NEW DEVELOPMENTS IN UPPER GI CANCER ENDOSCOPY

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3/12/05

OBJECTIVES: 1) TO UNDERSTAND THE ROLE OF ENDOSCOPIC ULTRASOUND IN DIAGNOSIS AND STAGING OF UPPER GI CANCERS
2)TO REVIEW THERAPEUTIC ENDOSCOPY IN THE MANAGEMENT OF UPPER GI CANCER

- EARLY AND LATE ESOPHAGEAL CANCER
- GIST
- GASTRIC CANCER
- PANCREATIC CANCER
- CELIAC PLEXUS BLOCK
- NEW DEVELOPMENTS IN IMAGING

Esophageal cancer

THE PROBLEM

- Worldwide > 300,000 new cases per year
- Wide geographical variation
- Approx. 50% present with locoregional disease – optimal therapy unclear
- 5 year OS rarely > 30%

INCIDENCE

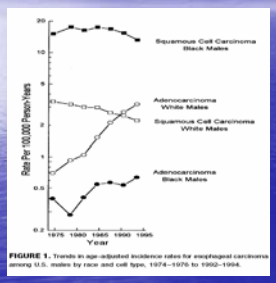


FIGURE 1. Trends in age-adjusted incidence rates for esophageal carcinoma among U.S. males by race and cell type, 1974–1976 to 1992–1994.

- SEER Database
- Smoking
- Alcohol
- Obesity
- Diet

CLASSIFICATION

- Squamous carcinoma
- Adenocarcinoma
  - Type 1
    - Intestinal metaplasia of tubular oesophagus
  - Type 2
    - True junctional tumours of the gastric cardia
  - Type 3
    - Subcardial tumours which infiltrate superiorly

STAGING

Primary Tumour (T) invades
- T1 l.propria/submucosa
- T2 m.propria
- T3 adventitia
- T4 adjacent structures

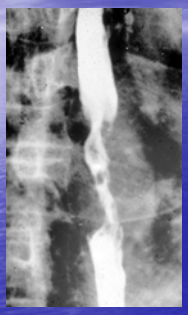
Regional LNs (N)
- N1 regional LN mets

Metastases (M)

Lower oesophagus
- M1a coeliac axis node
- M1b distant mets

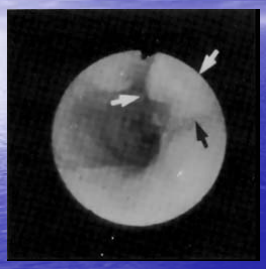
Mid/upper oesophagus
- M1a not applicable
- M1b distant metastases

DIAGNOSIS - Barium Swallow



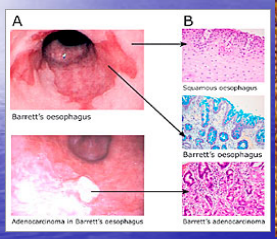
- Shouldering at both proximal and distal ends.
- Evidence of mucosal destruction and filling defects
- Free flow of barium

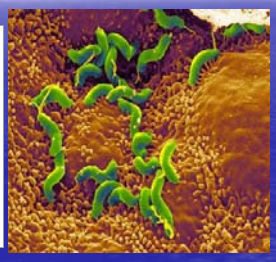
ENDOSCOPY



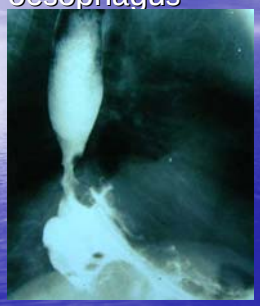
- Small flat tumour at distal end of oesophagus occupying < 25% lumen.

ADENOCARCINOMA



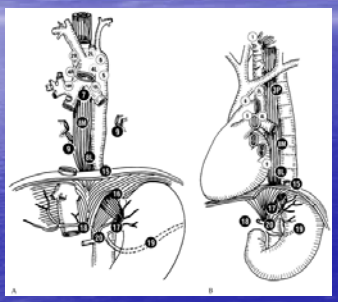


Barium Swallow – distal oesophagus



- Typical apple core lesion seen with distal esophageal adenocarcinoma associated with chronic reflux disease.

LYMPH NODE MAPPING



PATTERNS OF SPREAD

- Lymphatic
- Radial
- Longitudinal

- Rice et al, 1998
  - N=359
  - Tis N+ (0%)
  - T1 N+ (10.8%)
  - T2 N+ (43.2%)
  - T3 N+ (77.2%)
  - T4N+ (66.7%)

DISTANT METASTASES

- Lymphatic and haematogenous spread appear to be independent (not sequential)
- Bone marrow studies at time of surgery

Staging cont.

Routine

- CT
- EUS

Selected

- CXR
- Abdominal US
- MRI
- Bronchoscopy
- Laparoscopy
- PET

CT

T stage

- Can predict mediastinal invasion in >80%
- Cannot delineate component layers of oesophageal wall or microscopic invasion in T1-3 tumours
- Detection of coeliac, portal nodes and distant metastases

N stage

- Accuracy 38 – 70%

Endoscopic Ultrasound (EUS)

T stage

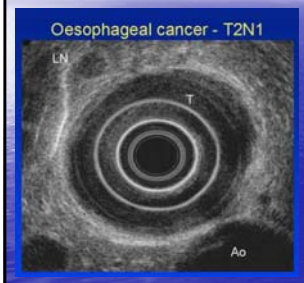
- Overall accuracy 84% : T1 (81%), T2 (76%), T3 (92%), T4 (86%)
- Superior to CT for T staging (84% v 58%)
- Limitation : obstructing tumours (<25%)
- With neoadjuvant therapy accuracy of determining T stage decreases to 40% (fibrosis, inflammation, nonviable residual cancer)

