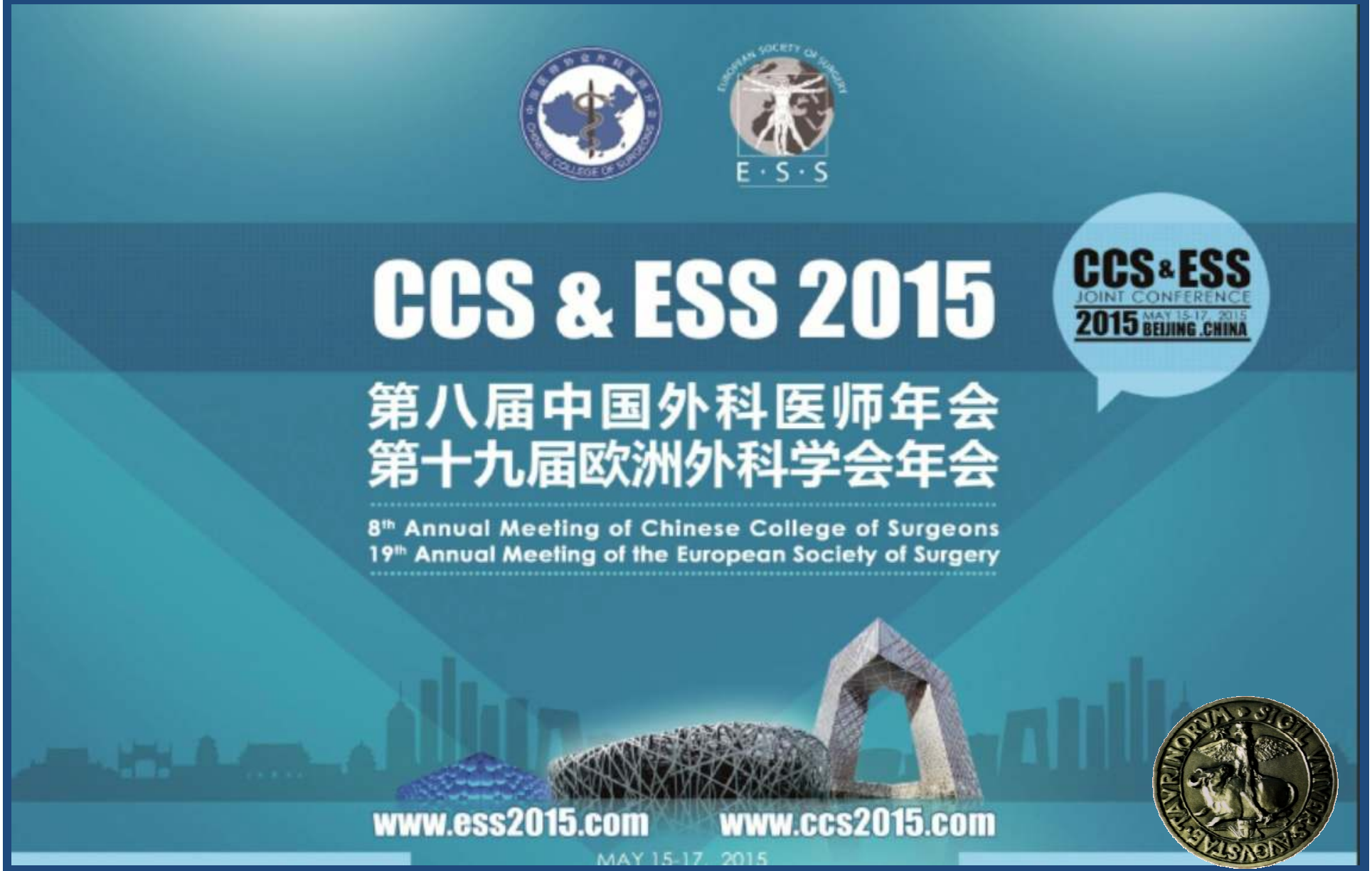
Carcinoma of the esophagus and cardia



Prof. Guido Gasparri, MD, FACS University of Turin, Italy

Carcinoma of the esophagus and cardia

Oesophageal cancer is the eighth most common cancer worldwide; in both sexes there are more than 20-fold differences in incidence between the different regions of the world.
0.8 per 100,000 in Western Africa to 17.0 per 100,000 in Eastern Asia with a very poor survival (the highest mortality rates occurring in Eastern Asia, 14.1 per 100,000)

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65:5-29.

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Carcinoma of the esophagus and cardia

In the United States the incidence of squamous esophageal cell carcinoma is decreasing; in contrast the incidence of adenocarcinoma arising out of Barrett's esophagus is rising dramatically. You can observe the same data in Italy.

Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev 2010; 19:1468.

Prof. G. Gasparri, MD, FACS University of Turin, Italy

Carcinoma of the esophagus and cardia

Major risk factors for esophageal SCC are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. Also smoking and excessive alcohol consumption are considered to be important, particularly in Western countries.

