

# Management of G.E. Junction – Adenocarcinoma

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# Adenocarcinoma gastroesophageal junction

- \* Increasing incidence in the western world
- \* Borderline location
- \* Controversy exists in many aspects
  - \* Definition of site
  - \* Classification
  - \* Management

# Gastroesophageal junction (GEJ) - Definition

- Not standardized.
- Anatomically
  - At angle of His, tubular esophagus joins the cardia.
- Physiologically
  - The distal border of the lower esophageal sphincter, as determined by manometry.
- Endoscopically
  - The most proximal extent of the longitudinal gastric folds
- Pathologically
  - The most proximal aspect of the gastric folds.

# Gastroesophageal junction (GEJ) adenocarcinoma - Definition

- \* AJCC 7<sup>th</sup> edition
  - \* “Cancers whose epicenter is in the lower thoracic esophagus , GEJ or within the proximal 5 cm of stomach that extent into the GEJ or esophagus are stage grouped similar to adenocarcinoma of the esophagus”






# Siewert's Classification

- \* Alarming rise in the incidence and prevalence of adenocarcinoma at the oesophagogastric junction.
- \* Much discrepancy exists in the current literature about the classification and optimal management of this tumour.
- \* Inability of the current Union Internacional Contra la Cancrum (UICC/AJCC) system to classify and stage these lesions.
- \* A clear range of tumors arise in the oesophagus, the oesophagogastric junction, and the stomach in terms of epidemiology, genetics, patterns of spread, and prognosis.

# Siewert's Classification

- \* Type I tumour
  - \* Adenocarcinoma of the distal esophagus which usually arises from an area with specialized intestinal metaplasia of the esophagus (i.e. Barrett's esophagus) and which may infiltrate the esophagogastric junction from above.
- \* Type II tumour
  - \* True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the esophagogastric junction; this entity is also often referred to as 'junctional carcinoma'.
- \* Type III tumour
  - \* Subcardial gastric carcinoma which infiltrates the esophagogastric junction and distal esophagus from below

# Justification for the Siewert's classification

	Type 1	Type 2	Type 3
Mean age	60·9	60·2	62·0
Sex ratio (M :F)	8·2 :1	5·1 :1	2·4 :1
Hiatus hernia (%)	72	28	21
History of GORD (%)	84	42	29
Barrett's oesophagus (%)	81	11	2
intestinal metaplasia gastric cardia (%)	75	32	9
undifferentiated tumors (%)	51	56	71
'non-intestinal' growth pattern (%)	24	34	45
direction of lymphatic spread	 	 	