EUS

N stage

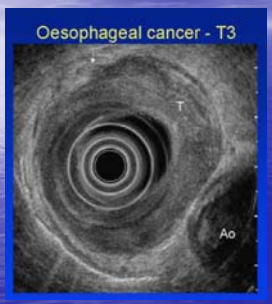
- Overall accuracy 77% : N0 (69%), N1 (89%)
- Sensitivity 75%, specificity 70%
- Well defined margins, >1cm, rounded, hypoechoic = likely to be involved.
- Can be biopsied

EUS – T2N1



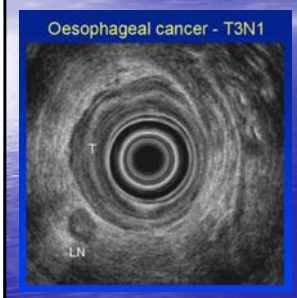
- Tumour involving m.propria
- A small rounded, hypoechoic lymph node (sonographically malignant)

EUS - T3N0



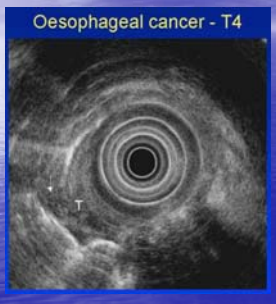
- Large, circumferential, heterogenous tumour
- Distinct cleavage plane between tumour and aorta.

EUS - T3N1



- Circumferential tumour in the mid-oesophagus with invasion through the muscularis.
- Discrete, rounded lymph node .

EUS - T4



- Tumour breaches the pleura in one section
- Invasion of the pleura was not identified by CT scan.

ESOPHAGEAL CANCER THERAPY –EARLY CA

Emerging Therapies for Barrett's Esophagus

BARRETT'S ESOPHAGUS THERAPY

Barrett's Esophagus is a definite risk for the development of adenocarcinoma of the esophagus, increasing cancer risk about 40 fold.
The risk of carcinoma developing in BE is about 0.5% per year.

The incidence of adenocarcinoma of the esophagus is increasing since 1970s. Approximately 7000 new cases of esophageal adenocarcinoma are reported yearly in North America.

Barrett's Esophagus

Barrett's Esophagus is a definite risk for the development of adenocarcinoma of the esophagus, increasing cancer risk about ***40*** fold.

The risk of carcinoma developing in BE is about ***0.5%*** per year.

Barrett's Esophagus Therapy

Surgical therapy eg Esophagectomy is the "gold standard" of therapy of patients with high grade dysplasia in Barrett's Esophagus.

Endoscopic therapy is emerging as a possible alternative to esophagectomy in appropriately selected patients

Barrett's Esophagus with HGD Esophagectomy

Operative mortality is between 4% - 7%.

Early morbidity is approximately 15% -32%

Long term morbidity approx 10 %

Recurrence of BE after esophagectomy

- Four patients out of 45 pts post esophagectomy developed recurrence of BE 1,4,8 and 9 yrs later
- Recommendation: post esophagectomy younger pts should be observed for BE

ENDOSCOPIC THERAPY OF BARRETT'S ESOPHAGUS

- Summary of methods:
  - Photodynamic therapy
  - Laser ablation
  - Argon Plasma Coagulation
  - Multipolar electrocoagulation
  - Endoscopic mucosal resection
  - Combination of procedures

Photodynamic Therapy

PDT uses a photosensitising drug which is activated by light of a specific wavelength.

PDT was orinally described by Raab who described the lethal effect of light on paramecia treated with acridine dye.

It is a "cold" photochemical reaction eg there is no heating of tissues.

Photodynamic Therapy

The photosensitiser is activated by light and interacts with molecular oxygen to produce a reactive singlet oxygen. This moiety is highly cytotoxic and also produces microvascular damage. This combined action then leads to formation of necrotic tissue which eventually sloughs away and there is subsequent re- epithelialisation of the treated site.

Endoscopic Therapy of Barrett's Esophagus
Photodynamic Therapy

Photochemical method of ablation of Barrett's Esophagus using
1) porfimer sodium (Photofrin) for deep tissue penetration (mucosa and submucosa)
2)5-aminolevulinic acid(5-ALA) for shallow tissue penetration(mucosa)

Photofrin remains in body tissues for approximately 6-8 weeks
5-ALA photosensitivity is limited to several days.

ENDOSCOPIC THERAPY OF BARRETT'S ESOPHAGUS

PHOTODYNAMIC THERAPY

Photofrin is injected IV then followed by endoscopy in 48 hrs.
Dye- laser red light(630nm) is delivered via a fiberoptic probe.
Cylindrical diffuser may be used to uniformly diffuse the laser light

Light delivery may be repeated in 48 hrs if additional areas need treatment.

5-ALA is administered orally followed by laser light exposure in 4 hrs.