Zhai R, Chen F, Liu G, Su L, Kulke MH, Asomaning K, Lin X, Heist RS, Nishioka NS, Sheu CC, Wain JC, Christiani DC. Interactions among genetic variants in apoptosis pathway genes, reflux symptoms, body mass index, and smoking indicate two distinct etiologic patterns of esophageal adenocarcinoma. J Clin Oncol 2010; 28:2445.

Carcinoma of the esophagus and cardia

***The increase of the adenocarcinoma of the esophagus , particularly in Western countries, is known to be attributed to risk factors such as overweight, a history of smoking and alcohol consumption, gastroesophageal reflux disease, and a diet* that was low in fruits and vegetables .**

Zhai R, Chen F, Liu G, Su L, Kulke MH, Asomaning K, Lin X, Heist RS, Nishioka NS, Sheu CC, Wain JC, Christiani DC. Interactions among genetic variants in apoptosis pathway genes, reflux symptoms, body mass index, and smoking indicate two distinct etiologic patterns of esophageal adenocarcinoma. J Clin Oncol 2010; 28:2445.

Carcinoma of the esophagus and cardia

Interactions between risk factors may be more important than the individual risk factors. But in a study of 305 patients with esophageal adenocarcinoma and 339 age- and sex-matched controls, reflux was the strongest individual risk factor.

Zhai R, Chen F, Liu G, Su L, Kulke MH, Asomaning K, Lin X, Heist RS, Nishioka NS, Sheu CC, Wain JC, Christiani DC. Interactions among genetic variants in apoptosis pathway genes, reflux symptoms, body mass index, and smoking indicate two distinct etiologic patterns of esophageal adenocarcinoma. J Clin Oncol 2010; 28:2445.

Carcinoma of the esophagus and cardia

There is still some difficulty in treating the problem of the adenocarcinoma of the esophagogastric junction. In some articles this tumor is treated with squamous cell carcinoma of the esophagus or, in other series, as a gastric tumor in spite of the fact that it has its own well-defined identity. There are now two classifications of this tumor.

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1) Carcinoma of the esophagus and cardia

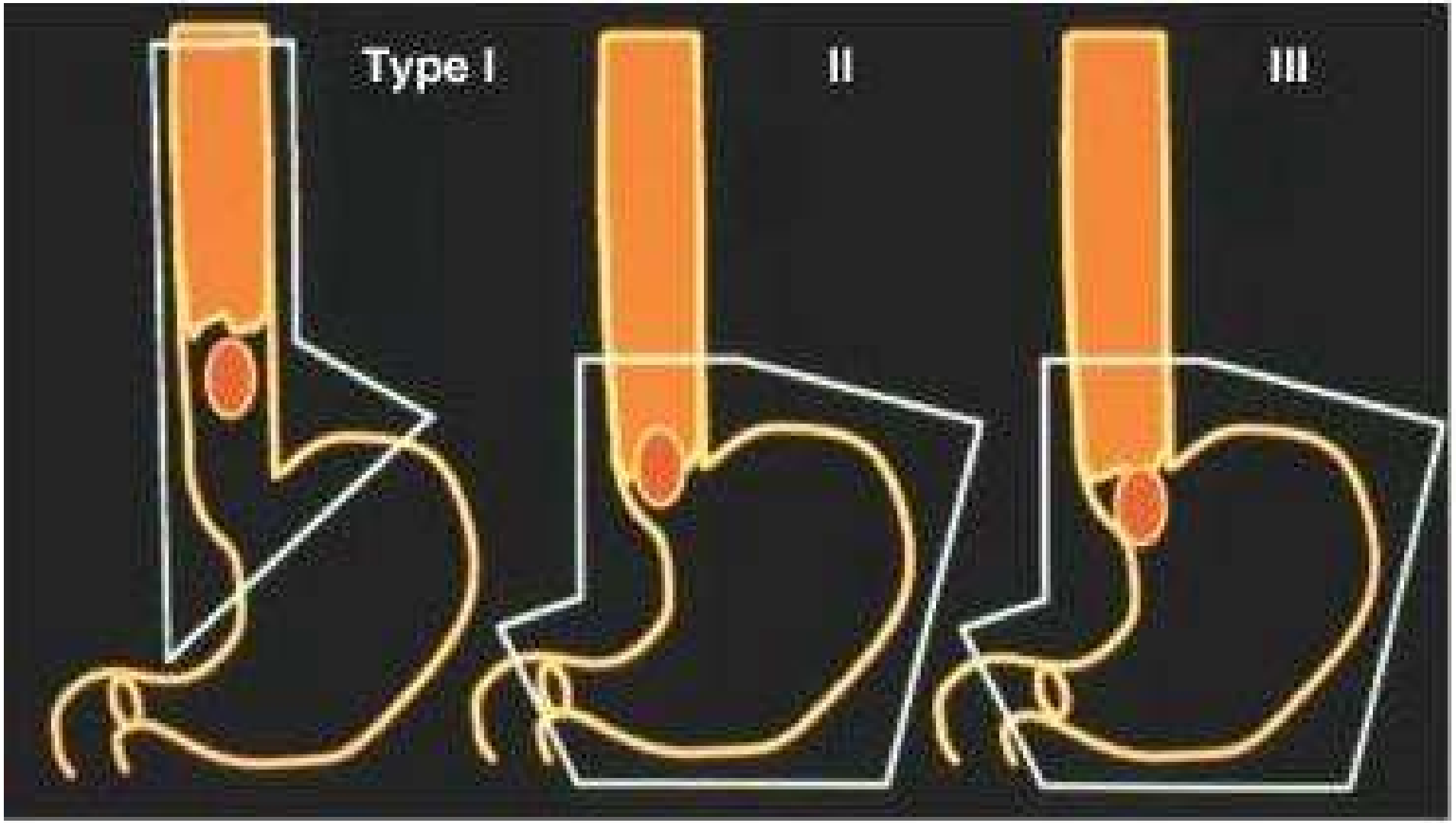
Type I tumor *located between 5 and 1 cm proximal to the anatomical cardia. Adenocarcinoma of the distal esophagus that usually arises from an area with specialized intestinal metaplasia of the esophagus (Barrett's esophagus) and that may infiltrate the EGJ from above.*

