# Esophageal cancer an overview

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# Background

- Morbid disease with poor prognosis
- ~ 25% five year survival even with complete resection in localized disease
- Emerging role of neo-adjuvant therapies and non-surgical treatment options
- Coexisting malnutrition and co-morbidities play a role in treatment decisions
- Intensive supportive care

# Risk factors / pathology

- Smoking
- Alcohol use
- Barrett’s esophagus

Pathology

- Squamous
- Adenocarcinoma

# Symptoms

Dysphagia

Recurrent vomiting

Anorexia

Weight loss

GI blood loss

Cough

Change in voice

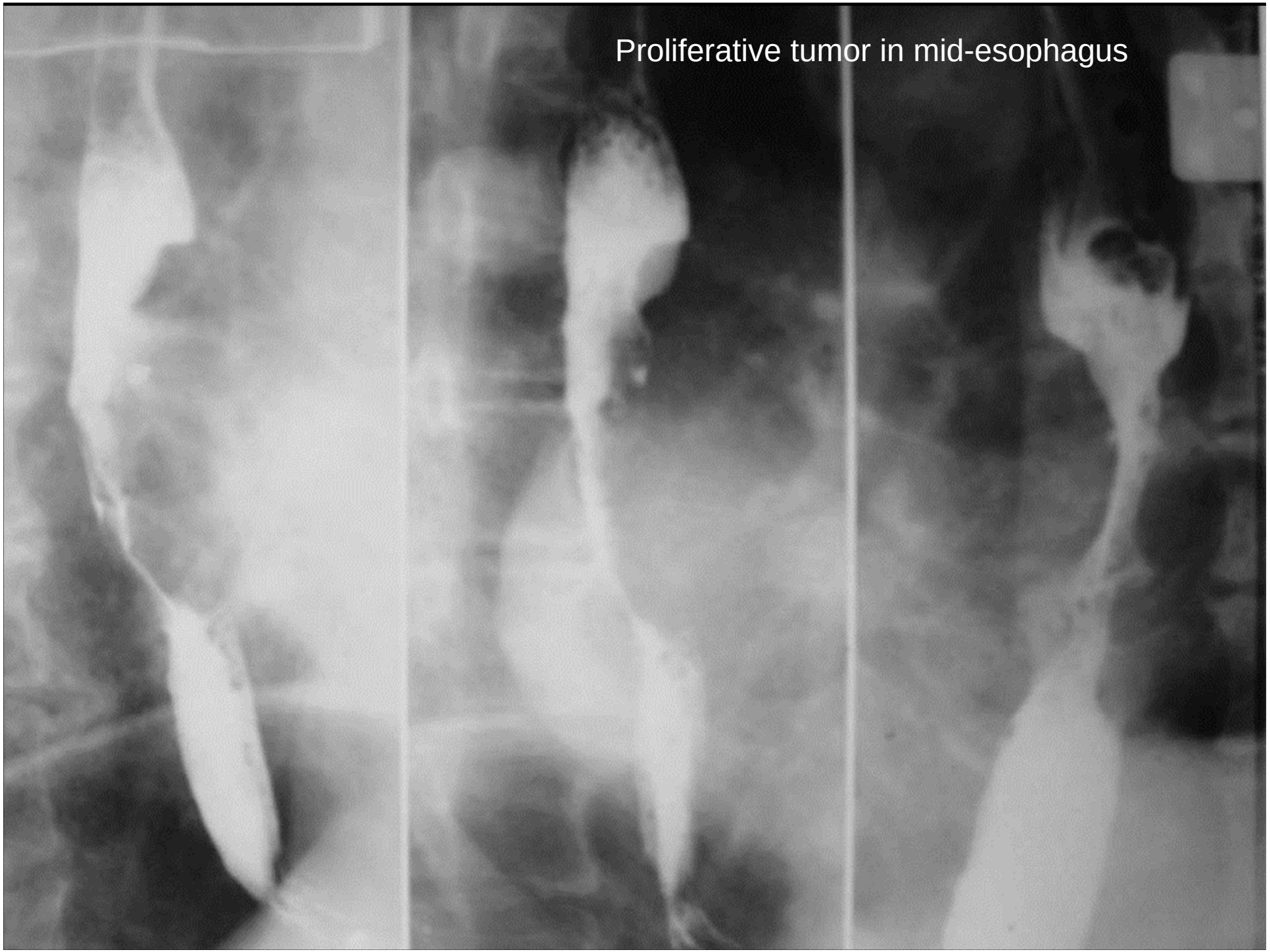
# Clinical examination

- General condition
- Performance status
- Nutritional status
- Assessment of co-morbidities

- Cervical lymphadenopathy
- Liver metastases

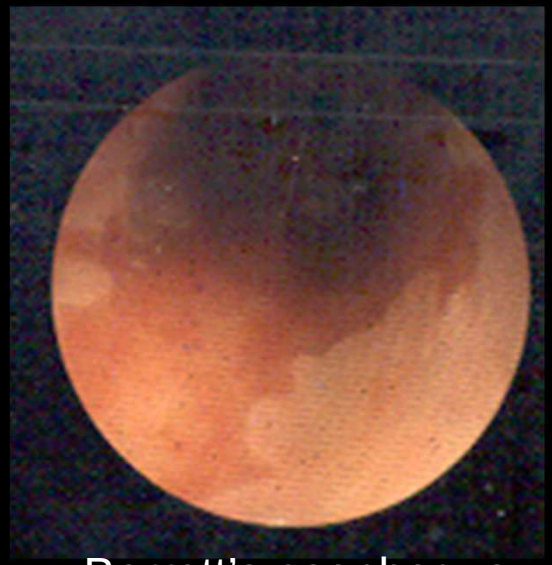
# Investigations

- Diagnostic
  - Barium swallow
  - Upper GI scopy + biopsy
- Staging
  - CT scan chest + upper abdomen
  - Endoscopic ultrasonography
  - Bronchoscopy – for upper and mid third lesions, or patients with change of voice

