



GASTRIC CANCER

Prof. Kamal Bani-Hani

Faculty of Medicine
Hashemite University
February 2022

EPIDEMIOLOGY 1: INCIDENCE

- Although it is **steadily declining** in incidence, GC remains one of the most common and deadly neoplasms in the world.
 - GC is the **third** leading cause of **cancer deaths** worldwide, following only lung and colorectal cancer in overall mortality.
 - GC has the **fifth** highest **incidence** among cancers (and the 7th most prevalent).
 - Over a **million** new cases of GC are diagnosed, worldwide, each year.
- GC is also one of the most **behaviorally influenced**, and thus **preventable**, of major cancers.



EPIDEMIOLOGY 2:

- GC is more prevalent in **males**. In **developed** countries, GC is **2.2** times more likely to be diagnosed in males than females. In **developing** countries, this ratio is **1.83**.
- GC are more frequently diagnosed in **developed nations**. The average incidence rate among high-middle Human Development Index (HDI) nations is **20 per 100,000** for males, while the average rate among low-middle HDI nations is **6.6 per 100,000**.
- The incidence of GC is highly variable by **region** and **culture**.
 - Incidence rates are highest in **Eastern and Central Asia and Latin America**. In East Asia, the average incidence of GC is **32.1** per 100,000 among males and **13.2** among females.
 - In North America, this incidence is **5.6** per 100,000.
 - The rate is lowest in North and East Africa, with only **4.7** annual diagnoses per 100,000 males.
- The **Republic of Korea** has the highest national incidence with almost **60 per 100,000** new cases annually for **males**. While **female** incidence rates are lower (only **25** per 100,000 in Korea).

EPIDEMIOLOGY 3

- Estimated new cases and deaths from gastric cancer (GC) during **2021** in the **USA**.

	Male	Female	Both sex
New cases	16160	10400	26560
Deaths	6740	4440	11180

PATTERN OF GASTRIC CANCER IN JORDAN 1996-2017

Year	Total No. of Cancer cases			Gastric Cancer-Male		Gastric Cancer-Female		Gastric Cancer-All	
	Male	Female	All	Freq.	%	Freq.	%	Freq.	%
1996	1704	1598	3302	79	4.6	49	3.0	128	3.9
1997	1699	1655	3354	83	4.9	51	3.0	134	4.0
1998	1777	1603	3380	81	4.5	53	3.3	134	4.0
1999	1560	1582	3142	78	5.0	47	3.0	125	4.0
2000	1680	1690	3370	82	4.8	51	3.0	133	3.9
2001	1740	1672	3412	84	4.8	35	2.1	119	3.5
2002	1760	1670	3430	106	6.0	47	2.8	153	4.5
2003	1743	1735	3478	76	4.4	46	2.7	122	3.5
2004	1763	1828	3591	78	4.4	38	2.1	116	3.2
2005	1818	1860	3678	67	3.7	45	2.4	112	3.0
2006	2047	2151	4198	79	3.9	64	3.0	143	3.4
2007	2048	2284	4332	96	4.7	55	2.4	151	3.5
2008	2274	2332	4606	95	4.2	73	3.1	168	3.6
2009	2280	2518	4798	68	3.0	77	3.1	145	3.0
2010	2330	2519	4849	90	3.9	62	2.5	152	3.1
2011	2194	2481	4675	81	3.7	49	2.0	130	2.8
2012	2346	2667	5013	86	3.7	50	1.9	136	2.7
2013	2564	2852	5416	100	3.9	75	2.6	175	3.2
2014	2718	2977	5695	99	3.6	53	1.8	152	2.7
2015	2668	2888	5556	101	3.8	56	1.9	157	2.8
2016	2815	3184	5999	91	3.2	58	1.8	149	2.5
2017	2990	3362	6352	127	4.2	84	2.5	211	3.3
Total	46518	49108	95626	1927	4.1	1218	2.5	3145	3.3

**Ten most common cancers among
Jordanians both genders, 2017**

No	Site	Freq	%
1	Breast	1302	20.5
2	Colorectal	678	10.7
3	Lymphoma	485	7.6
4	Trachea, Bronchus, Lung	473	7.5
5	Thyroid	293	4.6
6	Bladder	248	3.9
7	Prostate	236	3.7
8	Leukemia	233	3.6
9	Stomach	211	3.3
10	Brain, Nervous system	185	2.9

**Ten most common cancers among
Jordanians, Males, 2017**

No	Site	Freq	%
1	Colorectal	371	12.4
2	Trachea, Bronchus, Lung	366	12.2
3	Prostate	236	7.9
4	Bladder	215	7.2
5	Non-Hodgkin lymphoma	159	5.3
6	Leukemia	158	5.3
7	Stomach	127	4.2
8	Kidney	117	3.9
9	Brain, Nervous system	102	3.4
10	Hodgkin disease	97	3.2

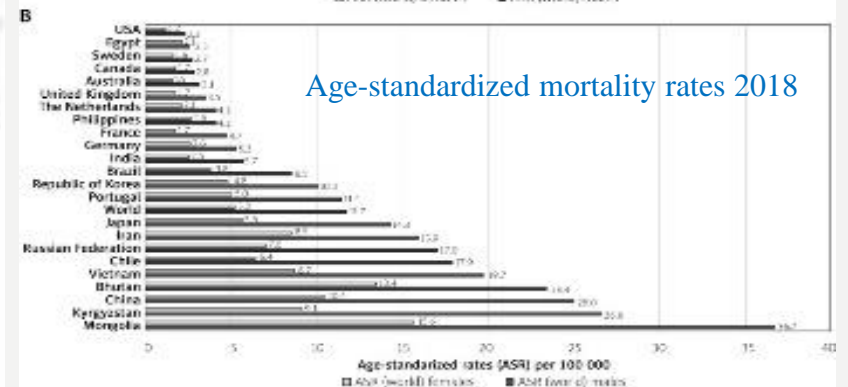
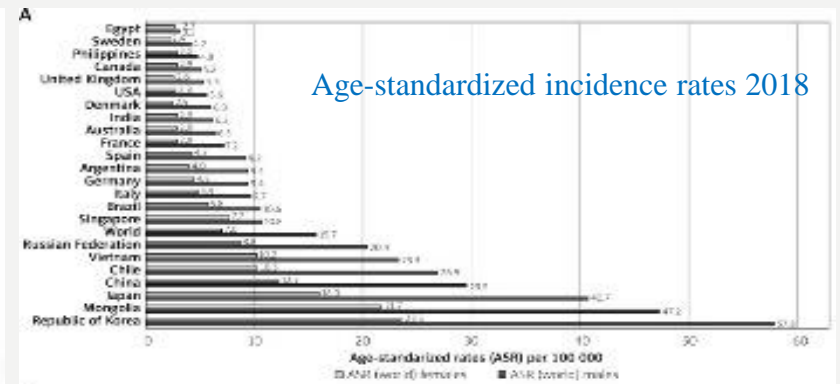
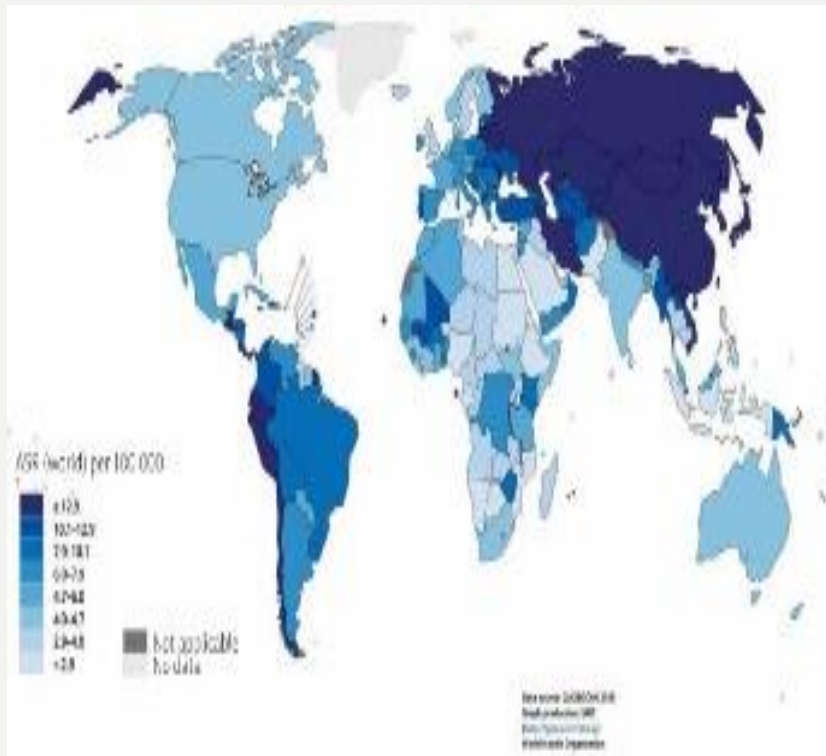
**Ten most common cancers among
Jordanian Females, 2017**

