Esophageal Cancer

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Content- Theme – Esophageal Cancer

Anatomy

Epidemiology

Diagnostics

Curative Therapy

Palliation

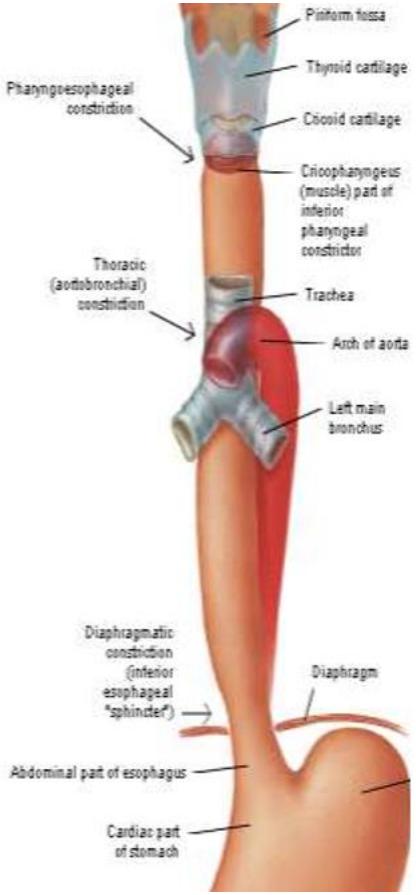
ANATOMY

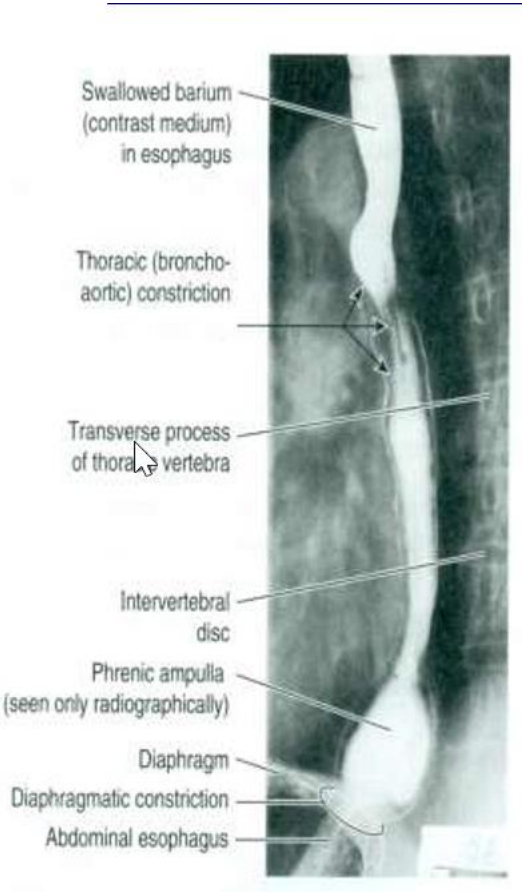
Esophagus has 4 constrictions, namely ……

Muscular tube,
about 25 cm in length
narrowing…..

- **at starting =**

  cricopharyngeal junction
- **Crossed by aortic arch**
- **Crossed by left bronchus**
- **Piercing the diaphragma**





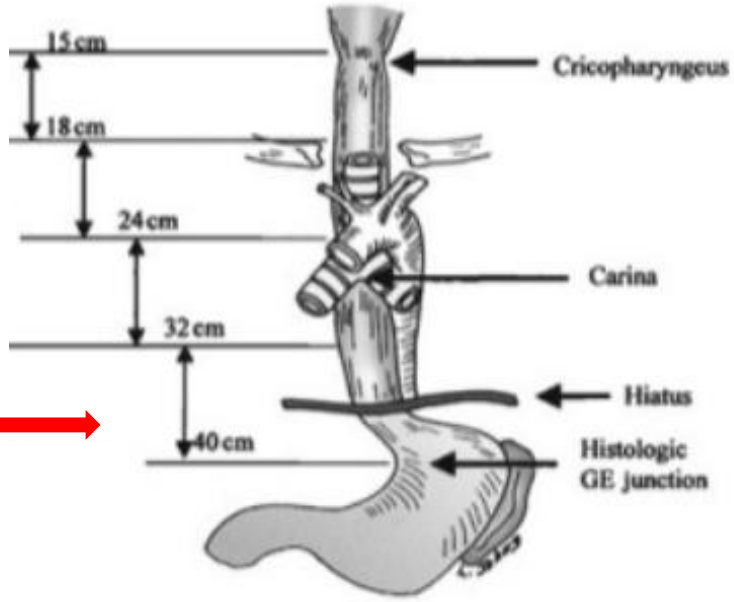
Esophagus has 4 anatomic regions, namely ……

Cervical

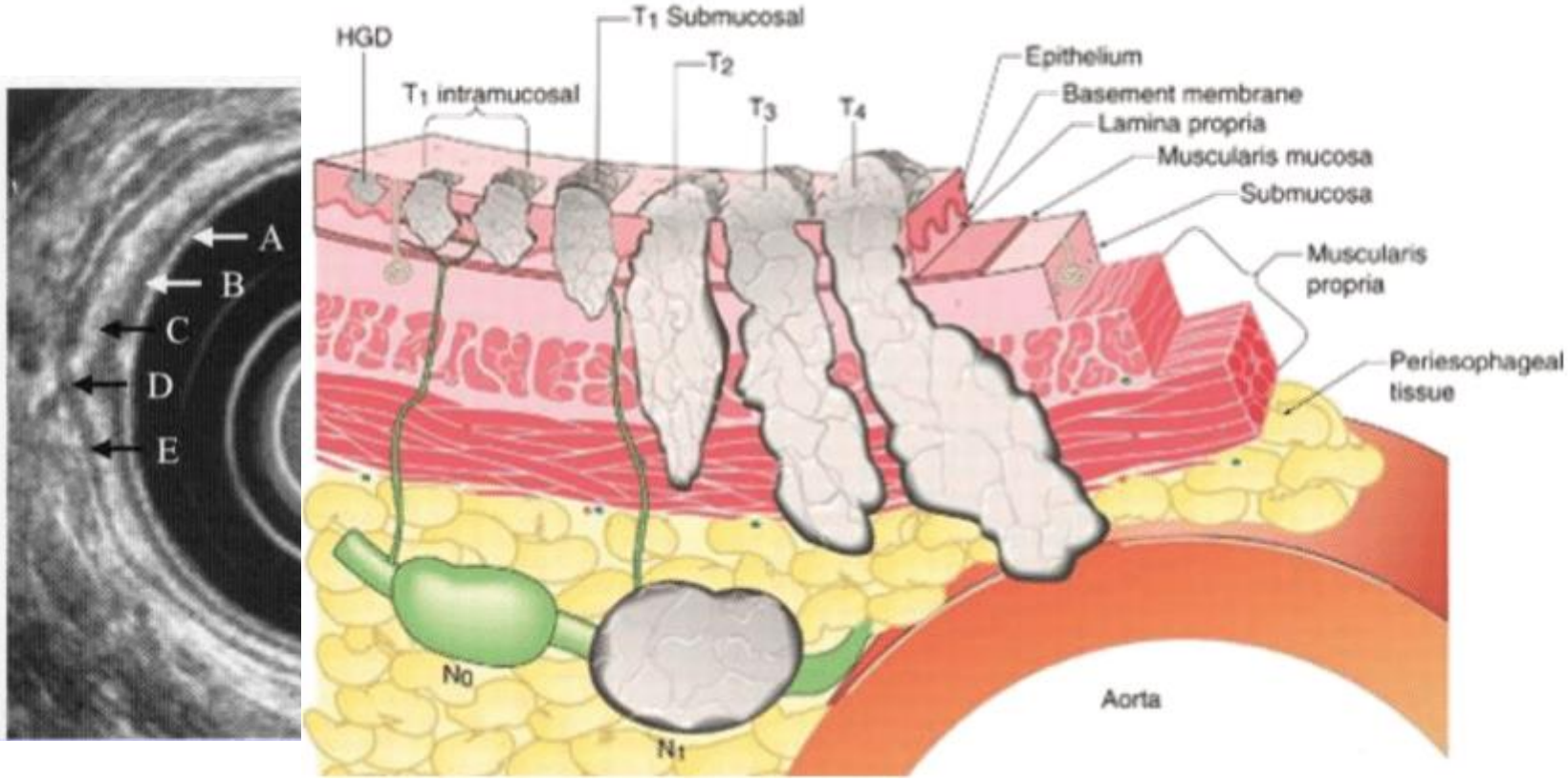
Upper thoracic

Mid-thoracic

Lower thoracic/abdominal

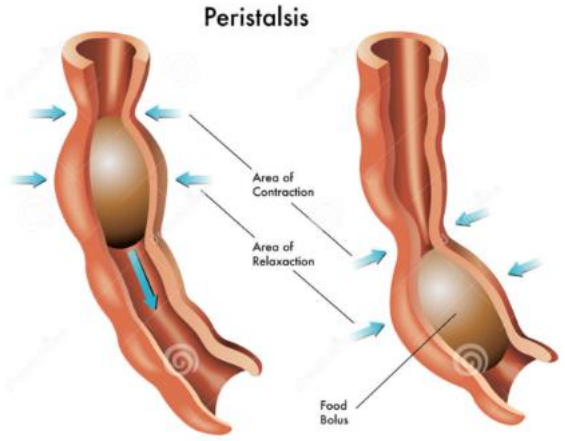


Esophagus has 4 layers, namely ……



Thickness esophageal wall: 2 mm !

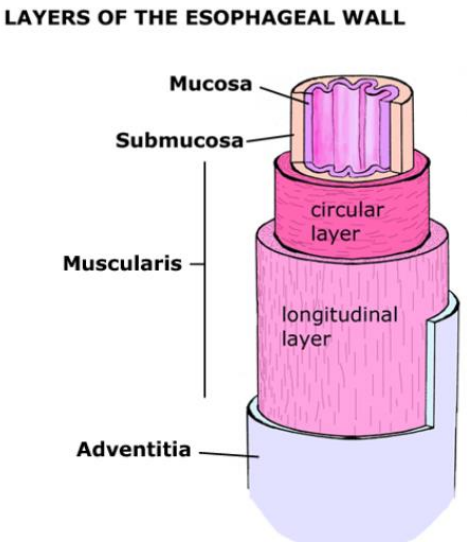
Esophagus muscle layers – function and anatomic differences



