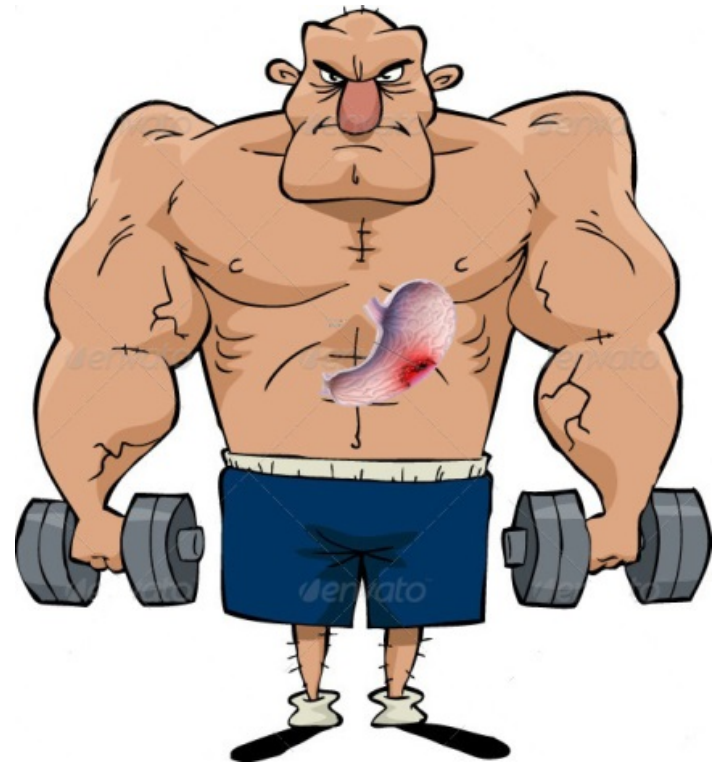


GASTRIC CANCER

DR AMIR ASHRAFI



Epidemiology

Aetiologic factors

Classification

Clinical features

Investigations

Staging

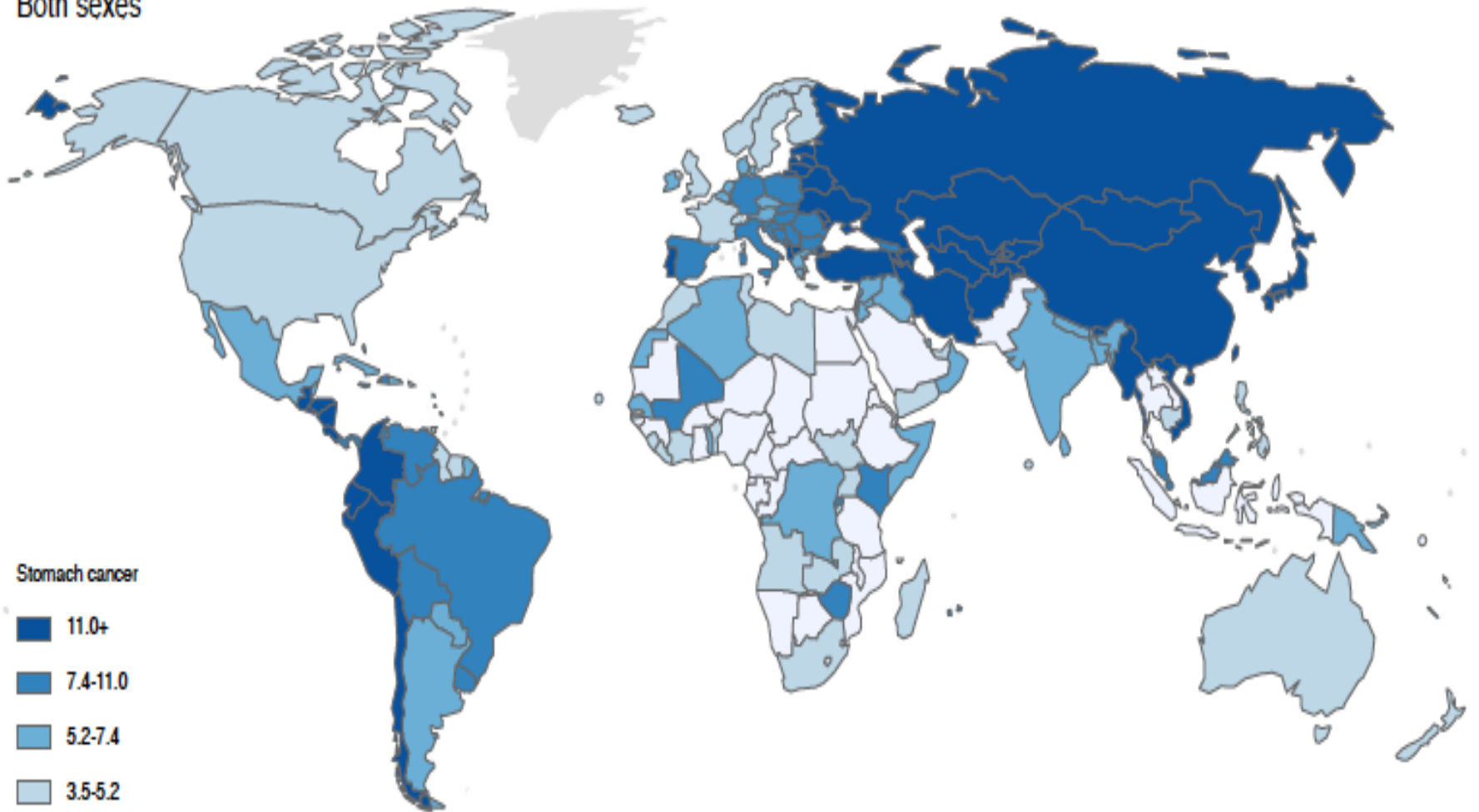
Treatment

EPIDEMIOLOGY AND FACTS

- ✓ Worldwide, gastric cancer is the fourth most common cancer and the second leading cause of cancer death.
- ✓ It is especially prevalent in East Asia and South America and has been increasing in developing countries, which now have almost two thirds of all distal gastric cancer cases.
- ✓ Among developed countries, Japan and Korea have the highest rates of the disease. Gastric cancer is the most common cancer in Japan but mortality dropped 50% with screening in 1970s.
- ✓ In 2010, there were 1,999 new cases of stomach cancer in Australia (1,314 new cases in men and 685 new cases in women), accounting for 1.7 per cent of all new cancers
- ✓ Stomach cancer is more common in men:
In 2010, 11.9 cases per 100,000 men, compared with 5.2 cases per 100,000 women.
- ✓ It is a disease of older individuals, with peak incidence in the seventh decade of life.
- ✓ In 2011, there were 1,140 deaths from stomach cancer (715 men and 425 women), accounting for 2.6 per cent of all cancer deaths in Australia.
- ✓ Between the periods 1982–1987 and 2006–2010, five-year relative survival increased in Australia from 17.2 % to 26.7%

Incidence ASR

Both sexes



Stomach cancer

- 11.0+
- 7.4-11.0
- 5.2-7.4
- 3.5-5.2
- <3.5
- No Data

International Agency for Research on Cancer



WHAT CAUSES GASTRIC CANCER?

FACTORS INCREASING OR DECREASING GASTRIC CA

Increase risk

Family history

Diet (high in nitrates, salt, fat)

Familial polyposis

Gastric adenomas

Hereditary nonpolyposis colorectal cancer

Helicobacter pylori infection

Atrophic gastritis, intestinal metaplasia, dysplasia

Previous gastrectomy or gastrojejunostomy (>10 y ago)

Tobacco use

Ménétrier's disease

Blood Group A

Decrease risk

Aspirin

Diet (high fresh fruit and vegetable intake)

Vitamin C

GASTRIC CANCER GENETIC MUTATIONS

Deletion or suppression of *p53*

Overexpression of COX-2

CDH1

BOX 49-3 Factors Associated With Increased Risk for Developing Stomach Cancer

Nutritional

Low fat or protein consumption
Salted meat or fish
High nitrate consumption
High complex carbohydrate consumption

Environmental

Poor food preparation (smoked, salted)
Lack of refrigeration
Poor drinking water (e.g., contaminated well water)
Smoking

Social

Low social class

Medical

Prior gastric surgery
H. pylori infection
Gastric atrophy and gastritis
Adenomatous polyps

Other

Male gender



The presence of the cytotoxin-associated gene A (*cagA*) is associated with increased virulence and risk of gastric cancer.