PDT for Barrett's Esophagus f/u in 100 patients B.F.Overholt et al

- 78 men,22 women treated with PDT were followed for ~19 mos
- PDT technique: 48 hrs after injection of photofrin ,630nm laser light is endoscopically delivered using a cylindrical diffuser. Second treatment may be given to" skip areas"in 48 hrs

PDT FOR BARRETT'S ESOPHAGUS

- 2/100 patients developed a small island of glandular epithelium with HGD under areas of squamous epithelium
  1 pt developed subsquamous AdCa, retreated with PDT with no tumor recurrence
- 75-80% of treated mucosa was replaced with squamous epithelium

LONG TERM STUDY OF PHOTODYNAMIC THERAPY OF HIGH GRADE DYSPLASIA OF BARRETT'S ESOPHAGUS SINGLE CENTRE STUDY, E.OVERHOLT

71 patients --- followed for approximately 58 months.
59 patients with HGD --- in 53 patients HGD was eliminated (90%)
3 patients(5%) developed subsquamous adenoca (expected 25-50%)

Strictures developed in 18% of patients with one PDT,50% with 2 PDTs
Barrett's mucosa was reduced by approx. 7.2 cm(0-19cm)

Photodynamic Destruction of High Grade Dysplasia and Early Carcinoma of the Esophagus after the Oral Administration of 5ALA Gossner et al.

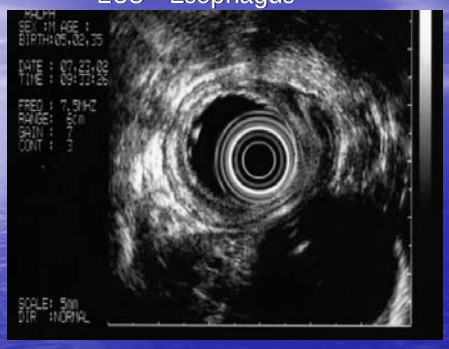
27 patients with HGD and early carcinoma were treated with PDT using 5ALA. Approximately 6 hrs after ingestion of 5ALA, laser light irradiation of the affected area of the esophagus was performed.

HGD was eliminated in 9/9 patients. 19 mucosal tumors in 18 pts were treated and eradicated succesfully in 10 patients with a follow up of 16.9 months (range, 3-37 months)
There was no related morbidity and mortality observed.

Barrett's Esophagus -PDT Case study-BCCA

•53 y/o man with longstanding hx of reflux was dg to have Barrett's Esophagus 5y/a.
• Started on Omeprazole 20mg/day with good control of symptoms.
• Endoscopy in Dec/98 revealed no change in the appearance of BE but biopsies showed multifocal HGD. Omeprazole was increased to 20 mg bid and he was subsequently referred for PDT.
•His GI and systemic enquiry was negative
•Physical exam was normal. EUS of the esophagus and CT chest/abdomen were normal.

EUS - Esophagus

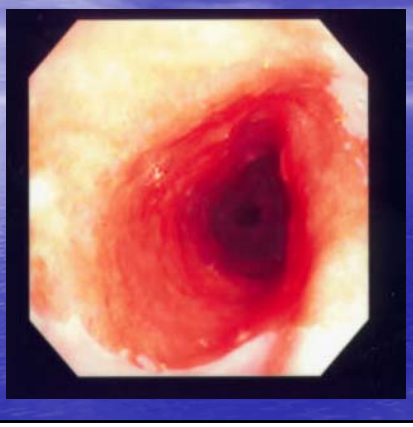


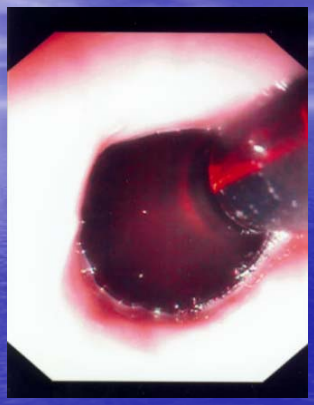
BC Cancer Agency
CARE & RESEARCH

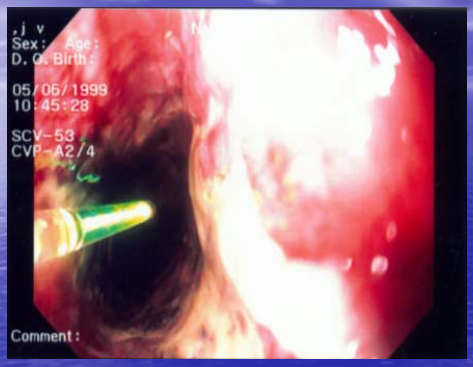
Barrett's Esophagus
Case study

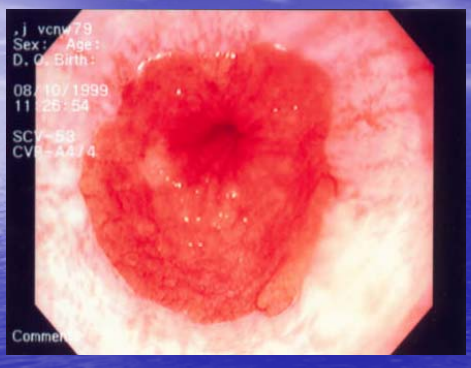
- Endoscopy defined the Barrett's mucosal segment as 10 cm long
- PDT treatment was given to the distal 7cms segment in May/99 and to the remaining 3 cms in August/99. Patient tolerated the treatment well. He had a brief episode of dysphagia in Sept/99. Endoscopy did not reveal any areas of narrowing .He has been continued on Omeprazole 20 mgm bid.

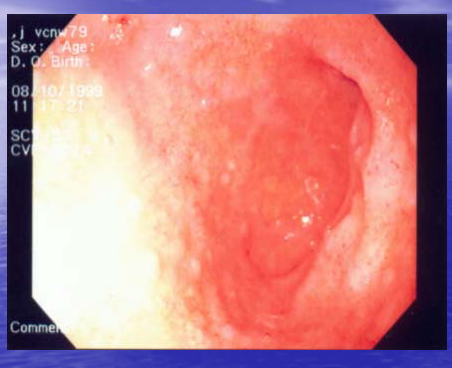
- Follow up for 6 years -endoscopies revealed a complete resolution of BE mucosa and four quadrant biopsies q 2cm revealed squamous mucosa.