<u>Internal = circular:</u>
contraction causes increase in luminal pressure

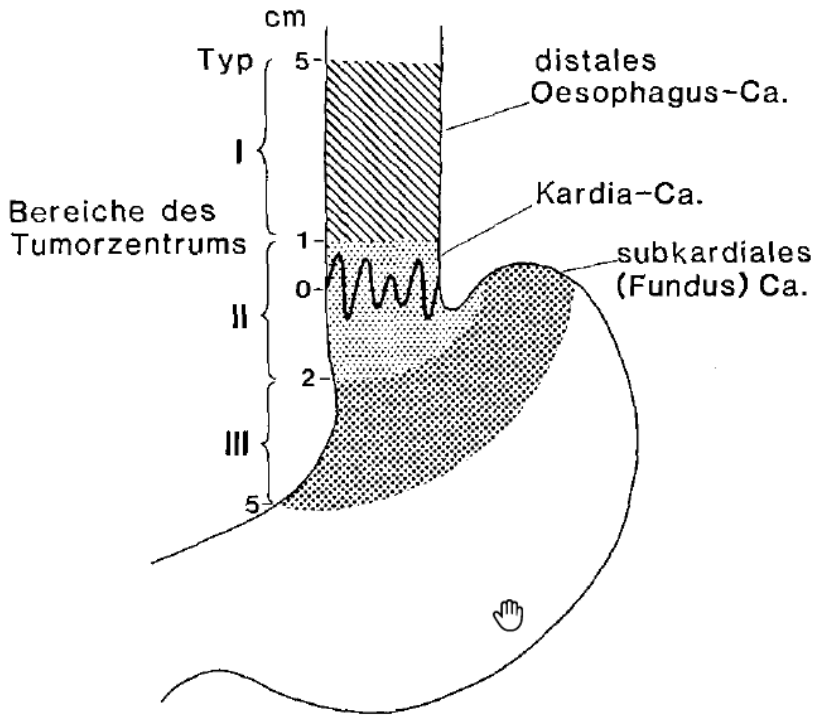
<u>External = longitudinal:</u>
contraction causes shortening with

together create wave pushes bolus down



superior third: voluntary striated muscle
middle third: voluntary striated + smooth muscle
inferior third: only smooth muscle

AGE-classification by Siewert
Adenocarcinoma of gastroesophageal junction



Siewert I and II:
esophageal guideline

Siewert III:
gastric cancer guideline

Siewert JR et al. Der Chirurg 1987

EPIDEMIOLOGY

Basic epidemiology facts on esophageal cancer

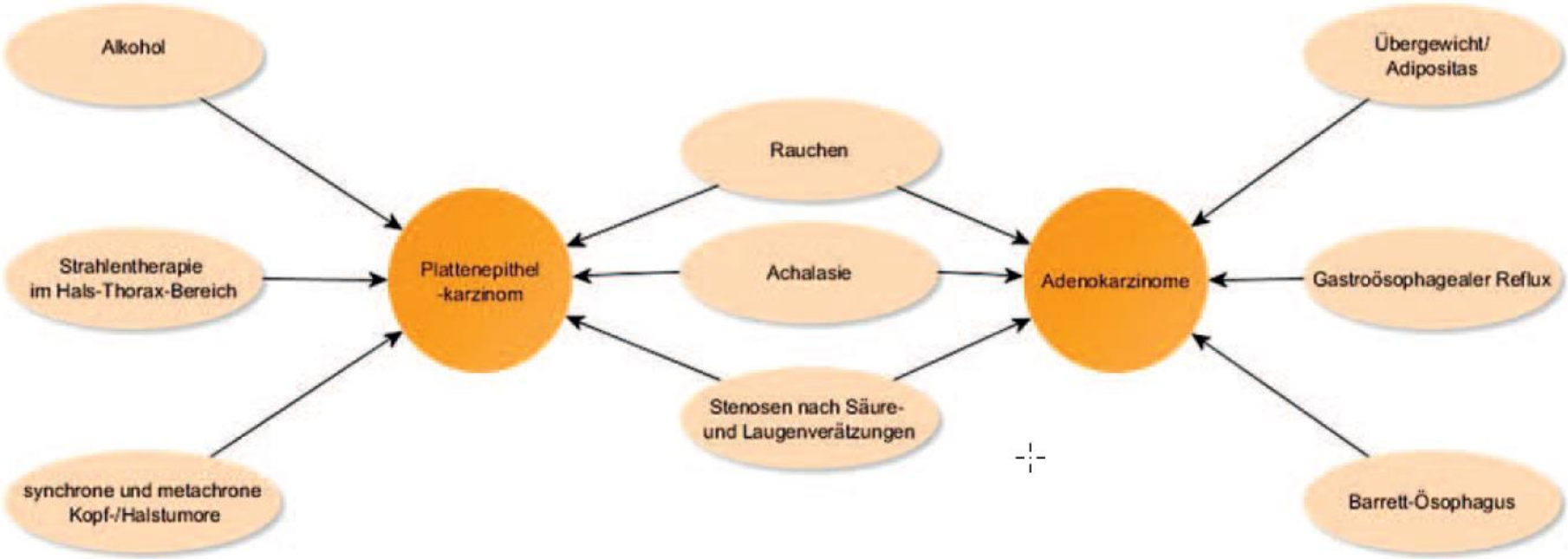
- Esophageal cancer is the 7th leading cause of cancer death
- Accounts for about 1% of all malignancies, 6% of GI cancer
- Most common in china, iran, india, former sovjet union
- Incidence rises steadily with age , reaching a peak in 6-7th decade
- Male : femaile = 3.5 : 1
- African-american males: white males = 5:1

Frequency of location of esophageal cancer

SCC:
usually in the middle 3rd of the esophagus
upper : middle : lower = 15: 50 : 35

Adenocarcinoma (AC):
most common in lower 3rd of esophagus
here about 2/3 of all cases

What are risk factors for esophageal cancer ?



Smoking – alcohol and esophageal cancer …..?

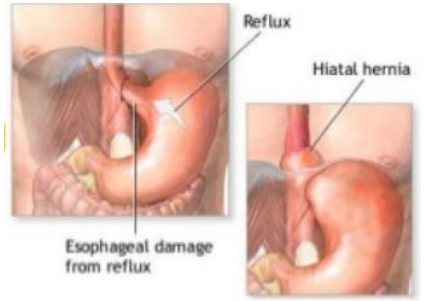
Risk/ increase	Squamous-Ca	Adeno-Ca
smoking	**6-8.5 times**	1-1.8
alcohol		
< 12.5 g/d	1.3	
12.5-50 g/d	2.3	?
> 50 g/d	**4.9**	
Smoke+ alcohol	**Up to 24-times**	?

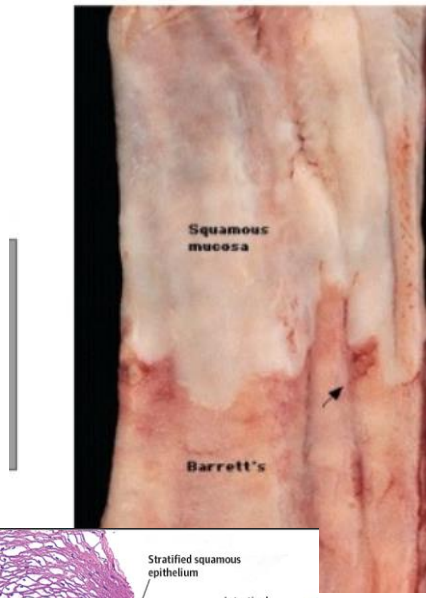
Sewram V et al. Cancer Epidemiol 2016; Tramacere I et al. Epidemiology 2011

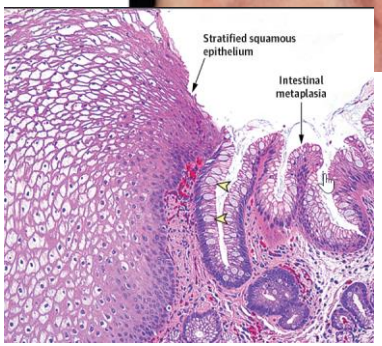
Risk factors for adenocarcinoma are ?

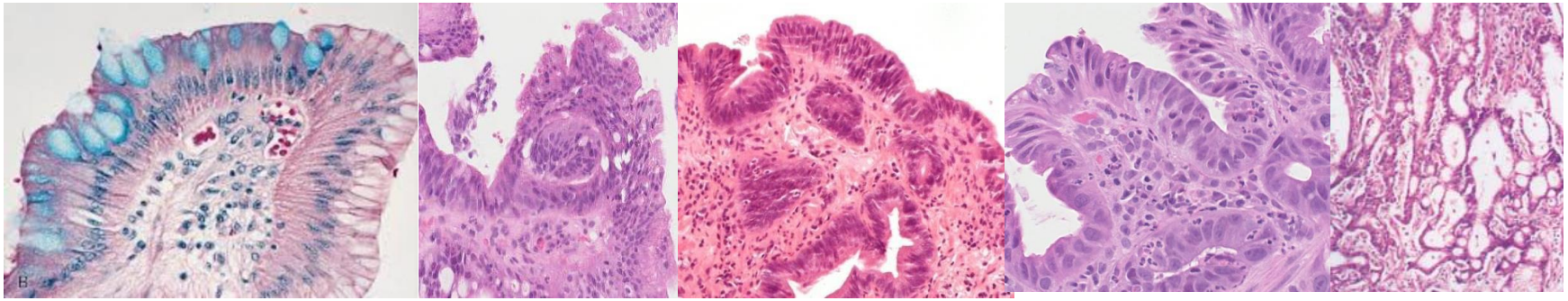
Adipositas: BMI > 30 kg/m²
About 3-fold increase in incidence AC
+ stimulates progression Barrett-> AC

Barrett-mucosa per se
About 3-100-fold increase in AC
Risk progression to HGD 0.9%/year



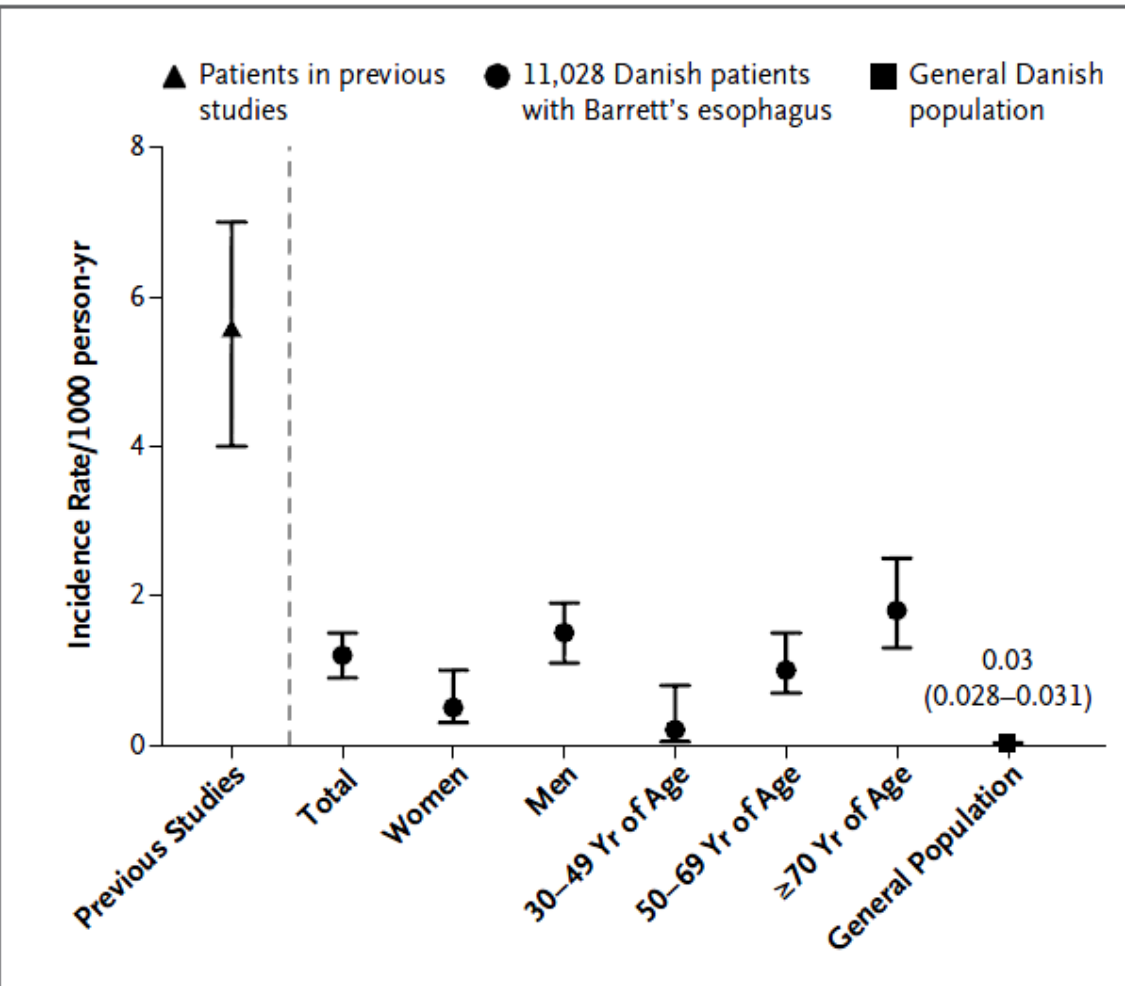






BE	indefinete	LGD	HGD	adenocarcinoma

Incidence ratio of AC
up to 11.3



follow up: 5,2 years

Incidence of Adenocarcinoma among patients with Barrett's Esophagus

lower than in historical data

0.12 % vs 0.5 %

Frederik Hvid-Jensen et al. N Engl J Med 2011

Pattern of spreading in esophageal cancer ?