Countries with high levels of gastric cancer, such as Japan, have a much higher rate of *cagA*-positive *H. pylori* infection

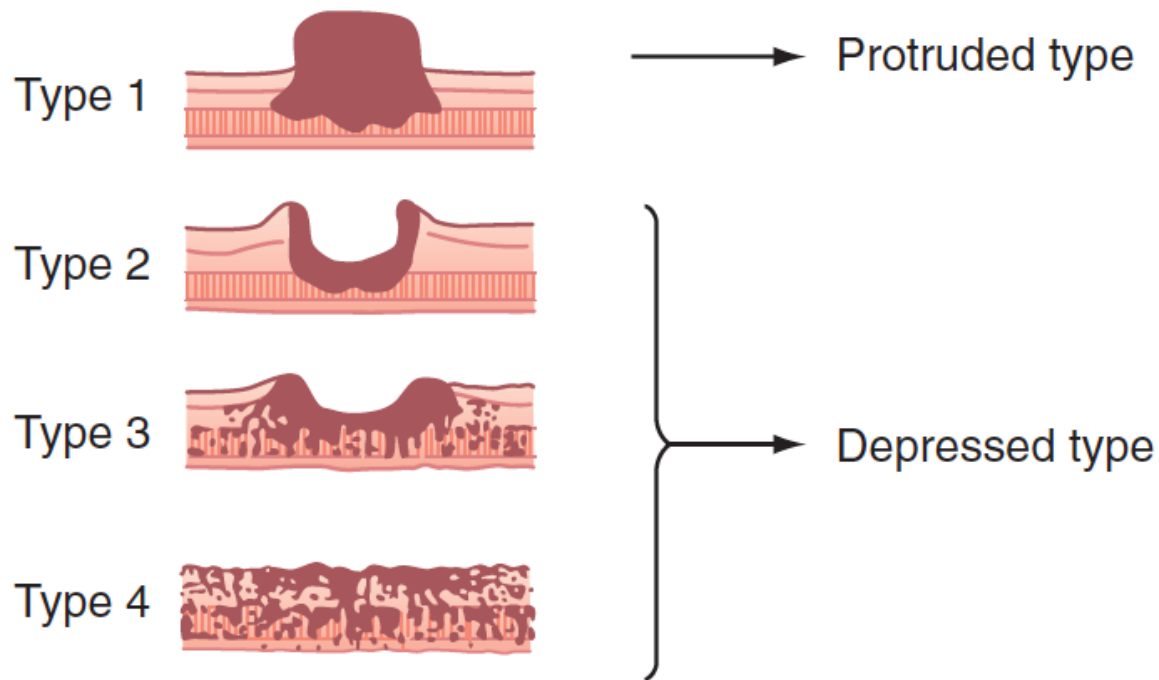
There is likely synergism between diet and *H. pylori* infection, with the bacteria increasing carcinogen production and inhibiting its removal. *H. pylori* has been shown to promote the growth of the bacteria that generate the carcinogenic N-nitroso compounds.

Patients on long term PPI can colonize *H. pylori* which leads to corpus gastritis and 1/3 will get atrophic gastritis which is a risk factor for gastric Ca. So they should be monitored for and have eradication of *H. Pylori* (Still no evidence)

CLASSIFICATION

BORRMANN CLASSIFICATION SYSTEM (1926)

Borrmann's classification



LAUREN CLASSIFICATION SYSTEM (1967)

- 1. *Intestinal:*** resembles colon cancer, can be polypoid or ulcerated, occurs usually in the distal stomach and has a prolonged pre-cancerous phase.
- 2. *Difusse:*** Extends widely with no distinct margins and the glandular structure is rarely present. Patients tend to be younger and have a worst prognosis.

LAUREN CLASSIFICATION SYSTEM (1967)

INTESTINAL	DIFFUSE
Environmental	Familial
Gastric atrophy, intestinal metaplasia	Blood type A
Men > women	Women > men
Increasing incidence with age	Younger age group
Gland formation	Poorly differentiated, signet ring cells
Hematogenous spread	Transmural, lymphatic spread
Microsatellite instability	Decreased E-cadherin
<i>APC</i> gene mutations	
<i>p53</i> , <i>p16</i> inactivation	<i>p53</i> , <i>p16</i> inactivation

WHO SYSTEM

Adenocarcinoma (papillary, tubular, mucinous, and signet ring)

Adenosquamous cell carcinoma

Squamous cell carcinoma

Undifferentiated carcinoma

Unclassified carcinoma

DIAGNOSIS

approximately 50 percent have disease that extends beyond locoregional confines, and only one-half of those who appear to have locoregional tumor involvement can undergo a potentially curative resection

Surgically curable early gastric cancers are usually asymptomatic and only infrequently detected outside the realm of a screening program.

Countries with screening program: Japan, Venezuela, and Chile.

NON-SPECIFIC CLINICAL FEATURES
(FOUND AT AN EARLY STAGE)

INDIGESTION, HEARTBURN, BLOATING OF THE STOMACH AFTER MEAL OR VAGUE EPIGASTRIC DISCOMFORT



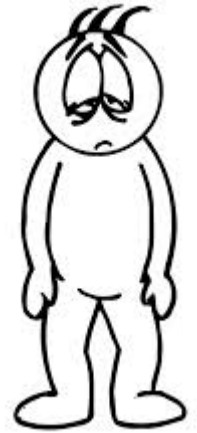
**CONSTANT, NON-RADIATING UPPER
ABDOMINAL PAIN (USUALLY NOT SEVERE)
WHICH IS NOT RELATED TO FOOD INTAKE**



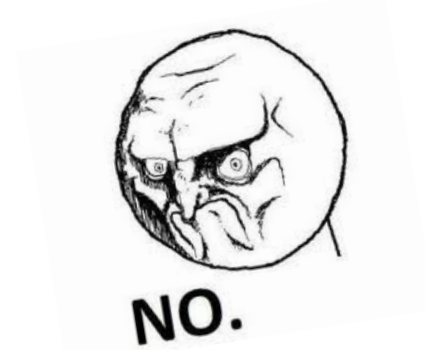
WEIGHT LOSS



WEAKNESS AND FATIGUE



LOSS OF APPETITE



EARLY SATIETY



CLINICAL FEATURES

Presenting symptoms of gastric cancer in 18,363 patients

Symptom	Percent
Weight loss	62
Abdominal pain	52
Nausea	34
Dysphagia	26
Melena	20
Early satiety	18
Ulcer-type pain	17

Adapted from Wanebo, HJ, Kennedy, BJ, Chmiel, J, et al, Ann Surg 1993; 218:583.

Graphic 67702 Version 1.0

Occult GI bleeding with or without IDA is common

overt bleeding (melena or hematemesis) is seen in less than 20 percent of cases.

***Pseudoachalasia syndrome:* may occur as the result of involvement of Auerbach's plexus due to local extension or to malignant obstruction near the gastroesophageal junction.**

So in older patients coming with Achalasia think of Gastric Cancer

25 % of patients have a history of gastric ulcer. All gastric ulcers should be followed to complete healing, and those that do not heal should undergo resection

METASTATIC DISTRIBUTION

Common sites:

liver

Peritoneal surfaces

Non-regional or distant lymph nodes.

Less commonly:

ovaries

central nervous system

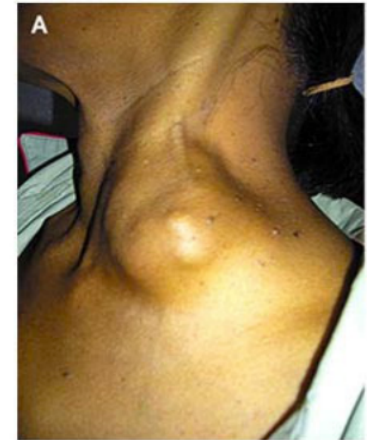
bone

pulmonary

soft tissue

LYMPHATIC SPREAD

- **left supraclavicular adenopathy**
(a Virchow's node or signal node)



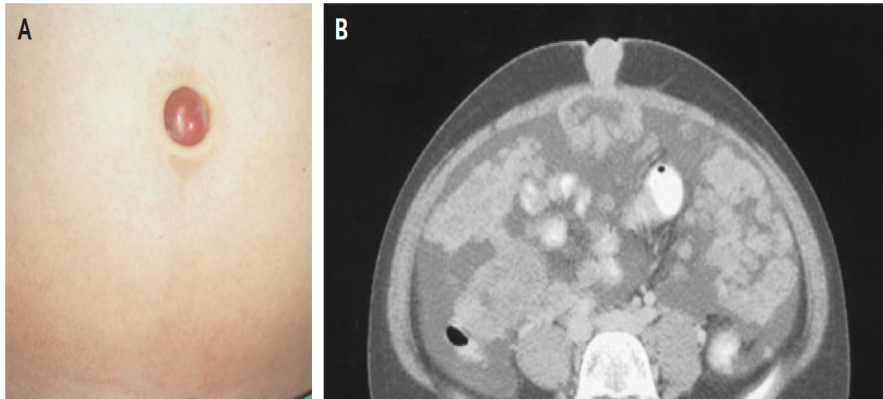
- **Left Anterior Axillary node (Irish node)**





Rudolph Virchow

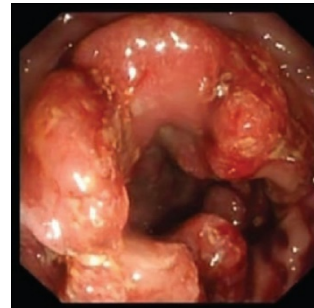
- **Periumbilical nodule (Sister Mary Joseph's node)**



PERITONEAL SPREAD

can present with :

- enlarged ovary (Krukenberg's tumor)
- mass in the cul-de-sac on rectal examination (Blumer's shelf)
- Ascites can also be the first indication of
- peritoneal carcinomatosis.



Liver:

-A palpable liver mass can indicate metastases, but metastatic disease to the liver is often multifocal or diffuse.

-Liver involvement is often, but not always, associated with an elevation in **ALP.**

- Jaundice or clinical evidence of liver failure is seen in the preterminal stages of metastatic disease.

PARANEOPLASTIC MANIFESTATIONS

sudden appearance of diffuse

seborrheic keratoses
(sign of Leser-Trelat)



Acnathosis Nigricans

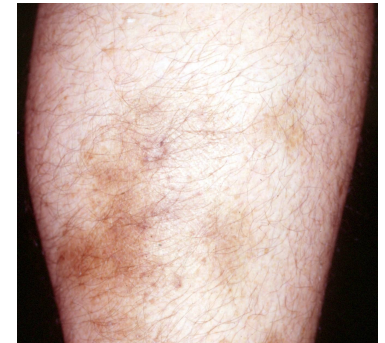


microangiopathic hemolytic anemia

hypercoagulable states

Polyarteritis nodosa

(single manifestation of an early and surgically curable gastric cancer)



DIAGNOSTIC MODALITIES

- ❖ **Endoscopy**
- ❖ **Barium Studies**
- ❖ **Endoscopic Ultrasound (EUS)**
- ❖ **CT Abdo/Pelvis**
- ❖ **Tumor Markers**
- ❖ **PET/CT**
- ❖ **Laparoscopy**

ENDOSCOPY

5 % of malignant ulcers appear benign grossly

A single biopsy has a 70% sensitivity

Seven biopsies from the ulcer margin and base: >98%

Sensitive (Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Graham DY, et al, Gastroenterology. 1982;82(2):228.)