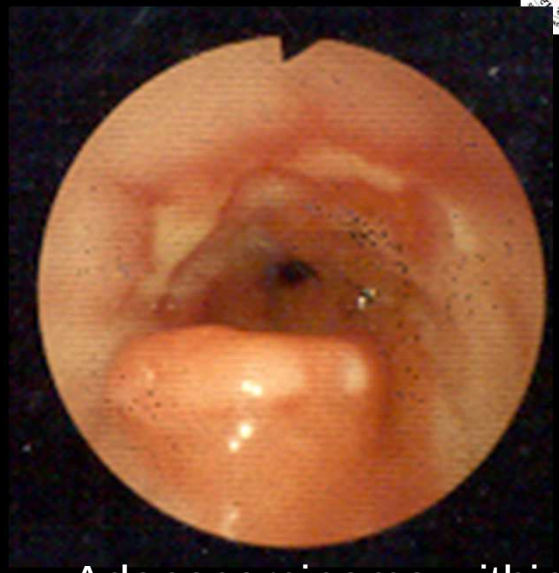

Proliferative tumor in mid-esophagus

# Flexible upper GI Endoscopy

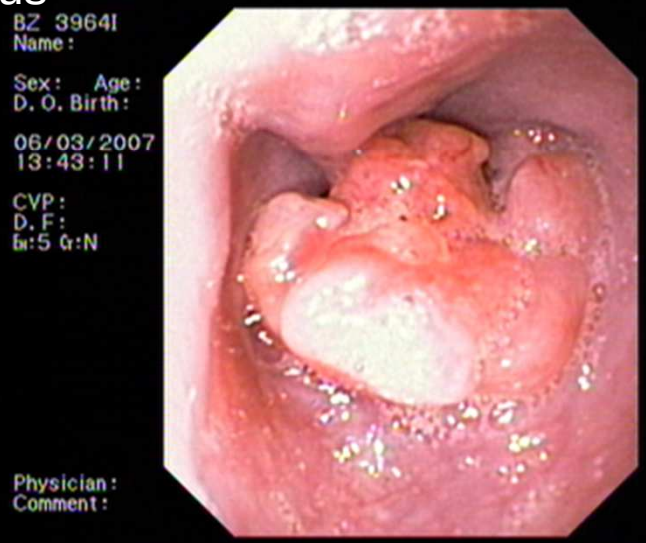
- Direct visualization of the tumor and the upper GI tract
- Multiple biopsies and cytology (if required)
- Skip lesions
- Vocal cords
- Fistulous openings



Barrett's esophagus



Adenocarcinoma within Barrett's esophagus



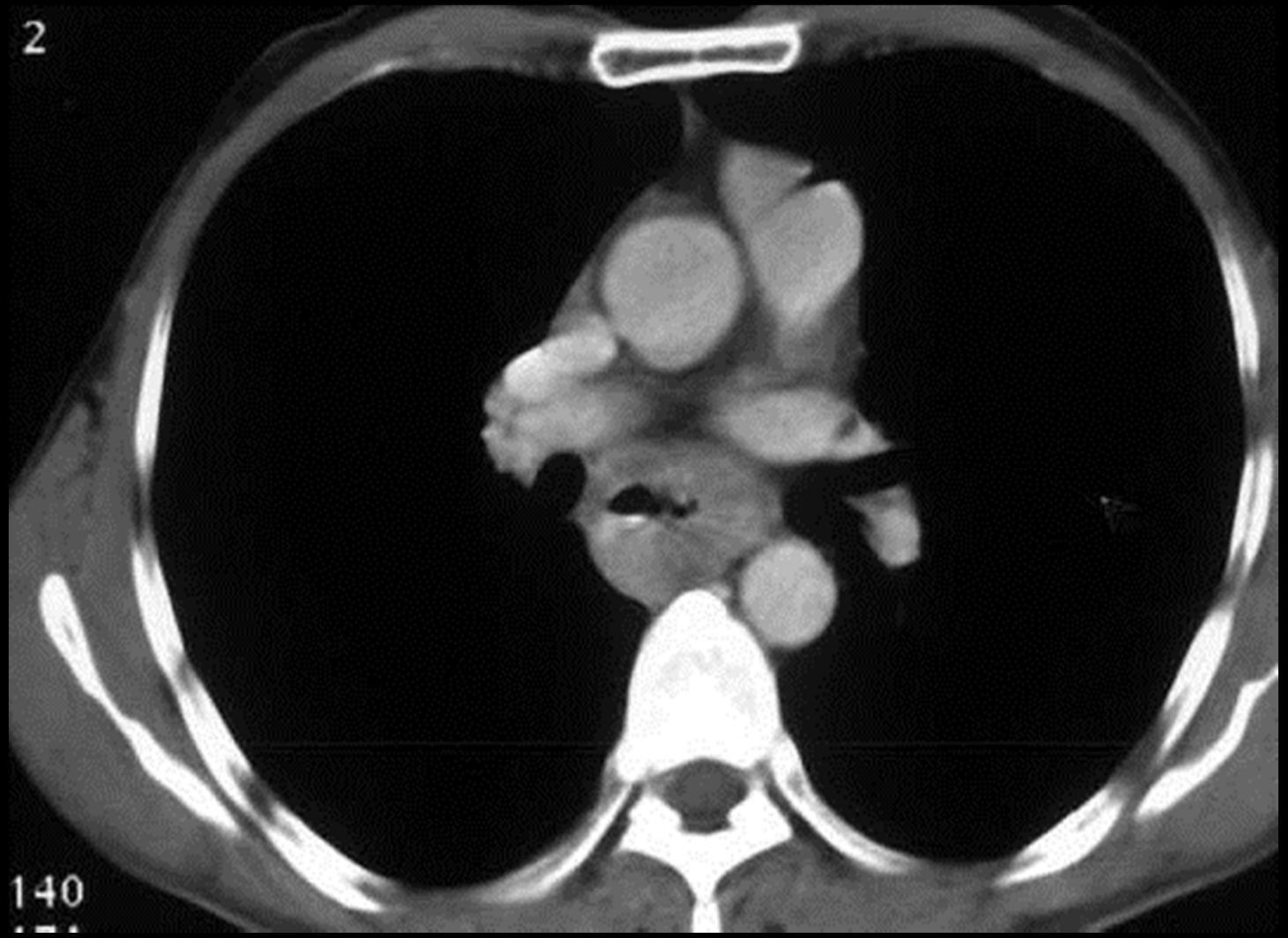

Proliferative tumor in the esophagus

# CECT scan

- CT scan mandatory in staging patients with esophageal cancer
- Thorax and upper abdomen need to be imaged
- IV contrast
- Gastric distension with oral contrast