- No serosal covering

= more easy/early direct invasion contiguous structures

- LN involvement increases with T-stage
- 25-30% hematogenous metastases at time of presentation
- Most common sites of metastasis are:

lung, liver, pleura, bone, kidney

Lymphatic drainage in esophageal cancer

rich mucosal and

submucosal lymphatic system

submucosal plexus drains

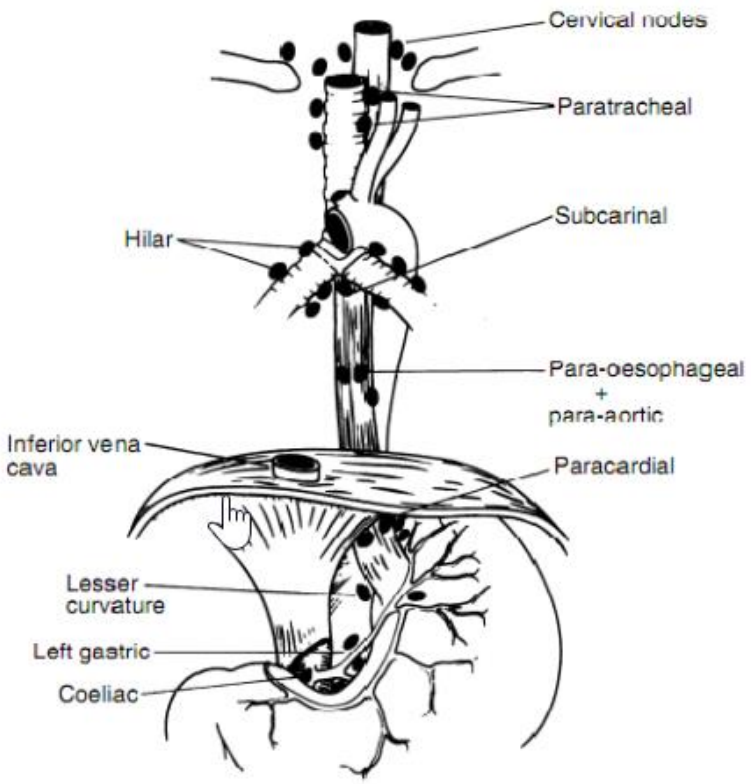
into regional LN in the

cervical, mediastinal,

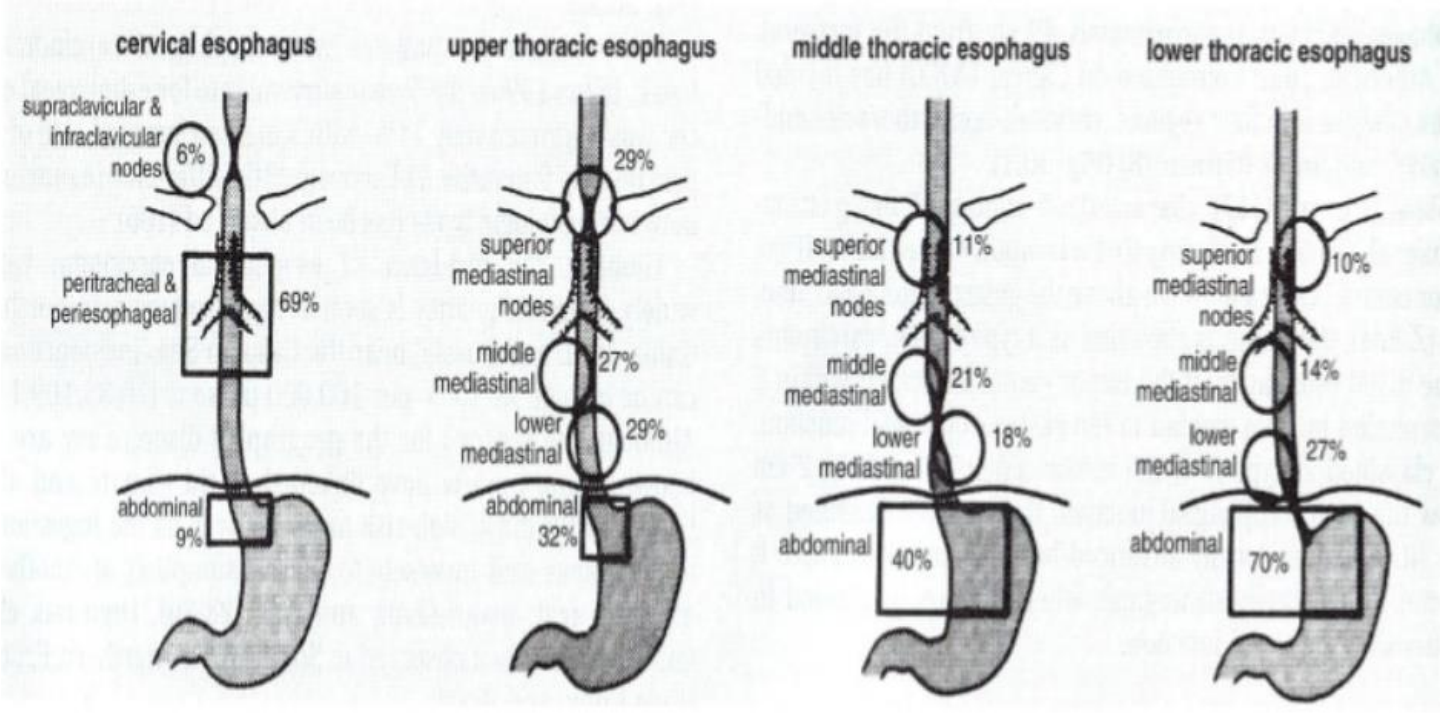
para-esophageal,

left gastric +

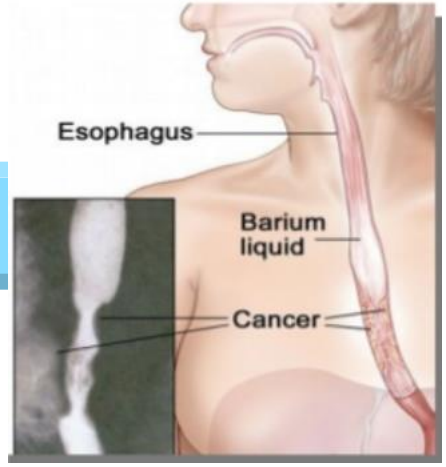
celiac axis region

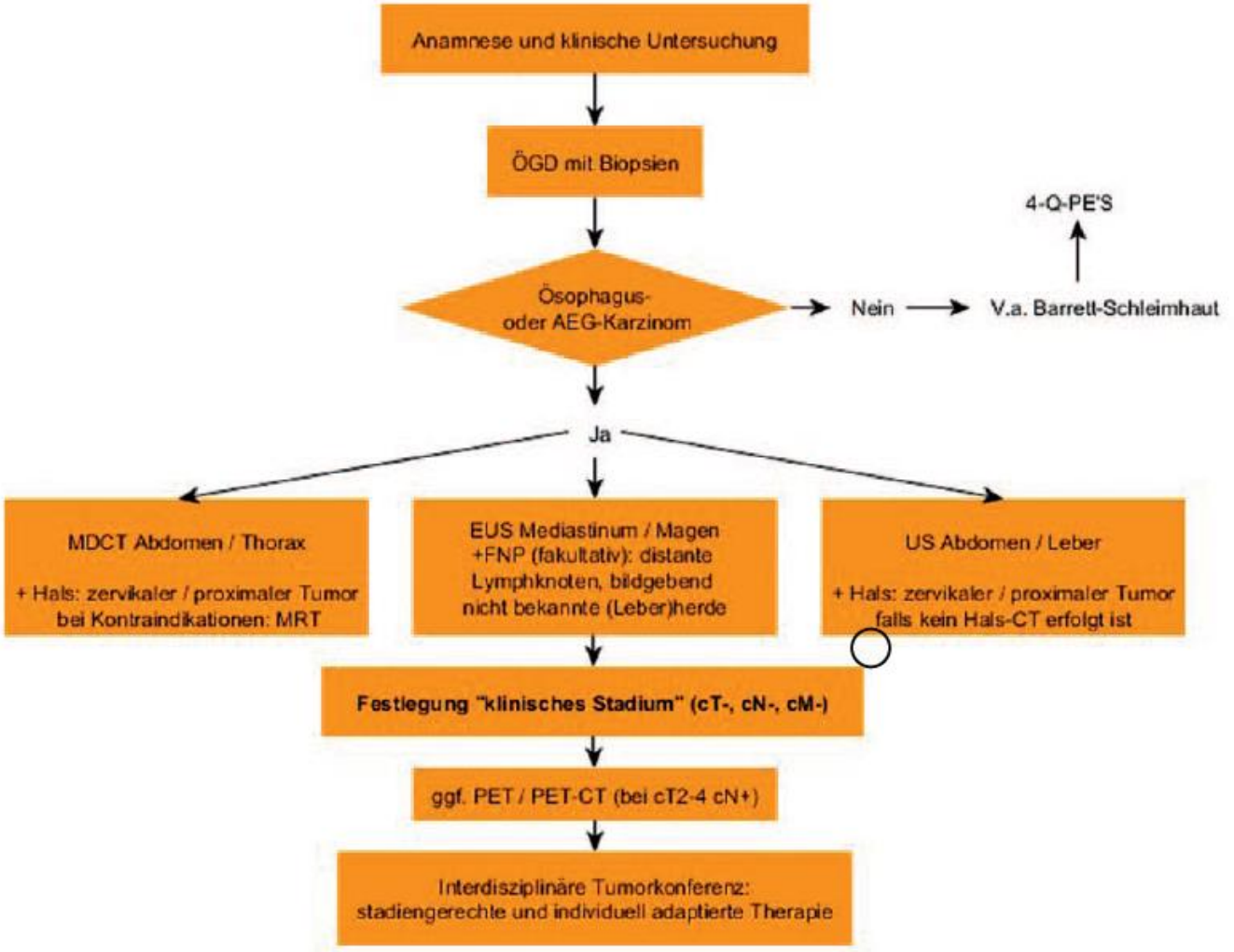


Site-wise nodal involvement in esophageal cancer



DIAGNOSTIC

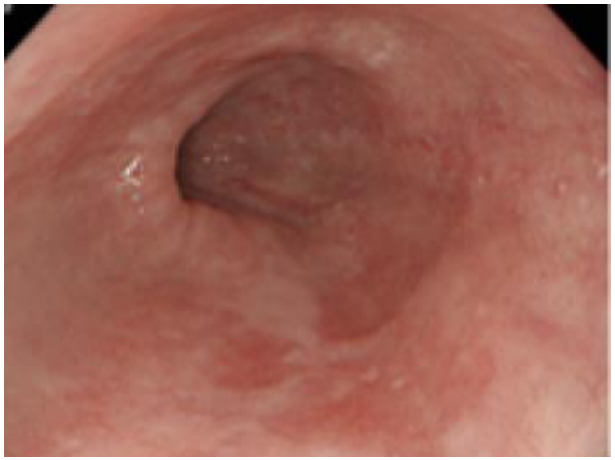


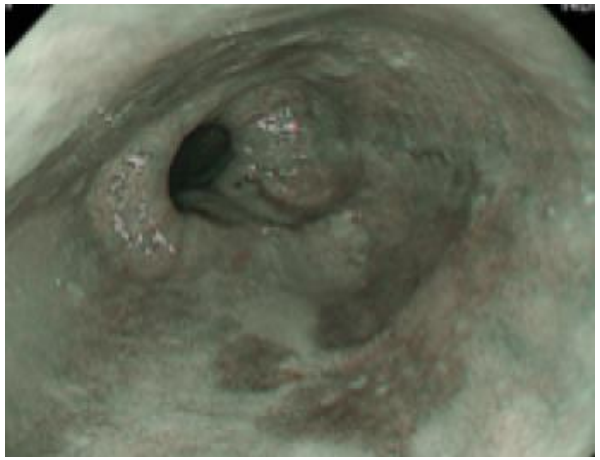


Abkürzungen:
AEG = Karzinome des gastro-ösophagealen Übergangs (adenocarcinoma of esophagogastric junction);
CT = Computertomographie; EUS = endoskopischer Ultraschall; FNP = Feinnadel Biopsie; MDCT = Multi-detector Computed Tomography;
MRT = Magnetresonanztomographie; ÖGD = Ösophagogastroduodenoskopie; PET = Positronen-Emissions-Tomographie;
US = Ultraschall; 4-Q-PE'S = 4- Quadranten Probeexzisionen

Squamous esophagus: 3 steps to do (see, capture ……)

White Light HD

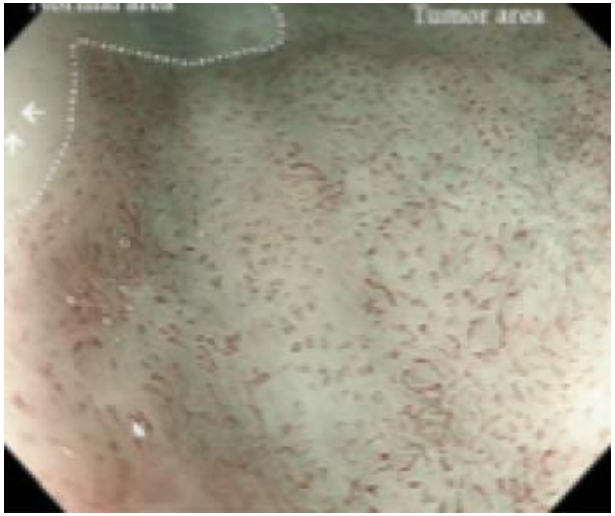


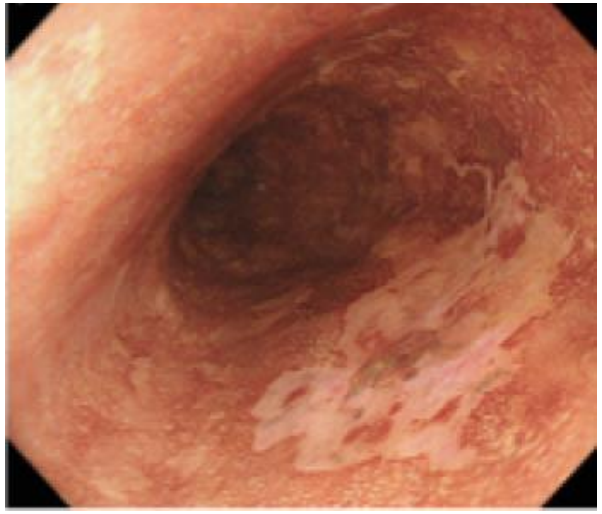


NBI

SSC-HGD/Ca B1 = without Sm-involvment

Near Fokus



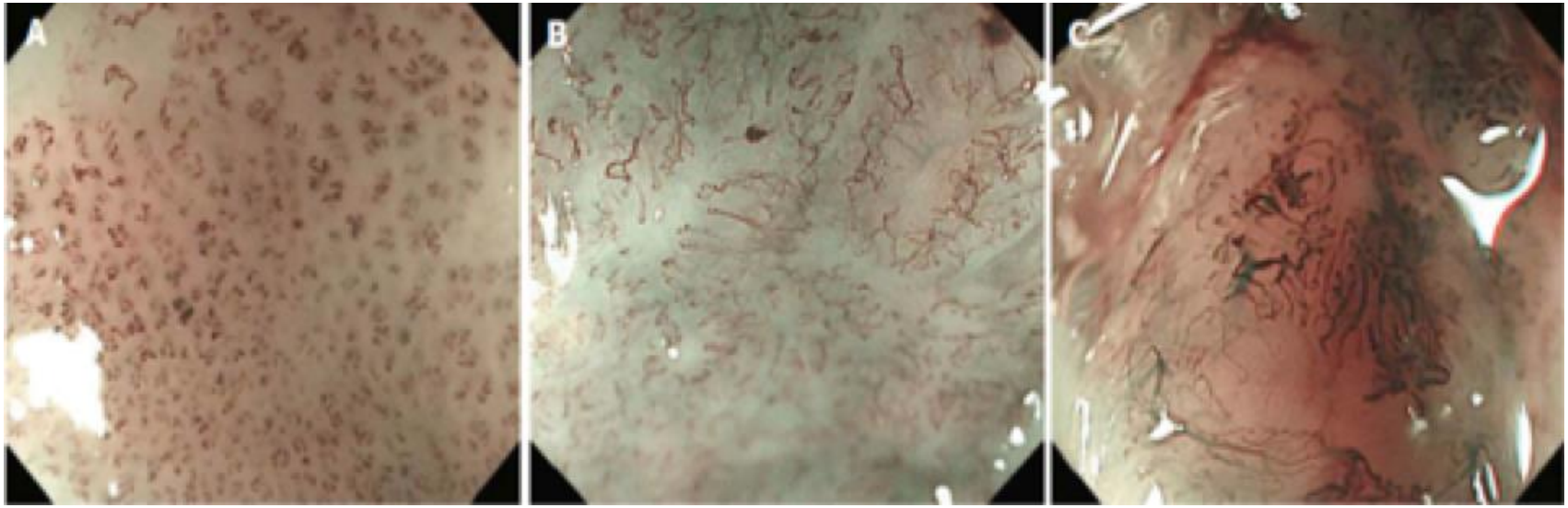


Lugol

Japanese Classification superficial squamous cell carcinoma (SSCCa) by magnifying NBI