Linitis Plastica (5% of cases) is difficult to diagnose endoscopically and superficial biopsies will be negative

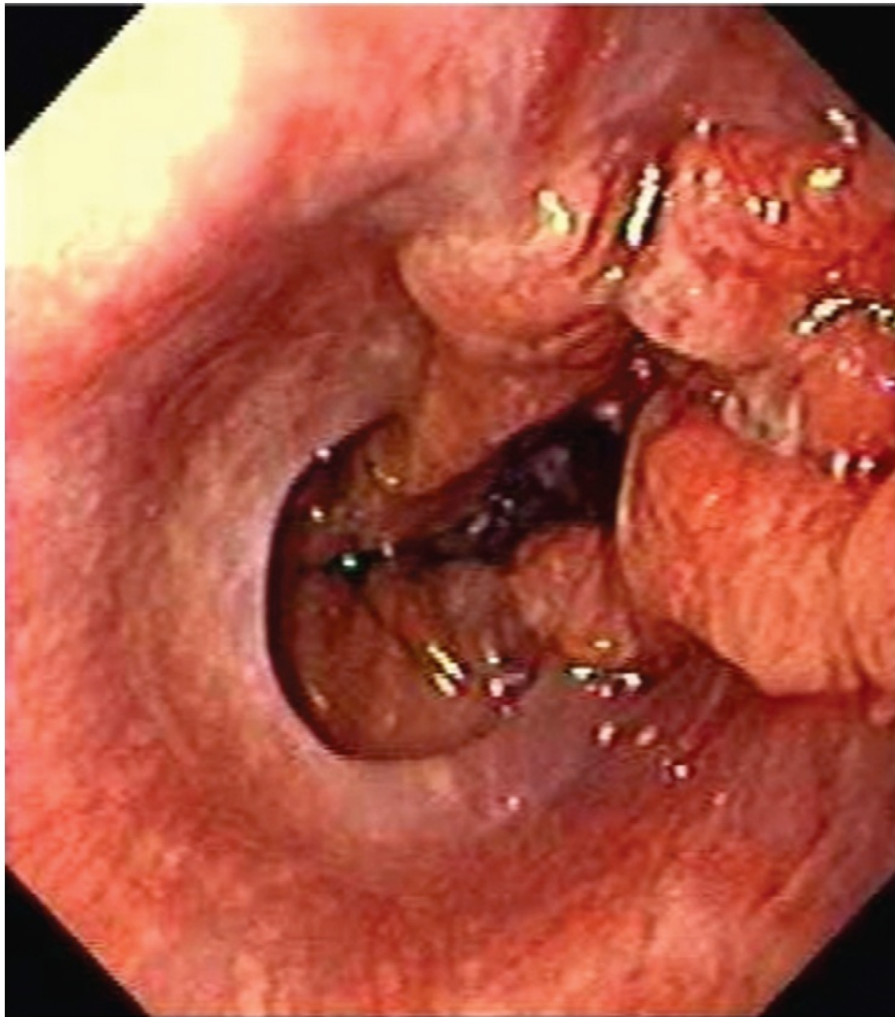


FIGURE 49-21 Endoscopic view of intestinal-type adenocarcinoma of the gastric cardia. (Courtesy Dr. David Bentrem, Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago.)

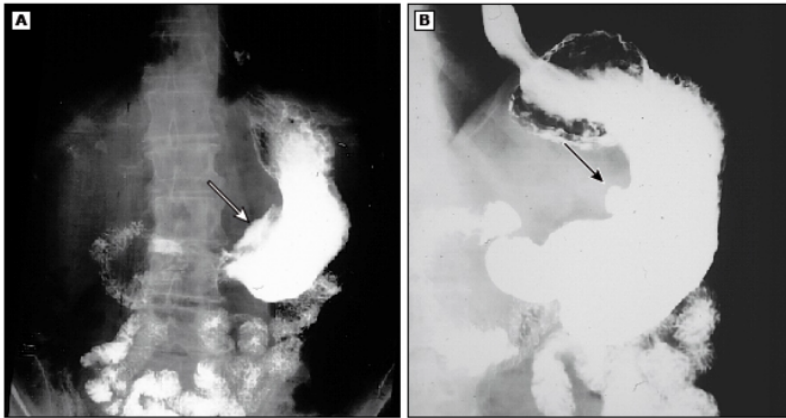
BARIUM STUDIES

can identify both malignant gastric ulcers and infiltrating lesions

50% False negative

sensitivity of barium meals as low as 14 percent in early stages

Malignant and benign gastric ulcer as seen on upper gastrointestinal (UGI) series



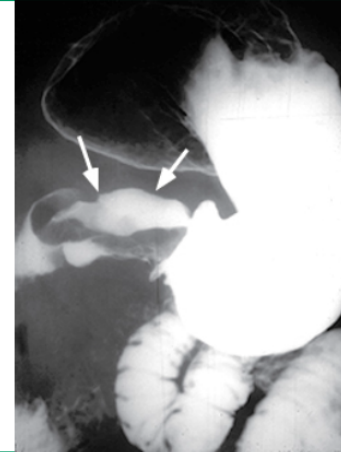
Upper GI series showing the differences between a malignant and benign gastric ulcer.
(A) Malignant gastric ulcer of the distal lesser curvature. There is the biconvex meniscus sign with a nodular ulcer mound (arrow).
(B) Benign gastric ulcer of the lesser curvature. The ulcer crater has smooth margins and projects beyond the gastric wall (arrow).

Normal upper GI series



Normal air-contrast upper gastrointestinal study showing normal gastric folds and small intestinal anatomy, and no masses.

Malignant gastric ulcer



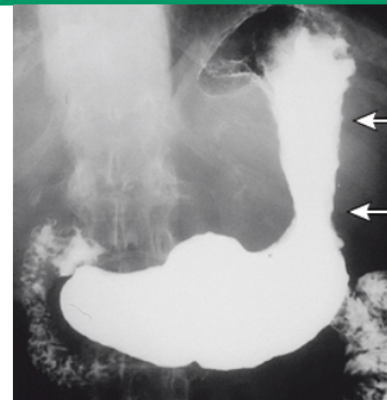
Double contrast upper GI study demonstrates a large barium-filled ulcer crater (arrow) surrounded by edematous mucosa. The ulcer is extending from the stomach, across the pylorus and into the duodenum, features that are not seen with benign ulcers.

BARIUM STUDIES

Superior to upper endoscopy in patients linitis plastica.

decreased distensibility of the stiff, "leather-flask" appearing stomach is more obvious on the radiographic study, and the endoscopic appearance may be relatively normal

Linitis plastica of the stomach as seen on upper gastrointestinal (UGI) series



Upper gastrointestinal study reveals fixed narrowing of the entire proximal stomach (arrows) due to submucosal invasion by a gastric cancer. Other malignancies, such as breast and lung metastases to the stomach, may have a similar appearance.

STAGING SYSTEMS

Japanese classification:

based upon refined anatomic location, particularly of the lymph node stations

TMN:

The staging schema of the AJCC/UICC is based upon tumor (T), node (N), and metastasis (M) classifications

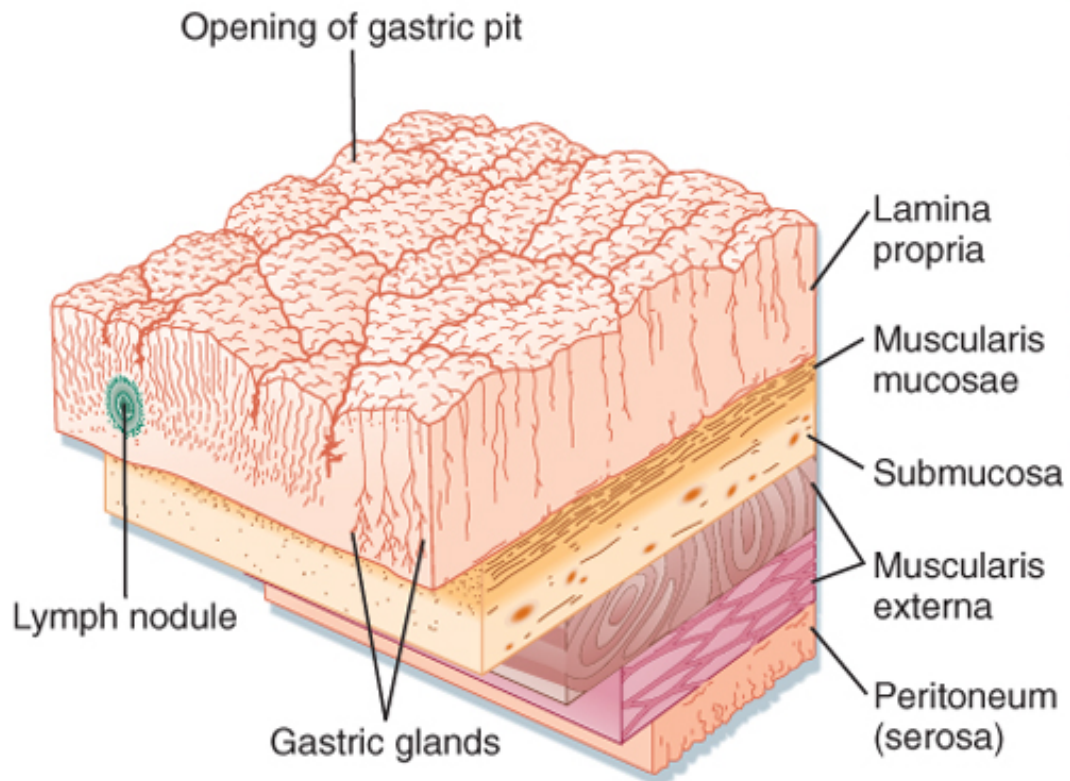
T stage is dependent on depth of tumor invasion and not size.