Type II tumor *located between 1 cm proximal and 2 cm distal to the anatomical cardia. True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ; this entity is also often referred to as "junctional carcinoma."*

Type III tumor *located between 2 and 5 cm distal to the anatomical cardia. Subcardial gastric carcinoma that infiltrates the EGJ and distal esophagus from below.*

Siewert JR, Hölscher AH, Becker K, Gössner W. Cardia cancer: attempt at a therapeutically relevant classification. Chirurg 1987; 58:25.
Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998; 85:1457.

Siewert classification



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2) Carcinoma of the esophagus and cardia

Recently, the 7th Edition of the TNM classification by American Joint Committee on Cancer (AJCC) has simplified the classification of the carcinoma at proximal stomach based on the location of tumor epicenter and the presence or absence of EGJ involvement.

Rice TW, Rusch VW, Ishwaran H, Blackstone EH; Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 2010; 116:3763.

2) Carcinoma of the esophagus and cardia

The tumor is to be stage grouped as esophageal carcinoma if its epicenter is in the lower thoracic esophagus or EGJ or within the proximal 5 cm of stomach (i.e. cardia) with the tumor mass extending into EGJ or distal esophagus. If the epicenter is >5 cm distal to the EGJ, or within 5 cm of EGJ but does not extend into EGJ or esophagus, it is stage grouped as gastric carcinoma

Rice TW, Rusch VW, Ishwaran H, Blackstone EH; Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 2010; 116:3763.

Carcinoma of the esophagus and cardia

- **Treatment of early cancer**
- **Multimodality treatment**
- **Surgical treatment**
- **How to improve morbidity, mortality and survival.**

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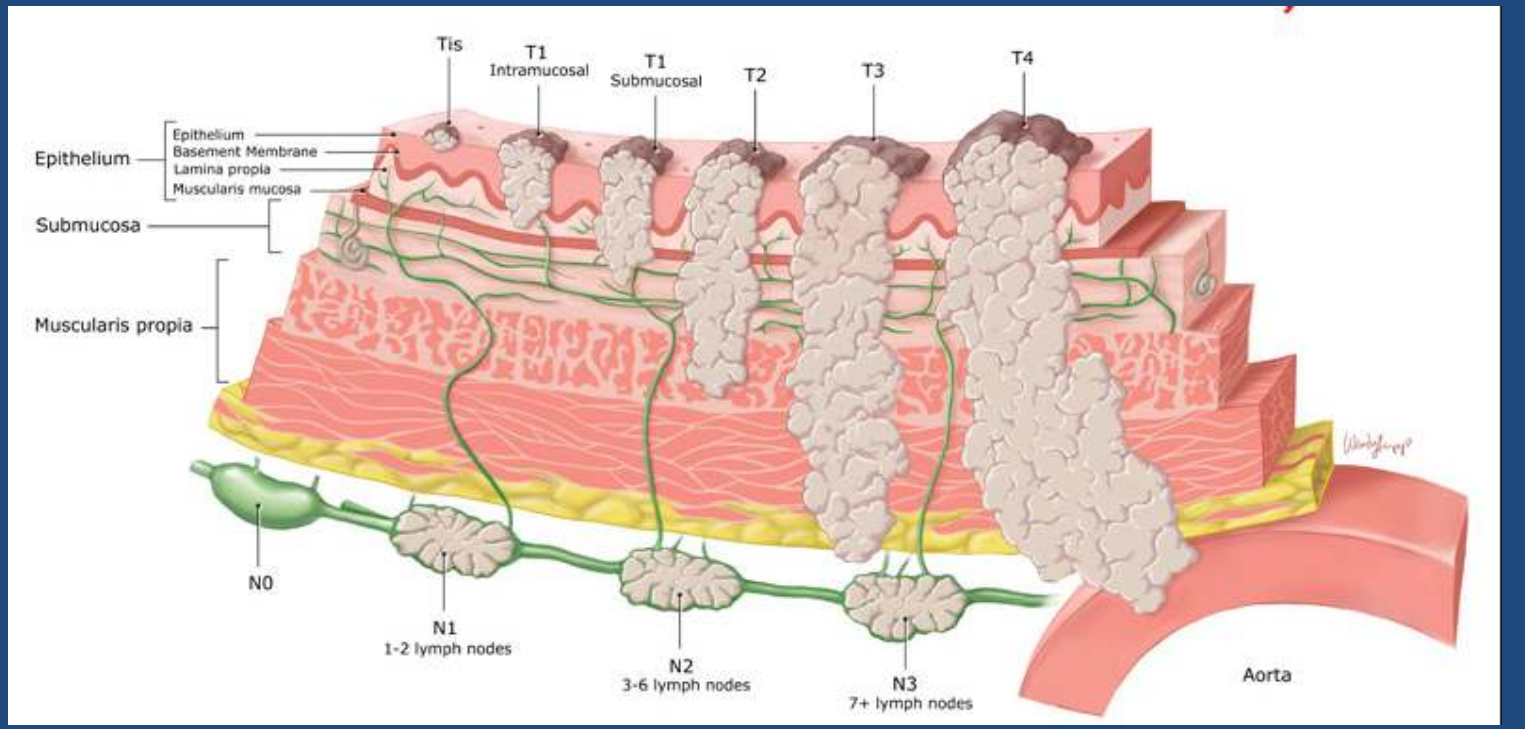
Treatment of early cancer