What is B1-3 Grading ?

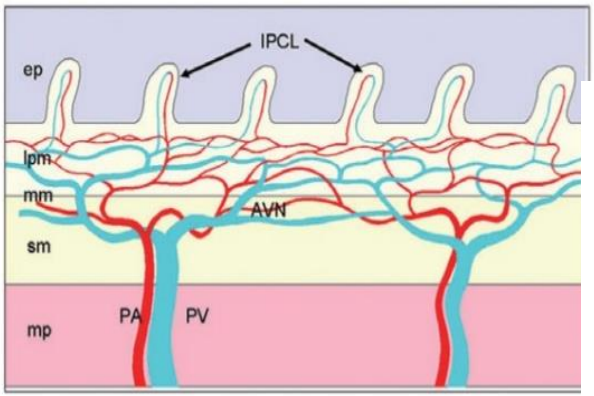
B1 **B2** **B3**



Oyama T et al. Esophagus 2017

Diagnostic Accuracy of Japanese Classification for superficial squamous cell carcinoma (SSCCa) by magnifying NBI

Intra-papillary capillary loops (IPCL)



AVM: arborescent vascular network, PA: perforating artery, PV: perforati

Kim S et al.
WJG 2017

Endoscopic resection ?? **Surgical resection**

Table 2 Comparison of pretreatment diagnosis by magnifying endoscopy with narrow-band imaging and histopathology of superficial esophageal squamous cell carcinoma

ME-NBI	No. of cases	Histopathology, *n*		
		m1-m2	m3-sm1	sm2
B1	20	20	0	0
B2	31	8	17	6
B3	19	0	1	18

ME-NBI: Magnifying endoscopy with narrow-band imaging.

What does Lugol stain – and why is it used ?

Iodine-based solution incorporated in the glycogen

Glycogen abundant in non-keratinized squamous epithelium

Dysplasia/Cancer depleted glykogen storage -> demarcated

Lugol-Chromoendoscopy (CE) for squamous cell carcinoma detection

- Prospective study in 62 centers, 1095 High-Risk patiens: St.n. SSCa or BC, chronic pancreatitis, Head-Neck-Tumors, or C2-Nicotin-abuse
- 35 SSCCa: 7 (20%) early lesions
- **20% only detected after Lugol-Chromoendoskopy (p=0,002)**
- Overall prevalence LGIEN 2,4%
- **77% only detected by Lugol-CE (p<0,001)**

Lugol-CE increases sensitivity for SSC-dysplasia/Ca!

Dubuc et al., Endoscopy 2006

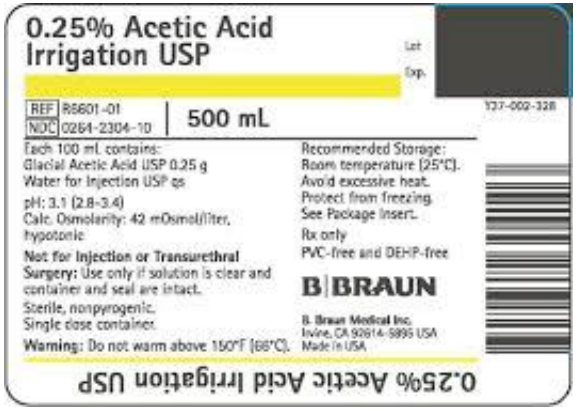
Head-/neck-tumors and esophageal squamous neoplasia ?