Nodal stage is based upon the number of positive lymph nodes rather than the proximity of the nodes to the primary tumor

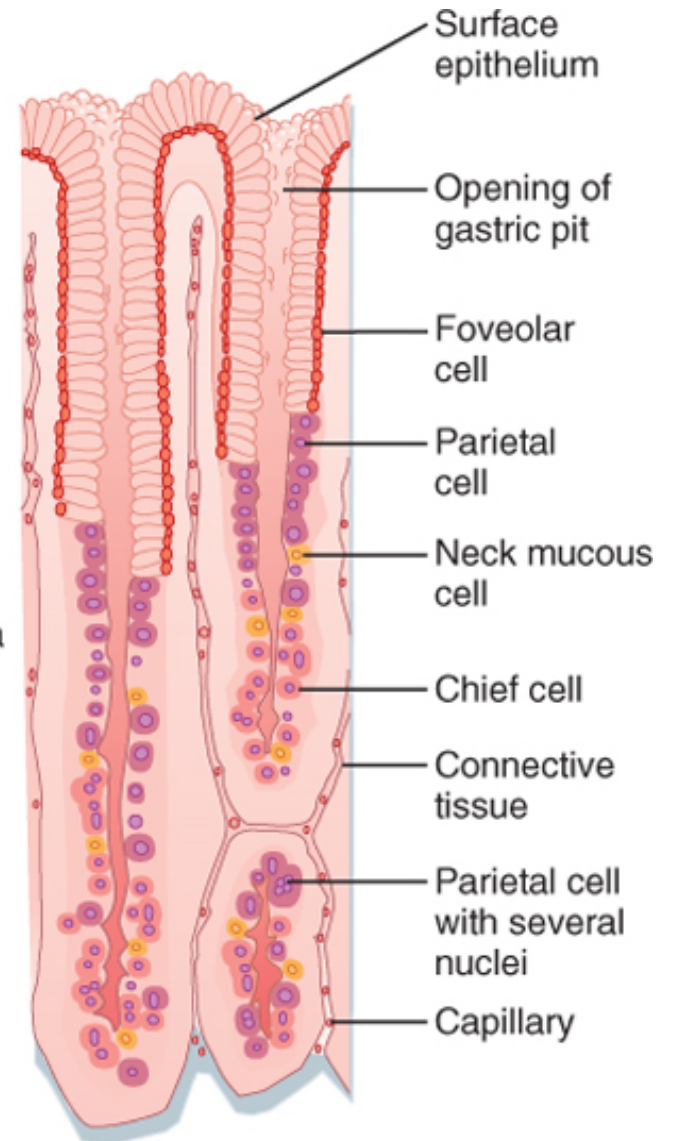
GASTRIC CANCER

TNM STAGING

Tis	Intaepithelial tumour
T1	Tumour invades LP or submucosa
T2	Tumour invades muscularis propria or subserosa
T3	Tumour penetrates serosa without invasion of adjacent structures
T4	Tumour invades adjacent structures



A



B

GASTRIC CANCER

TNM STAGING

N0	No regional lymph node metastases
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes

GASTRIC CANCER

TNM STAGING

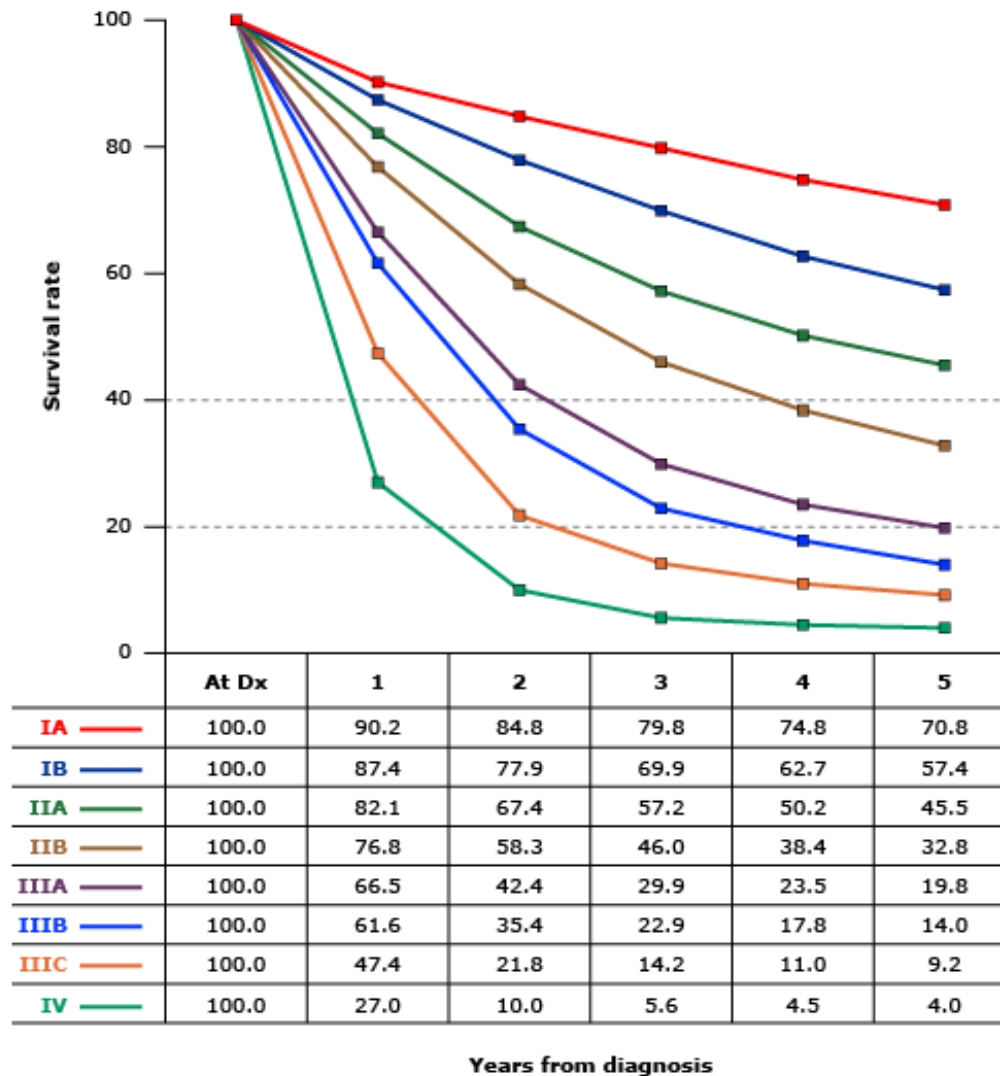
M0	No distant metastasis
M1	Distant metastasis

TNM staging for gastric cancer

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* ^Δ		
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures* ^Δ		
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 1-2 regional lymph nodes		
N2	Metastasis in 3-6 regional lymph nodes		
N3	Metastasis in seven or more regional lymph nodes		
N3a	Metastasis in 7-15 regional lymph nodes		
N3b	Metastasis in 16 or more regional lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

Observed survival rates for 10,601 surgically resected gastric adenocarcinomas



CLINICAL STAGING AND THE SELECTION OF TREATMENT

locoregional disease (stage I to III) after preoperative testing are potentially curable

All patients with a primary tumor that is considered to invade through the submucosa (T2 or higher) or with a high suspicion of nodal involvement on pretreatment staging studies should be referred for multidisciplinary evaluation to identify the best treatment strategy.

Patients with advanced stage IV disease are usually referred for palliative therapy depending on their symptoms and functional status.

PREOPERATIVE EVALUATION

Indicators of unresectability:

- **distant metastases**
- **invasion of a major vascular structure, such as the aorta, disease encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery.**
- **Distal splenic artery involvement is not an indicator of unresectability; the vessel can be resected en bloc with a left upper quadrant exenteration: stomach, spleen and distal pancreas.**

PREOPERATIVE EVALUATION

Patients who have bulky adenopathy fixed to the pancreatic head that might indicate the need for a Whipple procedure are at a high risk for occult metastatic disease.

In these cases, it is probably best to consider staging laparoscopy or upfront chemotherapy or combined modality therapy rather than surgery initially. (Performance of a Whipple for gastric cancer is an extremely rare occurrence.)

Linitis plastica has an extremely poor prognosis, and many surgeons consider its presence to be a contraindication to potentially curative resection.