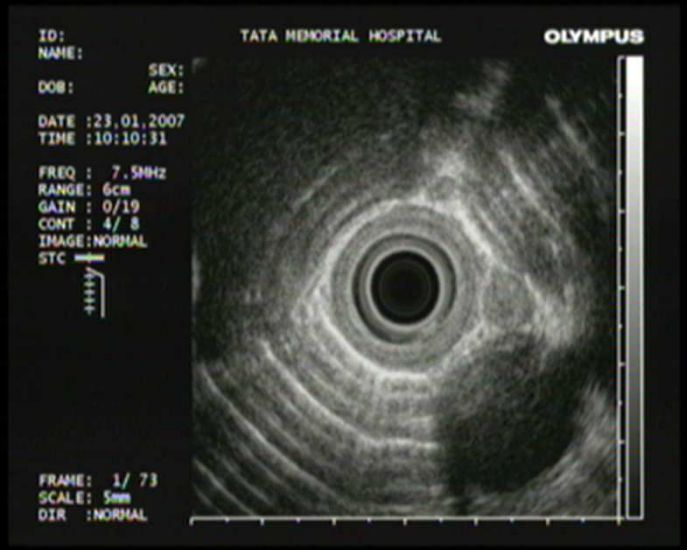
- Can CECT be avoided in some patients?
    - Advanced disease, poor general health

# CT scan – mid esophageal ca

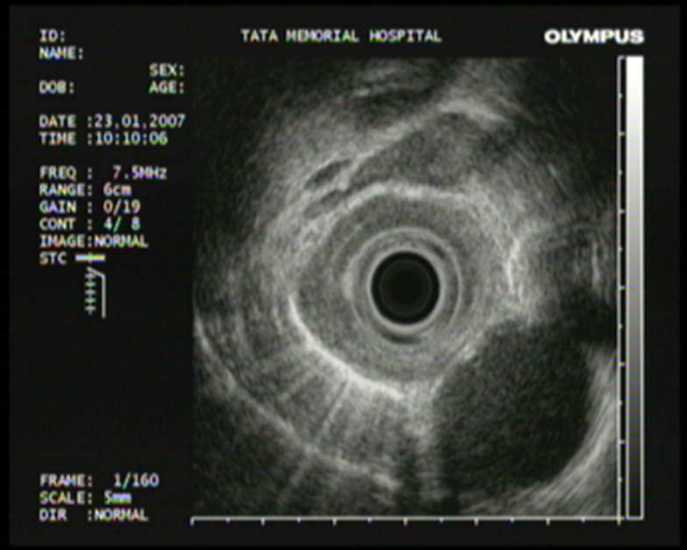


# Endoscopic ultrasound EUS

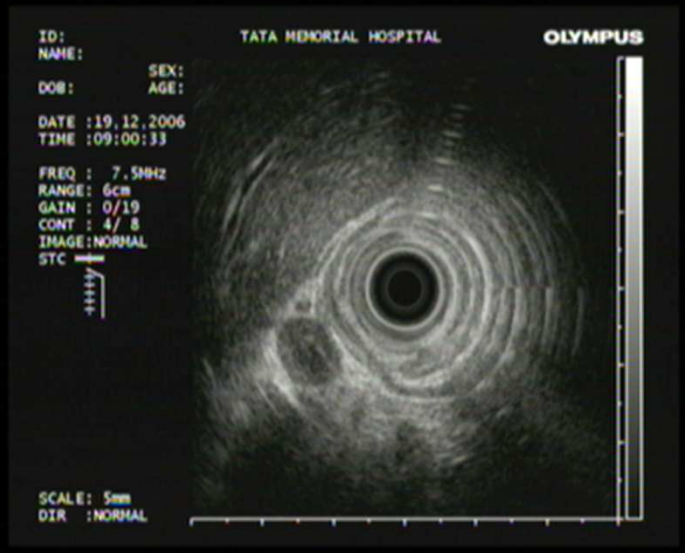
- Most accurate tool for tumor staging
- 75-85% accurate for T staging (the depth of penetration of the tumor)
- 65-75% accurate for N staging (the presence of enlarged peri-esophageal lymph nodes)
- The only staging modality for assessing early ($T_{is}$ or $T_1$) tumors
- EUS guided FNAC for mediastinal and celiac nodes
- Restaging after neoadjuvant therapy




T3N0 tumor




T4N1 tumor




Celiac nodes T3N1M1a

# Treatment of esophageal cancer

- Localized disease
  - Surgery
  - Radiotherapy or CT+RT
- Loco-regionally advanced disease
  - NACT or NACT > RT + surgery or CT+RT
- Metastatic disease
  - Radiotherapy
  - Stenting