Lymph node involvement

Tis 0%

T1a 0-2%

T1b 30%



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- *Treatment of early cancer*

EMR: long term results

Pech et al. Gut 2008;57:1200

Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus

Table 2
Acute and long-term results

Characteristic	
Patients treated with ER (n)	279
Treated with PDT (n)	55
Treated with ER+PDT (n)	13
Treated with APC (n)	2
Endoscopic resections (n)	734
ERs per patient	2.1
Piecemeal resections (n)	100/279 (35.8%)
Major complications (n) (eg, major bleeding)	2 (0.6%)
Minor complications (eg, minor bleeding, slight stenosis, odynophagia sunburn)	58 (16.6%)
CLR (patients)	337/349 (96.6%)
Time until CLR (months)	4.2 (SD 5.6)
Follow-up (months)	
25% percentile	49.5
75% percentile	80.0
Mean	63.6
Median	63.0
Metachronous lesions	74/349 (21.5%)
Long-term CLR after repeat ET	330/349 (94.5%)

APC, argon plasma coagulation; CLR, complete local remission; ER, endoscopic resection; ET, endoscopic treatment; PDT, photodynamic treatment; SD, standard deviation.

Treatment of early cancer

You must consider patient factors:

- ✓ ***Endoscopic treatment requires long term follow up***
- ✓ ***Patient could desire a « one off » treatment***
- ✓ ***Patient does not like or does not have the opportunity to travel (experts in EMR are found in few cities)***
- ✓ ***For young patients the operative risk is low and the follow up very long considering the age***

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Multimodality treatment

Gebski reported a 7% 2-year survival advantage for preoperative chemotherapy and a 13% 2-year advantage for chemoradiotherapy. The current data confirm that this level of benefit for preoperative chemotherapy is maintained up to 5 years.

Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J, Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. Lancet Oncol 8:226-234, 2007

Multimodality treatment

Stahl describes a trial in which patients were randomly assigned to neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy. Although the study closed early due to poor accrual, there were more complete pathologic responses in the chemoradiotherapy group (17% compared with 2.5% after chemotherapy) and this was associated with prolonged survival (3-year survival 43% v 27%). A limitation of chemoradiotherapy is the associated higher operative mortality.