No	Site	Freq	%
1	Breast	1292	38.4
2	Colorectal	307	9.1
3	Thyroid	223	6.6
4	Corpus Uteri	148	4.4
5	Non-Hodgkin lymphoma	136	4.0
6	Ovary	109	3.2
7	Trachea, Bronchus, Lung	107	3.2
8	Hodgkin disease	93	2.8
9	Stomach	84	2.5
10	Brain, Nervous system	83	2.5

PATTERN OF GASTRIC CANCER IN JORDAN 1996-2017

- Stomach cancer occurred more frequently in males than in females, with a male to female ratio of **1.6: 1**.
- The overall ASR for stomach cancer was **3.9/100,000** (4.9/100,000 for males and 2.9/ 100,000 for females). The overall median age at diagnosis was **60 years** (60 years for males and 61 years for females).
- The incidence of gastric cancer in Jordan is **low** (3-4/100,000) compared to regional estimates and remained relatively constant between 1996 and 2017.

EPIDEMIOLOGY 4



EPIDEMIOLOGY 5: SURVIVAL

- The 5-year survival rate for GC is **31%** in the US. Average survival rates reflect the fact that **most cases diagnosed are already metastatic**.
- The 5-year survival rate for pre-metastatic diagnosis is **67%**.
- Survival is highly variable **based on stage** during surgical intervention. The 5-year survival rates for stage **IA** and **IB** tumors treated with surgery are **94%** and **88%**, respectively. On the other hand, stage **IIIC** tumors treated with surgery had a 5-year survival rate of **18%**.

ETIOLOGY AND RISK FACTORS

1	Sex	M > F
2	Age	Advanced age
3	Class	Lower
4	Environmental factors	
5	Diet and smoking	High in salted, smoked, or preserved foods Low in fruits and vegetables
6	H. pylori	3-6 fold
7	Chronic atrophic gastritis and Int. metaplasia	
8	Adenomatous gastric polyps and FAP	10-20%
9	Previous gastric surgery	2-6 fold
10	Pernicious anemia	10%
11	Ménétrier's disease (Giant hypertrophic gastritis)	10%
12	Family history of gastric cancer	10%
13	Blood type A	
14	Hypogammaglobulinemia	47-fold

DIET

Appears to be correlated with a high intake of:

(a) **Preserved foods** (↑salt, nitrates, nitrites).

(b) **Pickled vegetables**

(c) **Salt**

- Nitrates and nitrites → **n-nitrosamines** (carcinogens)
- Free radical–induced injury by nitrosamines are potentially damaging.
- Ascorbic acid can prevent the conversion of nitrites to nitrosamines).
- **Ascorbic acid** and **beta-carotene** act as antioxidants.

HELICOBACTER PYLORI

- Parallels between rates of GC and H. pylori infection.
- H. pylori infection rate is ↓ over time in the US, in parallel with the ↓ in GC.
- **3-6-fold ↑** risk of GC in individuals with H. pylori.
- Infection causes > 80% of chronic gastritis cases. → chronic atrophic gastritis → metaplasia → GC.
- Toxins such as **ammonia** and **acetaldehyde** are produced, which → inflammation and epithelial damage.
- It causes epithelial cell proliferation and production of growth regulatory peptides. Recruitment of inflammatory cells (neutrophils) are augmented. These neutrophils generate **free radicals** and **chloramine**, both of which cause direct DNA damage.
- **35-89% of GC could be prevented by eradication.**
- Associated more with **intestinal** than the diffuse type. More with Ca of the **antrum**, fundus, and **body** than Ca of the **cardia**.

ADENOMATOUS GASTRIC POLYPS

- 5th – 7th decades, and have few symptoms or signs.
- DX is usually made on barium meal or coincidentally during endoscopy
- Risk for malignant degeneration is **10-20%** and **↑** for polyps **≥ 2 cm**.
- Pedunculated polyps should be removed endoscopically for pathologic exam.
- Sessile polyps **> 2 cm**. treated with **wedge resection** + a margin of normal mucosa.
- Patients with multiple polyposis should be considered for gastrectomy.

PREVIOUS GASTRIC SURGERY

- Gastric surgery for benign conditions ↑ the risk by 2-6 folds. Mostly 15-20 years after Billroth II
- Events analogous to H. pylori infection is present. Partial gastrectomy and vagotomy causes hypo- or achlorhydria, allowing bacterial overgrowth with ↑ conversion of nitrites to nitrosamines
- Ca in the gastric remnant have a poor prognosis (tend to present at a more advanced stage and in older patients)
- Surveillance in postgastrectomy patients may improve survival.

HYPOGAMMAGLOBULINEMIA

- It is a disorder caused by **low serum immunoglobulin** or **antibody** levels.
- Igs are the main components of the humoral immune system and are able to recognize antigens to trigger a biological response and eradicate the infectious source.
- Hypogammaglobulinemia is the most common primary immunodeficiency and encompasses a majority of immune-compromised patients.
- This condition predisposes children and adults to recurrent infections, allergies, neoplasms, and autoimmunity.
- Hypogammaglobulinemia can be of primary or secondary origin.
 - **Primary immunodeficiencies** result from genetic disorders and/or chromosomal anomalies during the development of the immune system.
 - **Secondary causes** are usually induced by an external or acquired factor such as a **corticosteroid** or **immunosuppressant drug**, **nutritional disorders**, **infections**, **chemotherapy**, **malignancy**, **nephrotic syndrome**, other **metabolic diseases**, and hazardous **environmental** conditions.