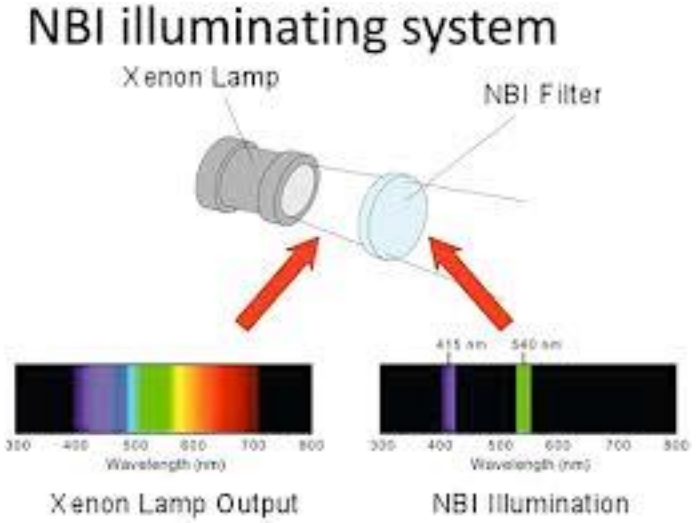
5-14% risk for simultanous or metachronous SCC per se
Radiation adds risk-equivalents Steinberg J et al. Tumor Diagn Ther 2008

In each HNO-tumor-patient getting PEG what you do ?

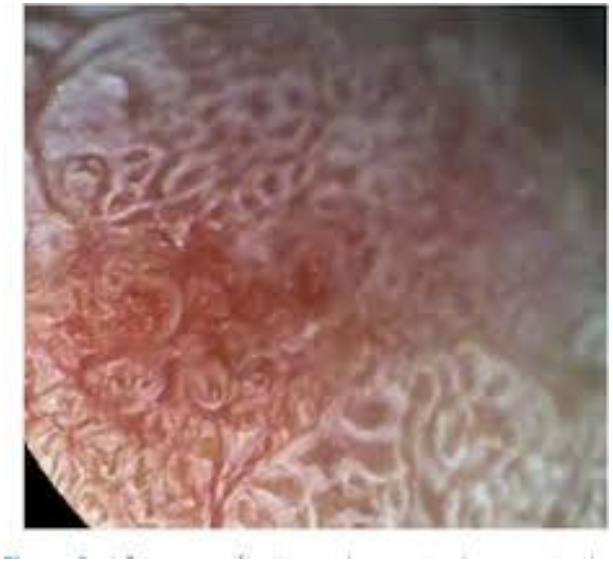
chromoendoscopy (virtual + lugol) esophagus
plus magnifying seeking dys/neoplasia

Barrett esophagus: 3 steps to do (see, capture ……)





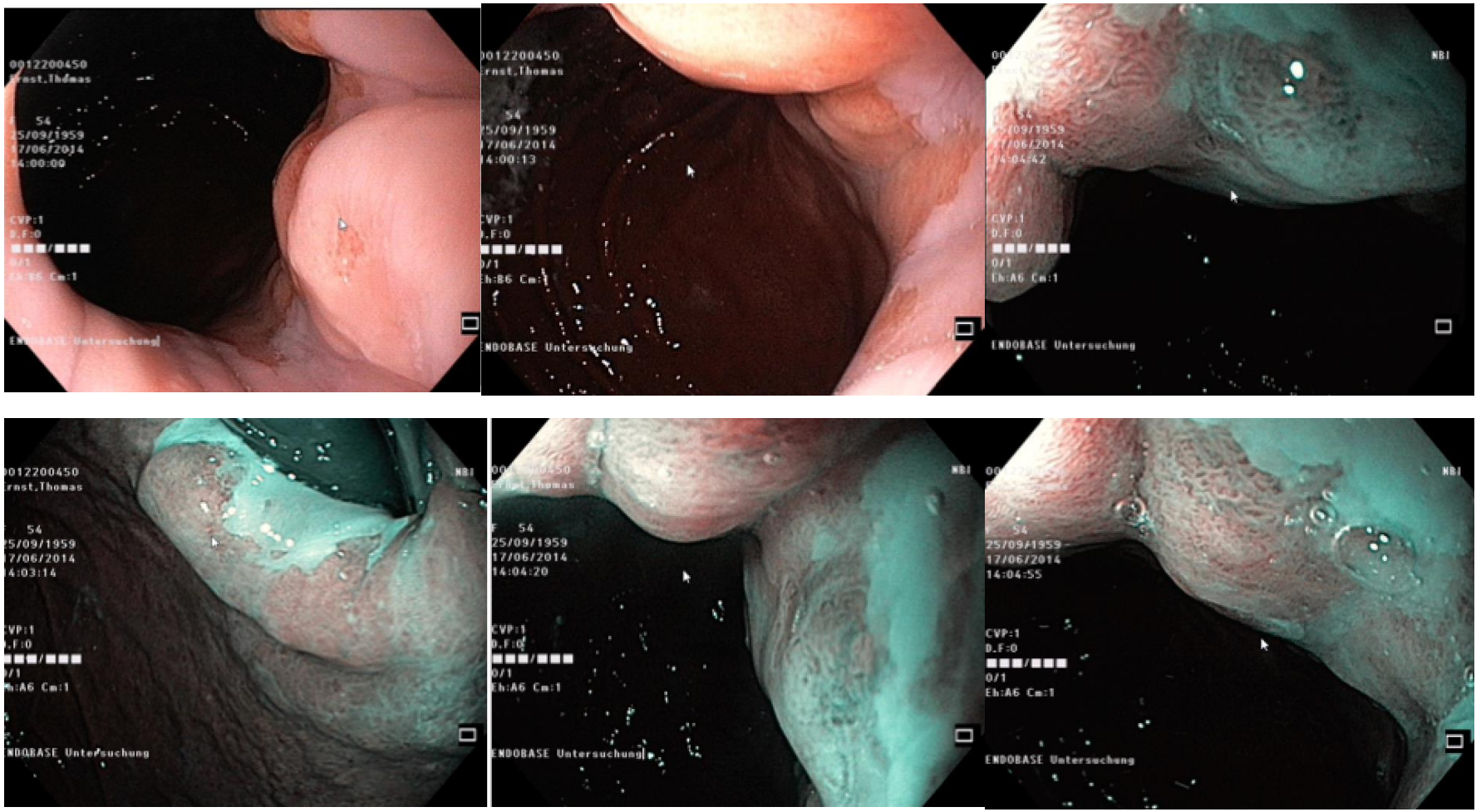
Near Focus



How long does it take for “loss-of-whitening” ?

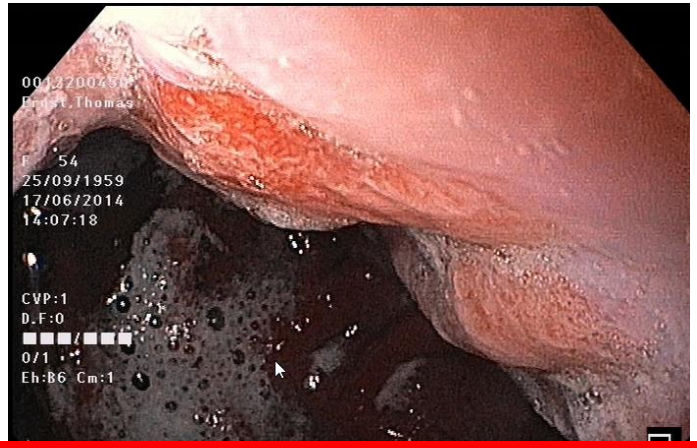
Up to 2 min (for Dysplasia)

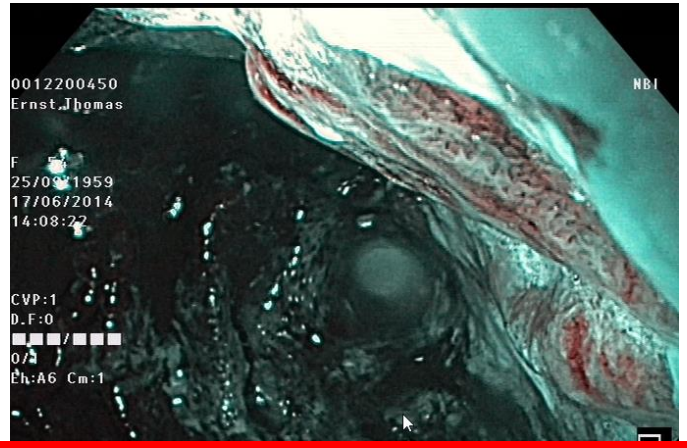
GE-junction – normal or not ?



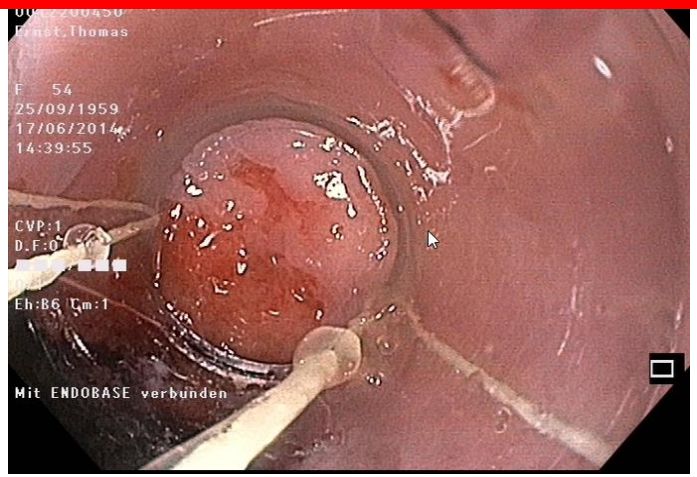
Ernst Thomas 25.9.1959

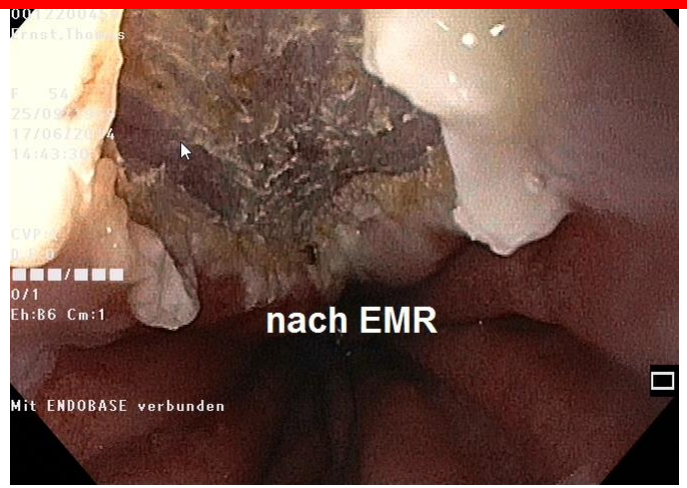
Barrett-Esophagus-Carcinom





Moderate differentiated Adeno-Carcinom
T1a N0L0V0 G2 R0





Ernst Thomas 25.9.1959

Barrett-Esophagus: Acetic Acid increases diagnostic sensitivity for Neoplasia

Meta-Analysis (13 studies): acetic acid for HGD-EIN and Early AC sensitivity 92% and specificity 96%

Coletta et al. GIE 2016

Diagnostic accuracy of EUS for T- and N-staging

Metaanalysen zum EUS	Anzahl Patienten/ Studien	Sensitivität/Spezifität T-Kategorie	Sensitivität/Spezifität N-Kategorie
Thosani et al., 2012 [92]	1019/19	Frühe Karzinome[1] (T1a/T1b): T1a: 85 %/87 % T1b: 86 %/86 %	n. a.
Puli et al.,2008 [93]	2585/49	T1: 82 %/96 %	EUS: 85 %/85 %
		T2: 81 %/94 %	
		T3: 91 %/94 %	EUS-FNP: 97 %/96 %
		T4: 92 %/97 %	
Van Vliet, 2008 [			er „M1a“): 85 %/96 %
Tranchemontagr 2009 [95]			er „M1a“): 75 %/94 %
Luo et al. 2016 [95, 97]		T1a: 84 %/91 % T1b: 81 %/89 % T4: 84 %/96 %	n. a.