PDT for Barrett's Esophagus

AdCa	prePDT	POST PDT Ca	HGD	LGD	ND	NoBE
T1	12	3	0	1	8	4
T2	1	0	0	0	1	0
HGD	73	0	7	8	56	32
LGD	14	0	1	0	13	7
TOTAL	100	3	8	9	78	43

PDT FOR BARRETT'S ESOPHAGUS

- Complications:
  - esophageal stricture in 34 patients
  - 3 patients developed atrial fibrillation
  - transient pleural effusion are common
  - photosensitivity
  - postprocedure retrosternal pain

Barrett's Esophagus-PDT

Case study 2

•67 y/o man presented with hx of mild heartburn approx 2x/week. He also had experienced mild decrease of appetite and weight loss. He underwent UGI endoscopy which revealed a small nodule at the GE junction. Biopsy revealed HGD in a short segment of BE.

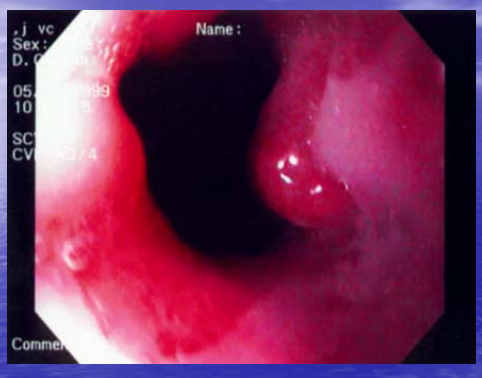
•Patient was started on Omeprazole 20 mgm bid and referred for PDT.

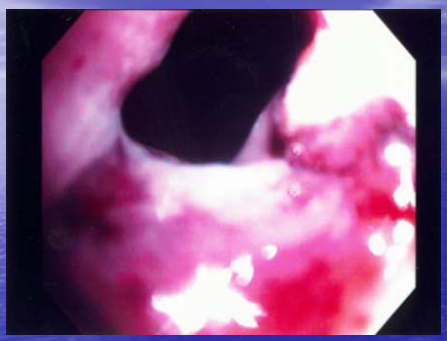
•PMHx: CABG 1983, HepC, DM.

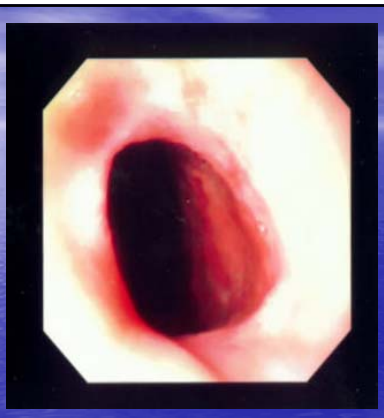
•Phys exam was negative. EUS of the esophagus, CT chest was neg.

Barrett's Esophagus- PDT

Patient underwent PDT in Aug/99. He tolerated it well and had no complications. Subsequent UGI endoscopies over the last 2 years revealed elimination of the Barrett's mucosa and HGD. He is continuing to take Omeprazole 20mgm bid.







Thermal Ablative Therapy for Barrett's Esophagus

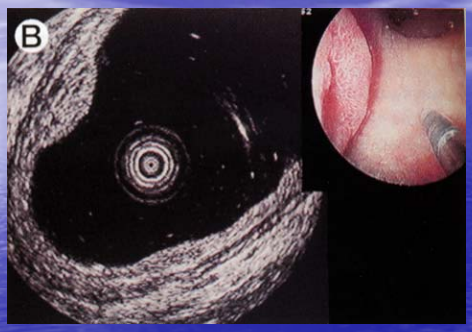
Electrocoagulation: multicenter trial- R.Sampliner et al

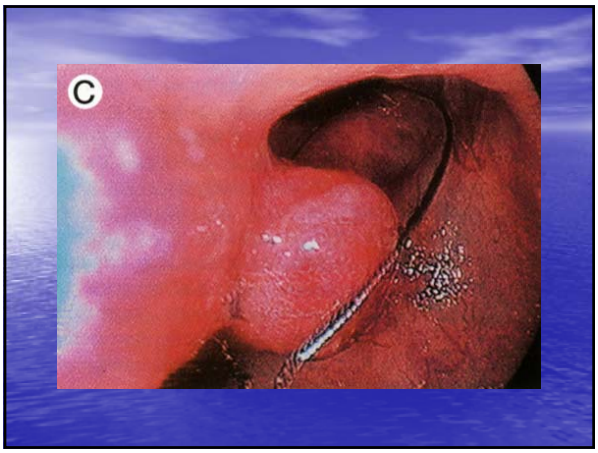
Multipolar electrocoagulation was used with omeprazole 40 mg bid to reverse BE.
58 patients with 2-6cm of BE were treated. 85% had visual reversal and 78% had both visual and histological reversal.
One patient developed a stricture requiring dilation.
Problems with this method : large number of therapeutic sessions(6) and unequal depth of mucosal injury.