PATHOLOGY

▪ Site

- Formerly arose more in the antral and pyloric regions. Recently ↑ rate of involvement of the cardia and GEJ.
- 10-15% of tumors are diffuse in character (linitis plastica).
- Lesser curve is more commonly involved than the greater curve.
- There is a much higher incidence of tumors of the **cardia** in **smokers** than of tumors elsewhere in the stomach.

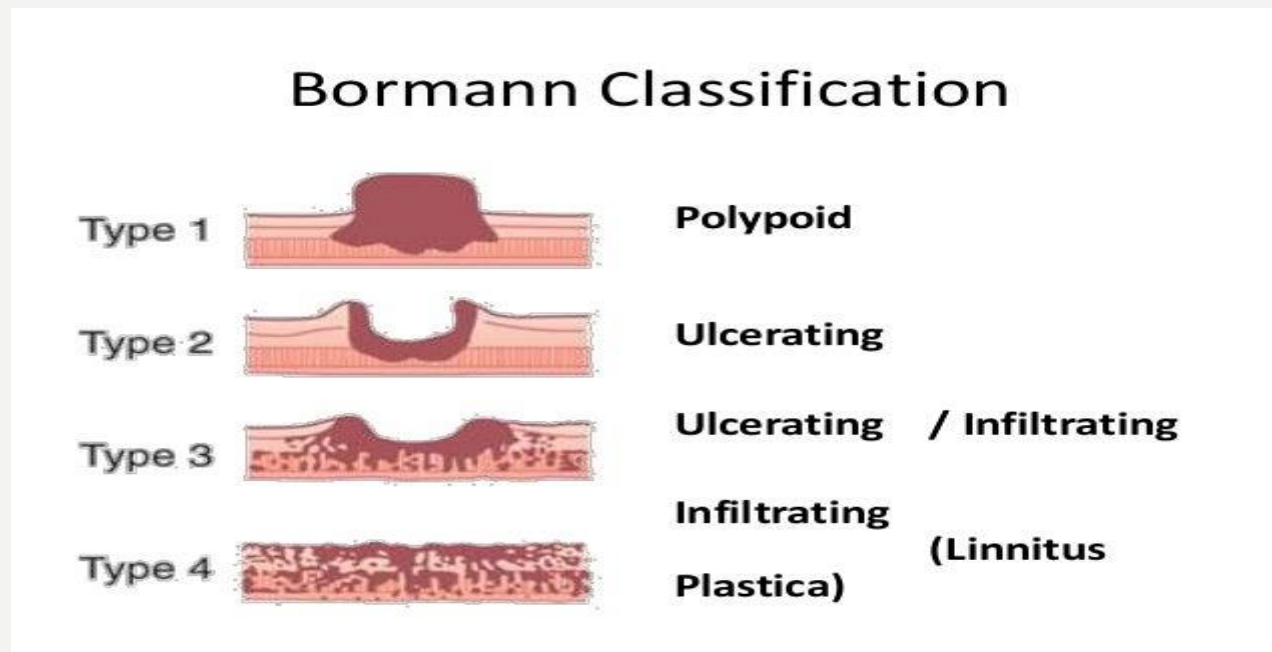
▪ Macroscopic

Adenocarcinomas can be divided into the following subtypes:

1. Fungating or polypoid.
2. Ulcerating.
3. Superficial spreading.
4. Diffusely spreading (linitis plastica).

PATHOLOGY (CLASSIFICATION)

- ❑ Bormann classification
- ❑ Broeder's histologic grading system
- ❑ Ming's classification
- ❑ Lauren classification



LAUREN CLASSIFICATION

Intestinal-type tumors	Diffuse-type tumors
Glandular structure	Tiny clusters of small cells
Diffuse inflammatory cell infiltration and frequent intestinal metaplasia	Widespread through the mucosa, less inflammatory infiltration
Preceded by a pre-cancerous process and predominate in regions with ↑ incidence of gastric Ca	More often in women , in younger patients, and in regions where gastric cancer is less common
As regional gastric cancer risk is ↓, it experiences most of the reduction.	As the incidence of gastric Ca in the cardia ↑, it is seen with ↑ frequency.
	Frequent lymphatic invasion, intraperitoneal metastases, have a poorer prognosis .

HISTOPATHOLOGIC TYPES:

- Adenocarcinoma (intestinal, diffuse, and mixed).
- Papillary, tubular, or mucinous adenocarcinoma.
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma.
- Small cell carcinoma.
- Mixed adenocarcinoma and choriocarcinoma
- Undifferentiated carcinoma (Anaplastic).

Grades : G1-G4 for **well**, **moderately**, **poorly**, and **undifferentiated** tumors.



GIST



Gastric Leiomyoma

PATHOLOGY (METASTASIS)

1. Regional lymphatics.
2. Hematogenous (**portal** and **systemic** circulation)
3. Within the gastric wall
4. Direct invasion of adjacent organs.
5. Involved gastric serosa can seed metastases throughout the peritoneum.

Ovary (**Krukenberg's tumor**)

Pelvic cul-de-sac (**Bloomer's shelf**).

Umbilical adenopathy (**Sister Mary Joseph's node**).

Left supraclavicular adenopathy (**Virchow's node**).

MOLECULAR GENETICS

- Molecular and chromosomal alterations → development of gastric Ca
- Deletion of p53 or expression of aberrant p53 protein is associated with transformation. LOH at the p53 locus is found in **68%** of gastric tumors
- Overexpression of EGFR and C-erbB-2 are **early events**, whereas p53 mutation is a **late event** in gastric carcinogenesis

STAGING (TNM CLASSIFICATION)

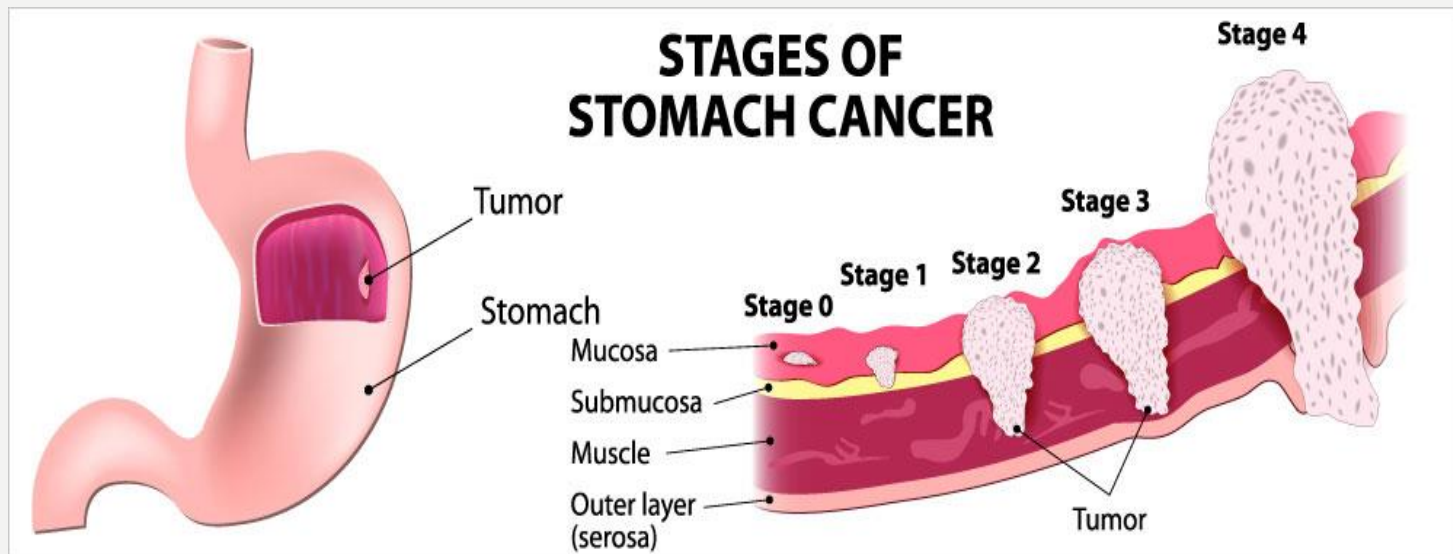
- Gastric cancer is staged according to the characteristics of the primary tumor (T), nodal metastases (N), and presence of metastatic disease (M)
- The most important **prognostic indicators** remain the **depth of penetration**, local regional **lymph nodes metastasis**, and involvement of **adjacent organs**.

