Gastric cancer

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- Gastric cancer encompasses a heterogeneous collection of etiologic and histologic subtypes associated with a variety of known and unknown environmental and genetic factors.
- It is a global public health concern, accounting for 700,000 annual deaths worldwide, and currently ranks as the fourth leading cause of cancer mortality, with a 5-year survival of only 20%.
- The incidence and prevalence of gastric cancer vary widely, with Asian/Pacific regions bearing the highest rates of disease.

- Approximately 3% to 5% of gastric cancers are associated with a hereditary predisposition, including a variety of Mendelian genetic conditions and complex genetic traits.

- Gastric cancer has traditionally been subtyped pathologically according to Lauren's1 classification published in 1965 and revised by Carneiro et al.2 in 1995.
- The four histologic categories include:
- (1) glandular/intestinal,
- (2) border foveal hyperplasia,
- (3) mixed intestinal/diffuse, and
- (4) solid/undifferentiated.

- More clinically relevant, the majority of gastric cancers can be subdivided into intestinal type or diffuse type.
- Diffuse gastric tumors frequently feature signet ring cells
- The intestinal subtype is seen more commonly in older patients, whereas the diffuse type affects younger patients and has a more aggressive clinical course.

ETIOLOGY

- Environmental Risk Factors

  diet and lifestyle variables.

- Infectious Risk Factors

  H. pylori infection

  Epstein-Barr virus

Genetics

- More than 70% of cases occur in developing countries, and men have roughly twice the risk of women.
- In 2008, estimates of gastric cancer burden in the United States were 21,500 cases (13,190 men and 8,310 women) and 10,880 deaths. The median age at diagnosis for gastric cancer is 71 years, and 5-year survival is approximately 25%.
- Only 24% of stomach cancers are localized at the time of diagnosis, 30% have lymph node involvement, and another 30% have metastatic disease. Survival rates are predictably higher for those with localized disease, with corresponding 5-year survival rates of 60%.

PATHOLOGY AND TUMOR BIOLOGY

- Approximately 95% of all gastric cancers are adenocarcinomas.

PATTERNS OF SPREAD

- Carcinomas of the stomach can spread by local extension to involve adjacent structures and can develop lymphatic metastases, peritoneal metastases, and distant metastases.
- These extensions can occur by the local invasive properties of the tumor, lymphatic spread, or hematogenous dissemination.

CLINICAL PRESENTATION AND PRETREATMENT EVALUATION

- Because of the vague, nonspecific symptoms that characterize gastric cancer, many patients are diagnosed with advanced-stage disease.
- Patients may have a combination of signs and symptoms such as weight loss (22% to 61%)37; anorexia (5% to 40%); fatigue, epigastric discomfort, or pain (62% to 91%); and postprandial fullness, heart burn, indigestion, nausea, and vomiting (6% to 40%). None of these unequivocally indicates gastric cancer. In addition, patients may be asymptomatic (4% to 17%). Weight loss and abdominal pain are the most common presenting symptoms at initial encounter. Weight loss is a common symptom, and its clinical significance should not be underestimated.
- Dewys et al. found that in 179 patients with advanced gastric cancer, >80% of patients had a >10% decrease in body weight before diagnosis. Furthermore, patients with weight loss had a significantly shorter survival than did those without weight loss

- Up to 25% of the patients have history/symptoms of peptic ulcer disease. A history of dysphagia or pseudoachalasia may indicate the presence of a tumor in the cardia with extension through the gastroesophageal junction. Early satiety is an infrequent symptom of gastric cancer but is indicative of a diffusely infiltrative tumor that has resulted in loss of distensibility of the gastric wall.

- Delayed satiety and vomiting may indicate pyloric involvement. Significant gastrointestinal bleeding is uncommon with gastric cancer; however, hematemesis does occur in approximately 10% to 15% of patients, and anemia in 1% to 12% of patients. Signs and symptoms at presentation are often related to spread of disease.

- Ascites, jaundice, or a palpable mass indicate incurable disease. The transverse colon is a potential site of malignant fistulization and obstruction from a gastric primary tumor. Diffuse peritoneal spread of disease frequently produces other sites of intestinal obstruction.

- A large ovarian mass (Krukenberg's tumor) or a large peritoneal implant in the pelvis (Blumer's shelf), which can produce symptoms of rectal obstruction, may be palpable on pelvic or rectal examination.