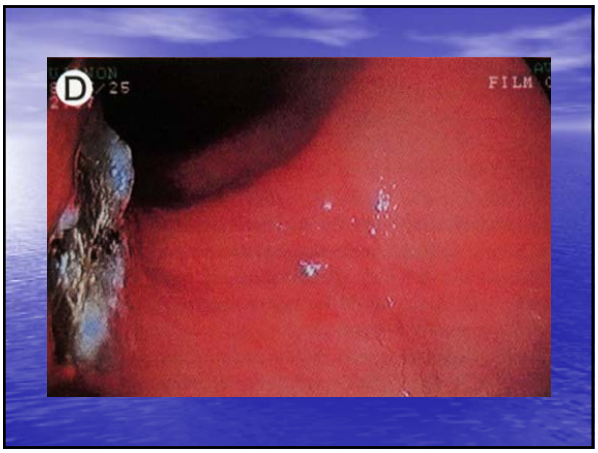
Endoscopic Mucosal Resection of Early Cancer and HighGrade Dysplasia in Barrett's Esophagus. Ell et al

- 64 pts with early carcinoma or high grade dysplasia were treated with EMR.
- 35 patients were low risk
  1) diameter 20mm or less
  2)well or moderately differentiated adenocarcinoma
  3)lesion limited to mucosa
  4)I,II a,b,c.
- 29 pts were high risk.

ENDOSCOPIC MUCOSAL RESECTION OF ESOPHAGEAL CANCER







ENDOSCOPIC THERAPY OF ADVANCED ESOPHAGEAL CANCER

- Laser therapy
- Argon Plasma coagulation
- Stents
- PDT

ENDOSCOPIC LASER THERAPY OF ESOPHAGEAL CANCER

- **Introduction**: laser therapy is based on the interaction between the laser energy and tissue which results in heat.
- **Therapeutic variables**-- energy setting,the duration of delivery,the nature of the tissue, the wavelength used.

LASER THERAPY OF ESOPHAGEAL CANCER

- Laser therapy needs to be repeated, this depends on the initial tumor length and the tumor load.
- The **frequency** of the laser therapies and the **patient's condition** determine whether this therapeutic option should be continued or alternative treatments sought.

PALLIATION OF PATIENTS WITH ESOPHAGOGASTRIC NEOPLASMS BY INSERTION OF A COVERED MODIFIED GIANTURCO-Z ENDOPROSTHESIS. Bartelsman et al .

- Methods: short and long term outcomes in 153 pts Rx with 164 stents.
- Results: Dysphagia score decreased from 3.7 to 2.2
- Complications:early in ~30%
  late in~ 28%

STENT THERAPY OF PATIENTS WITH ESOPHAGEAL CANCER

- **Early complications:**
  stent -migration~4%
  obstruction~6%
  pneumonia~5%
  bleeding~4%
  perforation~2%
  pain~ 16%

- **Late complications**
  stent-
  migration~3%
  obstruction~10%
  pneumonia~3%
  bleeding~7%
  perforation~1%
  pain~12%
  death~3%

EMR in Barrett's Esophagus

The mean number of treatment sessions per patient was 1.3+/-0.6 in group A and 2.8+/-2.0 in group B.
One major complication occurred ,a case of spurting bleeding

Complete remission was achieved in 97% of the patients in group A and in 59% of those in group B.

During a mean follow up of 12+/- 8 mos, recurrent or metachronous carcinomas were found in 14% of patients.

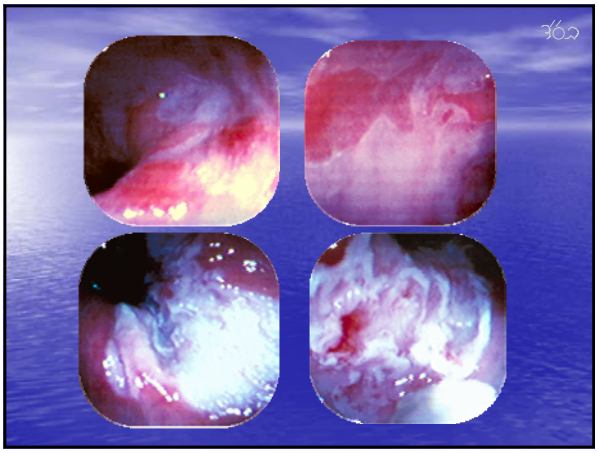
Conclusion: EMR of early carcinoma in BE is associated with low morbidity and may offer a therapeutic alternative to esophagectomy in selected patients with local, superficial carcinoma .

Ablation of Barrett's epithelium by argon plasma coagulation in combination with high-dose omeprazole.

•In 73 patients with histologically confirmed Barrett's esophagus APC was used in combination with omeprazole 40 mg tid.
In 69 of 70 patients (98%) complete squamous regeneration was achieved after a median of 2 sessions (range 1-5). Median follow up of 12 months. Three patients developed a mild stricture. Schulz et al.

•Van Lethem et al achieved complete remission of BE in 60% of pts

•Byrne et al in a study of 27 pts treated with APC demonstrated complete regeneration in 70% of pts.
Esophageal perforation occurred in 2 patients.



WHEN IS BARRETT'S MUCOSA TRULY ELIMINATED ? K.Wang et al

- 25 patients who had BE(~5cm length) eliminated by PDT were followed for a period of~23 mos
- Results:
  - 15/25 no recurrence
  - 10/25 recurred in ~10 mos
    8/10 no evidence of IM in the first set of bx, 2/10 had IM in the second sets of bx and in 6 pts IM was detected in the third sets of biopsies.
    Recommendation :
  - ***Absence of IM should only be accepted after min 3 neg sets of biopsies.***

Barrett's Esophagus Endoscopic Therapy

•**Endoscopic therapy of HGD in BE should be considered**

1) in patients who for reasons of frailty or comorbid condition
are at increased surgical risk from esophagectomy.