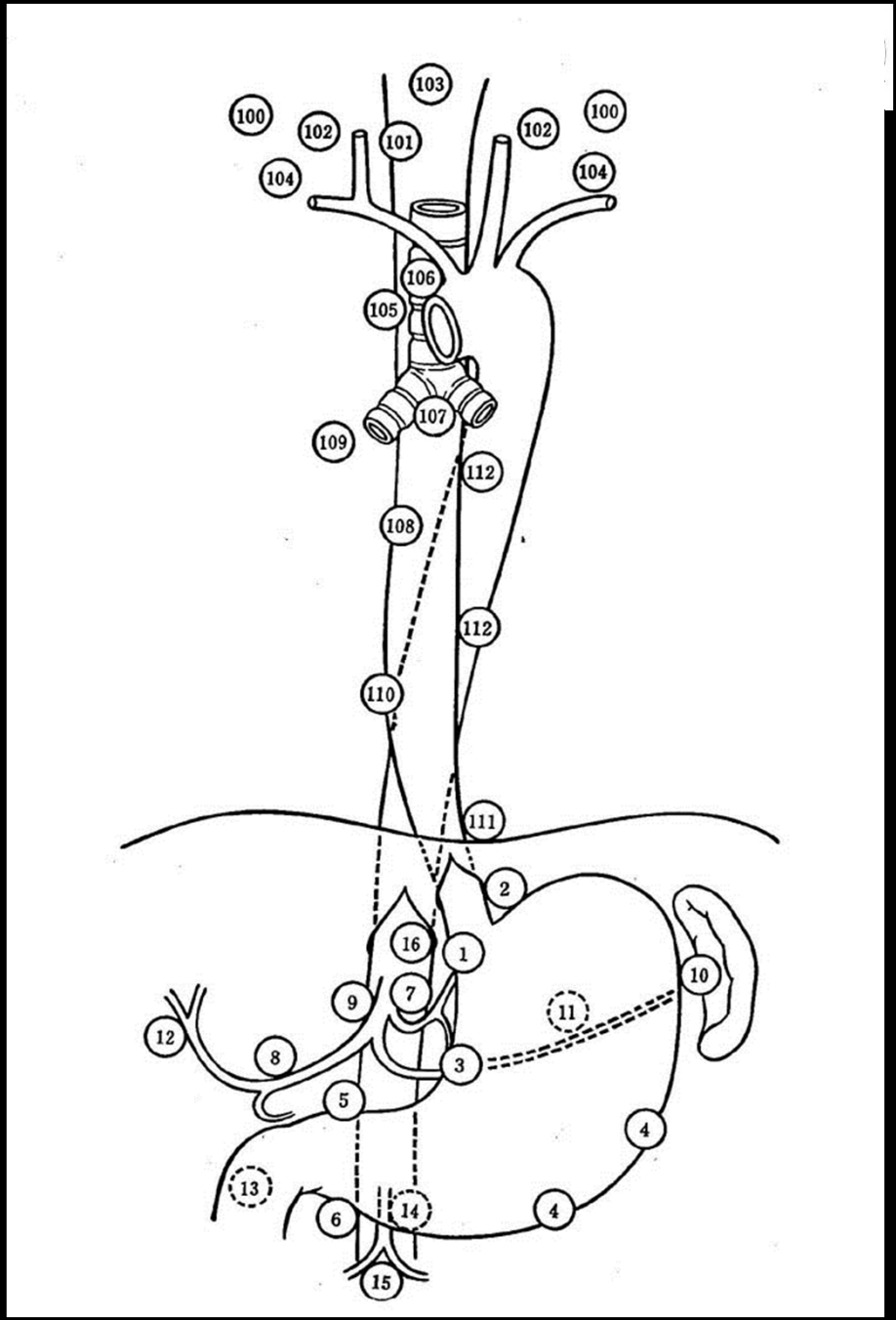
Localized disease

Surgery is the best treatment

check patient's fitness

Surgical approach

- Trans thoracic
- Transhiatal
- VATS
- RA



# Complications of surgery

- Anastomotic leak
  - Gastric tube ischemia
  - True anastomotic leak
- Pulmonary complications
  - Collapse
  - Pneumonia
- Chyle leak
- Recurrent laryngeal nerve paresis

# Which approach is best?

*Table 5. Long-Term Survival After Transthoracic or Transhiatal Esophagectomy for All Tumor Stages Combined*[a]

| | No. of Patients | | Surviving Patients (%) | | | |
|---|---|---|---|---|---|---|
| Survival | TTE | THE | TTE | THE | RR | 95% CI |
| 3-year | | | | | | |
| Randomized | 35 | 32 | 28.6 | 25.6 | 1.83 | 4.78–0.70 |
| Comparative | 375 | 250 | 29.1 | 22.0 | ... | ... |
| Overall | 1914 | 1119 | 26.7 | 25.0 | 0.94 | 0.83–1.07 |
| 5-year | | | | | | |
| Randomized | ... | ... | ... | ... | ... | ... |
| Comparative | 807 | 499 | 35.2 | 24.9 | 1.41 | 1.68–1.89 |
| Overall | 2677 | 2264 | 23.0 | 21.7 | 1.06 | 1.18–0.96 |

[a] Data were handled as outlined in the legend to Table 4.

CI = confidence interval; RR = relative risk; THE = transhiatal esophagectomy; TTE = transthoracic esophagectomy.

# Neoadjuvant treatment

## Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis

*Val Gebski, Bryan Burmeister, B Mark Smithers, Kerwyn Foo, John Zalcberg, John Simes, for the Australasian Gastro-Intestinal Trials Group*

*Lancet Oncol* 2007; 8: 226–34

Published Online February 15, 2007 DOI:10.1016/S1470-2045(07)70039-6

See Reflection and Reaction page 189

National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia (V Gebski MStat, K Foo FRANZCR, Prof J Simes FRACP); University of Queensland, Princess Alexandra Hospital, Brisbane, Australia (B Burmeister FRANZCR, B M Smithers FRACS); and Peter MacCallum Cancer Centre, Melbourne, Australia (Prof J Zalcberg FRACP)

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### Summary

**Background** Resectable oesophageal cancer is often treated with surgery alone or with preoperative (neoadjuvant) chemoradiotherapy or chemotherapy. We aimed to clarify the benefits of neoadjuvant chemoradiotherapy or chemotherapy versus surgery alone by a meta-analysis of randomised trial data.

**Methods** Eligible trials were identified first from earlier published meta-analyses and systematic reviews. We also used MEDLINE, Cancerlit, and EMBASE databases to identify additional studies and published abstracts from major scientific meetings since 1980. Only randomised studies with an analysis by an intention-to-treat principle were included, and searches were restricted to those databases citing articles in English. We used published hazard ratios if available or estimates from other survival data or survival curves. Treatment effects by type of tumour and treatment sequencing were also investigated.

**Findings** Ten randomised comparisons of neoadjuvant chemoradiotherapy versus surgery alone (n=1209) and eight of neoadjuvant chemotherapy versus surgery alone (n=1724) in patients with local operable oesophageal carcinoma were identified. The hazard ratio for all-cause mortality with neoadjuvant chemoradiotherapy versus surgery alone was 0·81 (95% CI 0·70–0·93; p=0·002), corresponding to a 13% absolute difference in survival at 2 years, with similar results for different histological tumour types: 0·84 (0·71–0·99; p=0·04) for squamous-cell carcinoma (SCC), and 0·75 (0·59–0·95; p=0·02) for adenocarcinoma. The hazard ratio for neoadjuvant chemotherapy was 0·90 (0·81–1·00; p=0·05), which indicates a 2-year absolute survival benefit of 7%. There was no significant effect on all-cause mortality of chemotherapy for patients with SCC (hazard ratio 0·88 [0·75–1·03]; p=0·12), although there was a significant benefit for those with adenocarcinoma (0·78 [0·64–0·95]; p=0·014).

**Interpretation** A significant survival benefit was evident for preoperative chemoradiotherapy and, to a lesser extent, for chemotherapy in patients with adenocarcinoma of the oesophagus. The findings provide an evidence-based framework for the use of neoadjuvant treatment in management decisions.

# Perioperative chemotherapy MAGIC trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

## Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

ABSTRACT

BACKGROUND

A regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) improves survival among patients with incurable locally advanced or metastatic gastric adenocarcinoma. We assessed whether the addition of a perioperative regimen of ECF to surgery improves outcomes among patients with potentially curable gastric cancer.