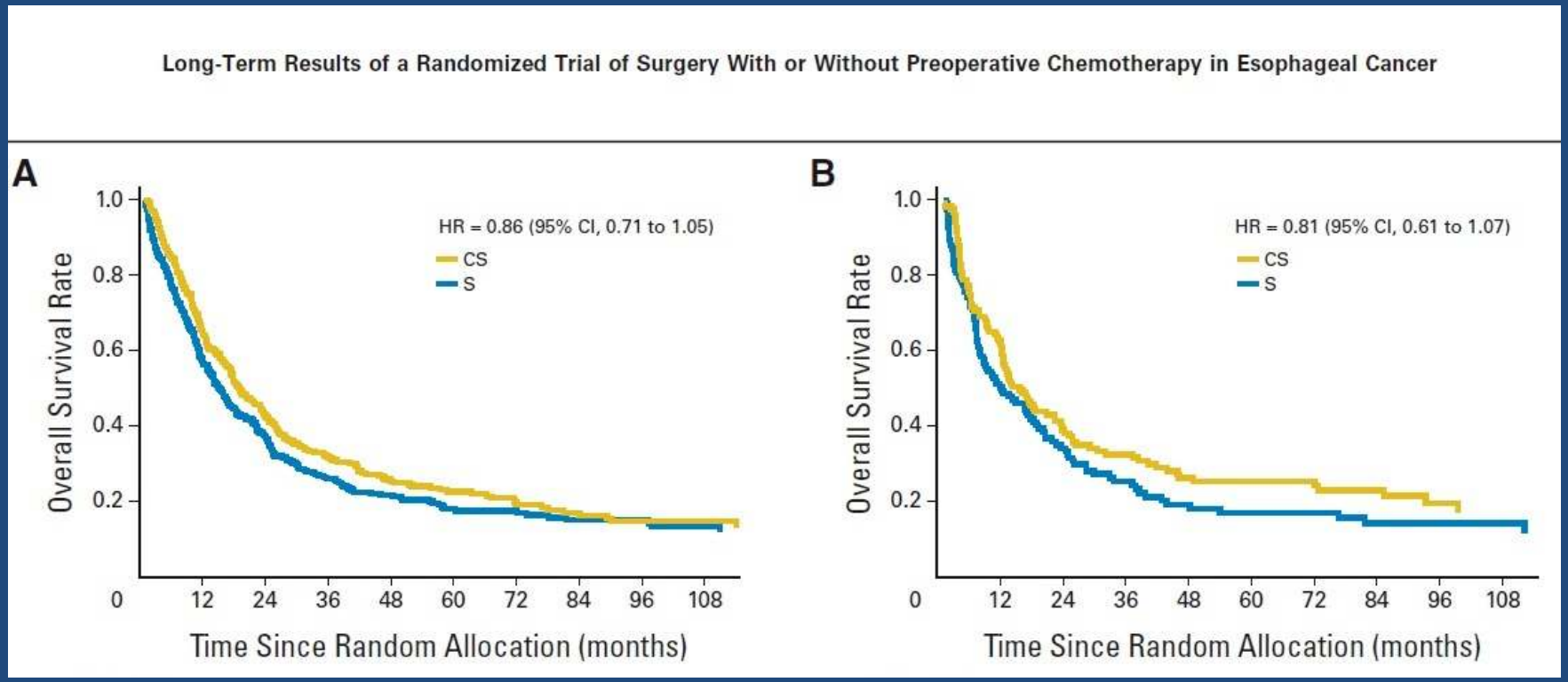
Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H:Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol , 2009; 20:851-6.

Multimodality treatment

✓*Potential benefit: locoregional reduction of tumor (down-staging) with the possibility of R0 resection and elimination of occult metastases*

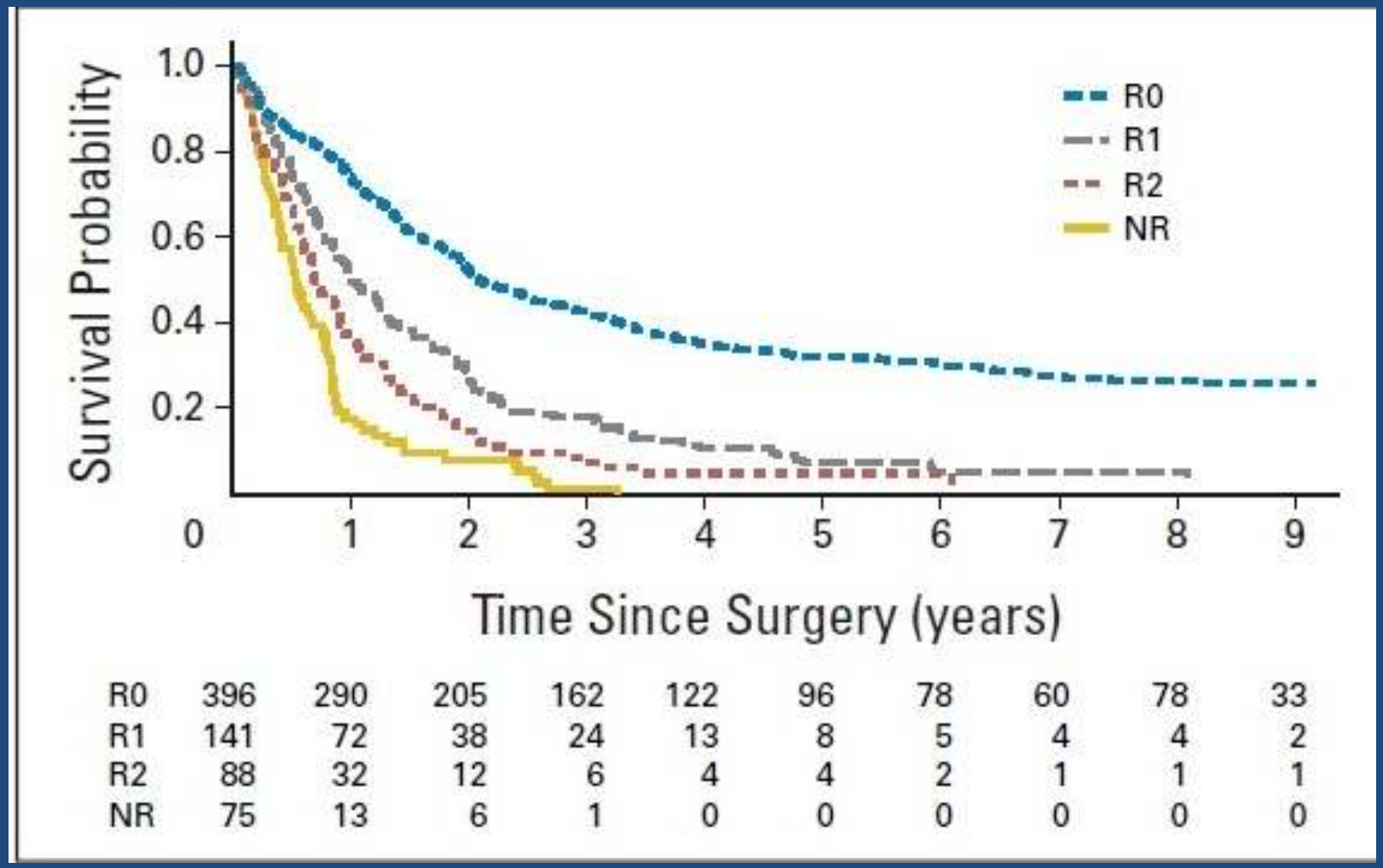
✓*Potential hazards: toxicity and deterioration of general condition, tumor progression, increased postoperative morbidity and mortality*