EUS is a must = Gold-Standard in diagnostic work-up

Takizawa K et al. JGH 2009

N-stage

Methode	Gepoolte Sensitivität (95 % KI)	Gepoolte Spezifität (95 % KI)	Gepoolte Treffsicherheit (95 % KI)
EUS-FNP	81 % (0,76 – 0,85)	73 % (0,63 – 0,80)	77 % (0,72 – 0,81)
MDCT	54 % (0,48 – 0,61)	87 % (0,79 – 0,92)	65 % (0,60 – 0,70)
FDG-PET	52 % (0,44 – 0,60)	82 % (0,65 – 0,92)	69 % (0,60 – 0,77)

Optimal EUS- (re-)staging can improve survival (up to 3 mo)

Endoscopy: quality criteria for report
e.g. Barrett- esophagus with macroscopic lesion + EUS

EGD QI (*N* = 11)	EUS QI (*N* = 8)
GEJ location	T-stage
Barrett's esophagus	Tumor thickness (mm)
Barrett's Prague classification	Nodal size (mm)
Tumor proximal margin	Nodal echogenicity
Tumor distal margin	Nodal shape
Luminal obstruction	Nodal location
Circumferential extension	Nodal FNA
Gastric extension	N-stage
Retroflexion	
Hiatal hernia	
Biopsy	

FNA, fine needle aspiration; *GEJ*, gastroesophageal junction

only 36% for EGD
and 46 % for EUS
good quality
> 6 fullfilled
quality criteria

Barbetta et al.
Gastro Surg 2019

Pre-operative other diagnostic measures ?

- **Nutritional status: deficit correlates with dysphagia**

  > 40% of cases lost > 10% body weight

  > 30% serum-albumin < 30 g/L

- **Assessment of functional organ reserve/resilience for cardia, respiratory, hepatic and renal function +**

- **Assurance cooperativity of patient**

Schroder W et al. Langenbecks Archiv 2006; Ancona et al. Cancer 2001

Nutrition pre/peri-operatively: increased «metabolic risk» for surgery exists if

One of the following is present

- ✓ Loss body weight > 10-15% inert 6 months
- ✓ BMI < 18.5 kg/m2
- ✓ SGA Grad C or NRS > 3
- ✓ Serum-albumin < 30g/L (excluding liver disease)

Intensified nutritional support improves outcome

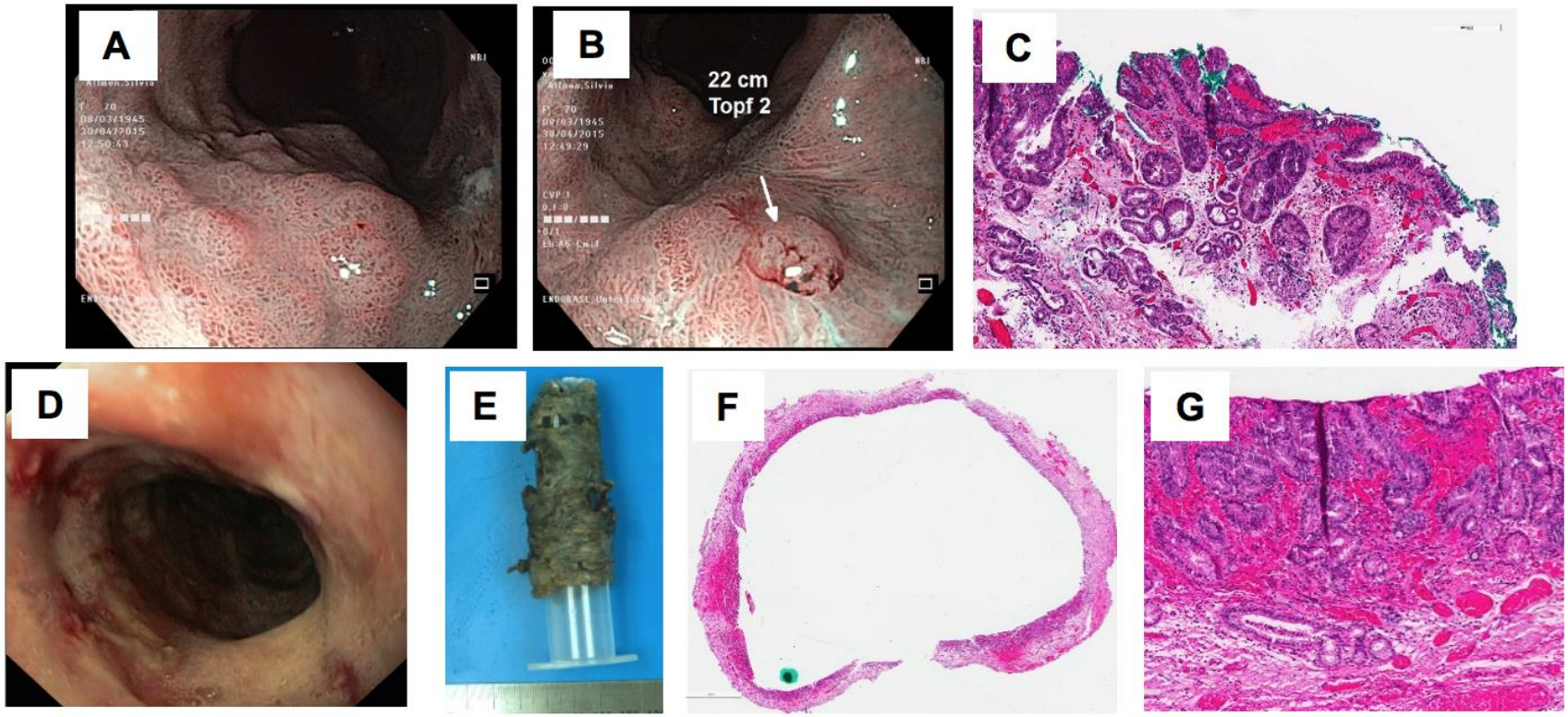
- ✓ Less severe complications (> IIIb Dindo) 32% vs. 60%
- ✓ Shorter Hospital-Stay

Lingthart et al. Dis Esophag 2013

Curative TREATMENT

Esophagus: circumferential extensive ESD

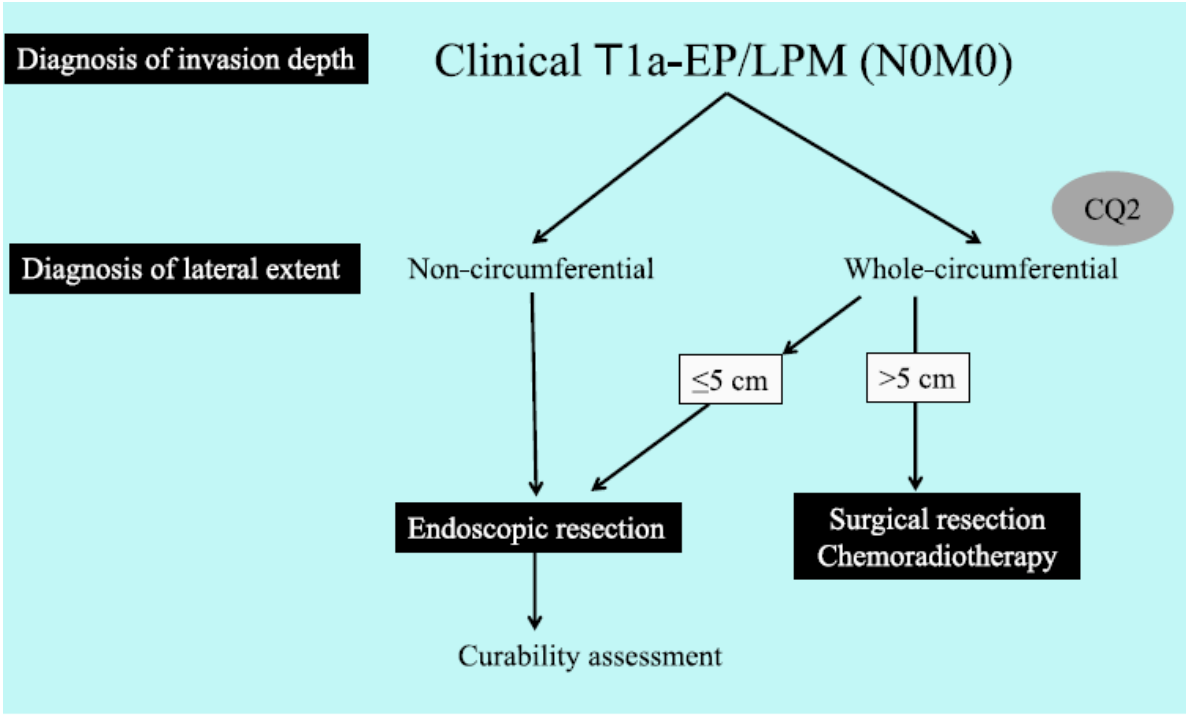
in Barrett C11M12 with multi-level HGD + carcinoma



14 cm long resected specimen incl. adenocarcinoma
T1a(M),Ly0,v0,HM0,VM0

Wiest R, Caca K et al
SGG 2017

Esophagus: circumferential extensive ESD- really ?



Japanese Guidelines Dig Endos 2020

Lesion-Limits for ESD ?

For Expert

- **Size/Area cm^2**
- **Location**

} **Not Really limiting**

- **Pre-treatment:**
- **Fibrosis.....**

} **Can be difficult/ limiting**

ESD best diagnostic procedure!
risk LN+ dependent on infiltration depth is……

SCC

Infiltration	LN+-rate
m1	0%
m2	3-4%
m3	12-15%
sm1	25-33%
sm2	35-40%
sm3	45-78%

ESD curative at m1-m3 ?

Undifferentiated

1-5%

ACa

Infiltration	LN+-rate
m1	0%
m2	0%
m3	0%
sm1	12%
sm2	20%
sm3	56%

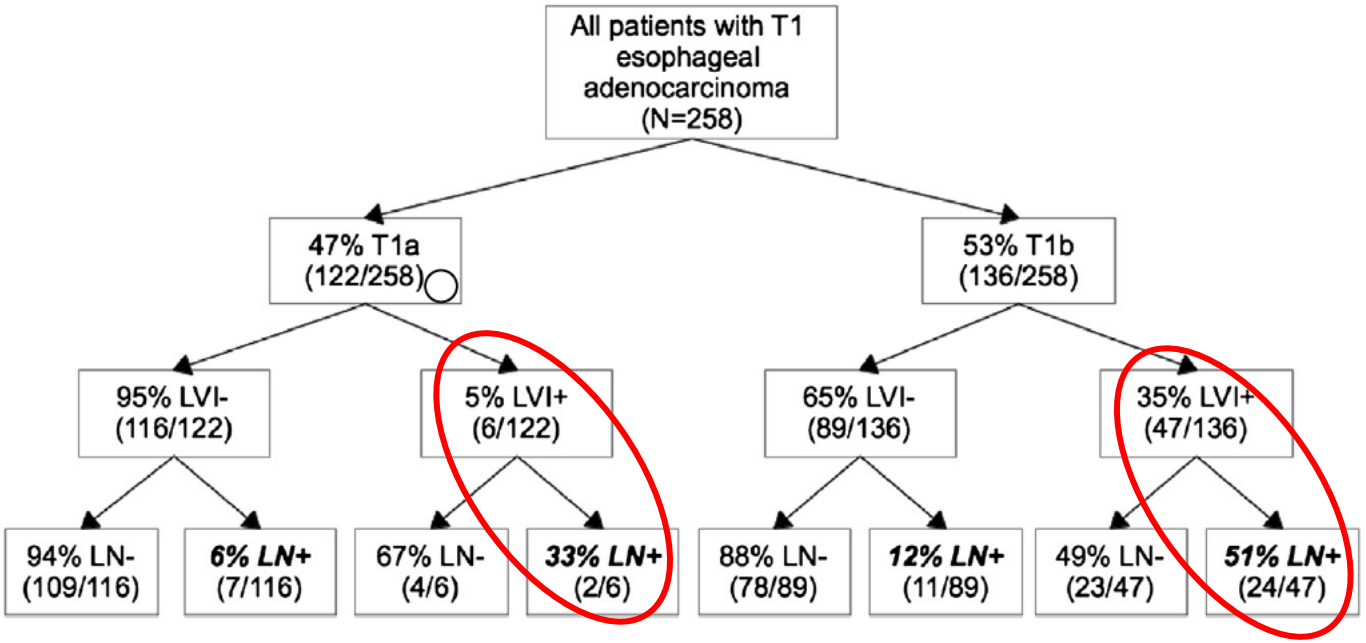
1% *

41% *

ESD curative at m1-sm1 ?