METHODS

We randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted

From the Departments of Medicine (D.C., Y.J.C.) and Surgery (W.H.A., J.N.T.), Royal Marsden Hospital, Surrey and London; the Medical Research Council Clinical Trials Unit, Cancer Group, London (S.P.S., R.E.L., M.V., S.W.); the Department of Oncology, Aberdeen Royal Infirmary, Aberdeen (M.N.); the Department of Medical Oncology, Christie Hospital, Manchester (J.H.S.); the Department of Medical Oncology, St. George's Hospital, London

# Non surgical options
# for
# localized disease

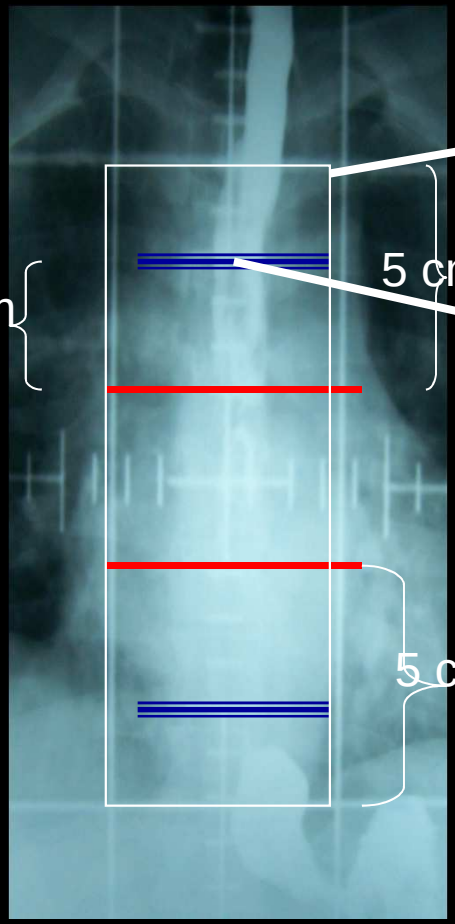
# Radiotherapy

- Traditionally results with RT alone - Dismal
- 3yr survival rate – 6%
- Evidence from single institution retrospective studies.
- Bias - patient selection for radiotherapy.
- With the advent of chemo-radiotherapy – limited role.
- Superficial, early tumors - Good cure rates with RT alone ( EBRT+/- ILBT).
- Also an option for a poor risk patients –

Not fit for multimodality therapy – But a candidate for Radical treatment.

**Not an Uncommon situation**

# What should be the target volume?




Phase- I- visible mucosal irrregularity on barium swallow +5cm cranio-caudal margins

Phase-II- Visible abnormality +3cm craniocaudal margins

1. Width of the field- encompasses majority of mediastinum - 7 cm/8 cm
2. Supracarinal Involvement- B/l SCF are included in the field
3. CO junction Involvement- Upper abd. nodes and prox. Stomach included in the field

Tailored treatment -

Include findings of CT and EUS

# What should be the beam arrangement?

Phase-I - Antero-posterior is preferred

4-F AP/PA with Oblique.

3-F AP with oblique or PA with oblique.

Phase-II - Oblique: Upper third- Ant. Oblique (in majority)

Lower third- Post oblique (in majority)

Aim:

- To deliver 60-65Gy to tumor
- To deliver < 46Gy to spinal cord
- To deliver least dose possible to lungs

# What should be the dose and dose per fraction?

Depends on the tolerance:

Traditionally EBRT dose - 60-64Gy

with the advent of chemotherapy dose – 50.4Gy

Dose/#:

To reduce late toxicity- preferable to avoid >2Gy/#. Routinely 1.8-2Gy/#.

Brachytherapy Boost ….

# Brachytherapy: Target volume

- Whether to boost the initial tumor bed or the residual volume is controversial
- The recommended active length documented by esophagoscopy is the visible mucosal tumor with a 1-2 cm proximal and distal margin
- Normal tissues - mucosa & underlying fibro-muscular wall

Though ILRT has been used as boost following ERT for many years, optimal dose & fractionation are unknown

# Timing / sequencing

- BT is usually given after EBRT in majority of patients to treat smaller Volumes
- Gap of
  - 2 to 3 wks following CTRT &
  - 1 to 2 weeks following EBRT

  to allow healing of mucositis
- BT after EBRT has the advantage:
  Entubing & dilating relatively normal tissue

# Postoperative radiotherapy

ORIGINAL ARTICLES: GENERAL THORACIC

## Value of Radiotherapy After Radical Surgery for Esophageal Carcinoma: A Report of 495 Patients

Ze Fen Xiao, MD, Zong Yi Yang, MD,* Jun Liang, MD, Yan Jun Miao, MD, Mei Wang, MD, Wei Bo Yin, MD, Xian Zhi Gu, MD, De Chao Zhang, MD, Ru Gang Zhang, MD, and Liang Jun Wang, MD

Departments of Radiation Oncology and Thoracic Surgical Oncology, Cancer Institute (Hospital), Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

*Background.* Despite three decades of debate, no conclusion has been reached concerning the effectiveness of postoperative radiotherapy for resected esophageal carcinoma. From 1986 through 1997, a prospective randomized study was carried out with 495 patients in an attempt to define the value of this therapeutic modality.

*Methods.* A total of 495 patients with esophageal cancer who had undergone radical resection were randomized by the envelope method into a surgery-alone group (S) of 275 patients and a surgery plus radiotherapy group (S + R) of 220 patients. Radiation treatment was started 3 to 4 weeks after the operation. The portals encompassed the entire mediastinum and bilateral supraclavicular areas. A midplane dose of 50 to 60 Gy in 25 to 30 fractions was delivered over 5 to 6 weeks.

*Results.* The overall 5-year survival rate was 31.7% for the S group and 41.3% ($p = 0.4474$) for the S + R group. The 5-year survival rates of patients who were lymph node positive were 14.7% and 29.2% ($p = 0.0698$), respectively. Five-year survival rates of stage III patients were 13.1% and 35.1% ($p = 0.0027$), respectively.

*Conclusions.* Postoperative prophylactic radiotherapy improved the 5-year survival rate in esophageal cancer patients with positive lymph node metastases and in patients with stage III disease compared with similar patients who did not receive radiation therapy. These results were almost significant for patients with positive lymph node metastases and highly significant for patients with stage III disease.