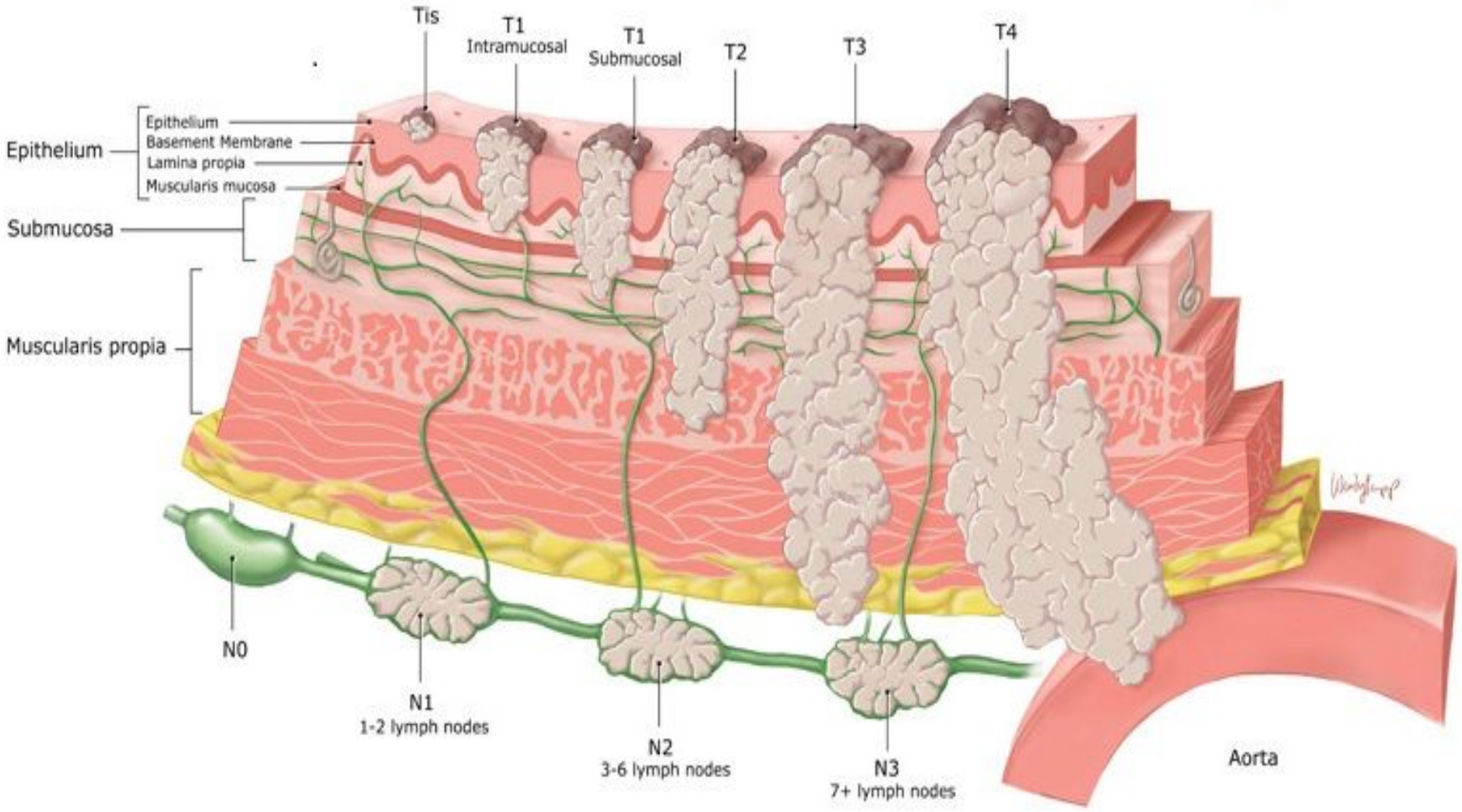
- Nodular metastases in the subcutaneous tissue around the umbilicus (Sister Mary Joseph's node) or in peripheral lymph nodes such as in the supraclavicular area (Virchow's node) or axillary region (Irish's node) represent areas in which a tissue diagnosis can be established with minimal morbidity. There is no symptom complex that occurs early in the evolution of gastric cancer that can identify individuals for further diagnostic measures. However, alarming symptoms (dysphagia, weight loss, and palpable abdominal mass) are independently associated with survival;

- increased number and the specific symptom is associated with mortality.

PRETREATMENT STAGING

- Tumor markers – CEA, CA19-9,CA125
- EUS
- CT
- MRI
- PET-CT
- Staging Laparoscopy and Peritoneal Cytology

STAGING, CLASSIFICATION, AND PROGNOSIS



TREATMENT OF LOCALIZED DISEASE

- Stage I Disease (Early Gastric Cancer)
- Endoscopic Mucosal Resection
- Limited Surgical Resection
- Gastrectomy