2) may be particularly useful in patients with short Barrett's Esophagus.

3) in patients who refuse surgery

A Prospective Randomized Study Comparing Three Types of Covered Metal Stents for the Palliation of Malignant Dysphagia. P.D.Seersema et al

- Comparison of 3 stents--Cook-Z stent,Ultraflex and Wallstent were placed in 100 pts.
- Results: At 4 weeks the mean dysphagia score improved significantly (3 to 1). No differences between the stents in the incidence of major complications (33%-24%-18%; bleeding,perforation,pain).
- Recurrence of dysphagia due to stent migration or tumor overgrowth developed in 24%-26%- 33% of patients. Median survival was similar in all 3 groups approx. 110 days.

GASTRIC TUMORS

Endoscopic Mucosal Resection Of Early Gastric Cancer. Kondo et al

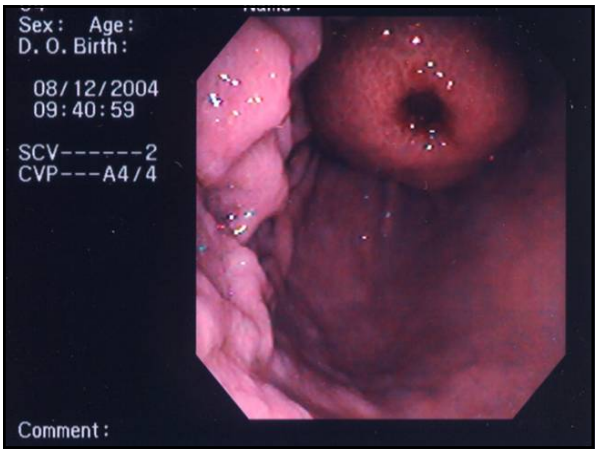
- EMR applied to lesions of up to 30mm in diameter that were not invading the submucosa.
  479 ca/11 year period -submucosal invasion in 74 tumors.
- Local recurrence in 17 pts treated with endoscopy or surgery. There were no GC related deaths over a median follow up period of 38 months. Bleeding and perforation developed in 5% of patients, no treatment related deaths.

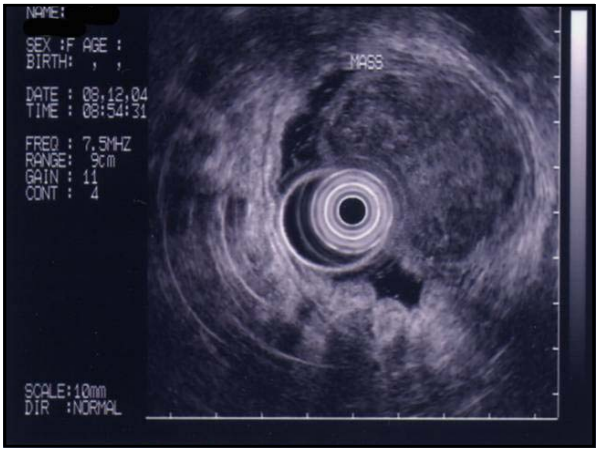
Gastric tumors

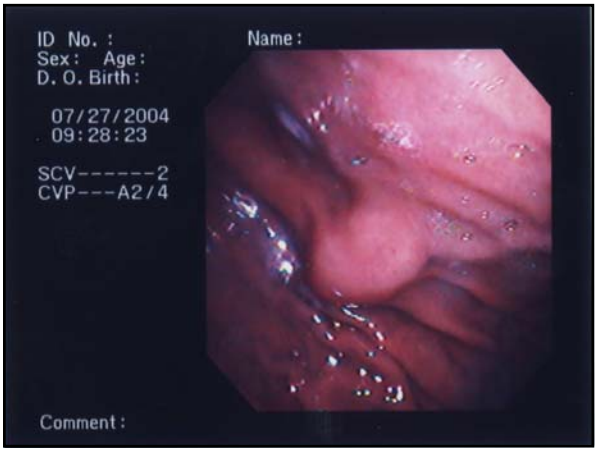
- Subepithelial mass 1)GIST- most common tumor about 70% occur in the stomach
  10-30% are cancerous
  Determination of malignant potential:
  related to size>2-3 cm and number of mitoses >5/HPF

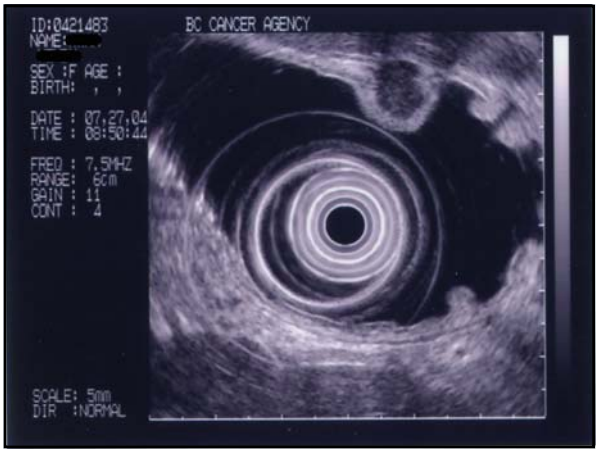
Gastric tumors

- EUS helpful in establishing dg:
  anechoic (cysts)
  hyperechoic mass – lipoma
  these do not need any further f/u
- *Hypoechoic*- define from which layer it arises; if from 2nd/3rd layer may be removed endoscopically. Mass arising from the 4th layer needs a laparoscopic removal