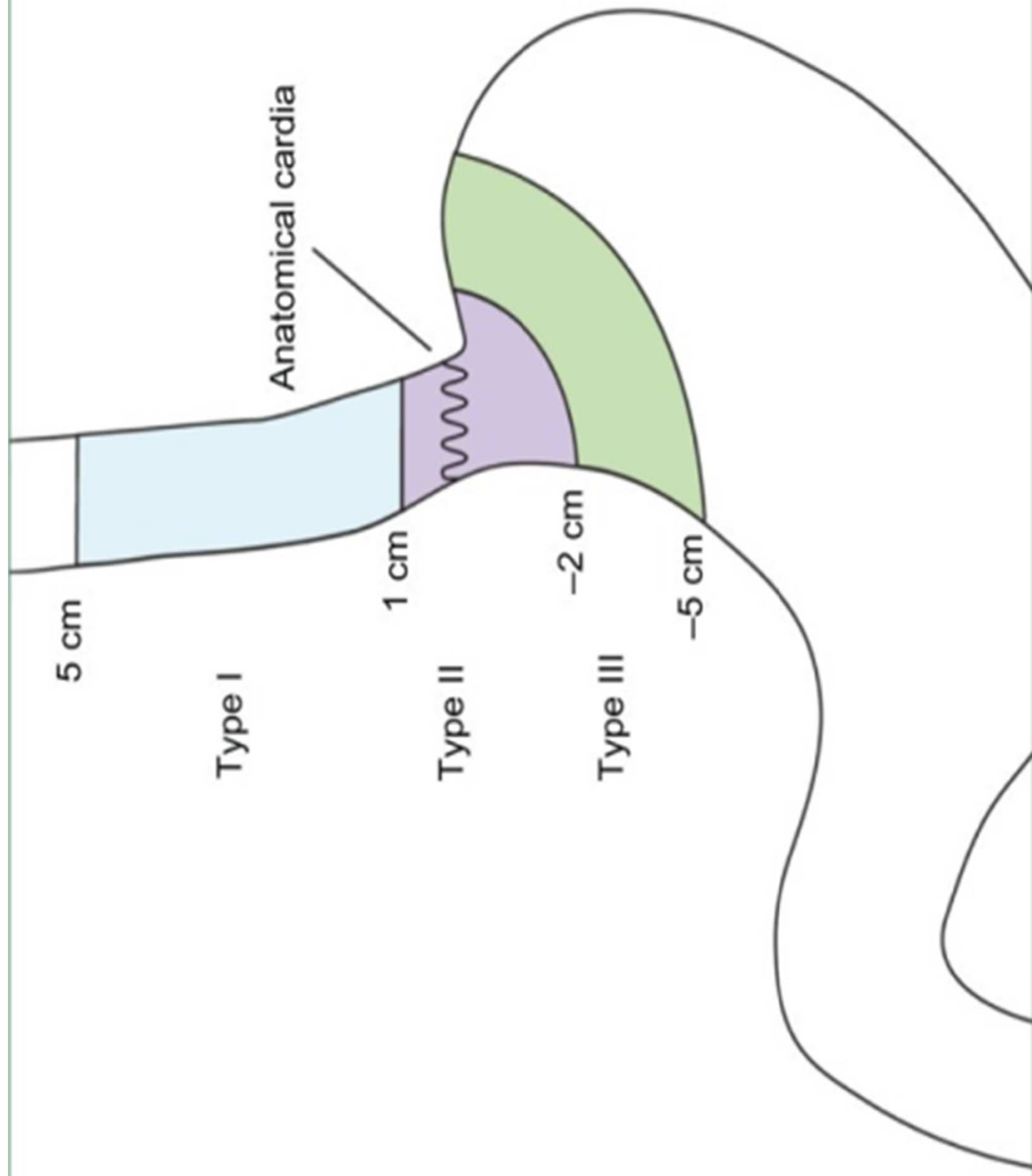
# Siewert's Classification

- \* This classification is morphological based on location of tumor centre
- \* Performed by
  - \* Contrast radiography
  - \* Endoscopy
  - \* CT scan
  - \* Intraoperative appearance
- \* International Gastric Cancer Association (IGCA) and the International Society for Diseases of the Esophagus (ISDE) consensus conference in 1998 agreed that the classification outlined above should form the basis for defining, assessing and reporting treatment of adenocarcinoma arising in the vicinity of the esophagogastric junction.



# Modified Siewert's classification: (C J. Shearer)

- \* **Gastro-esophageal junction (GEJ):-** The proximal margin of the gastric folds and the point at which the tubular oesophagus flares into the sac-like stomach
- \* **Type 1 :-** The centre of the cancer or more than two-thirds of the identifiable tumour mass is located more than 1 cm proximal to the anatomical GEJ
- \* **Type 2 :-** The centre of the cancer or tumour mass is located within an area extending from 1 cm proximal to the GEJ to 2 cm distal to it.
- \* **Type 3 :-** The centre of the tumour or more than two thirds of the tumour mass is located more than 2 cm below the GEJ.