PRIMARY TUMOR (T)

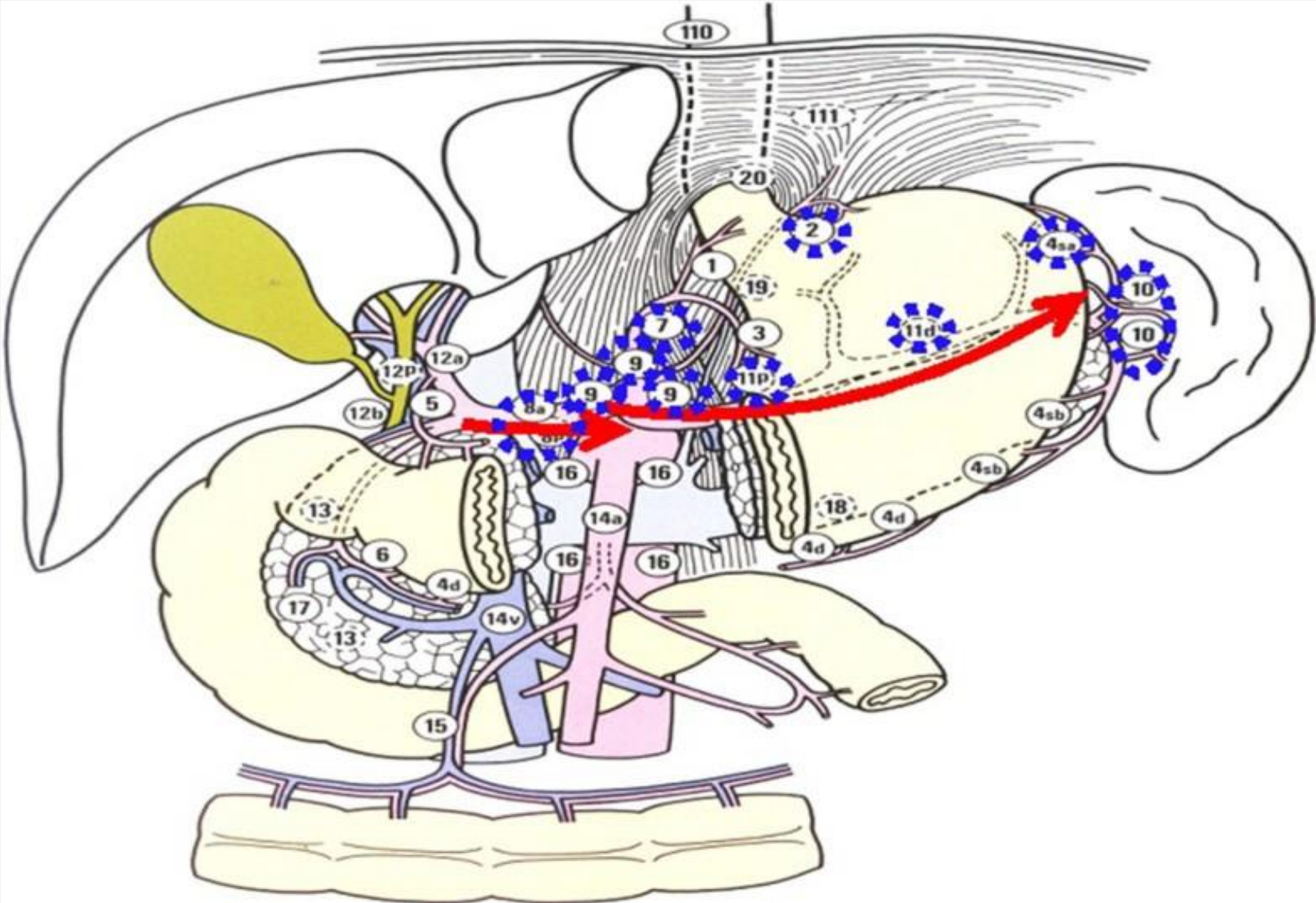
TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis:	● <i>Carcinoma in situ</i> : intraepithelial tumor without invasion of the lamina propria
T1:	● Tumor invades lamina propria or submucosa
T2:	
T2a:	Tumor invades muscularis propria
T2b:	Tumor invades subserosa
T3:	Tumor penetrates the serosa (visceral peritoneum) without invading adjacent structures
T4:	Tumor invade adjacent structures

NODAL INVOLVEMENT (N)

- The **regional lymph nodes** are the perigastric nodes, found along the **lesser** and **greater curvatures**, and the nodes located along the **left gastric, common hepatic, splenic, and celiac arteries**
- Involvement of **other intra-abdominal lymph nodes**, such as the hepatoduodenal, retropancreatic, mesenteric, and para-aortic, is classified as **distant metastasis**.



LYMPH NODE STATIONS



NODAL INVOLVEMENT (N)

NX:	Regional lymph node (s) cannot be assessed
N0:	No regional lymph node metastasis
N1:	Metastasis in 1-6 regional lymph nodes
N2:	Metastasis in 7-15 regional lymph nodes
N3:	•Metastasis in > 15 regional lymph nodes

DISTANT METASTASIS (M)

MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
M1:	Distant metastasis

AJCC STAGE GROUPINGS

Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T1, N1, M0 T2a, N0, M0 T2b, N0, M0
Stage II	T1, N2, M0 T2a, N1, M0 T2b, N1, M0 T3, N0, M0
Stage IIIA	T2a, N2, M0 T2b, N2, M0 T3, N1, M0 T4, N0, M0 T3, N2, M0
Stage IIIB	
Stage IV	T4, N1, M0 T4, N2, M0 T4, N3, M0 T1, N3, M0 T2, N3, M0 T3, N3, M0 Any T, any N, M1

TNM Staging Classification

T
(Tumor size and penetration)

N
(Cancer spread to nearby lymph nodes)

M
(Spread to other parts of the body—metastasis)

Tis: Tumor "in situ:" caught very early and has not grown beyond stomach lining.

T1: Tumor has grown through lining and into connective tissue.

T2: Tumor has grown into thick inner muscle.

T3: Tumor has spread through outer lining but not to any nearby organs or tissues.

T4: Tumor has spread into nearby tissues or organs.