ABDOMINOPELVIC CT SCAN

performed early in the preoperative evaluation after the diagnosis of Gastric Ca

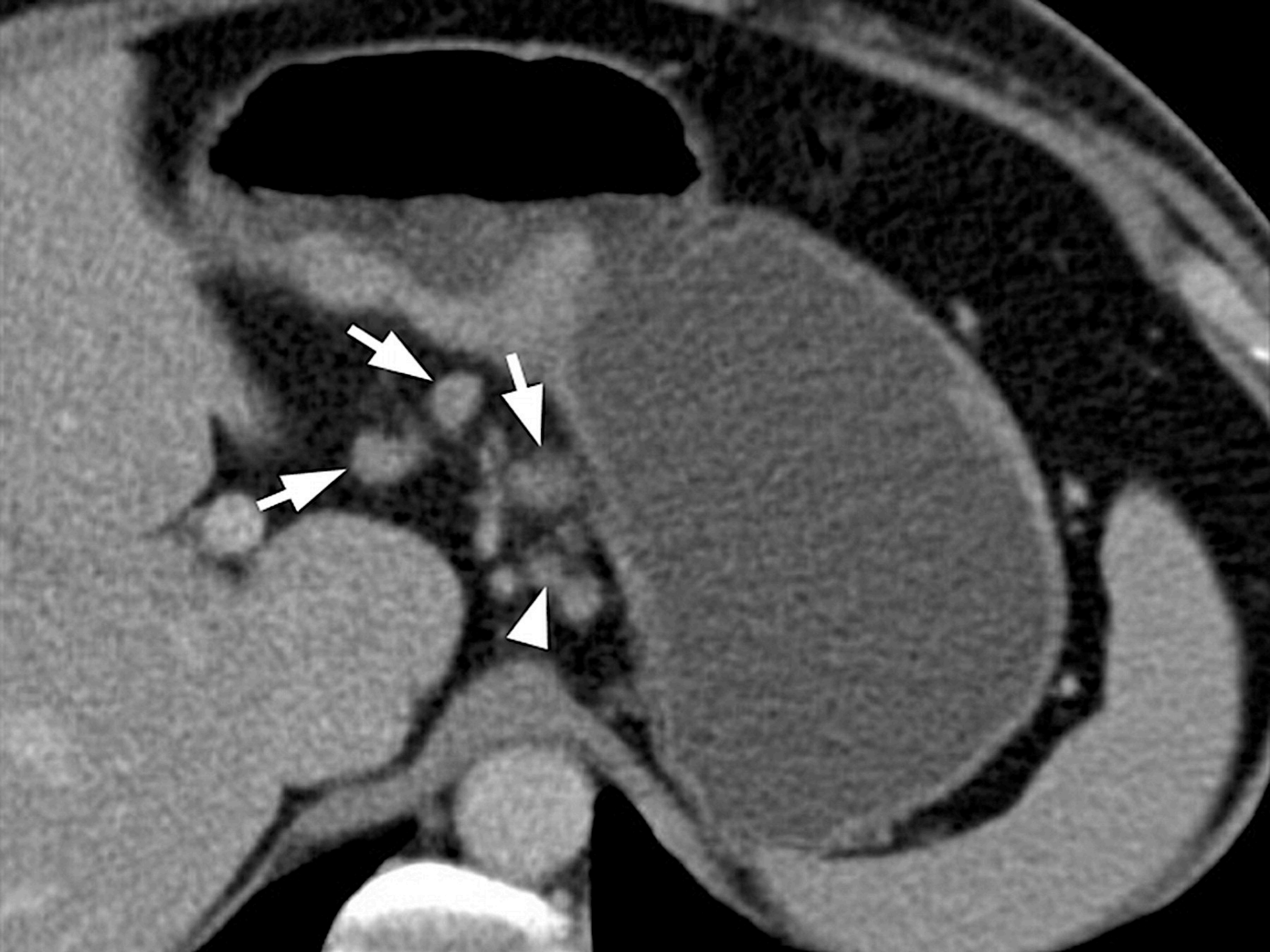
hepatic or adnexal metastases, ascites, or distant nodal spread can be identified and unnecessary surgery avoided

Peritoneal metastases and hematogenous metastases smaller than 5 mm are frequently missed by CT

negative CT : 20 to 30 % of chance of intraperitoneal disease to be found at either staging laparoscopy or at open exploration

CT accuracy in T stage of the primary tumor : only 50 to 70 %

for regional nodal metastases: sensitivity 65 to 97 %, and specificity 49 to 90 %



ENDOSCOPIC ULTRASONOGRAPHY

- **most reliable nonsurgical method available for evaluating the depth of invasion of primary gastric cancers, particularly for early (T1) lesions**
- **The accuracy of EUS for differentiation of individual tumor stages (T1 to T4) ranges from 77 to 93 percent depending on the operator experience**
- **newer CT techniques (such as three-dimensional multidetector row CT) and MRI may achieve similar results in terms of diagnostic accuracy in T staging**
- **accuracy for nodal staging (65 to 90 %) is only slightly greater with EUS as compared to CT**
- **Neoadjuvant chemotherapy or chemoradiotherapy may be recommended for patients with a primary tumor that is considered to invade into the muscularis propria (T2 or higher) or with a high suspicion of nodal involvement on pretreatment staging studies.**
- **EUS is also of value for patients with early gastric cancer because accurate assessment of submucosal invasion is essential before considering the option of endoscopic mucosal resection.**

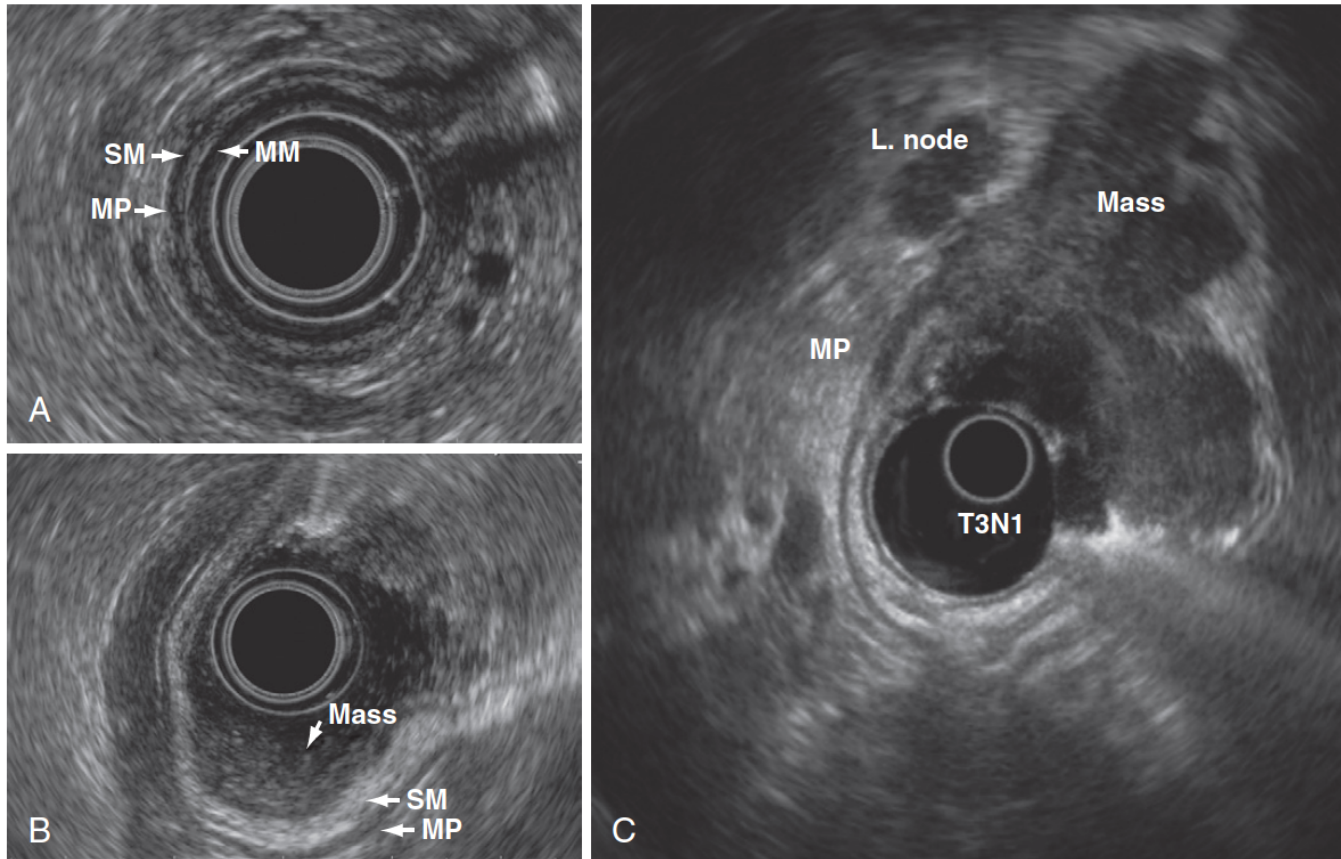


FIGURE 49-22 Endoscopic ultrasound views of normal stomach **(A)**, T1 N0 gastric cancer **(B)**, and T3 N1 gastric cancer **(C)**. (Courtesy Dr. Rajesh Keswani, Division of Gastroenterology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago.)