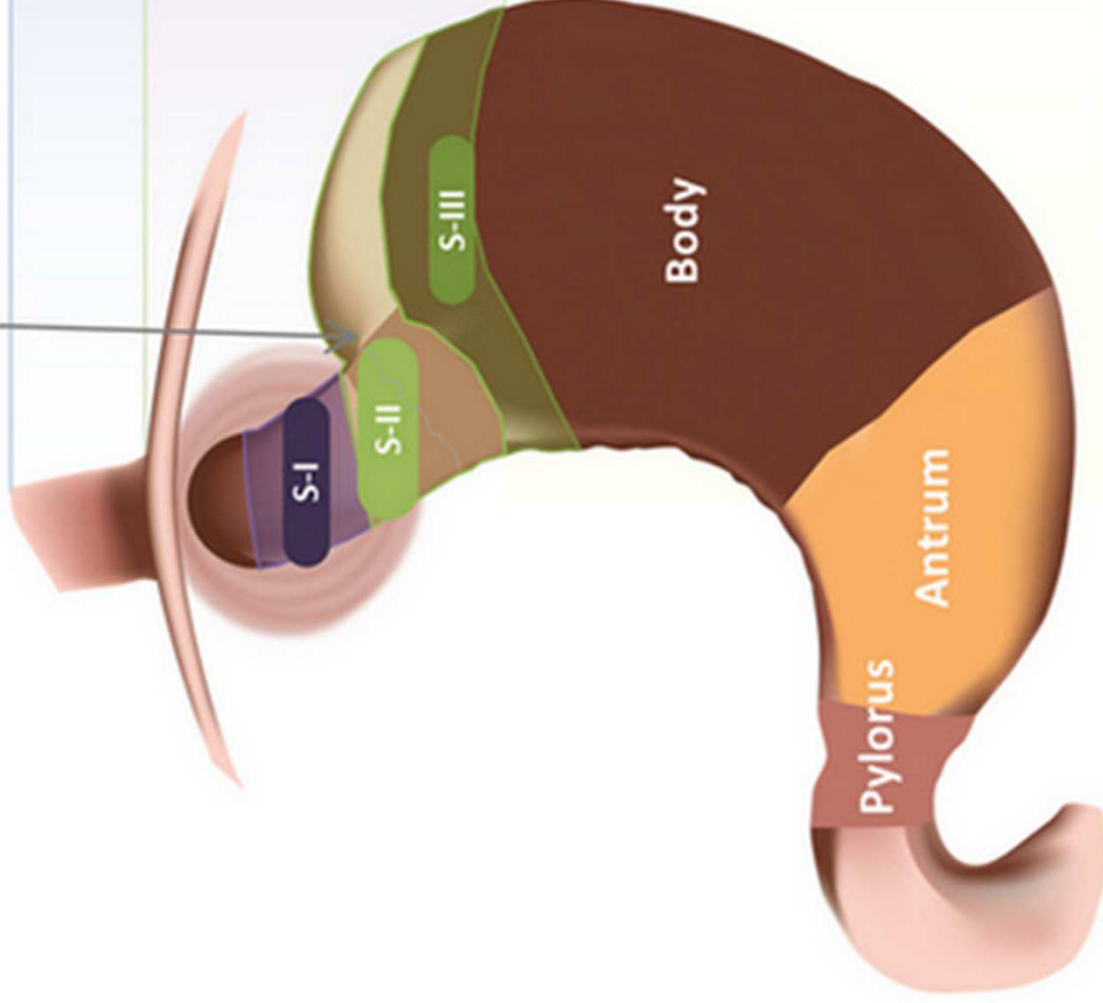


Anatomical  
EGJ

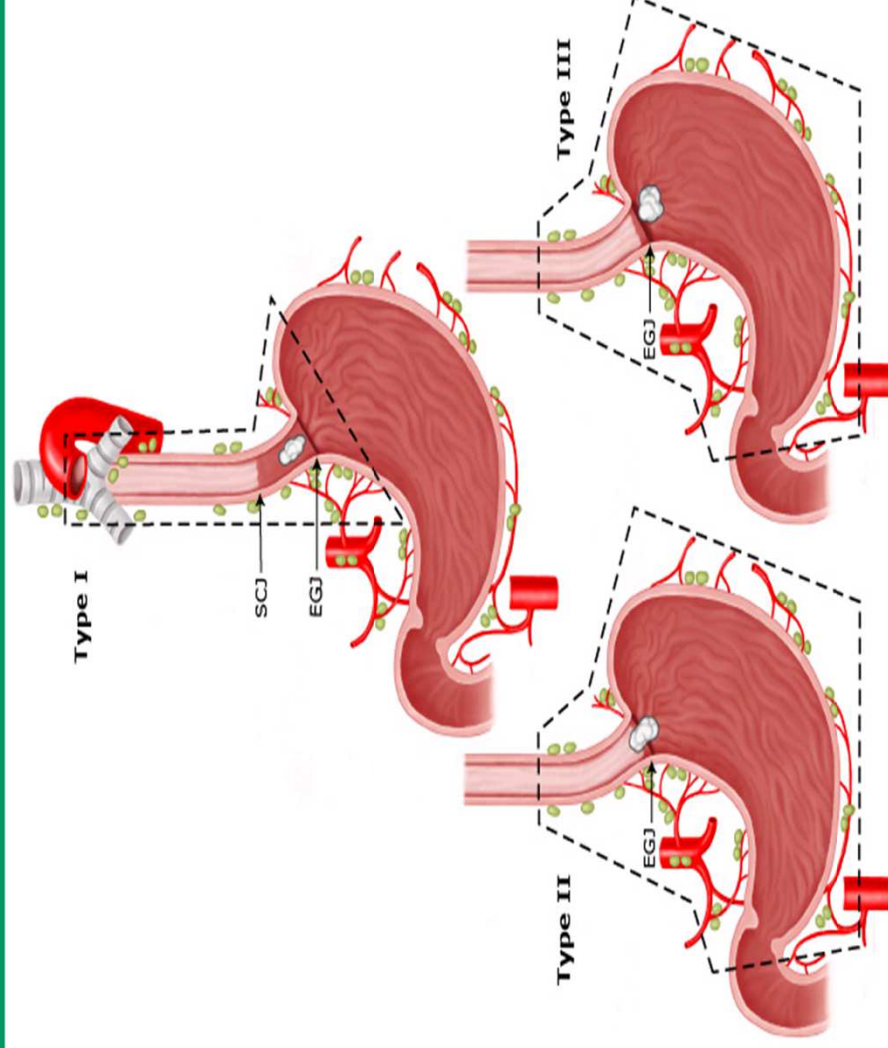
Esophageal  
(SCC)

EGJ (AC)  
With Siewert (S)  
Classification

Gastric/Stomach  
(AC)



## Definition and extent of resection for type I, II, and III adenocarcinoma of esophagogastric junction



These figures represent the Siewert classification for tumors arising at the esophagogastric junction (EGJ) and the extent of the surgical resection for an EGJ adenocarcinoma, including regional lymph nodes, based upon the Siewert classification.

Type I adenocarcinoma is located in the distal esophagus and is resected by a subtotal gastrectomy, subtotal esophagectomy, and regional lymphadenectomy.

Type II adenocarcinoma arises from the cardia or the EGJ and is resected by a total gastrectomy, distal esophagectomy, and regional lymphadenectomy.

Type III adenocarcinoma originates in the subcardial gastric location, infiltrates the EGJ and distal esophagus from below, and is resected by a total gastrectomy, distal esophagectomy, and regional lymphadenectomy.

Based on information from: Mariette C, Biesse N, Gronnier C, Triboulet JP. Oesophagogastric junction adenocarcinoma: which therapeutic approach? *Lancet Oncol* 2011; 12:296.

# Adenocarcinoma of the Esophagogastric Junction: Surgical Therapy Based on 1602 Consecutive Resected Patients

M Feith, H J. Stein, J.R Siewert

- \* Between July 1982 and December 2005,
- \* Prospectively collected data of curative surgery of 1602 patients.
- \* Department of Surgery, Technische University Munich.
- \* Classified according to the Siewert's type.

# Adenocarcinoma of the Esophagogastric Junction: Surgical Therapy Based on 1602 Consecutive Resected Patients

M Feith, H J. Stein, J.R Siewert

## \* Procedure

- \* Type I :- Radical transmediastinal or transthoracic en bloc esophagectomy with resection of the proximal stomach.
- \* Type II :- Extended gastrectomy with transhiatal resection of the distal esophagus.
- \* Type III :- Extended total gastrectomy with transhiatal resection of the distal esophagus

# Results

	Type 1 621	Type 2 485	Type 3 496	Total 1602	p
Age	61 ± 10.5	62 ± 11.4	64 ± 12.1	62 ± 11.3	ns
Male: female ratio	10.7:1	4.9:1	2.2:1	4.5:1	<.01
intestinal metaplasia	79.5%	5.6%	0.8%	32.7%	<.01
intestinal growth pattern	80.9%	55.4%	38.5%	60.1%	<.01
undifferentiated tumors	54.4%	60.2%	73.4%	62%	<.01