N0: Cancer has not spread to nodes.

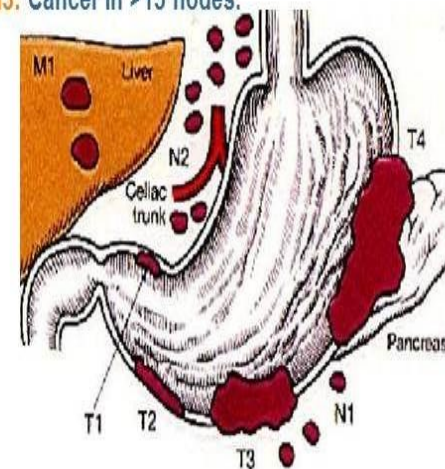
N1: Cancer in 1 to 6 nodes.

N2: Cancer in 7 to 15 nodes.

N3: Cancer in >15 nodes.

M0: No metastasis

M1: Metastasis



EARLY GASTRIC CANCER

- 5.2 million screened→6414 have Ca, and 98.7% had operations. (54% of detected cases, 62% of which were early Ca).
- Defined as disease involving the **mucosa** or **submucosa** (may be fairly large).
- 5-6% of mucosal and 15 -20% of submucosal early Ca are accompanied by **positive** lymph nodes.

EARLY GASTRIC CANCER 1

- Three types of macroscopic lesions are described:
 - ❖ (a) Protruded (Type I).
 - ❖ (b) Superficial (Type II).
 - ❖ (c) Excavated (Type III).
- It represents only **10-15%** of diagnosed cases in the west.
- Five-year survival after resection ranges from **70-95%**, depending on the presence of nodal involvement.