Stage II and Stage III Disease

- GASTRECTOMY

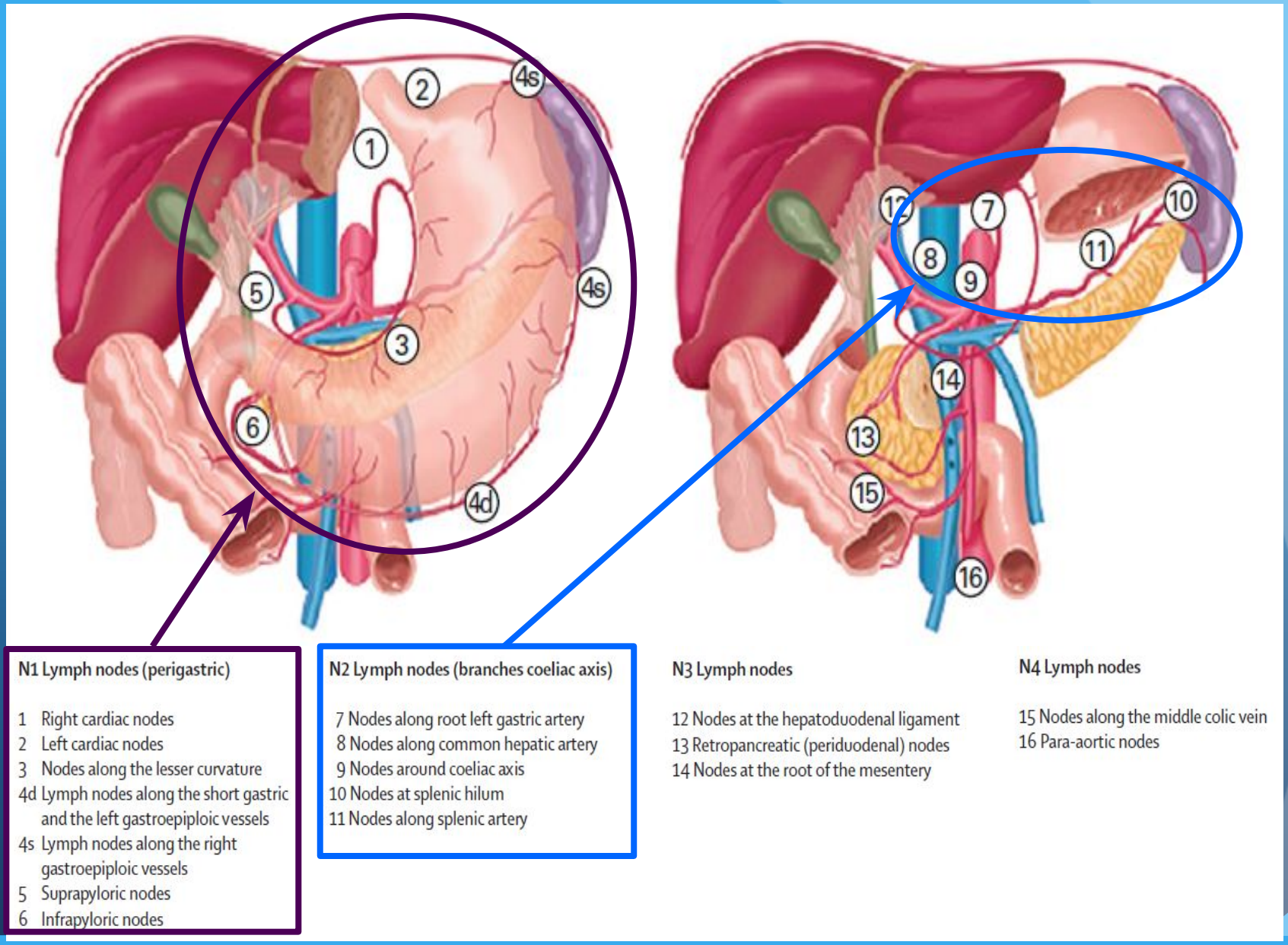
Adjuvant Therapy

- Adjuvant therapy indicates administration of a treatment following a potential curative resection of the primary tumor and regional lymph nodes.
- Therapy after resections that leave microscopic or gross disease are not adjuvant treatment, but rather therapy for known disease, which is palliative in nature.
- Neoadjuvant chemotherapy involves the use of systemic treatment before potentially curative surgery.

- There are several theoretical reasons for beginning adjuvant therapy soon after operation (perioperative chemotherapy). Studies have shown a rapid increase in cell growth of metastases after a primary tumor has been removed related to a decline in certain circulating factors, which serve to inhibit angiogenesis or other cell-cycle promotors, once the primary tumor is removed.
- Perioperative or neoadjuvant chemotherapy has been studied because the ability to perform a R0 resection in gastric cancer is difficult. In addition, a substantial number of patients undergoing gastrectomy have prolonged recovery.

- Neoadjuvant chemotherapy has a dual goal: allowing a higher rate of R0 resections and treatment of micrometastatic disease early in the course of treatment.

D1 vs D2 Lymphadenectomy



N1 Lymph nodes (perigastric)

1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4d Lymph nodes along the short gastric and the left gastroepiploic vessels
4s Lymph nodes along the right gastroepiploic vessels
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)

7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around coeliac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes

12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (periduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes

15 Nodes along the middle colic vein
16 Para-aortic nodes

Rationale for Preoperative Therapy in Proximal Gastric Cancer

- Studies demonstrating benefit of preoperative chemotherapy over surgery alone[1]
- Evidence of role of induction chemoradiation therapy in distal esophageal CA[2]

[1] MAGIC Trial. Cunningham et al. Radiother Oncol 104 (2012)
[2] CROSS Trial. van Hagen et al. NEJM (2012)