Hölscher et al. Ann Surg 2011; Westerterp* et al. Virchow Archiv 2005

ESD best diagnostic procedure!
risk LN+ dependent on lymph-angioinvasion



Lymph-invasion independent risk factor for LN+

Lee Lawrence et al. J Am Coll Surg 2013

PULS of ESD

Non-curative ESD – Definition - Consequences

- **P**ositive vertical margin
- **U**ndifferentiated grading
- **L**ymphangioinvasion
- **S**m-positivity (SCC or AC: > sm 1)

High risk of recurrence and/or LN-positivity

Surgical resection with lymphadenectomy

Therapeutic standard of care for T3/T4- cancer ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

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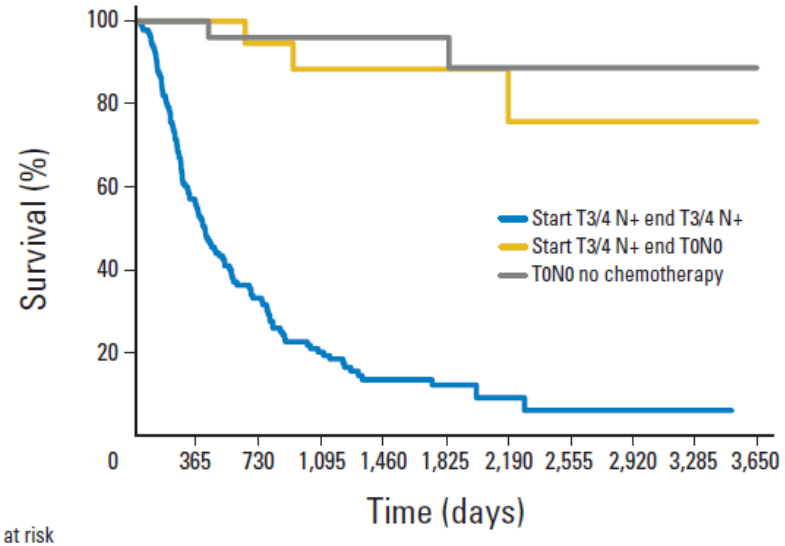
What is the strongest predictor for survival in patients with esophageal cancer undergoing neoadjuvant therapy ?

Tumor-Downstaging



No. at risk						
T3/4 N+ not downstaged	140	76	44	26	15	10
T3/4 N+ to T0N0	22	21	19	14	13	10
T0N0 no chemotherapy	28	28	25	22	14	14

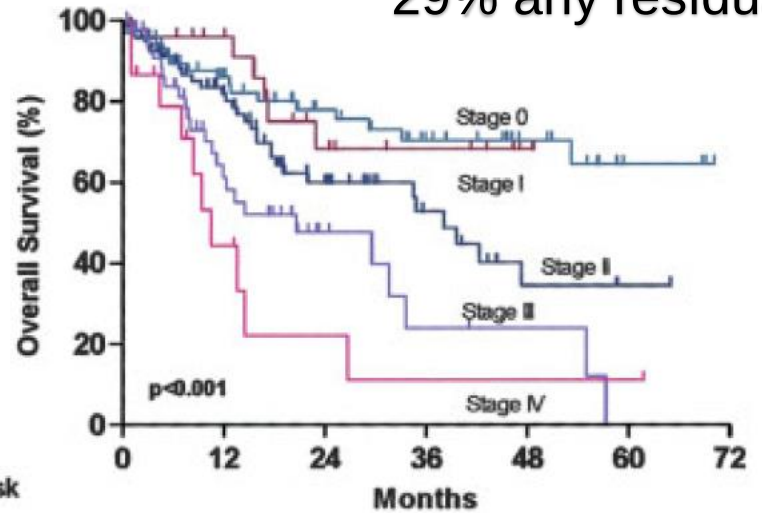
Tomasello et al. EJSO 2017/Davies et al JCO 2014

ypTNM Post-op

5y-survival

69% no residual

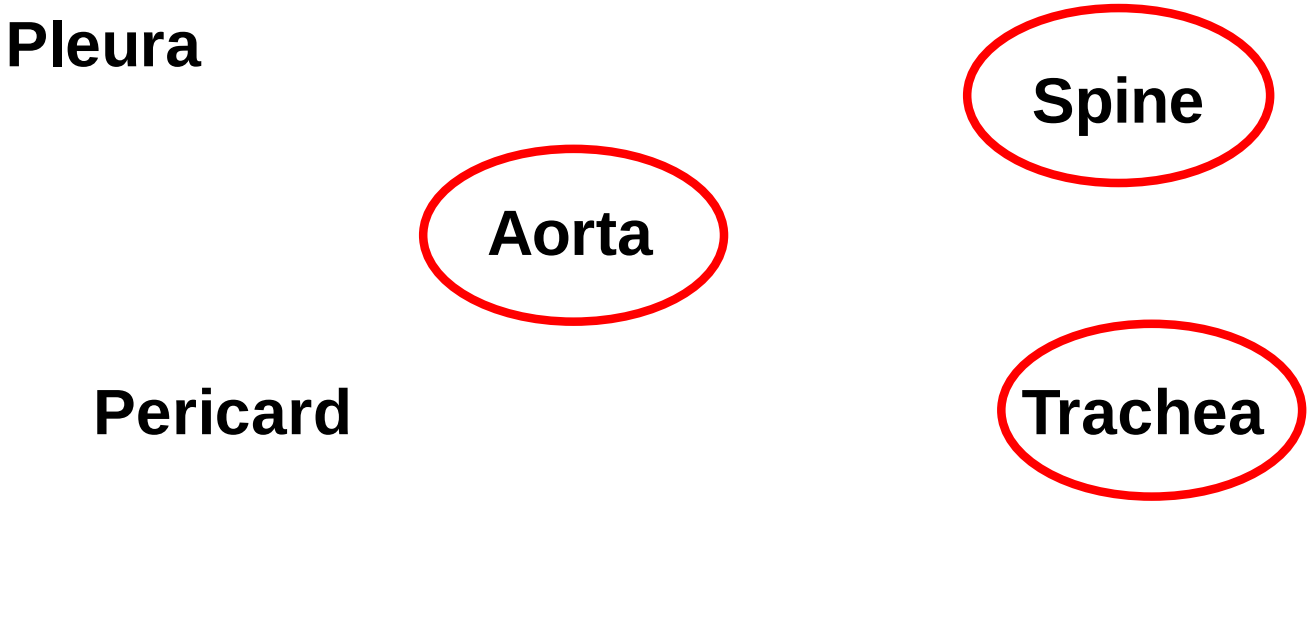
29% any residual



No. at Risk							
Stage 0	69	47	33	22	14	5	2
Stage I	25	20	10	7	3	1	1
Stage II	80	50	26	13	6	5	4
Stage III	46	20	7	3	2	0	0
Stage IV	15	5	2	1	1	1	0

Chirieac et al. Cancer 2005

Criteria making surgical resection inpractical….
The three bad sites of invasion



Adjuvant treatment after R0-resection ?

SCC: not recommended

AC: in neoadjuvant treated cases: not recommended

AC: only if understaging pre-operatively (emergency –surgery) ->

hence no neoadj RCTx then post-operatively (particularly if LN+)

after excluson of other metastasis

Palliative TREATMENT

What to test for optimizing treatment in metastatic adenocarcinoma?

- ✓ **HER2**
- ✓ **MMR**
- ✓ **PD-L1**

HER2-ranking-judgment (NCCN-guidelines)

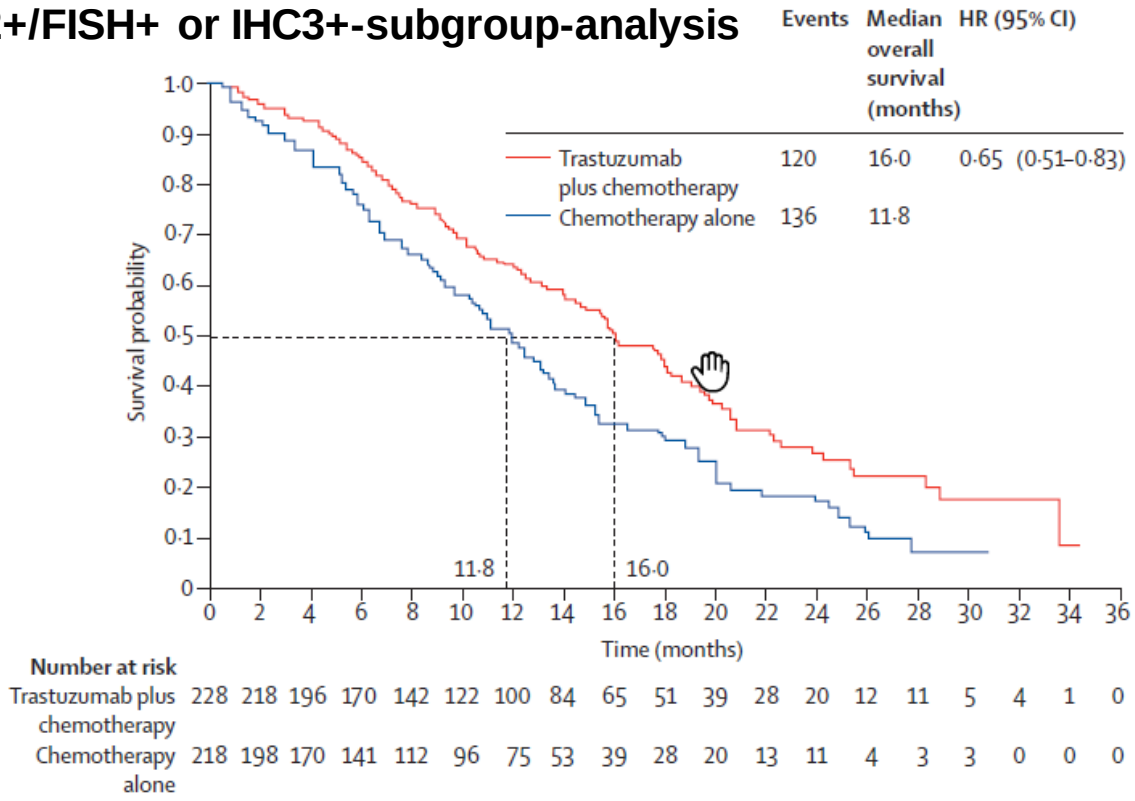
	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cluster of five or more cancer cells with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang, Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†*

IHC
0 or 1
no benefit

IHC2+/FISH+ or IHC3+-subgroup-analysis



AGE-I-tumors often HER2-positive

Lancet 2010

Role of checkpoint-inhibitors in esophageal cancer ?