PET SCAN

PET/CT imaging can be useful to confirm malignant involvement of CT-detected lymphadenopathy

a negative PET is not helpful since even large tumors with a diameter of several centimeters can be falsely negative if the tumor cells have a fairly low metabolic activity

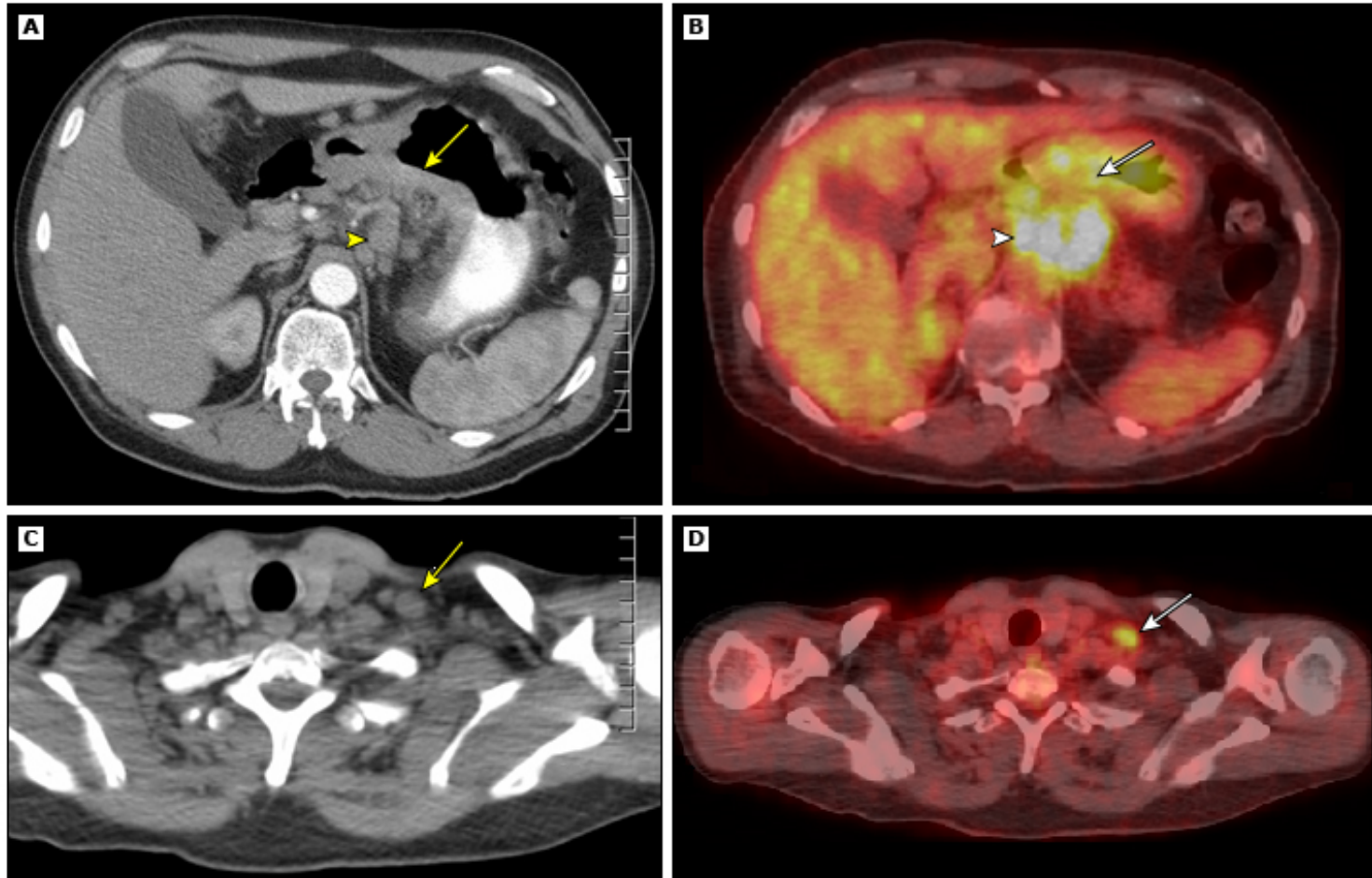
most diffuse type gastric cancers (signet ring carcinomas) are not FDG avid

The main benefit of PET is that it is more sensitive than CT for the detection of distant metastases

sensitivity of PET scanning for peritoneal carcinomatosis is only approximately 50 percent so cant replace staging laparoscopy

PET response to neoadjuvant therapy strongly correlates with survival, with PET response seen within 14 days of treatment. PET may be an effective modality for monitoring response to these therapies, sparing unresponsive patients further toxic treatment

Imaging metastatic gastric carcinoma with CT and PET CT



An axial CT image through the upper abdomen shows gastric wall thickening (arrow) and a group of large lymph nodes in the gastrohepatic ligament (arrowhead). Image B is a PET CT and shows a hypermetabolic mass in the stomach (arrow) and metastatic lymph nodes in the gastrohepatic ligament. Image C is an axial CT image through the thoracic inlet and shows a large lymph node in the supraclavicular region (arrow). Image D is a PET CT showing hypermetabolic activity in the supraclavicular node indicating metastatic disease.

CT: computed tomography; PET: positron emission tomography.

SEROLOGIC MARKERS

CEA

CA 125

CA 19 9

CA 72 4

AFP (Hepatoid Adenocarcinomas of the stomach, poor prognosis)

a drop in an elevated level of CEA and/or CA 125 may correlate with response to preoperative therapy,

STAGING LAPAROSCOPY

20 and 30 % of patients with T1 and above on EUS will be found to have peritoneal metastases despite having a negative CT scan

50% of T3-4 Gastric Ca will avoid unnecessary laparotomy

opportunity to perform peritoneal cytology in patients who have no visible evidence of peritoneal spread (predicts for early peritoneal relapse)

avoiding laparotomy also means avoiding a delay in starting chemotherapy for patients with metastatic disease and limited life expectancy

Many centers do it as a routine for the workup for most Gastric Ca patients and can be planned as a single stage procedure as resection

SUMMARY OF DIAGNOSTIC RECOMMENDATION

Abdominopelvic CT scan is indicated to look for metastatic disease (M stage); it should not be relied upon for assessing T / N staging or the presence of peritoneal metastases.

Suspicious visceral lesions require biopsy confirmation. Paracentesis for cytology should be performed when ascites is detected

A preoperative chest x-ray is recommended; chest CT scan is preferred (particularly for patients with a proximal gastric cancer

Endoscopic ultrasound (EUS) is better than CT at assessing tumor depth (T stage) and perhaps lymph node involvement (N stage), particularly if fine-needle aspiration is also performed.

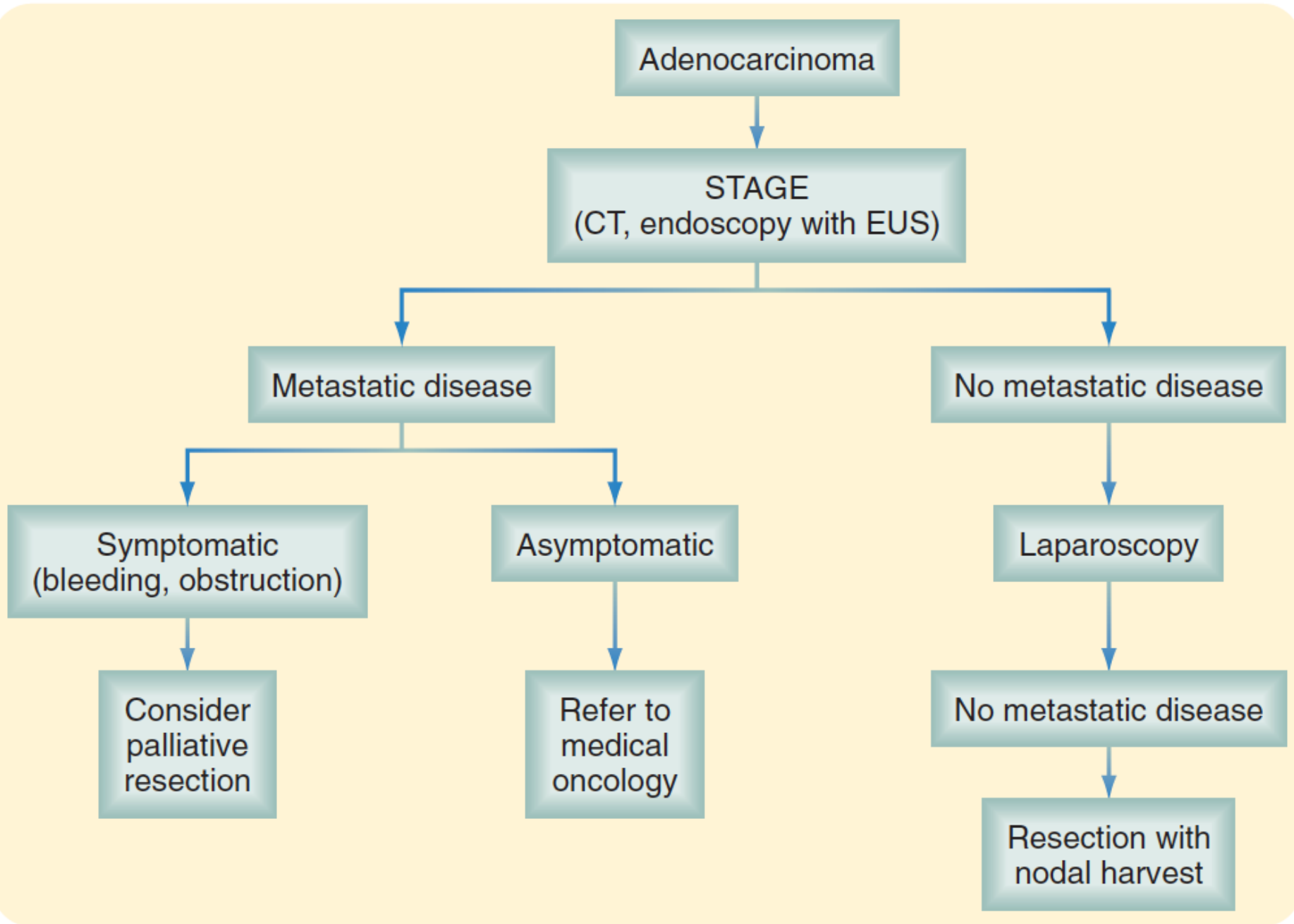
SUMMARY OF DIAGNOSTIC RECOMMENDATION

If the radiographic staging evaluation is otherwise negative for metastatic disease, integrated PET/CT is a reasonable addition to the preoperative staging evaluation for patients with \geq T2N0 disease, mainly to screen for distant metastases. As with CT, suspicious visceral lesions warrant biopsy.