Importance of Preoperative Staging When Considering Neoadjuvant Therapy

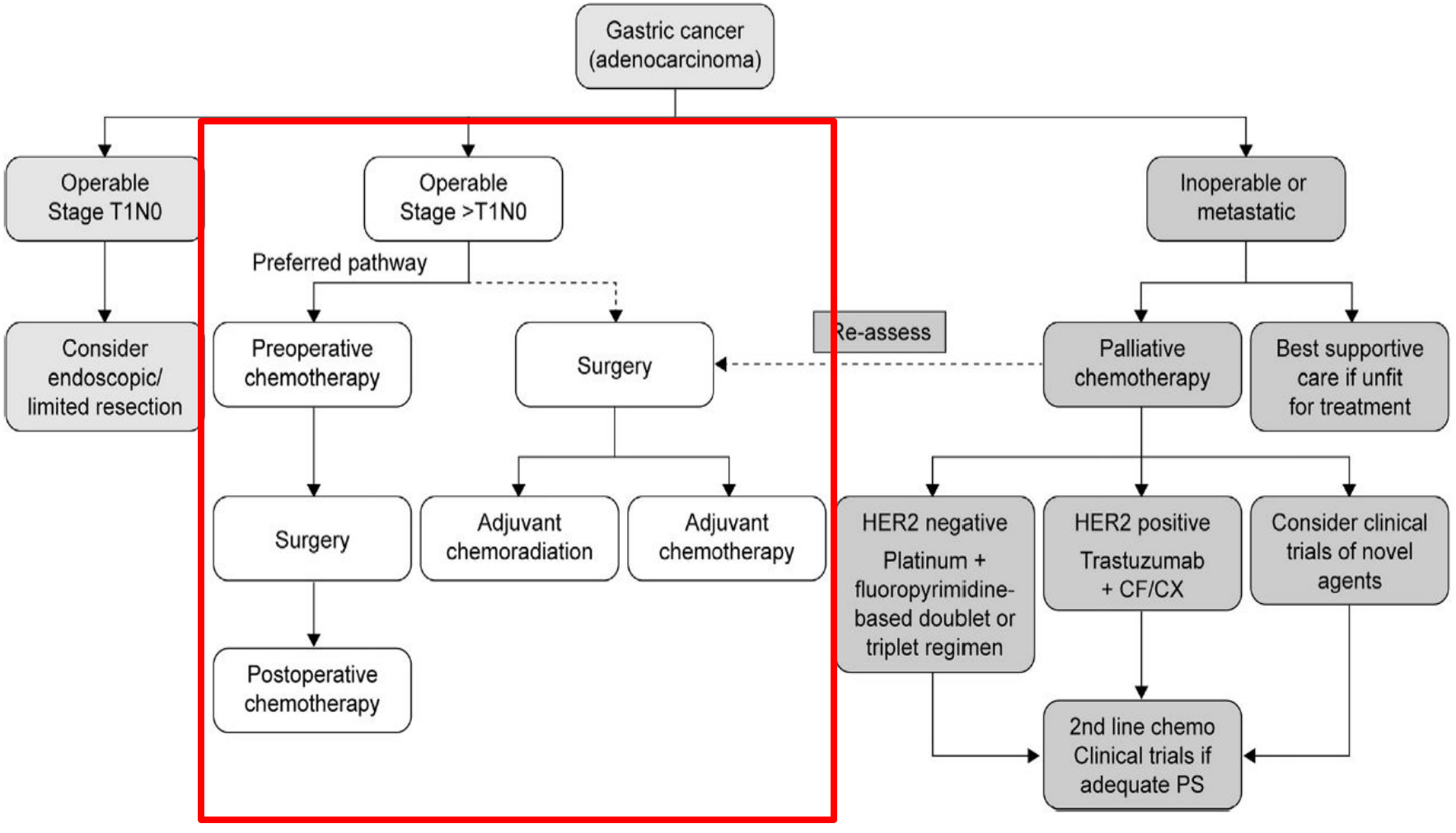
- Accuracy of predicting nodal involvement is 60-80%
- Surgery alone may be sufficient for Stage II disease
- Neoadjuvant therapy may be overtreating some patients