Survival



Allum WH, Stenning SP, Bancewicz J, Clark PI, and Langley RE Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer, J Clin Oncol, 2009;27: 5062-5067.

Survival



R0	396	290	205	162	122	96	78	60	78	33
R1	141	72	38	24	13	8	5	4	4	2
R2	88	32	12	6	4	4	2	1	1	1
NR	75	13	6	1	0	0	0	0	0	0

Allum WH, Stenning SP, Bancewicz J, Clark PI, and Langley RE Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer, J Clin Oncol, 2009;27: 5062-5067.

Surgical treatment

Esophagectomy as first line of therapy

The indications for an esophagectomy as the initial therapeutic approach to the patient with an esophageal cancer include:
Patients with clinical T1N0M0 lesions
Patients with clinical T2N0M0 lesions are candidates in many medical centers

Surgical treatment

Treatment of esophageal cancers (French Recommendations 2008)

- ✓**Preoperative staging: T1-T2-N0 SURGERY**
- ✓**Preoperative staging: T1-T2-N1 CRT + SURGERY or CT + SURGERY**
- ✓**Preoperative staging: T3N1-T4 N0 N1**
  SCC: exclusive CRT, salvage surgery
  ADC: CT + SURGERY

Surgical treatment

Esophagectomy post-adjuvant therapy

Patients who tolerate their induction well and have a response by CT scan, PET-CT, and endoscopy are generally candidates for a surgical resection four to six weeks after completion of the chemotherapy or chemoradiotherapy.

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Surgical treatment

Relative contraindications — The relative contraindications to an esophagectomy include:

Advanced age – Advanced age is associated with greater morbidity following esophagectomy. However, age alone should not determine operability as selected elderly patients have similar outcomes to younger patients.

2000-2012: 336 operations:

- 135 SCC
- 201 Cardia carcinoma

< 70 years	> 70 years
201 (59%)	135 (41%)

Complications <70 31.8% >70 49.2%
Mortality 2000-2012 → 4.4% (2.9 versus 6.6%)
Mortality 2007-2012: <70 0 >70 = 2.7%

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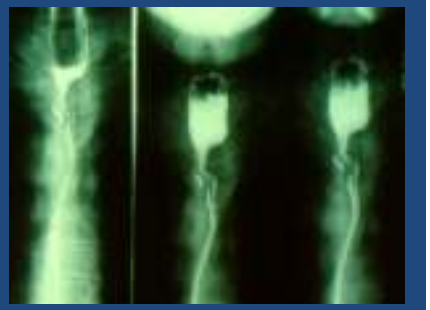
Surgical treatment

Relative contraindications — The relative contraindications to an esophagectomy include:

Comorbid illness – Comorbid illnesses increase the risk of postoperative complications (eg, cardiorespiratory complications, anastomotic leakage, reoperation rates, wound infection), and death following esophagectomy.