# Results

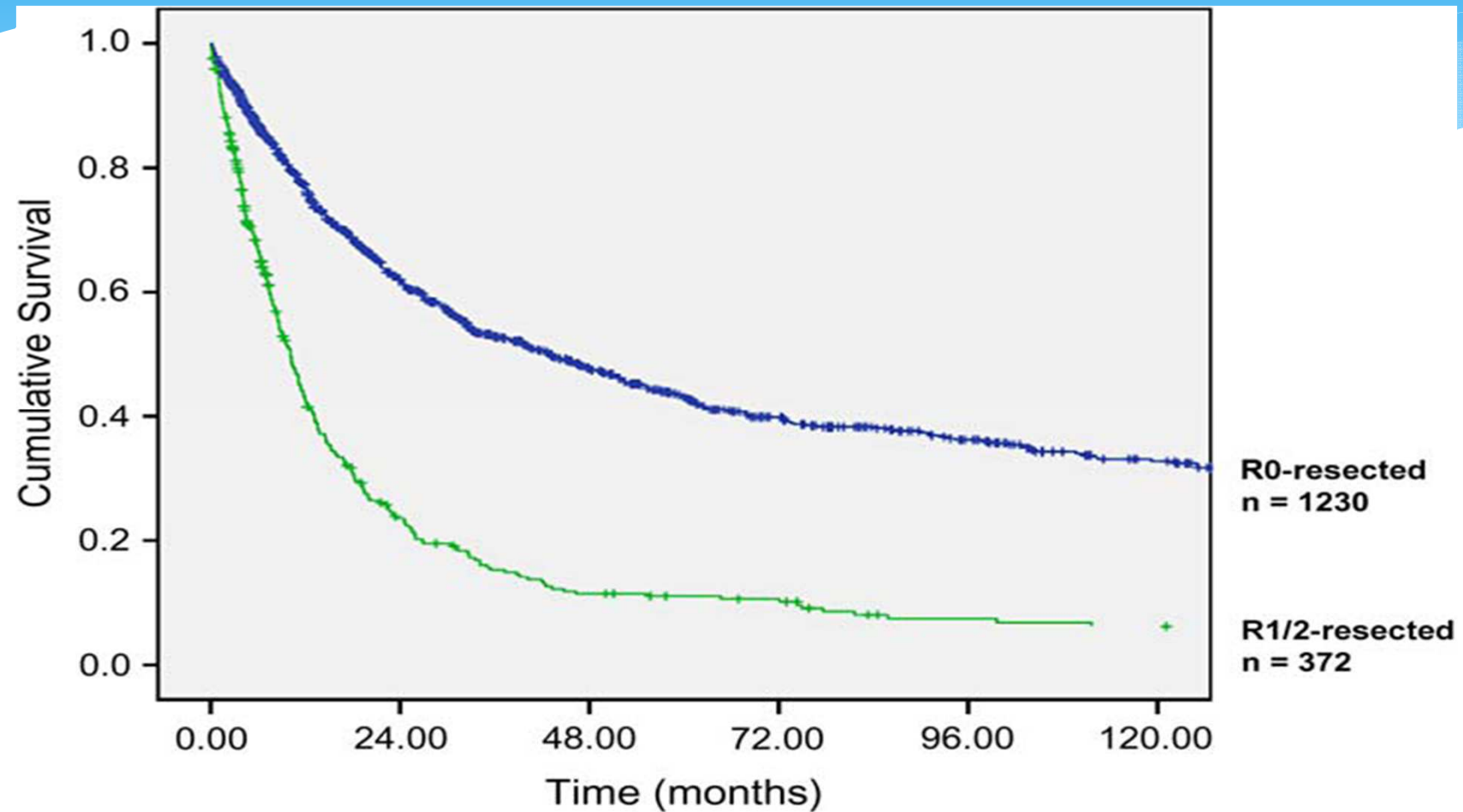
- \* Five year survival :- **37.7%**
- \* Ten year survival:- **26.4%**
- \* Multivariate analysis for independent prognostic factors
  - \* R0 resection
  - \* pN category
  - \* M category
  - \* T category