Gastric mass

- EUS biopsy – 75% sensitivity with >3 passes

Immunochemistry			
	CD 117 (cKIT), CD34	*SMA/Desmin*	
GIST	+		
Leiomyoma	-	+	
Schvannoma	-	-	*+ S100*
Glomus	-	+	*+ Vimentin*

Gastric tumors

- Techniques of endoscopic removal :
  1) cup suction method
  2) using a two channel scope –grasp and snare

Complications: Bleeding 20-24%
Perforation 0.5-5%
Transmural burn 0.5-1%

EUS IN THE DIAGNOSIS OF PANCREATIC CANCER

- Assesment of location, size, relationship to surrounding vasculature (portal,sma/smv involvement) ***T STAGE ACCURACY 69-94 %***
- Assesment of locoregional lymph nodes

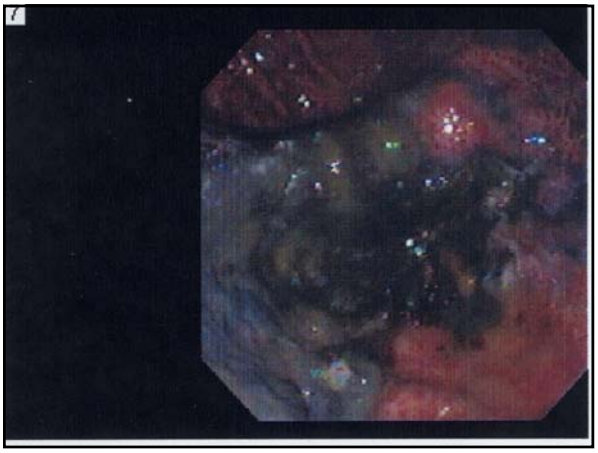
N STAGE ACCURACY 54-82 %

Pancreatic Cancer –Role of EUS

- EUS is superior to CT for diagnosing small lesions <3cms and is more accurate modality for T staging and for predicting vascular invasion.
- EUS guided FNA provides cytology for diagnosis.
- FNA is transduodenal, thus peritoneal cancer seeding does not occur
- Cost effective: influenced decision in approx 70% of patients and estimated cost saving of $3300

Pancreatic cancer

- *48 y/o man with hx of diabetes presented with hx of abdominal pain, weight loss and jaundice. Ct scan revealed diffuse changes of pancreatitis, ascites.and presence of varices suggestive of portal vein obstruction. He was treated with a CBD stent , he transiently improved but continued to be symptomatic and required admission to the hospital. The possibility of malignancy required further w/u with EUS.*



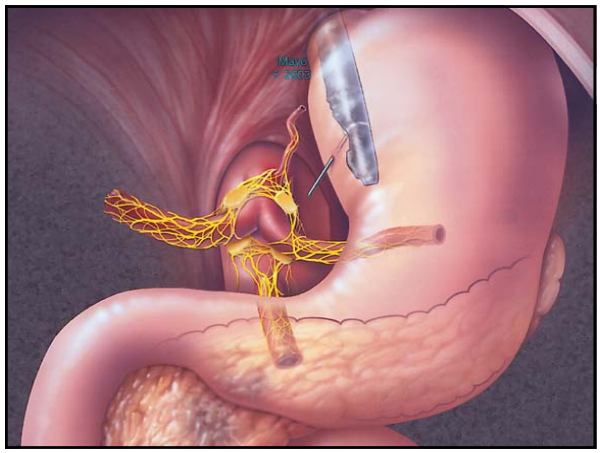
Celiac Plexus Neurolysis

- *CPN is performed for control of pancreatic cancer pain*

Technique : Under EUS guidance FNA is inserted through the stomach to the area of celiac plexus at the site of the celiac artery and a local anesthetic bipuvacaine and alcohol is injected under direct observation

Outcome: partial to complete pain control in 90% of patients in 3 months and 70-90% at time of death.

Complications : common but transient (hypotension, diarrhea)



EUS in lung cancer staging in NSCLC

- 10 % exploratory thoracotomies without resection; 25-35% recurrence therefore up to 45% of patients with NSCLC
- Chest/CT inadequate accuracy for advanced local disease.
- PET CT high sensitivity but low specificity(>20% false positive)