Surgical treatment

- ✓*Integrated anesthesia (general + thoracic epidural analgesia-TEA)*
- ✓*Aggressive Monitoring (invasive pressure, central venous pressure, urine output, blood volume control systems)*
- ✓*OLV type protective (the OLV is always accompanied by a significant inflammatory response in the lung ventilated and a possible trauma volume in non-ventilated lung once reexpanded, with a reperfusion syndrome*
- ✓*Fluid challenge intake patient-oriented*
- ✓*Immediate or early extubation*
- ✓*Immediate post operative in intensive / semi-intensive care unit*



Cervical esophageal cancer

Management of carcinoma arising in the cervical esophagus is more closely related to SCC of the head and neck than for tumors involving the distal esophagus. Radiation combined with chemotherapy is preferred over surgery for these patients since survival appears to be the same and major morbidity and mortality is avoided in most cases.

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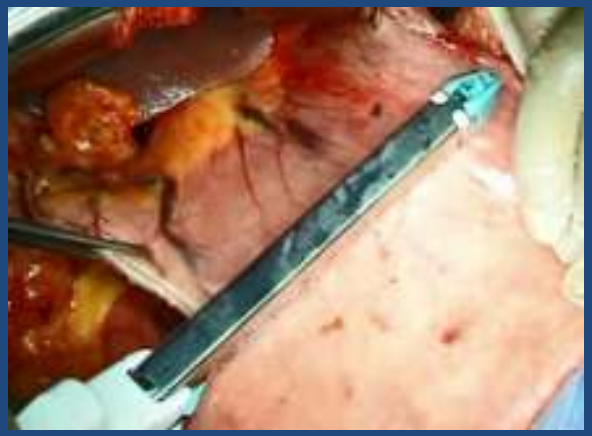
Surgical treatment

Depends on the localization of the cancer: excluding the cervical ones it could be: Three stages (Thoracotomy or Thoracoscopy, Laparotomy or Laparoscopy, Cervicotomy) for the middle thoracic tumor

Surgical treatment

Two stages (Thoracotomy or Thoracoscopy, Laparotomy or Laparoscopy with esophagogastric anastomosis) for the III° inferior of the esophagus or Siewert 1



Surgical treatment

Two stages (Thoracotomy or Thoracoscopy, Laparotomy or Laparoscopy with total gastrectomy for Siewert 2 and 3)

BUT

Patient selection is therefore fundamental and must include assessment of the likelihood of an R0 resection in the context of individual comorbidity and treatment, and management should be undertaken in centers where treatment-related morbidity and mortality are minimized.
In the future, assessments of molecular markers and functional imaging may enable prediction of treatment response.
Under these circumstances, further trials can be undertaken to optimize the perioperative regimens for the management of resectable esophageal cancer.

Allum WH, Stenning SP, Bancewicz J, Clark PI, and Langley RE Long-Term Results of a Randomized Trial of Surgery With or Without Preoperative Chemotherapy in Esophageal Cancer, J Clin Oncol, 2009;27: 5062-5067.

How to improve morbidity, mortality and survival.

The evidence for hospital volume as an important determinant of outcome in esophageal cancer surgery is strong. Concentration of procedures in high-volume hospitals with a dedicated setting for the treatment of esophageal cancer might lead to an overall improvement in patient outcome.

Wouters M. W. J. M, Gooiker, G.A., van Sandick J.W., Tollenaar R.A.E.M, The Volume-Outcome Relation in the Surgical Treatment of Esophageal Cancer, Cancer 2012; 118: 1754-63.

How to improve morbidity, mortality and survival.

Although there seems to be a lot of evidence on the volume-outcomes relationship for several surgical procedures,
there has also been a lot of criticism on the methodological quality of studies.

Pieper D, Mathes T, Neugebauer E, Eikermann M, State of Evidence on the Relationship between High-Volume Hospitals and Outcomes in Surgery: A Systematic Review of Systematic Reviews, J Am Coll Surg, 2013; 216: 1015-1025.

How to improve morbidity, mortality and survival.

The real problem is to select parameters for identifying centers in order to lower morbidity and mortality

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How to improve morbidity, mortality and survival.

Why don't surgeons do trials?

- ✓ *Certain of their decisions*
- ✓ *Skeptical of others*
- ✓ *Time consuming*
- ✓ *Extra resources*
- ✓ *Need to learn something new*
- ✓ *Long follow-up for cancer patients*

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How to improve morbidity, mortality and survival.

Randomized control trials

- ✓ *Hand vs stapler for anastomosis*
- ✓ *Pyloroplasty in gastric replacement*
- ✓ *Pyloroplasty vs pyloromyotomy*
- ✓ *Transthoracic vs transhiatal resection*
- ✓ *Neck drains after cervical anastomosis*
- ✓ *Postoperative radiotherapy*
- ✓ *Preoperative chemotherapy*

How to improve morbidity, mortality and survival.

Factors improving outcome

- ✓*Hospital volume*
- ✓*Surgeon volume*
- ✓*Qualified anesthetists*
- ✓*Bachelor degree of nurses*
- ✓*Epidural analgesia*
- ✓*Daily ward round*
- ✓*Fluid restriction*
- ✓*Normal albumin level*

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How to improve morbidity, mortality and survival.