EARLY GASTRIC CANCER 2

Macroscopic types of primary tumors

Subtypes of Type 0



Type 0 Ia: Protruded type



Type 0 IIa: Superficial elevated type



Type 0 IIb: Flat type



Type 0 IIc: Superficial depressed type



Type 0 III: Excavated type

Types of 1, 2, 3, and 4



Type 1 **polypoid tumors**



Type 2 **Ulcerated Ca**



Type 3 **Ulcerated Ca**

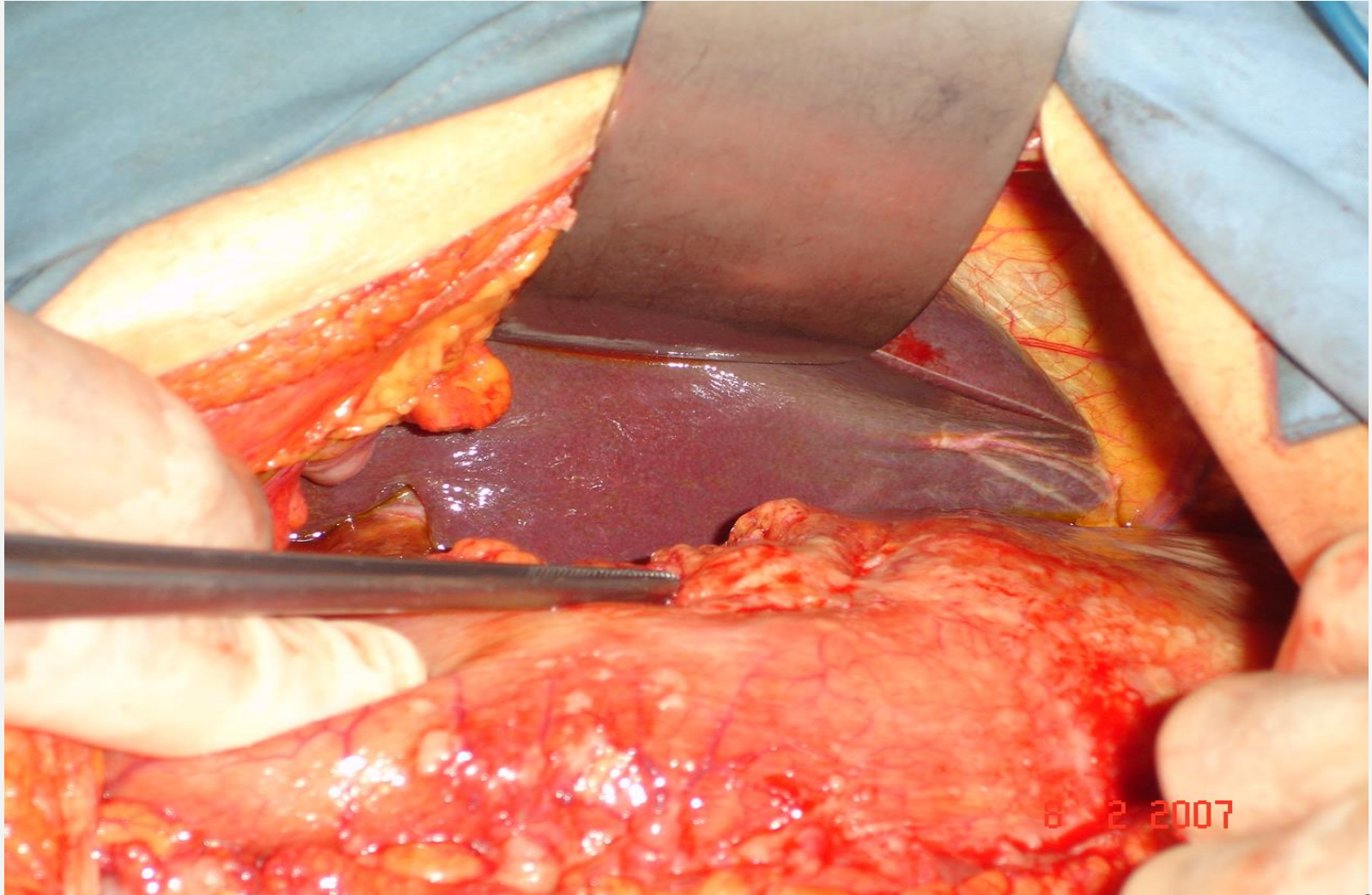


Type 4 **Diffusely infiltrating Ca**

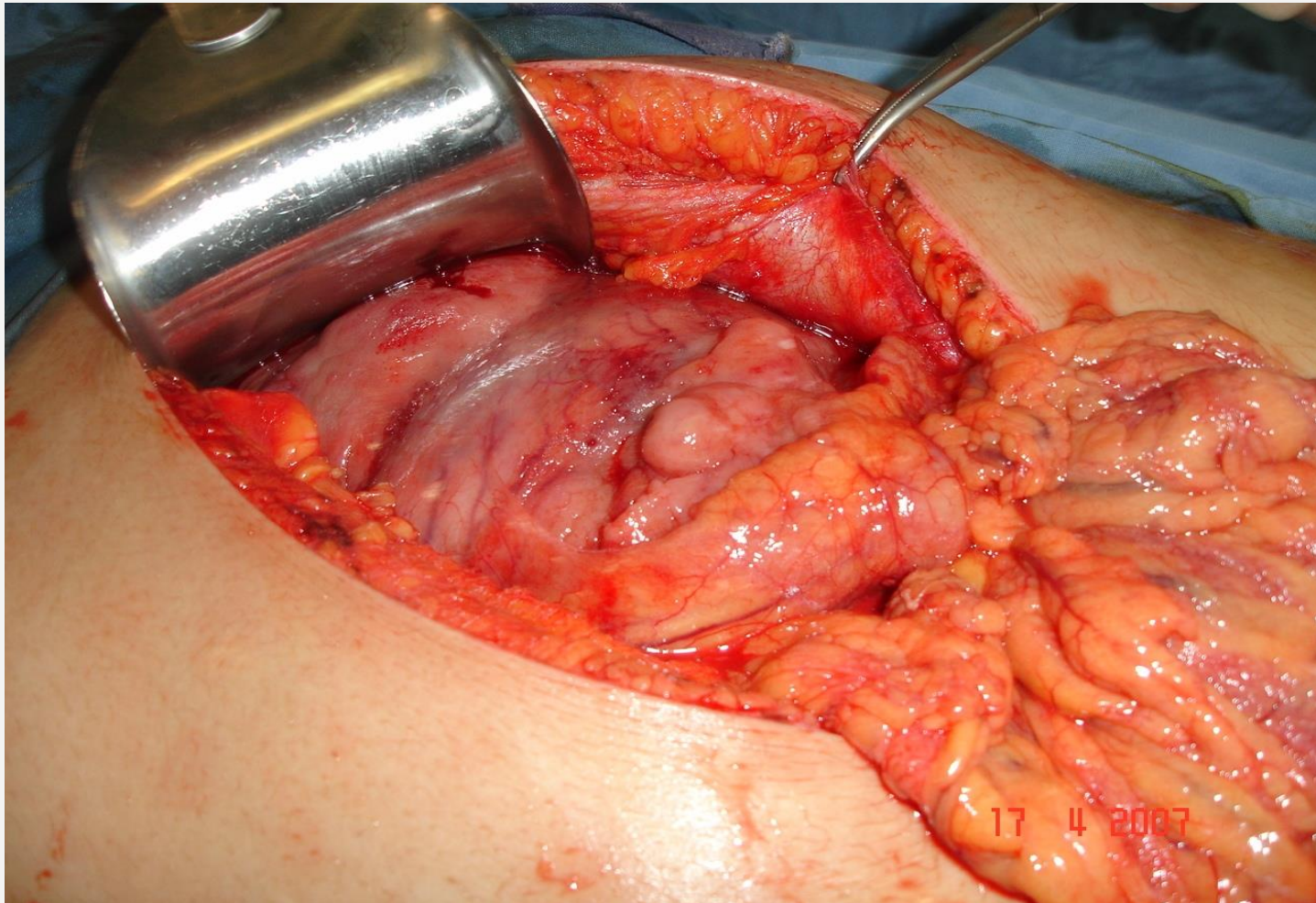
ADVANCED GASTRIC CANCER 1

- Suggests invasion of the muscularis or beyond
- Frequently associated with distant or contiguous spread, have a higher stage
- It represents < 50% of cases in Japan
- > 80% of cases in US are advanced gastric Ca at the time of diagnosis.

ADVANCED GASTRIC CANCER 2



ADVANCED GASTRIC LYMPHOMA



LINITIS PLASTICA



SYMPTOMS & DIAGNOSIS 1

- Symptoms of early gastric cancer are vague and unspecific. They may mimic symptoms of benign gastric ulcer
- Symptoms may not be evident until a tumor is of sufficient size to interfere with gastric motor activity, cause **obstruction**, or cause **bleeding** from an ulcerated tumor
- **Family history** of gastric cancer in 10% of patients

SYMPTOMS & DIAGNOSIS 2

1. Indigestion
2. Anorexia
3. Early satiety
4. Weight loss
5. Abdominal pain or discomfort and ulcer-type pain
6. Bloating of the stomach after meals
7. Nausea and vomiting
8. Hematemesis and melena
9. Dysphasia
10. Weakness and fatigue / Asthenia
11. Signs or symptoms of dissemination



ROUTINE LABORATORY TESTS

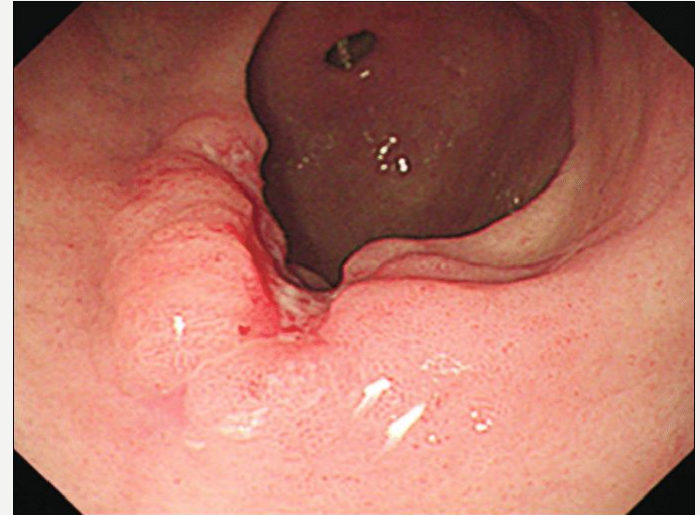
- Hematocrit, CBC, liver function tests, and stool guaiac (A stool test is positive for blood)
- In advanced disease, laboratory evidence of anemia develops
- Liver function tests are usually abnormal with hepatic metastasis.

DOUBLE-CONTRAST BARIUM MEAL

- In Japan screening program, using this technique, 87% of initial subjects are cleared, and 13% are subjected to further examinations.
- Appearance:
 - (a) **Polypoid** mass.
 - (b) **Ulcer crater** lies in a mass and does not extend outside the boundary of the gastric wall. Mucosal folds do **not** radiate toward the centre of the crater, usually > 1 cm. and are surrounded by rigid gastric wall on fluoroscopy.
 - (c) **Nondistensible** stomach.

ENDOSCOPY AND BIOPSY/CYTOLOGY

- Gastritis-like malignant lesions
- Small, plaquelike lesions.
- Polyps or small ulcers.
- Ulcerated lesions have elevated margins with shaggy necrotic centres.
- Extensive tumor plaque or large polypoid mass.
- Linitis plastica is typified by a nondistensible stomach.



ENDOSCOPIC ULTRASONOGRAPHY



COMPUTED TOMOGRAPHY SCAN

- Gastric wall thickening (0.5-4 cm. and correlates with tumor penetration)
- Gastric ulceration (polypoid or sessile lesions)
- Invasion of the gastrohepatic ligament, spleen, or diaphragm
- Distal metastases.

OTHER DIAGNOSTIC MODALITIES.

- **Gastric acid analysis** can diagnose patients with **hypo-** and **achlorhydria**, which are associated with **↑** risk for gastric Ca (should be screened)
- **Molecular biologic techniques**, (e.g. cytologic evaluation for p53 or p21 protein)

TREATMENT 1

- Patients must be evaluated for **comorbid** conditions.
- Patients with profound weight loss and metabolic complications of their cancer should be treated.
- Patients **without** obstruction or bleeding but who have **distal metastases** should **not** be explored
- Patients **with** **obstruction** or **bleeding** should still be considered for exploration, as **palliative resection** is better than palliative bypass)
- In patients with metastatic obstructing proximal gastric tumors, prosthetic **endoesophageal tubes** or **endoscopic laser therapy** can be used

TREATMENT 2

- Surgical resection is the **only** potentially curative therapy.
- The extent of gastric resection should be tailored to the proximal extent of the primary lesion and geared toward obtaining **negative** proximal and distal margins.
- Different resections for distal, middle, and proximal lesions. In diffuse tumors, **total gastrectomy** may be the only option available to achieve adequate margins.