# Results

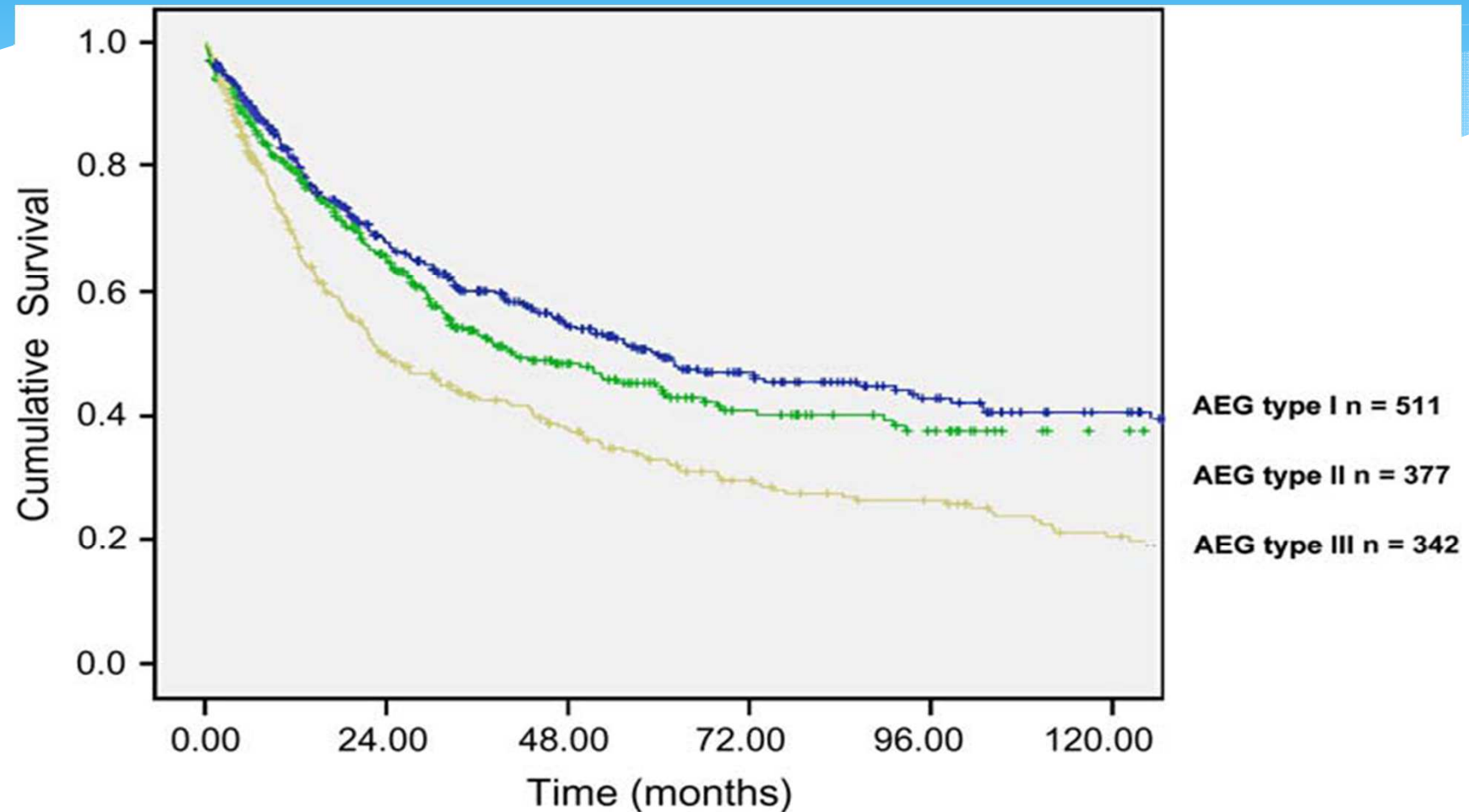
- \* On univariate analysis
  - \* long-term survival was significantly better in patients who had AEG types I and II tumors ( $P < .01$ ).
- \* On multivariate Cox regression analysis the tumor type had no independent effect on long-term prognosis.

Overall 10-year Kaplan Meier survival rates of 1602 consecutive patients who had resected AEG. Complete macroscopic and microscopic tumor resection (R0) versus microscopic or macroscopic residual disease after resection (R1/2);  $P < .0001$ .



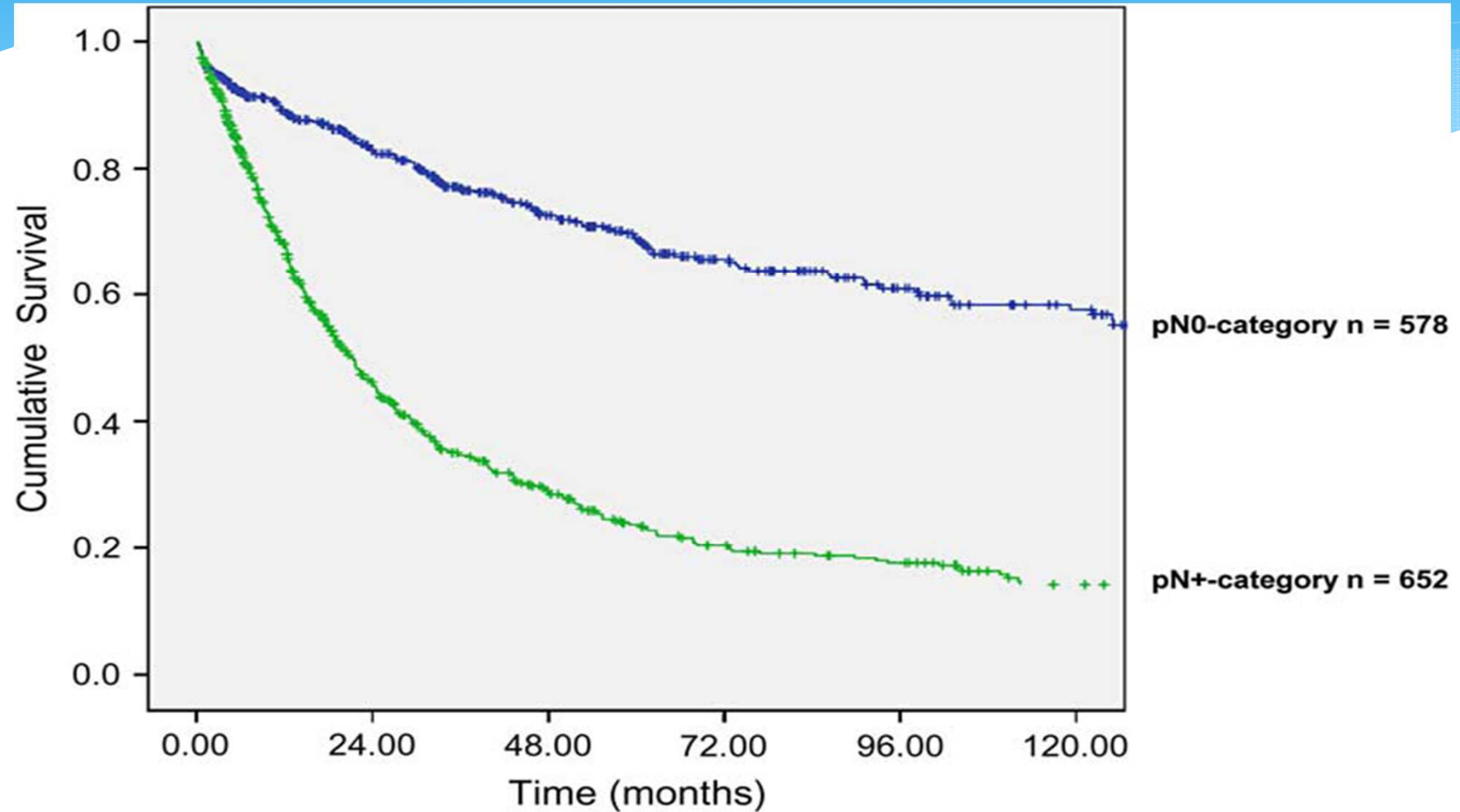
The 10-year Kaplan Meier survival rates of 1230 patients who had Ro-resected AEG.