What has helped improve outcome?

- ✓ ***Staging/ Imaging*** **++**
- ✓ ***Technology*** **+++**
- ✓ ***Added treatment*** **++**
- ✓ ***Pain control*** **+++**
- ✓ ***Airway clearance*** **+++**

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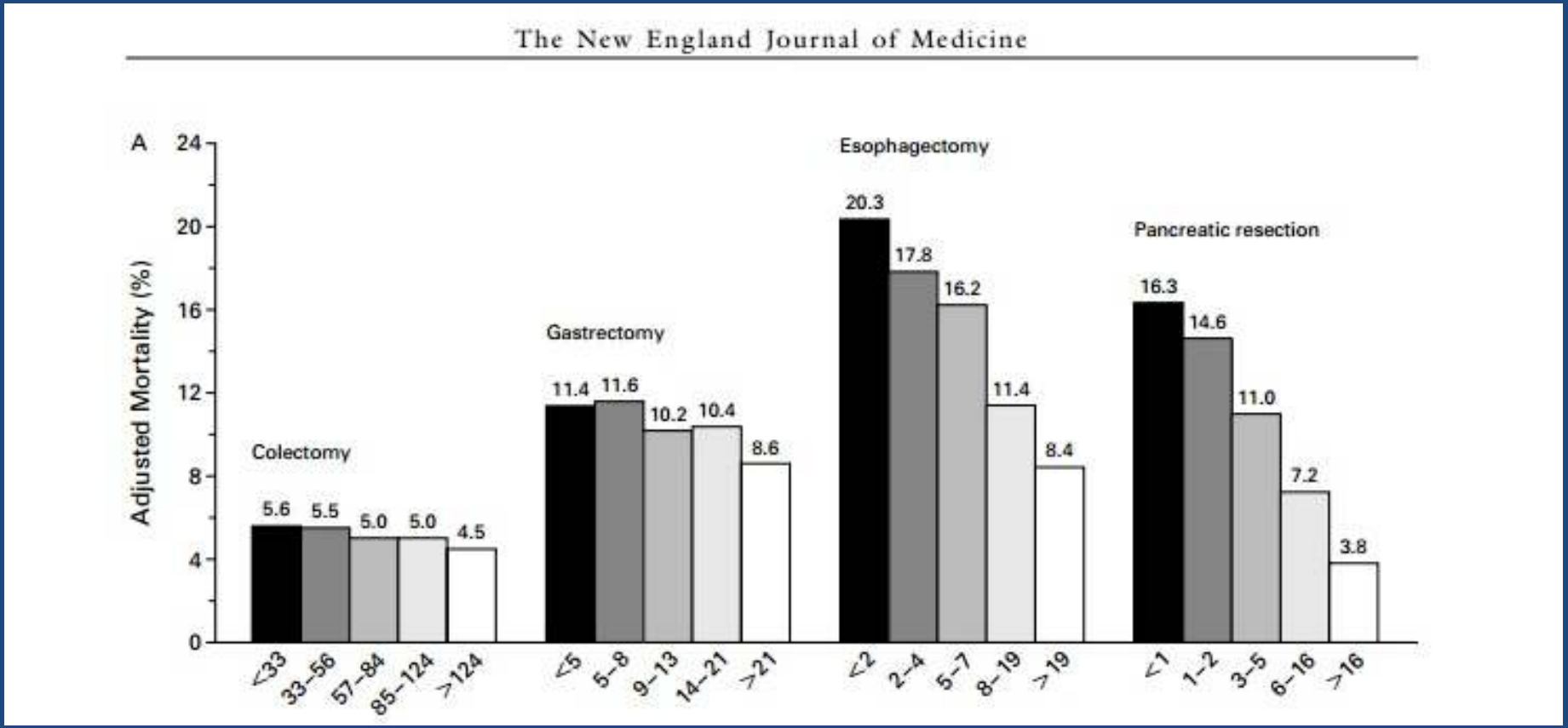
How to improve morbidity, mortality and survival.



Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE, Hospital volume and surgical mortality in the United States, N Engl J Med. 2002;11:1128-37.

How to improve morbidity, mortality and survival.

Esophagectomy mortality rates (Hong Kong Public Hospitals)

- ✓ *First audit (1997-2001) 11.2%*
- ✓ *Second audit (2002-2006) 5.5%*

- ✓ *High volume: 4.8%*
- ✓ *Mid volume: 5.0%*
- ✓ *Low volume: 8.7%*

Wong J, Icact 2009

How to improve morbidity, mortality and survival.

« You can walk on the water……
If you know where the rocks are »

There are no miracles in the treatment of esophageal cancer: recommendations are based on randomised trials

JP Triboulet, ICACT, Paris 2009

? ?

Grazie

Thank you

Prof. Guido Gasparri, MD, FACS University of Turin, Italy