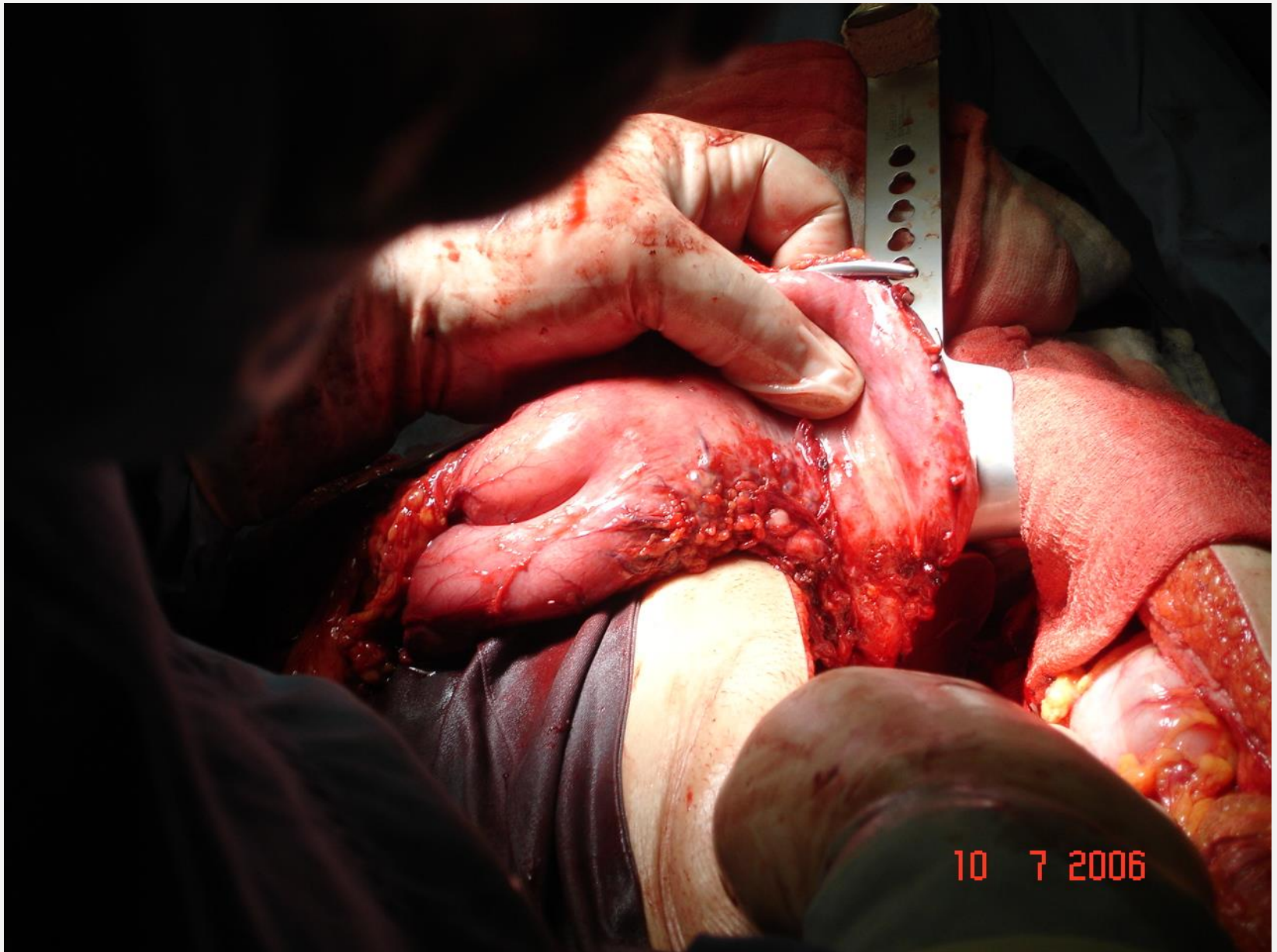
TREATMENT 3

□ Surgical resection and lymphadenectomy can be described as follows:

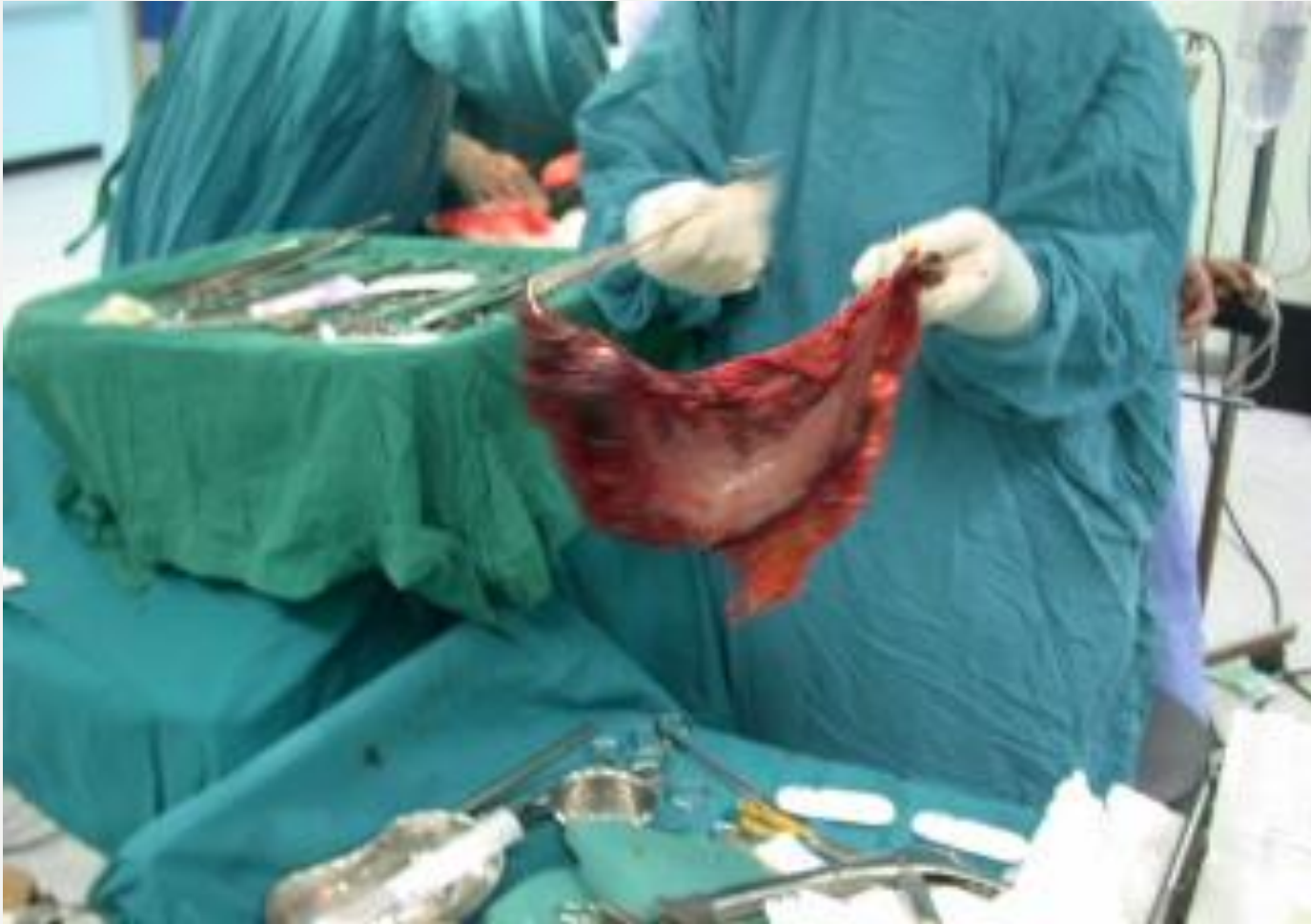
- **D0 resection** = incomplete removal of perigastric LN.
- **D1 resection** = complete removal of perigastric nodes.
- **D2 resection** = D1 +LN along the named arteries of the stomach.
- **D3 resection** = D2 + removal of the nodes of the celiac axis.
- **D4 resection** = D3 + para-aortic nodes.