Serum tumor markers (including CEA and CA 125) are of limited utility, and we do not routinely assay for them, unless a patient is undergoing neoadjuvant therapy.

staging laparoscopy is indicated in all medically fit patients > T1 lesion on EUS, no histologic confirmation of stage IV disease, (and who would not otherwise require a palliative gastrectomy)

Diagnostic laparoscopy should also be undertaken in patients who are being considered for neoadjuvant therapy.



SURGICAL MARGINS

Subtotal vs. Total Gastrectomy?

- **Factors Influencing Operation**

- **Extent of disease**
- **Histological type**
 - **Diffuse – total gastrectomy**
 - **Intestinal – potentially subtotal gastrectomy**
- **Location (for intestinal type)**
 - **Lower – subtotal gastrectomy**
 - **Mid – near-total gastrectomy**
 - **Upper – total gastrectomy**
 - **≤2 cm of GE junction- Esophagogastrectomy**

SURGICAL THERAPY

For cancers of the distal stomach, including the body and antrum, a distal gastrectomy is the appropriate operation.

The proximal stomach is transected at the level of the incisura at a margin of at least 6 cm, because studies have documented tumor spread as far as 5 cm laterally from the primary tumor.

The distal margin is the proximal duodenum.

The possibility of recurrence in the tumor bed (duodenal suture line and surface of the pancreas) suggest a Billroth II reconstruction rather than a Billroth I, which will result in less risk of gastric outlet obstruction secondary to tumor recurrence.

SURGICAL THERAPY

For proximal lesions of the fundus or cardia, a total gastrectomy with a Roux-en-Y esophagojejunostomy or proximal gastrectomy is equivalent from an oncologic perspective.

The postoperative anastomotic leak rate is higher for an esophagojejunostomy, but the margin will typically be larger than for a gastrojejunostomy

Laparoscopy has the same 5 yr survival as open but shorter time to start feeding and earlier DC from hospital

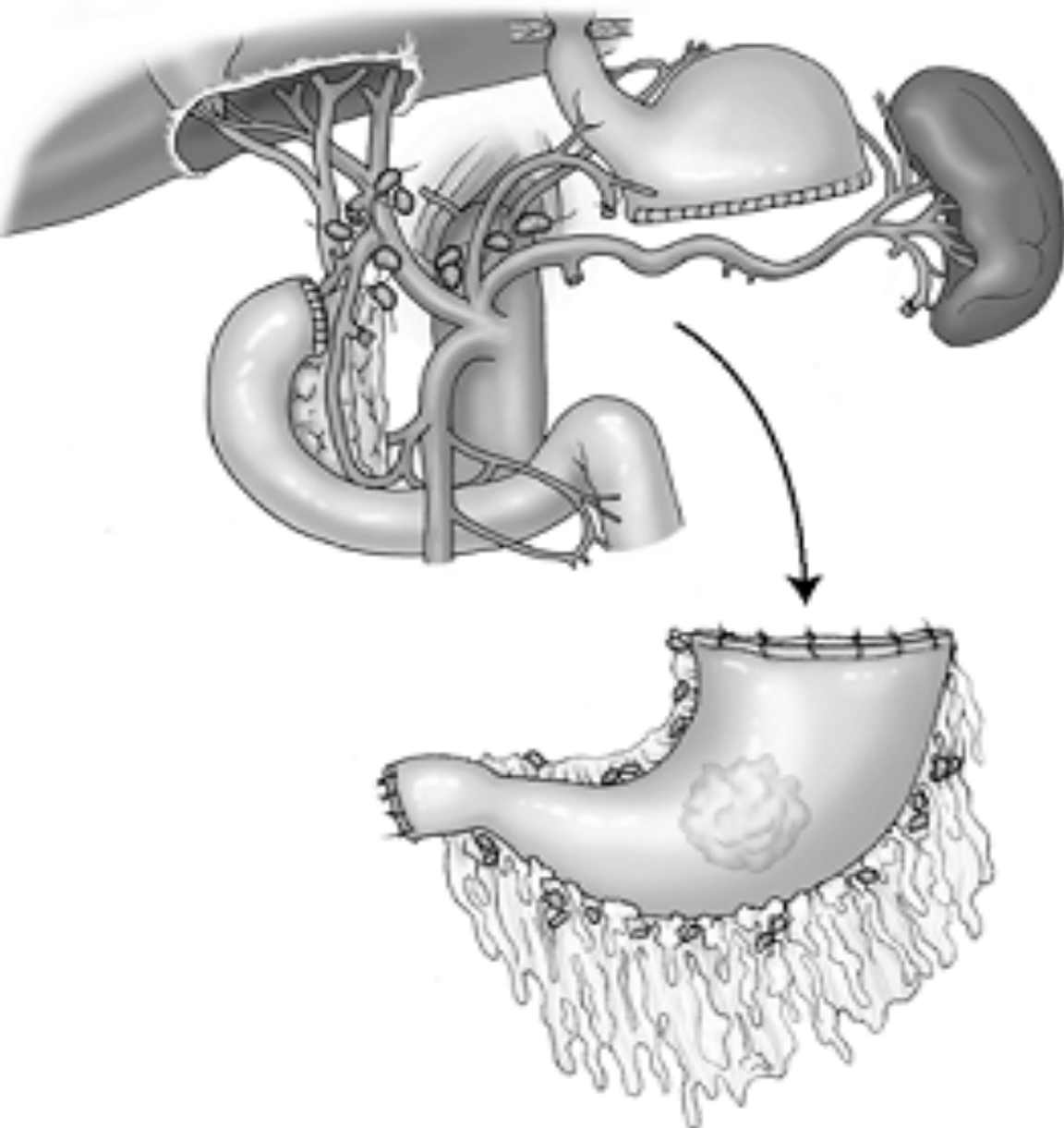


Fig. 15. Subtotal gastrectomy. The resection involves four-fifths of the stomach, including the omentum, the right and left hepatic arteries, and the lymph nodes at the lesser and greater curvature, as well as the lymph nodes in the gastroduodenal ligament. The left epiploic artery must be preserved.

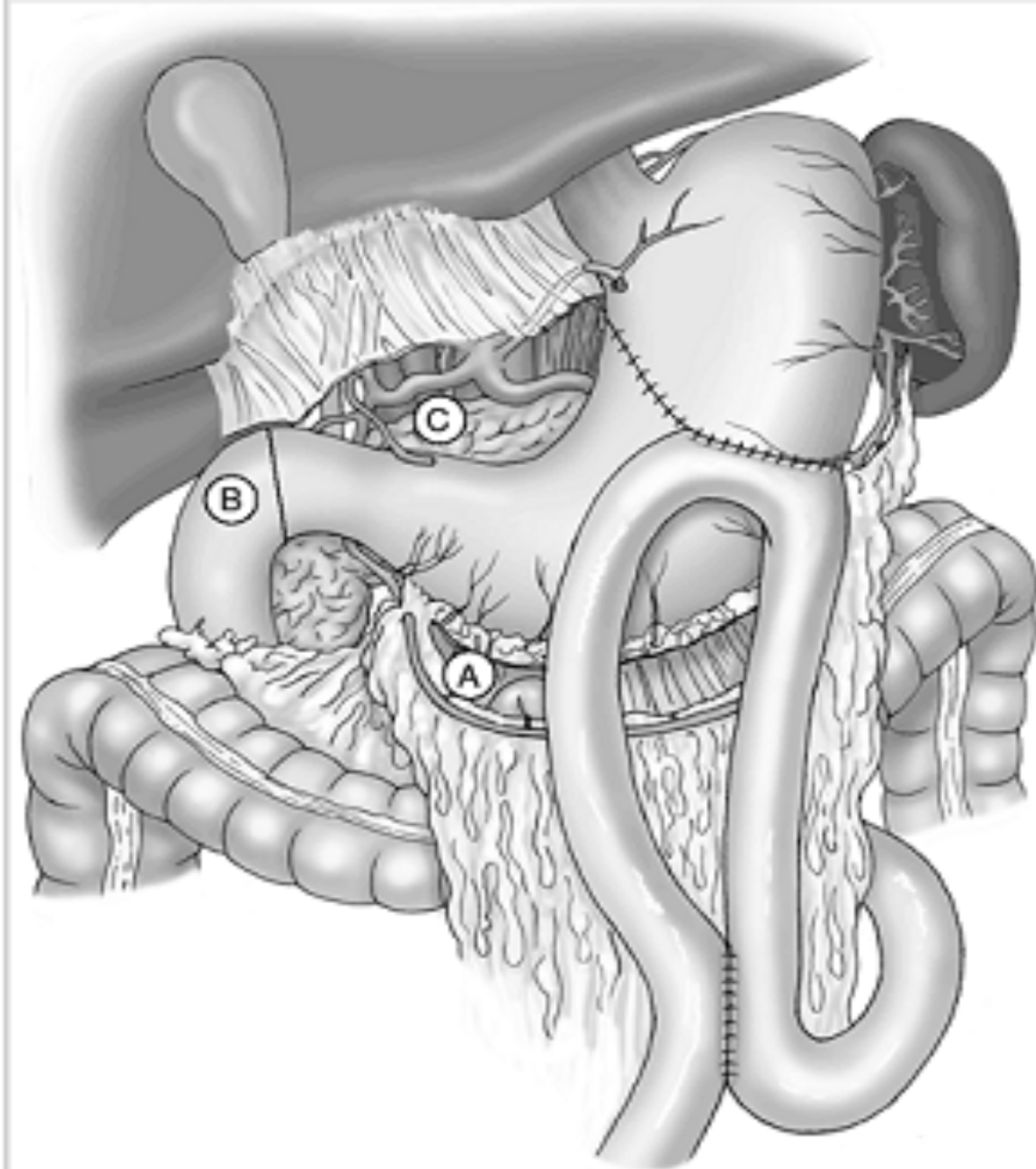


Fig. 12. The Billroth II reconstruction. The first or second jejunal loop of the jejunum is used, and a jejunojenuniostomy (according to Braun) should be accomplished in order to prevent bile reflux