Rationale for Up Front Surgery in Patients With Gastric Cancer

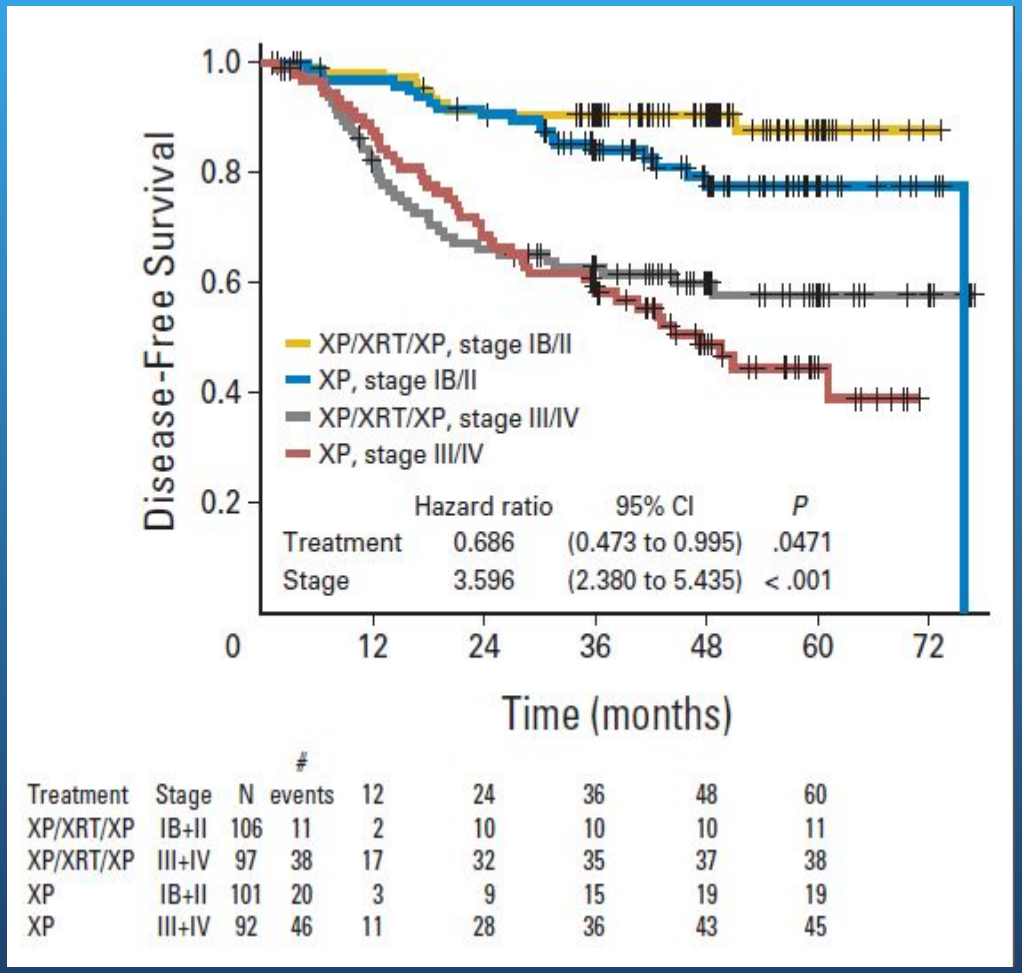
- Pathologic staging may result in more appropriate choice of adjuvant therapy (accurate stage II vs III, D1 vs D2, margins).
- Symptomatic patients may require initial surgery.
- In reality, gastrectomy is often performed before MDT consultation.

Algorithm for Management of Gastric Cancer*

*ESMO-ESSO-



Post-Operative Chemo vs Chemoradiation: ARTIST Trial



Treatment	Stage	N	# events	12	24	36	48	60
XP/XRT/XP	IB+II	106	11	2	10	10	10	11
XP/XRT/XP	III+IV	97	38	17	32	35	37	38
XP	IB+II	101	20	3	9	15	19	19
XP	III+IV	92	46	11	28	36	43	45

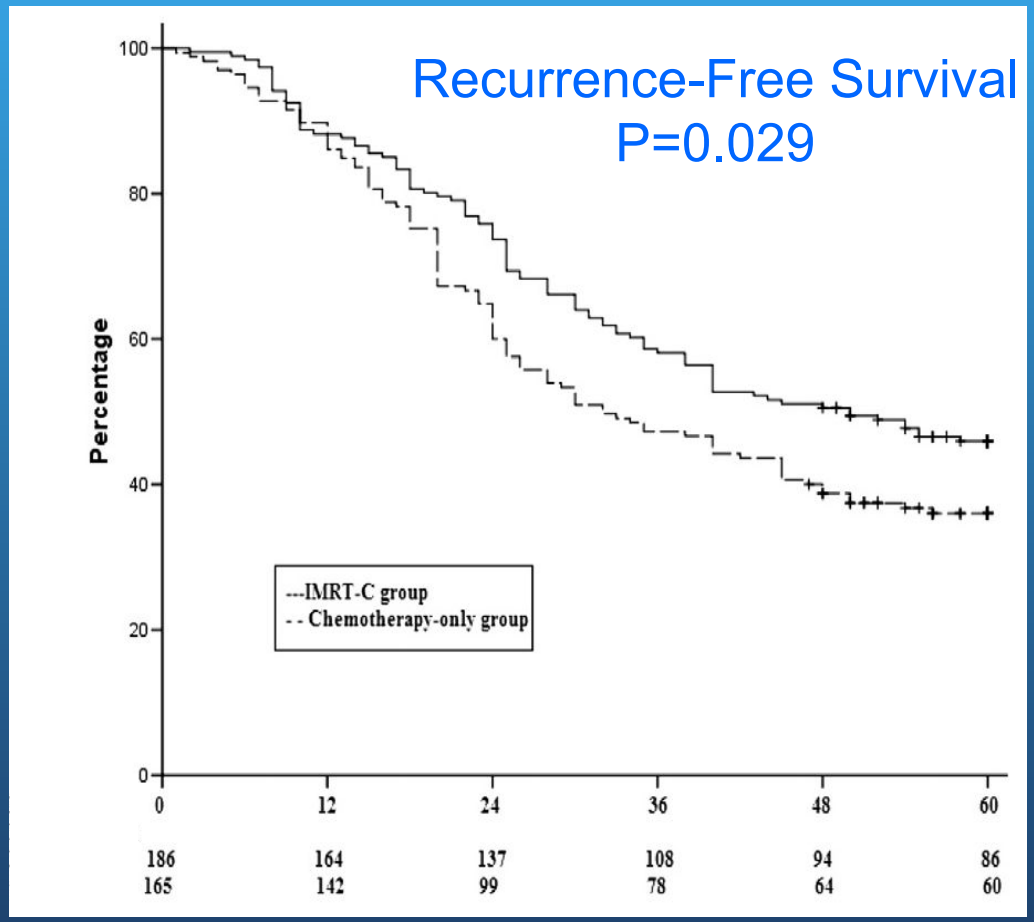
- Samsung University
- 458 patient RCT
- D2 gastrectomy
- ~5% proximal CA