AEG type I versus AEG type II versus AEG type III;  $P \neq .01$



The 10-year Kaplan Meier survival rates of 1230 patients who had R0-resected AEG.

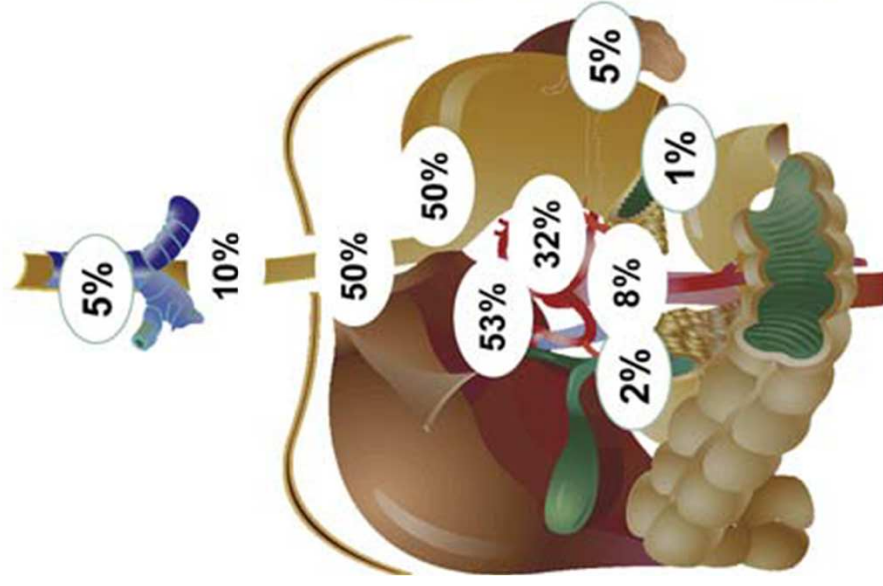
Lymph node status: pN0 category versus pN+ category;  $P < .0001$ .



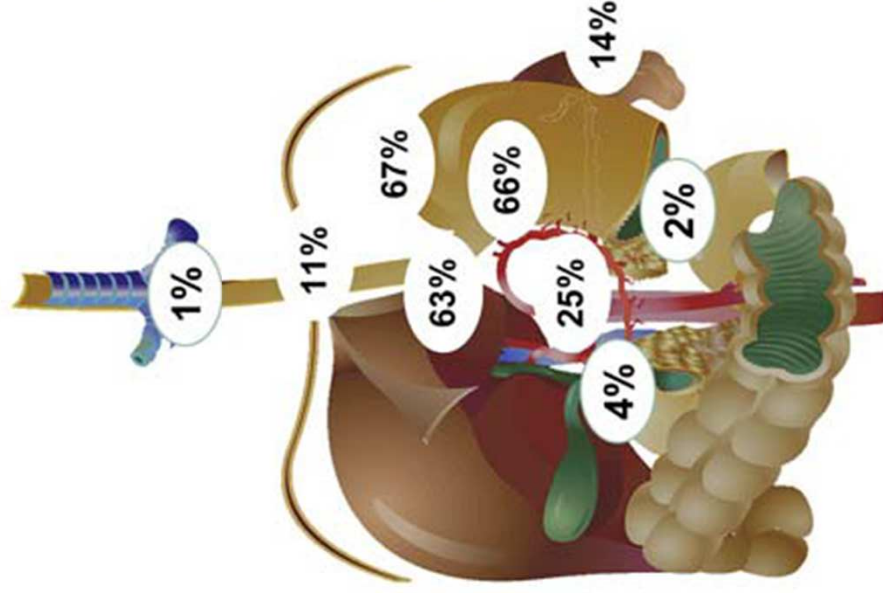
# Lymph node spread pattern

	Type 1	Type 2	Type 3
Left paracardial	50%	67%	49%
Right paracardial	53%	63%	52%
Lower post medi	50%	12%	
upper mediastinum	15%		
lesser curvature		66%	85%
L gas., spl.&celiac		25%	39%
great curvature			33%