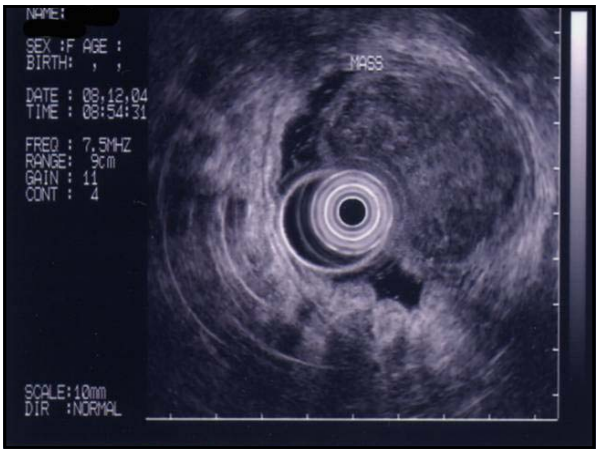
EUS in lung cancer

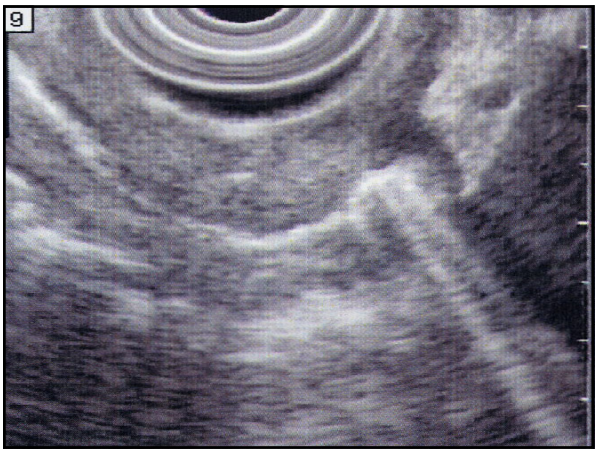
- Mediastinoscopy accesses the anterior mediastinum; in 10-15% of patients after negative mediastinoscopy N2/N3 disease is ascertained.
- EUS FNA paraesophageal space,subcarinal, aorto- pulmonary window,subcarinal, L atrium, celiac, left adrenal gland.

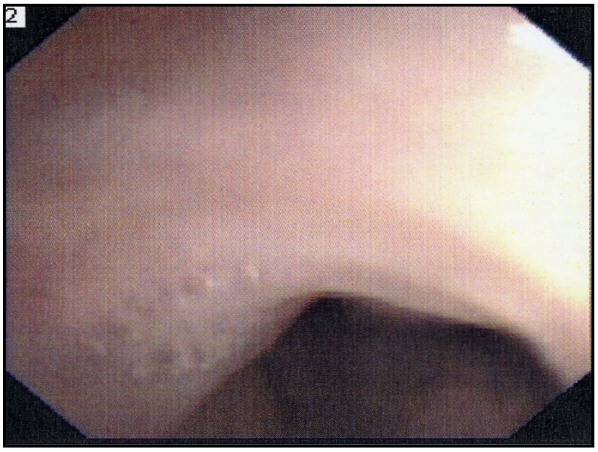
More then 40 studies report sens (median) 90%(0.6-1.0), spec 100% (0.71-100)

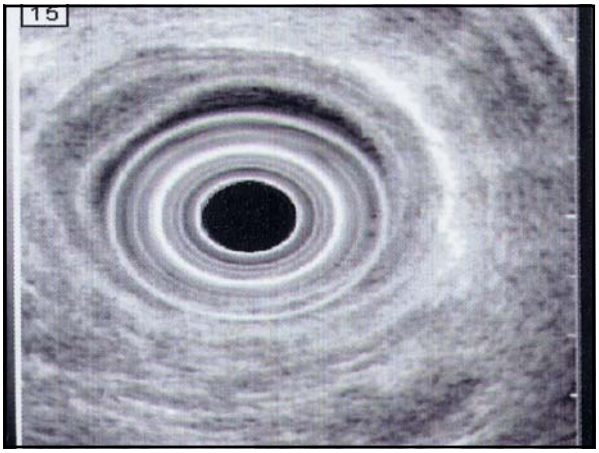
EUS in staging of lung cancer

- EUS FNA can prevent surgical intervention
- Less expensive then mediastinoscopy
- *Cost effective – if done intially in the staging of patients as it will eliminate patients with advanced disease from undergoing mediastinoscopy and surgery.*









EUS role in the staging of lung cancer.

Introduction:

- ***Exact staging of patients with NSCLC is important to improve selection of resectable and curable patients for surgery.***
- *Surgical resection is the best chance for cure for patients with NSCLC.*
- *Approx 10% of lung cancer operations result in explorative thoracotomies without tumor resection and in additional 25-35% disease recurs postoperatively.*

EUS in the diagnosis of NSCLC

- Chest CT alone is not accurate enough for dg of advanced lung cancer.
- PET CT is non invasive and offers the possibility of whole body scanning and thus detect distant metastases. This procedure has a high NPV.
- *PET CT has a considerable a false positive rate of 10-30%; thus a tissue dg is required before a patient is rejected from surgery*

A comparison of EUS guided biopsy and PET CT in lung cancer staging.
S.Larsen,PVilmannet al

- *Objectives: The aim of the study was to assess and compare the diagnostic values of PET CT and EUS FNA for diagnosing advanced lung cancer in patients who had both procedures performed.*
- *Methods: 27 patients with verified or suspected NSCLC underwent PET/CT and EUS-FNA. The respective findings were confirmed by surgery ,mediastinoscopy or f/u.*
- *Advanced lung cancer defined as T4and/ or N2/N3 and/or M1*

A comparison of EUS and PET/CT in lung cancer staging.

Results:

	PET/CT	***EUS-FNA***
Sensitivity for T4	***60%***	***60%***
N2/N3	***56%***	***100%***
M1	***100%***	***33%***

A comparison of EUS –FNA and PET/CT in NSCLC staging.

For diagnosis of advanced lung cancer

	PET/CT	EUS- FNA
Sensitivity	79%	79%
Specificity	61%	100%
PPV	69%	100%
NPV	73%	81%
Accuracy	70%	89%

A comparison of EUS and PET/CT in lung cancer staging

- *Conclusion: PET/CT and EUS- FNA had a comparable sensitivity and NPV for diagnosing advanced lung cancer but EUS – FNA had a superior specificity and PPV. The two methods seem to complement each other.*

NEW IMAGING TECHNIQUES

- Optical Coherence Tomography – *optical analog to ultrasound-mucosal imaging*
- Confocal Imaging- *point scanning laser analysis allows subsurface histological analysis*
- Narrow Band Imaging –*uses narrow bandwiths to visualize vasculature*
- Fluorescence Imaging


"Where does THIS piece go?"