Postoperative adjuvant Cap-Cis ± RT

- No difference in DFS
- No difference in locoregional rec

Lee et al. JCO Jan 2012

Post-Operative Chemo vs Chemoradiation: Nanjing University



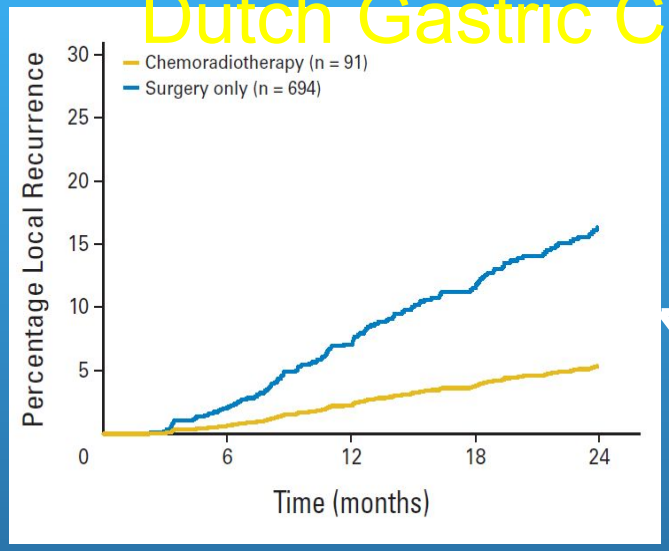
- 380 patients
- Randomized trial
- All D2 gastrectomy
- ~10% GE junction

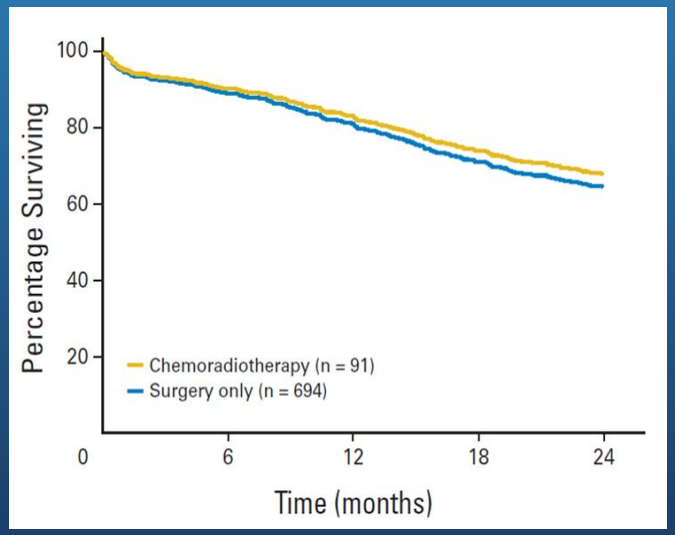
Postoperative adjuvant 5FU-LV ± IMRT

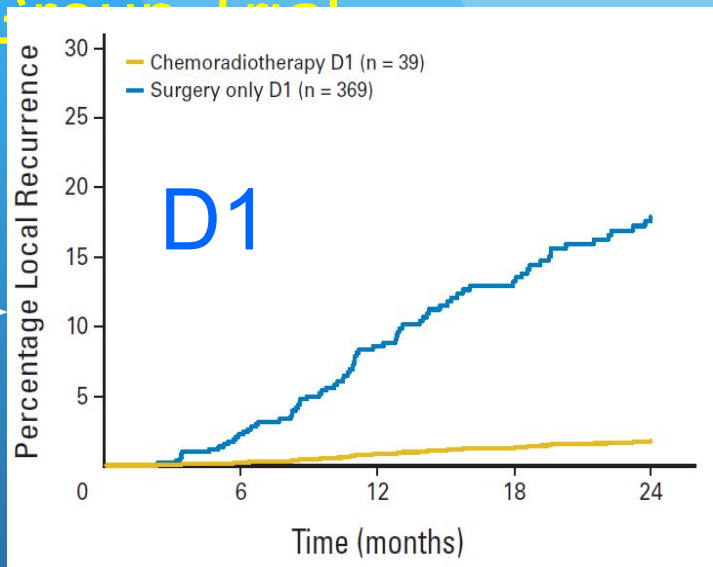
- Improved RFS with IMRT (50 vs 32 mo)
- No difference in