(Ann Thorac Surg 2003;75:331–6)

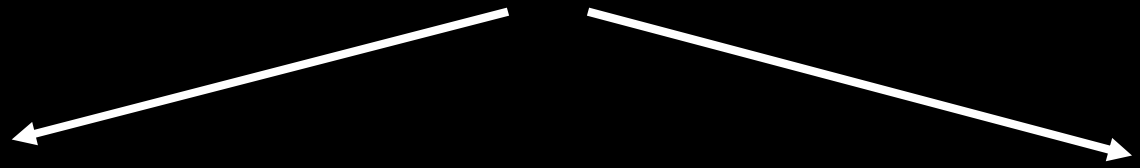
# Loco-regionally advanced disease

# Chemotherapy

- Neoadjuvant (Preoperative) chemotherapy
  - 5-FU / cisplatin
  - Taxane based regimen
- Neoadjuvant or Definitive chemo-radiation
  - 5-FU / cisplatin
  - Taxane based
  - Irinotecan based

# Rationale for Neo-adjuvant Therapy

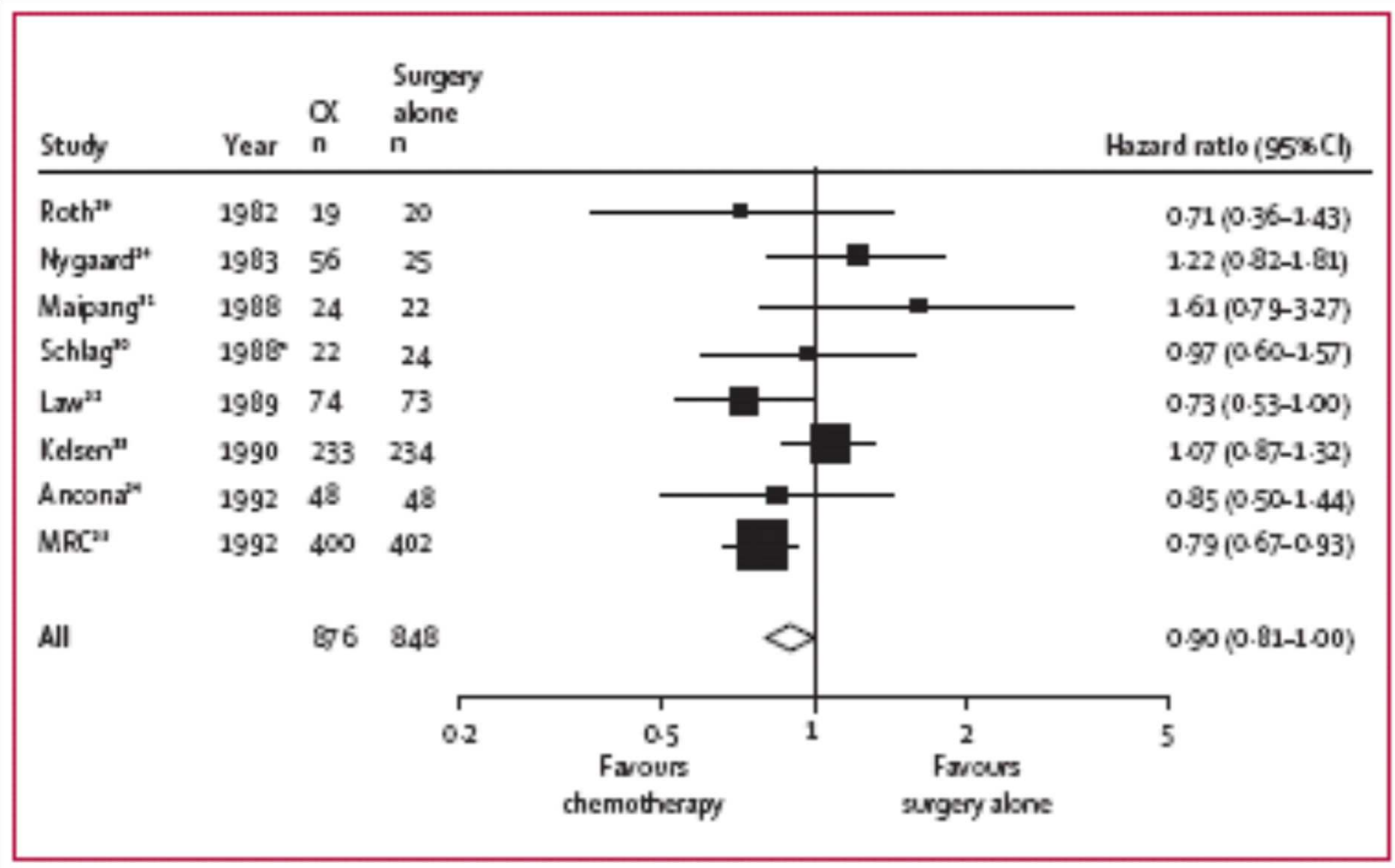
- **Reduction of local and micrometastic tumor deposits**
- **Down-staging the primary tumor by enhanced delivery of cytotoxic agents via intact microvasculature**
- **Possibility of less morbid surgery**
- **Many of the agents enhance radio-sensitivity**
- **Comprehensive pathologic assessment of - Imp in selecting patients for adj. therapy**