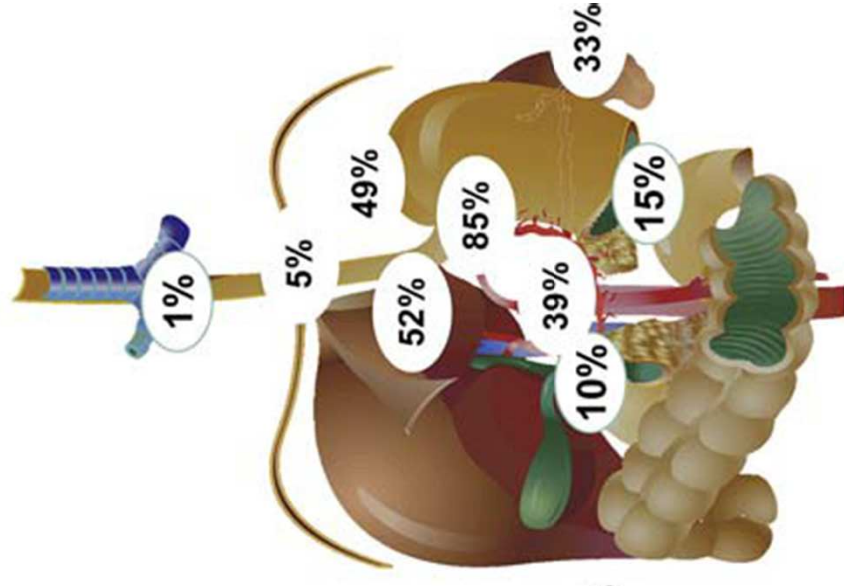
**AEG type I**



**AEG type II**



**AEG type III**



# Summary

- \* Siewert's typing is increasingly used world wide.
- \* Biologic and demographic data show differences between type I , type II and type III tumors.
- \* Type III tumors
  - \* Represent a special class of proximal gastric carcinoma,
  - \* High rate of advanced and undifferentiated tumors
  - \* Requires treatment according to the well-established gastric cancer guidelines.
- \* Surgical procedure followed in this study could produce R0 resection in 77% of cases.

# Observations

- \* Multivariate analysis for independent prognostic factors
  - \* R0 resection
  - \* TNM category
  - \* No significance for Siewert's type.
- \* Siewert's classification is pre-surgical.
  - \* Helpful in taking a treatment decision before surgery.
- \* AJCC- TNM staging is post surgical.
- \* AJCC- TNM staging is important in prognostication postoperatively.
- \* AJCC classify GEJ adenocarcinoma along with adenocarcinoma esophagus.



Clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the gastroesophageal junction and the distal esophagus  
Jessica M. Leers

- \* Concerns

- \* Siewert's classification system requires that the GEJ can be localized endoscopically, which can be difficult with large tumors.
- \* Whether an effort to distinguish between these tumors is warranted in clinical practice.

# Materials and methods

- \* Retrospectively reviewed the records of **613** patients who underwent resection for adenocarcinoma within 5 cm above or below the GEJ from January 1987 to June 2007.
- \* Siewert type I - 301
- \* Siewert type II - 208

# Materials and methods

- \* For eight patients the tumor was classified as a proximal gastric cancer (Siewert Type III), and these patients were excluded
- \* In 96 patients the size of the tumor precluded precise classification, and these patients were analyzed separately as an unclassified group.
- \* En bloc resection with 2-field lymphadenectomy.

# Results

- \* There were no significant differences in age, sex, or body mass index among patients with DE and GEJ tumors
- \* Patients with type 1 were
  - \* Significantly more likely to have reflux symptoms and Barrett's esophagus
  - \* Were more likely to have their tumors detected within a surveillance program compared with patients with GEJ adenocarcinoma.

# Results

- \* There were no significant differences in the median tumor length, type of resection, or use of neoadjuvant therapy.
- \* Prevalence and type of recurrence was similar for both GEJ and DE adenocarcinomas.
- \* Overall and disease-specific survival were similar for adenocarcinoma of the DE and GEJ.

# Results

- \* No significant difference in TNM staging and R status between Siewert's types.
- \* The prevalence of lymph node metastases and the number of involved lymph nodes were similar in patients with DE or GEJ adenocarcinoma.
- \* The prevalence of node involvement and the distribution of involved lymph nodes were similar for DE and GEJ tumors.

# Results

- \* Median follow-up in surviving patients was 37 months
- \* Survival at 5 and 10 years was 45% and 25% for patients with DE tumors compared with 38% and 31% for patients with GEJ tumors, respectively.
- \* Cox regression analysis showed no significant difference in survival between patients with GEJ adenocarcinoma and those with DE adenocarcinoma
- \* The type of recurrence was similar.
- \* No significant difference in recurrence rate.

# Discussion

- \* Difficult to define GEJ
- \* Discrepancies can be there between endoscopist, surgeon and pathologist regarding definition of GEJ
- \* Large tumors can obscure anatomy of the region.
- \* Effort to distinguish between adenocarcinoma of the DE and the GEJ is clinically unnecessary.
- \* Majority of patients (>95%) were treated similarly



# Discussion

- \* Mediastinal nodal involvement was present in 26% of DE adenocarcinomas and 25% of GEJ adenocarcinomas, with the majority of involved nodes located in the paraesophageal region for both tumor locations.
- \* Abdominal node involvement was present in 47% of DE adenocarcinomas and 52% of GEJ adenocarcinomas
- \* Siewert :- R0 resection in 75% of patients. This is substantially lower than the R0 resection rate of the present study :- greater than 90% when esophagectomy was the preferred resection technique.