- **Prognsosis better in cases/tumor with high level tumor-infiltrating lymphocytes** (TIL) v.a. cytotoxic CD8+- lymphocytes….. *D. Jiang et al. Science Rep. 2017*
- **Overexpression of PD-1 by cancer cells = escape from immune response** (eg. TIL-attack) is associated with poor prognosis *Gu L et al. PloSOne 2018*
- **Only minority of patients benefit**; response correlates with tumor mutations and neo-antigens *Alexander et al. Nature 2013*
- **1st line treatment: trials on-going**: Keynot 590: Phase III - blinded RCT Cis+5-FU with and without Pembrolizumab in SCC/ACa

Role of checkpoint-inhibitors in esophageal cancer ?

Keynote -181: RCT 2nd-line esophageal cancer
Pembrolizumab 200mg every 3 weeks vs. Investigator choice
(e.g. Paclitaxel, Docetaxel, Irinotecan)

In cases > 10% PD1-positive tumor cells (+MΦ)

	Pembrolizumab	Investigator Chemo-therapy
Overall survival (mo)	**9,3**	6.7
1-year survival (%)	**42**	20

Pembrolizumab FDA-approved as
2nd line in advanced SCC
2nd line in advanced ACa (MSI-H/dMMR-tumors)

Koijma T et al. J.Clin Oncol 2019

Ongoing Phase III-trials for PD1/PD-L1-inhibitors in upper –GI-cancers

Trial identifier	Phase	Line	Study population	Treatment arms	Primary endpoints
NCT02743494	III	Adjuvant	Oesophageal and OGJ	nivolumab vs. placebo	DFS, OS
NCT03221426	III	Peri-operative	Gastric and OGJ cancer	pembrolizumab plus chemotherapy (cisplatin and capecitabine/cisplatin and 5-FU/FLOT) vs. chemotherapy	pCR, EFS, OS
NCT03143153	III	1	Oesophageal cancer (squamous)	nivolumab plus ipilimumab vs. nivolumab plus chemotherapy (cisplatin plus 5-FU) or chemotherapy alone	PFS, OS
NCT03189719	III	1	Oesophageal cancer	pembrolizumab plus chemotherapy (cisplatin plus 5-FU) vs. chemotherapy	PFS, OS
NCT02746796	III	1	Gastric and OGJ cancer	nivolumab plus chemotherapy (SOX/CAPOX) vs. chemotherapy	PFS, OS
NCT02872116	III	1	Gastric and OGJ cancer	nivolumab plus ipilimumab vs. nivolumab plus chemotherapy (CAPOX/FOLFOX) vs. chemotherapy alone	PFS, OS
NCT02625610	III	1	Gastric and OGJ cancer	maintenance avelumab vs. continuation of first-line chemotherapy	OS
NCT03615326	III	1	Gastric and OGJ cancer	pembrolizumab plus trastuzumab and chemotherapy (cisplatin plus 5-FU/CAPOX/SOX) vs. trastuzumab plus chemotherapy	PFS, OS
NCT02569242	III	2	Oesophageal cancer	nivolumab vs. docetaxel/paclitaxel	OS

Palliative CTx for esophageal cancer – whom ?

AC

HER-negative
Platin (Oxaliplatin or Cisplatin) and Fluoropyrimidin-containing 2- or 3-combination therapy
should be used

e.g.
DCF
median survival 9.2 mo
progression-free survival 5.6 mo

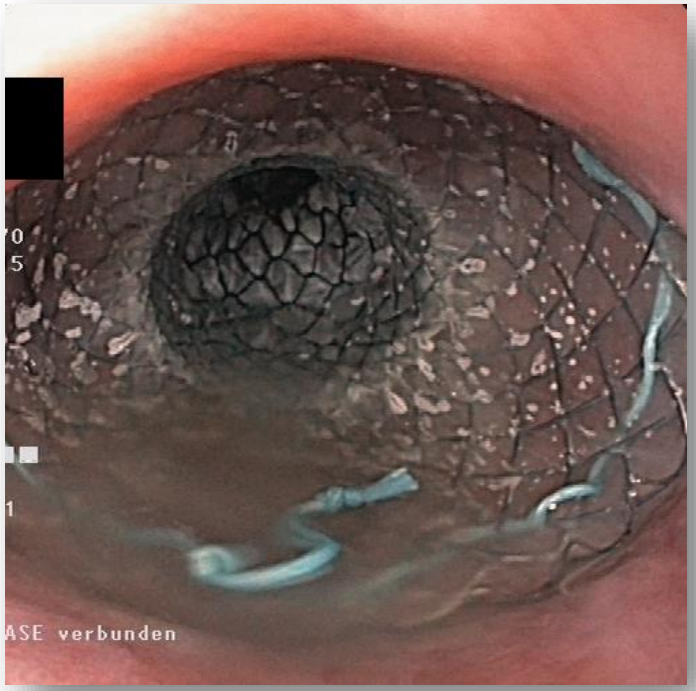
SCC

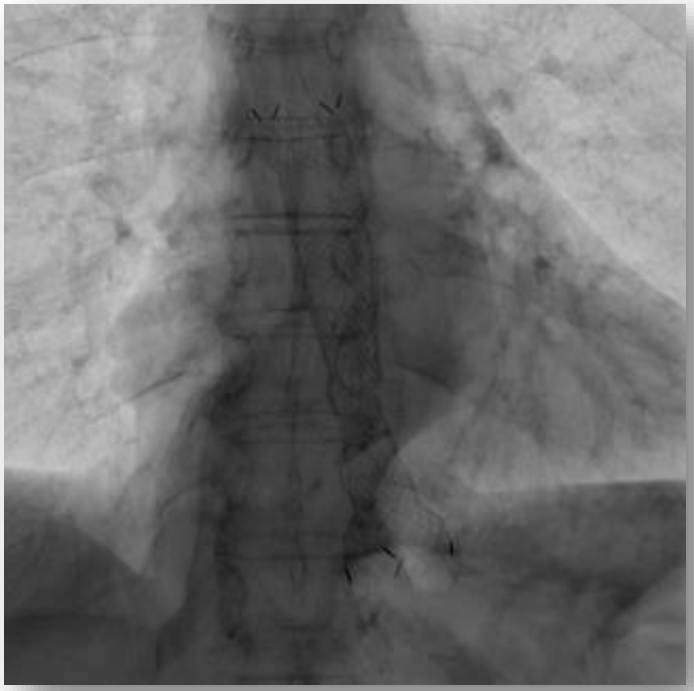
Cisplatin and Fluoropyrimidin combination-therapy

can be used

prolongation of overall survival is not proven

Severe Dysphagia and its palliation- what to do ?





Severe Dysphagia and its palliation- what to do ?

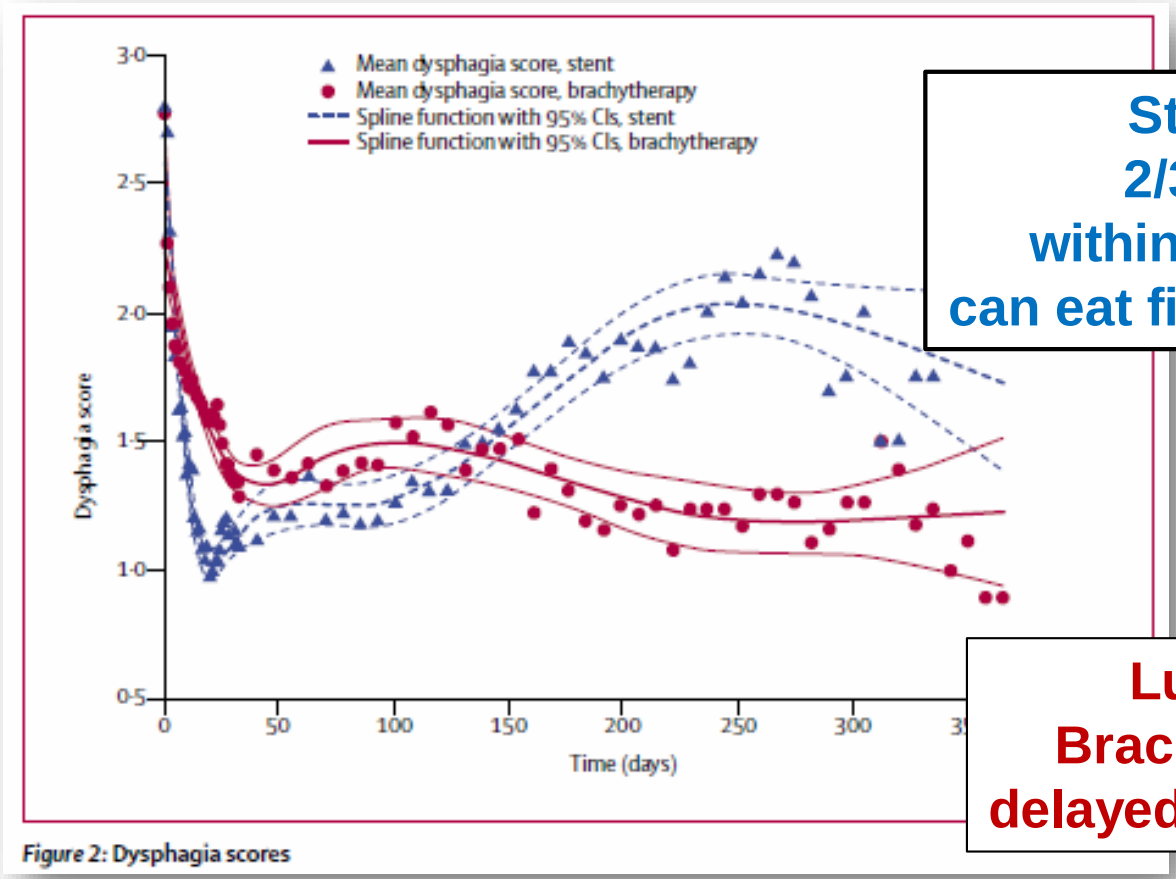


Figure 2: Dysphagia scores

Stenting:
2/3 of pts
within short time
can eat firm food again

Luminal Brachytherapy
delayed but durable

Hams et al. Lancet 2004

Severe Dysphagia and its palliation- what to do ?

Non-severe dysphagia: brachytherapy alone good benefits
Add-on APC plus Brachytherapy can improve efficacy
extended dysphagia free intervall
70 days vs. 35 days

Rupinski et al. Am J. Gastroenterol 2014

Stenting followed by single high-dose brachytherapy
Case-control study: >95% symptom-relief
for > 6 months

Bergquist et al. Dis Esophagus 2012

Stenting followed by radiation as normo-fractionized radio-therapy (with 5-FU): more sustained symptom relief
(7 vs. 3 months)

Javed A et al. J Gastro Cancer 2012