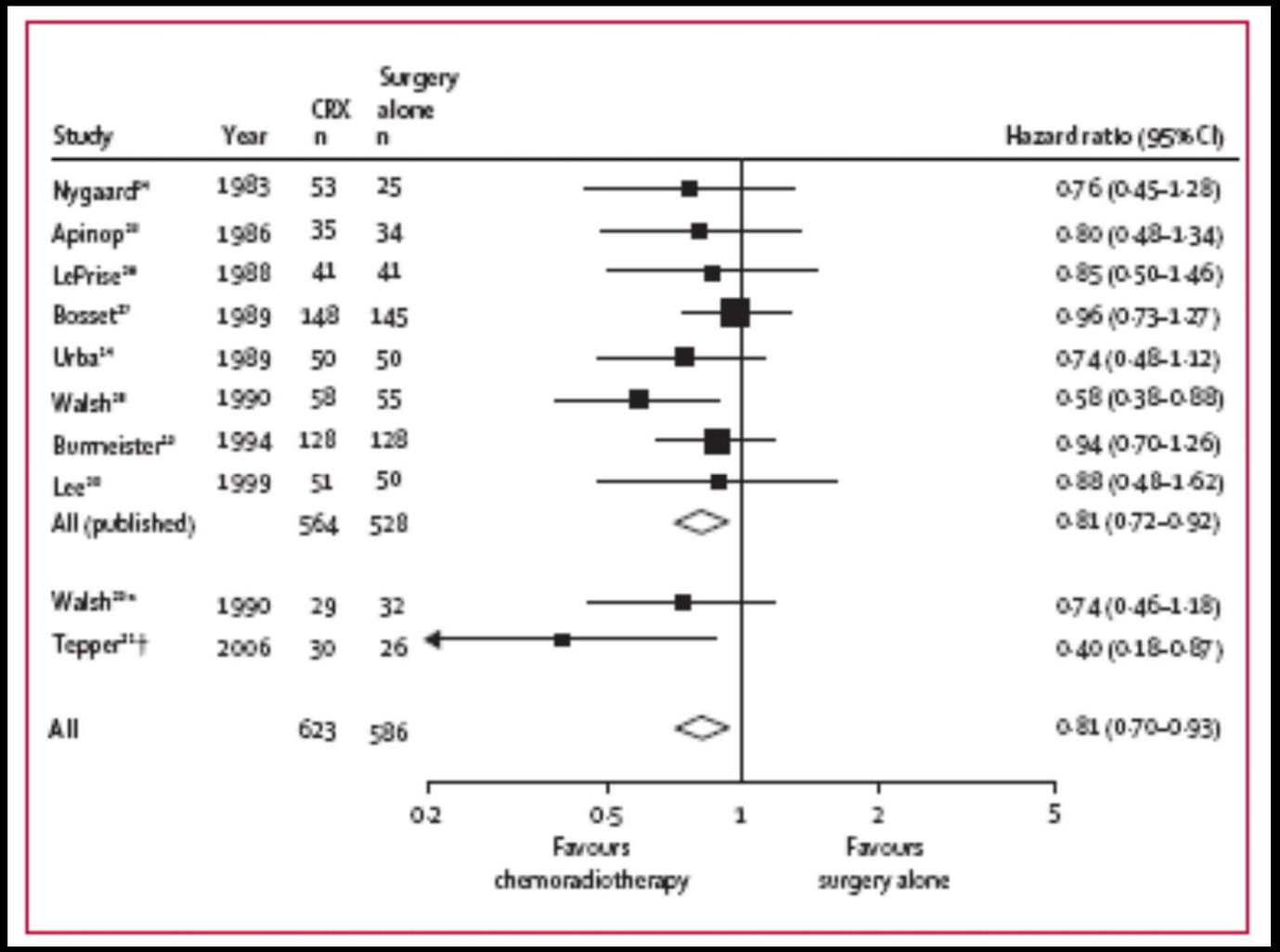
Neo-adjuvant Chemotherapy

Neo-adjuvant Chemo-radiotherapy

# Does neo-adjuvant chemotherapy help?



# Is neoadjuvant chemo-radiotherapy superior?



# Palliation and metastatic disease

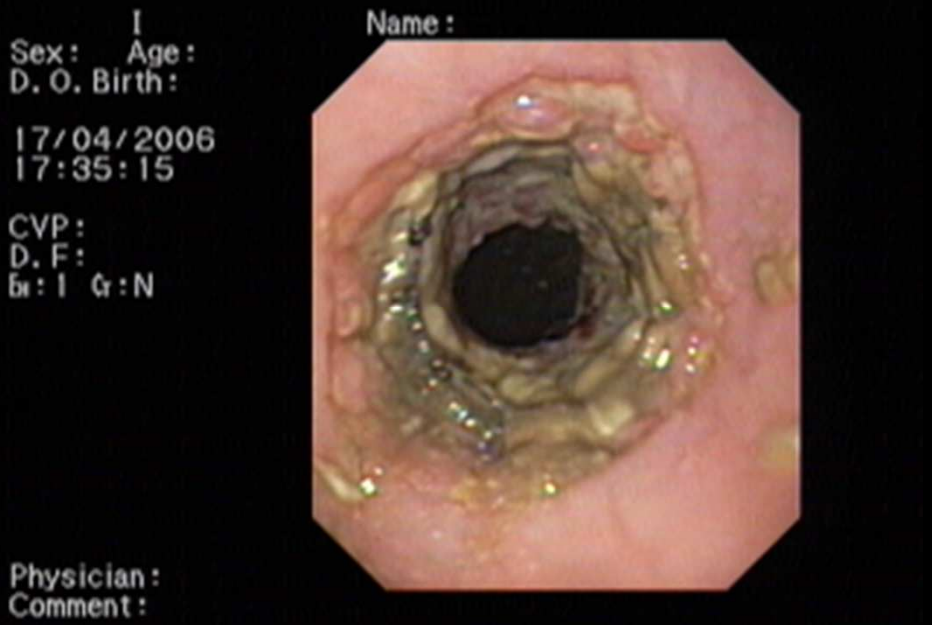
# Palliative Therapy Modalities

- Surgery
- Intubation (Self Expanding Metal Stents ‘SEMS’, Semirigid tubes)
- Thermal Ablation
  - Laser Therapy (Nd YAG / Diode)
  - BICAP probe
  - Argon Plasma Coagulation
- Photodynamic Therapy
- Radiotherapy (EBRT & BT)
- Dilatation
- Enteral Feeding (Nasogastric tube, PEG [Percutaneous Endoscopic Gastrostomy])

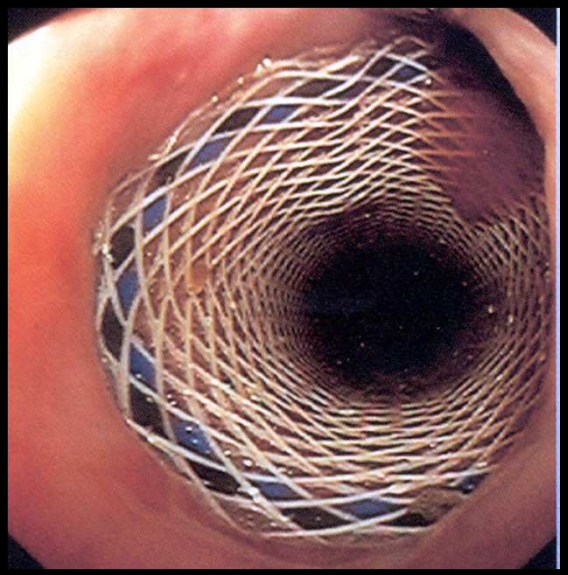
# Oesophageal Stenting

- Pre chemo-radiation
  - Self Expanding Plastic Stent
  - Temporary
  - Removable
- Palliative
  - Metal stent
  - Covered
  - Permanent
  - Dysphagia and TE Fistulae