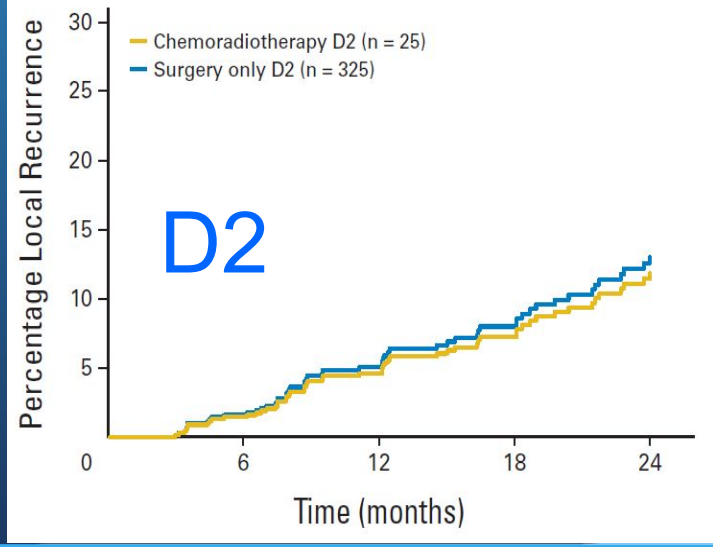
Zhu et al. Radiother Oncol 104 (2012)

Impact of Extent of Surgery and Postop Chemoradiation: Dutch Gastric Cancer Group Trial