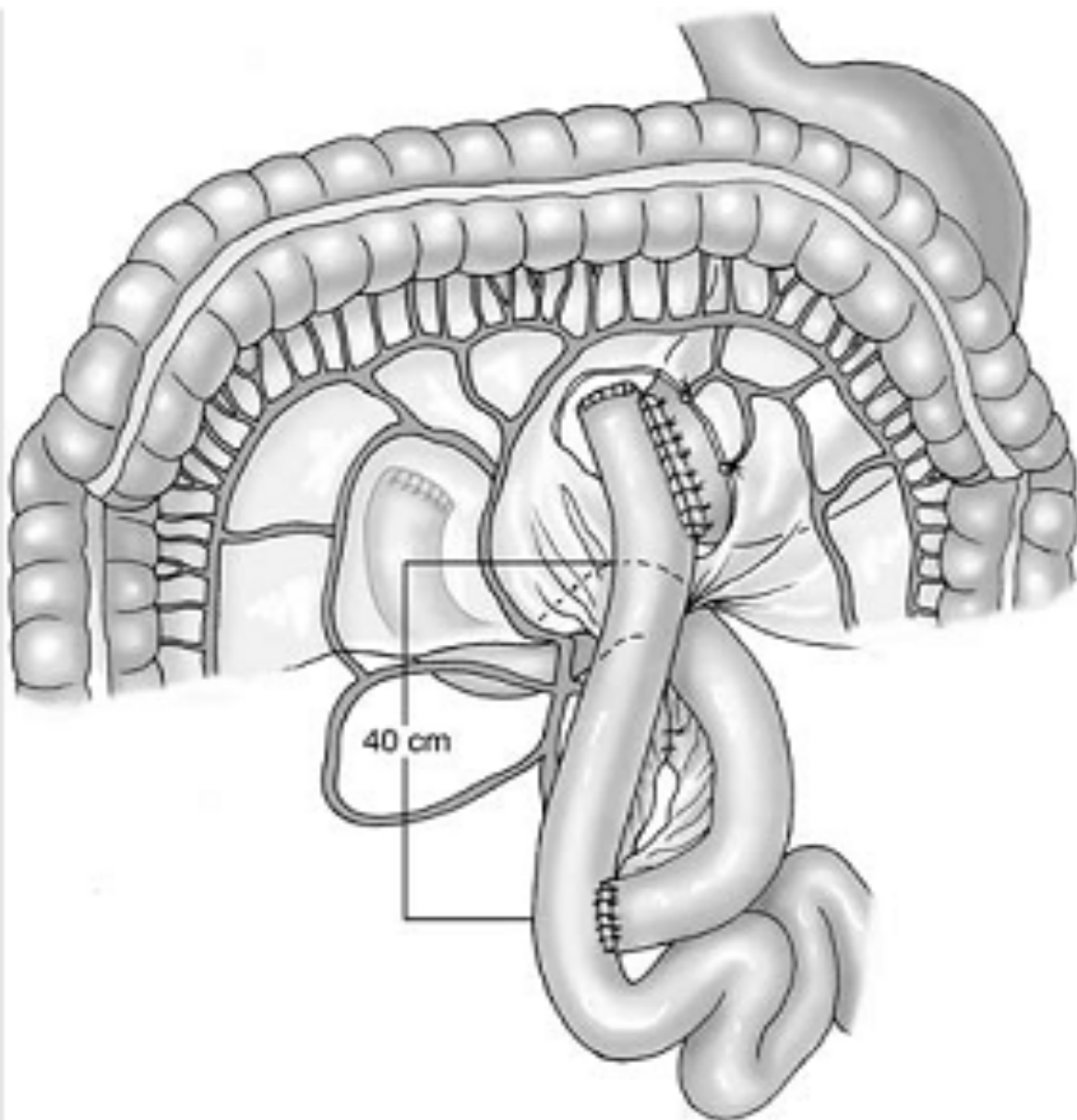


Fig. 13. The Roux-Y reconstruction. The first or second jejunal loop is disconnected and a gastrojejunostomy is performed end-to-side, as well as a jejuniojejunostomy end-to-side 40 cm aborally to the gastric anastomosis.

ENDOSCOPIC MUCOSAL RESECTION

For early gastric cancer with limited penetration of the gastric wall and no evidence of lymph node metastases, purely endoscopic mucosal resection

Widely practiced in Japan

no randomized controlled trials comparing endoscopic mucosal resection with gastrectomy for early gastric cancer

If no lymphatic vessel invasion, histologic ulceration of the tumor, and or larger size (≥ 30 mm) there is only 0.36% chance of Lymph node mets

GENERAL GUIDELINES FOR ENDOSCOPIC RESECTION OF EARLY GASTRIC CANCER

Based on these data, the are as follows:

- (1) tumor limited to the mucosa;
- (2) no lymphovascular invasion;
- (3) tumor smaller than 2 cm; and
- (4) no ulceration.

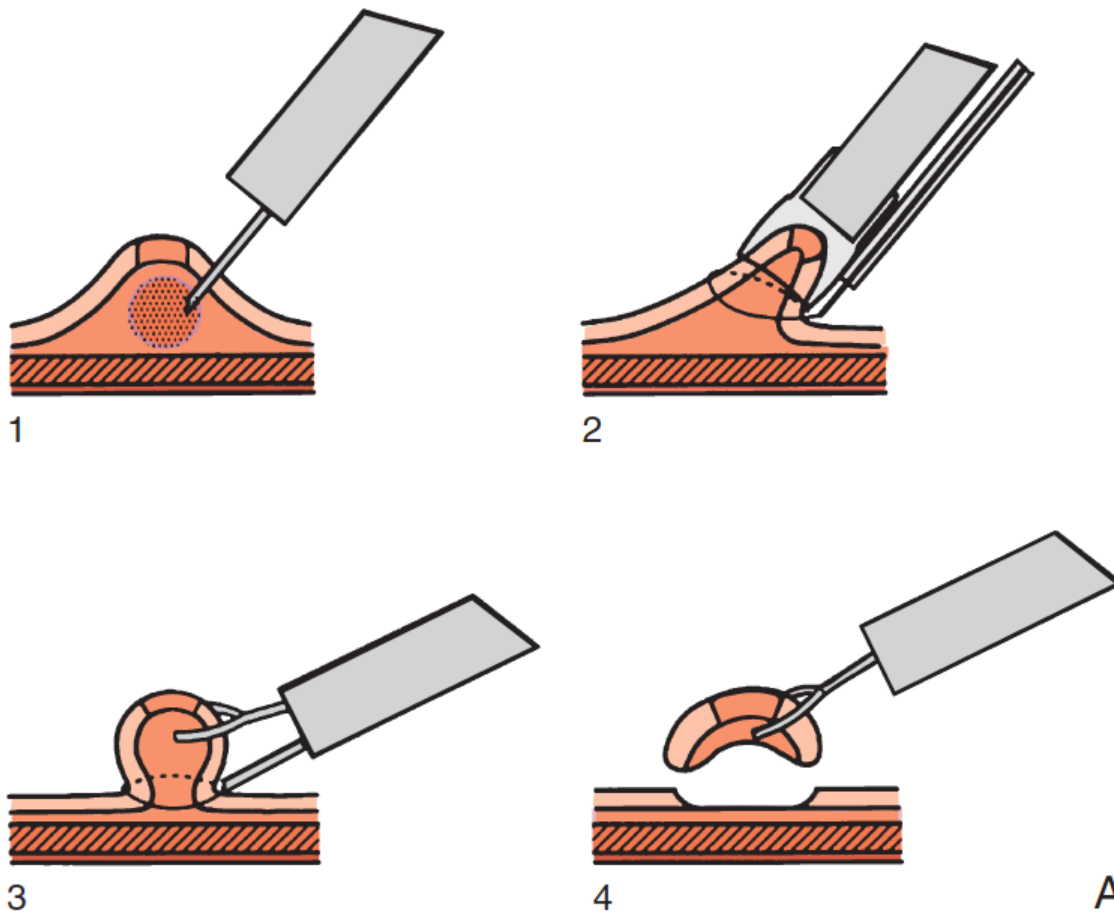


FIGURE 49-24 Endoscopic mucosal resection (EMR). A, EMR by strip biopsy: saline is injected into the submucosal layer, and the area is elevated (1). The top of the mound is pulled upward with forceps, and the snare is placed at the base of the lesion (2 and 3). Electro-surgical current is applied through the snare to resect the mucosa, and the lesion is removed (4). (From Tanabe S, Koizumi W, Kokutou M, et al: Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. *Gastrointest Endosc* 50:819–822, 1999.)

RECURRENCE

40% to 80%, recurrence rate after gastrectomy

Most recurrences occur within the first 3 years

Isolated distant metastases are uncommon because most patients with distant failure also have locoregional recurrence.

The most common sites of locoregional recurrence are the gastric remnant at the anastomosis, in the gastric bed, and in the regional nodes.

Hematogenous spread occurs to the liver, lung, and bone.

FOLLOW-UP

complete history and physical examination every 4 months for 1 year

every 6 months for 2 years, and then annually thereafter.

Laboratory tests: FBC, LFTs as clinically indicated.

Many clinicians obtain chest x-rays and CT scans of the abdomen and pelvis routinely, whereas others obtain studies only when clinically suspicious of a recurrence.

Annual endoscopy should be considered for patients who have undergone a subtotal gastrectomy.