# Summary

- \* **Inherent inaccuracies** in trying to determine the precise location of the GEJ and the relationship of the epicenter of a cancer to the GEJ.
- \* Given these difficulties and the lack of a significant difference in the biologic behavior between adenocarcinoma of the DE and GEJ, we suggest that **efforts to determine the precise origin of the tumor are not necessary** and that an esophagectomy, preferably an en bloc resection, is appropriate surgical therapy for adenocarcinoma in either location.

# Staging investigations

- \* Endoscopy and biopsy
  - \* Tumor location relative to the teeth and the EGJ
  - \* Tumor length
  - \* Extent of circumferential involvement
  - \* Degree of obstruction
  - \* Evidence of Barrett's esophagus
  - \* Siewert type (I, II, or III).

# Staging investigations

- \* CT scan
  - \* To evaluate the local extend of the primary disease
  - \* Regional nodal enlargement
  - \* Metastasis
- \* Endoscopic ultrasonography
  - \* The most accurate technique for locoregional staging of invasive esophageal cancer including tumors arising at the EGJ.

# Staging investigations

- \* PET and PET-CT
  - \* Useful to detect metastatic disease
  - \* Suspicious PET findings should be confirmed with biopsy before excluding a patient from surgical consideration given the high rate of false positive findings.
  - \* May be of clinical utility is in restaging after initial induction therapy.
- Routine brain imaging is not considered cost-effective or necessary as part of the routine staging evaluation unless symptoms or signs raise suspicion for brain metastases.

# Staging investigations

- \* Diagnostic laparoscopy
  - \* Controversial
  - \* NCCN:- optional for patients with EGJ tumors and no evidence of metastatic disease.
  - \* EORTC advocate diagnostic laparoscopy for all patients with locally advanced (T3/4) adenocarcinomas of the EGJ infiltrating the gastric cardia.

# Staging investigations

- \* The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) generally recommends diagnostic laparoscopy for all patients with esophageal and EGJ cancer who are considered candidates for curative resection based on non-invasive staging studies.

# Multimodality management of GEJ

- \* Complete surgical resection is a prerequisite for cure.
- \* Results with surgery alone are poor.
- \* Need adjuvant treatment to improve locoregional and systemic control and thus survival.
- \* Optimal multimodality treatment for EGJ adenocarcinomas is not well defined.



# Multimodality management of GEJ

- \* No randomized study until now has treated GE junction tumors as a separate entity.
- \* Clinical trials that have been carried out for tumors of this site have been divided between those aimed at treating gastric cancer and those aimed at treating esophageal cancer.
- \* Trials designed primarily for gastric cancer have included patients with GE junction tumors, but generally, the percentage of patients with GE junction tumors has been low, in the range of approximately 20%.

# Intergroup 01116

- \* Surgery alone versus surgery followed by adjuvant chemoradiotherapy
- \* GEJ primaries occurred in approximately 20% of patients.
- \* Median survival
  - \* 27 months for surgery alone group
  - \* 36 months for adjuvant chemoradiotherapy group
- \* Update, with a more than 10-year median follow-up showed continued strong benefit from postoperative radiochemotherapy.

# MAGIC trial

- \* Peri-operative chemotherapy with ECF schedule versus surgery alone
- \* GEJ primaries occurred in approximately 12% of patients
- \* Five-year survival
  - \* 36.3 % for perioperative-chemotherapy group
  - \* 23.0 % for surgery alone group.

# French FNLCC/FFCD trial

- \* Perioperative chemotherapy with cisplatin and a continuous intravenous infusion of fluorouracil or surgery alone
- \* 64% of patients had GEJ adenocarcinoma
- \* 5-year rate
  - \* 38% for perioperative chemotherapy
  - \* 24% for surgery alone

# CROSS trial

- \* Randomly assigned patients with resectable esophageal or esophagogastric-junction
  - \* Adenocarcinoma(75%)
  - \* Squamous cell carcinoma (23%)
  - \* Large-cell undifferentiated carcinoma (2%) tumors
  - \* Surgery alone or weekly administration of carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery.
- \* 24% GEJ tumors.
- \* Median overall survival
  - \* 49.4 months in the chemoradiotherapy– surgery
  - \* 24 months in the surgery group.

# German POET trial

- \* Adenocarcinoma of the lower esophagus or gastric cardia were randomly allocated to induction chemotherapy followed by surgery or chemotherapy followed by chemoradiotherapy followed by surgery.
- \* Study was closed prematurely after only 126 of the planned 354 patients were randomized because of poor accrual.
- \* Preoperative radiation therapy improved 3-year survival rate from 27.7% to 47.4%.

# Summary

- \* Incidence of adenocarcinoma of the esophagogastric junction is increasing rapidly.
- \* Seventh edition of the AJCC staging manual defines EGJ tumors as those tumors arising at the EGJ or in the cardia of the stomach within 5 cm of the EGJ that extend into the EGJ or esophagus. EGJ cancers are all staged as esophageal rather than gastric cancers.
- \* Siewert described three distinct categories of EGJ adenocarcinoma based upon anatomic location

# Summary

- \* The Siewert classification is useful for guiding the surgical strategy, but not for selection of the specific multimodality approach.
- \* Radical surgery is a prerequisite for cure.
- \* Results are poor with surgery alone.
- \* Surgery followed by adjuvant chemoradiotherapy as in intergroup-01116 or perioperative chemotherapy as in MAGIC trial or French FNLCC/FFCD trial are the recommended standard adjuvant treatments.





\*Thank you