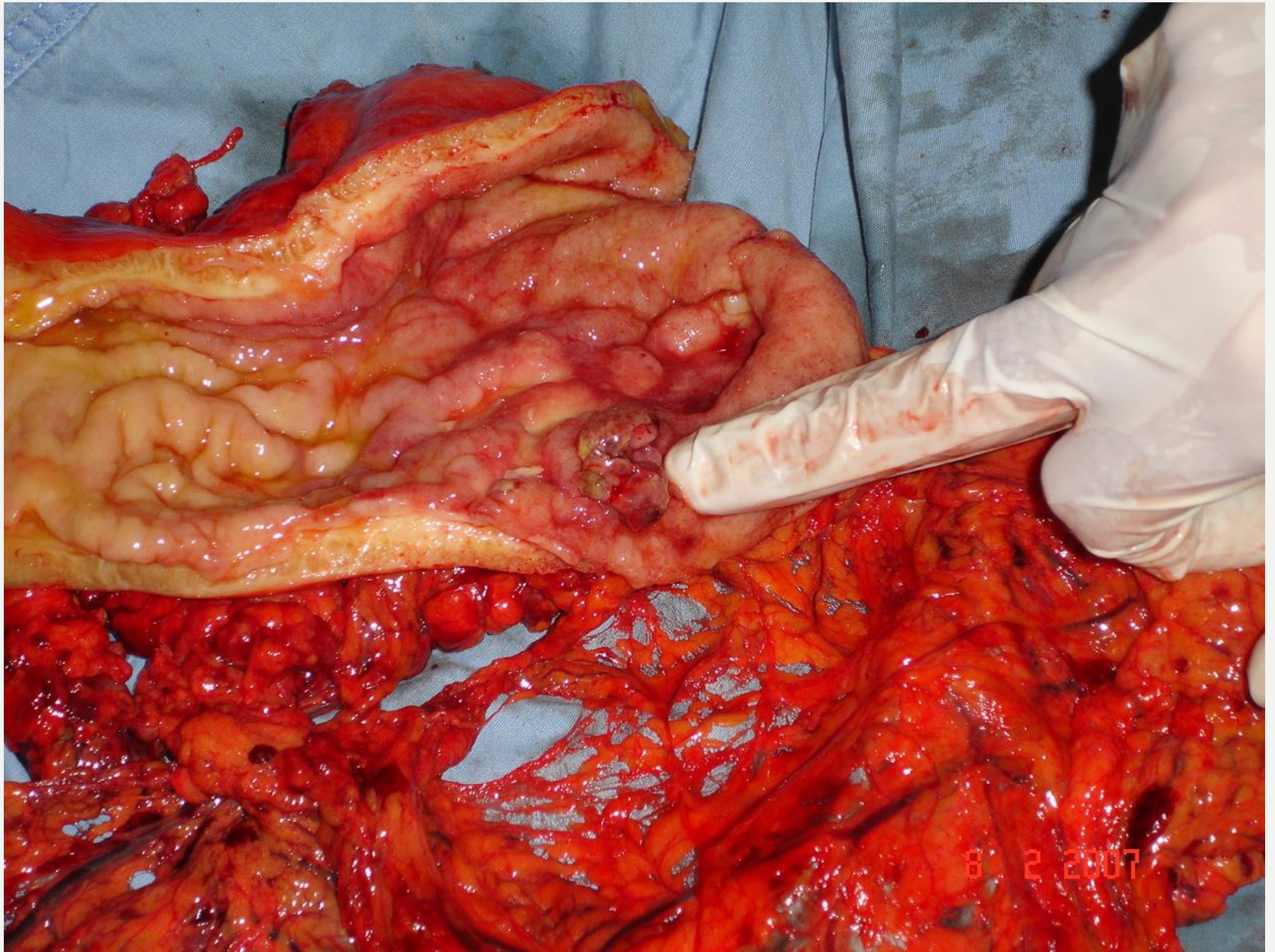
TREATMENT: EARLY GASTRIC CANCER

- D1 resection is usually curative (survival rates of 95%)
- Endoscopic treatment using cauterization, local injection of drugs, and laser therapy



TOTAL GASTRECTOMY





TREATMENT: ADVANCED CANCER

- Gastric resection includes:
 - (a) Subtotal gastrectomy for antral or pyloric lesions.
 - (b) Subtotal or total gastrectomy for middle-third lesions).
 - (c) Total gastrectomy with esophagojejunostomy for proximal-third, GEJ, or extensive middle-third lesions.
- In addition, the perigastric lymph nodes along the lesser and greater curvatures and the lymph nodes along the left gastric artery are typically removed. The lesser and greater omenta are resected.

TREATMENT (JAPANESE EXPERIENCE)

- Using a systematic approach, the standard operation in Japan for advanced cancer is the D2 dissection with removal of N 1 and N 2
- Using this standard operation, they reported a postoperative mortality rate of 0.4% for D2 and D3 resections
- The survival rates over the past 30 years have risen from 71% to 76% in Stage II, from 39% to 63% in Stage IIIA, from 28% to 39% in Stage IIIB, and from 2% to 10% in Stage IV disease

TREATMENT: GEJ CA

- Ca of the cardia and GEJ is becoming more prevalent, roughly doubling in incidence over the last 20 years
- The disease occurs in an older patient population with a high percentage of advanced tumors (50 to 74%)
- Treatment is by a radical operation, usually through a thoracoabdominal approach.

ADJUVANT THERAPY

▪ Chemotherapy

- ❖ Randomized trials showed a survival benefit for the treatment group
- ❖ There is a survival benefit for mitomycin C alone or fluorouracil and mitomycin C.

▪ Chemoradiotherapy

- ❖ Results are mixed.

▪ Chemoimmunotherapy

- ❖ The immune depression encourages the growth of tumor cells in certain patients.
- ❖ Numerous immunomodulators have been found to enhance T-cell function and stimulate natural killer cells.
- ❖ Immunotherapy alone has rarely been shown to be effective against residual tumors.
- ❖ The advantages are greatest in patients with Stage III and IV disease or patients who underwent R0 resection.