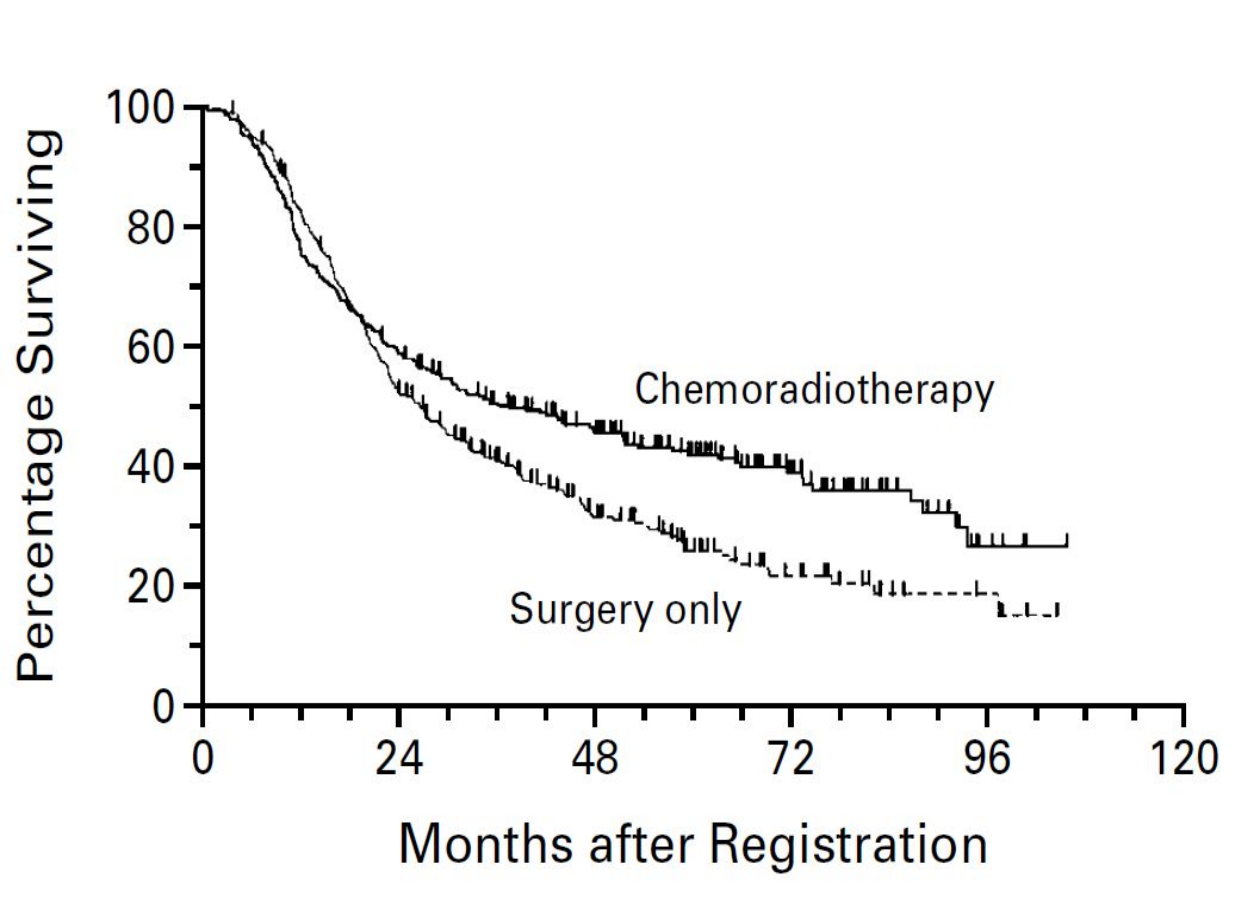






Dikken et al. JCO May 2010

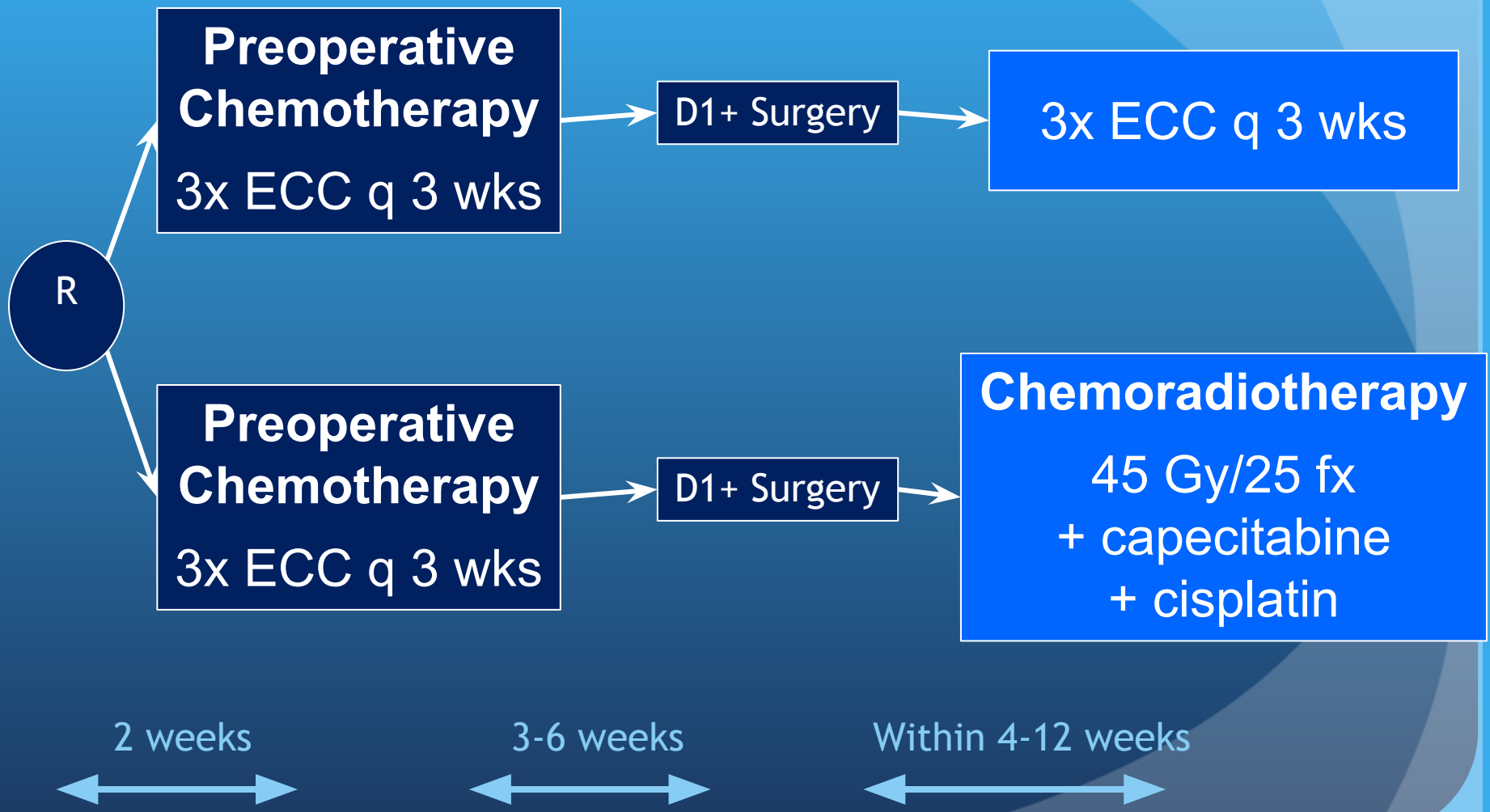
Chemoradiation After Surgery Versus Surgery Alone for Gastric and GEJ Adenocarcinoma



- 20% GE Junction
- Criticized for inadequate surgical radicality

MacDonald et al. NEJM 2001

CRITICS Study



Summary

1. While preoperative therapy may be preferred in most cases, initial gastrectomy is being commonly performed.
2. While R0 gastrectomy with D2 lymphadenectomy is recommended, less radical surgery is common.
3. Chemoradiation appears to have a role in reducing local recurrence.
4. Postoperative chemoradiation should be considered when managing a post-op patient, particularly when <D2 gastrectomy was performed.

Metastatic gastric cancer