# Oesophageal Stents




Self expanding metal stent



Self expanding plastic stent

# Palliative chemotherapy

- Palliative chemotherapy (Metastatic Cancer)
  - 5-FU based
  - Platinum based
  - Taxane based
  - Irinotecan based

# Palliative Radiotherapy

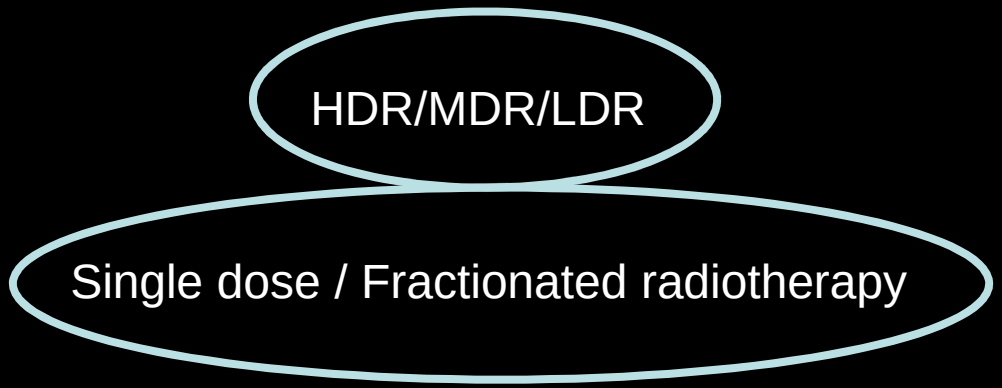
- External Beam Radiotherapy
- Brachytherapy
- Combination (EBRT + BT)

# Brachytherapy Dose Fractionation

Target Volume – Visible Mucosal tumor with 2cm craniocaudal margin.

Dose Prescription – 1 cm from mid-source or mid dwell position without optimization.

Several doses and fractionations have been used and ideal not known.



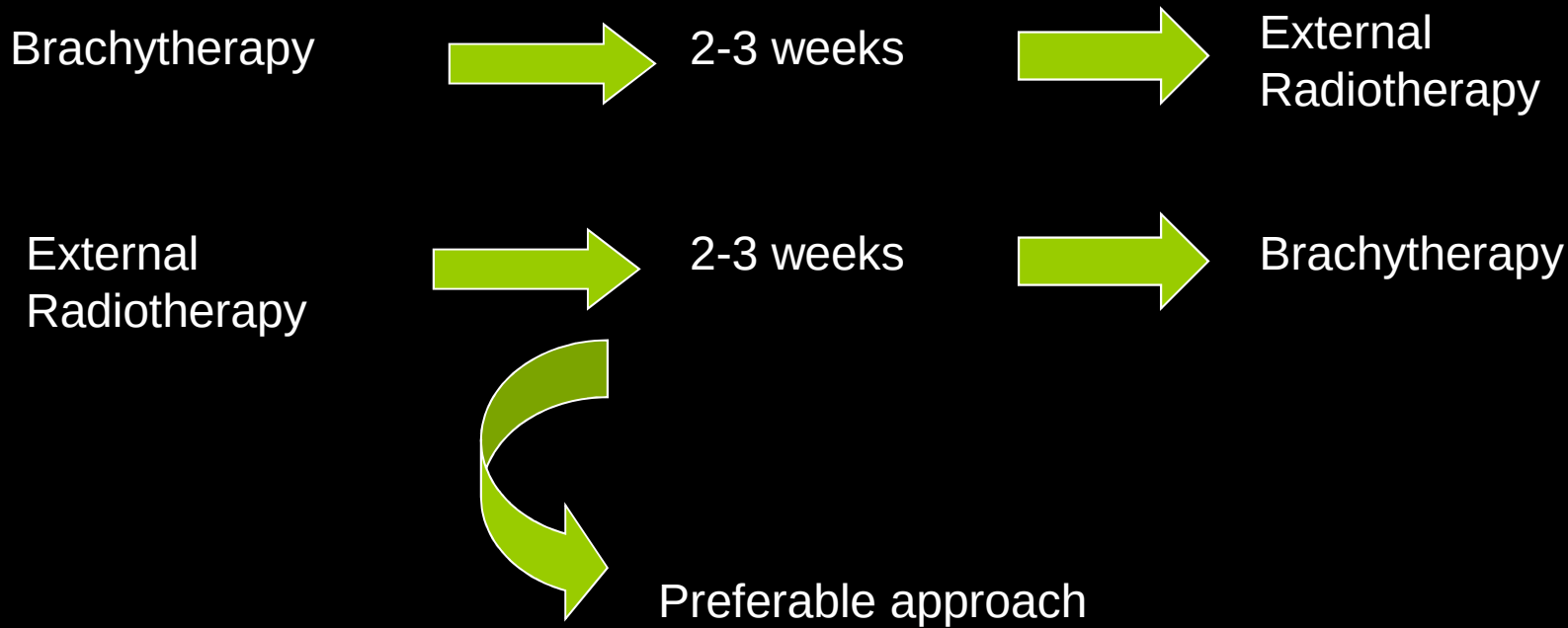

10Gy/15Gy-single dose as per previous external RT/ tolerance / life expectancy

Fractionated 6GyX2#, 6GyX3#, 8GyX2#,etc. ------- HDR. [10-14Gy in 1-2#-ABS]

20Gy single course at 0.4-1Gy/1h------ LDR. [ABS]

# Timing of Brachytherapy

Whenever given in combination with external radiotherapy- sequencing important




*Clin.Invest.Med.17(4):B115;1994

# Supportive Care

- IV hydration
- Gastrostomy/ Jejunostomy feeding encouraged
- Nutritional support if caloric intake is poor
- Antifungals / gargles as and when required
- Sucralfate/ local anesthetics
- Dilatations if required

# Summary

- Surgery is the mainstay of treatment
- Neoadjuvant chemotherapy and chemo-radiotherapy has promise in thoracic esophageal cancer
- Perioperative chemotherapy improves outcomes in adenocarcinomas of GE jn and stomach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