



KASTURBA MEDICAL COLLEGE

MANIPAL

(A constituent unit of MAHE, Manipal)



Manipal Comprehensive
Cancer Care Centre

Precise. Precision. Person-Centred. Population.

Carcinoma Esophagus- Tailoring the treatment

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MCCCC, Kasturba Medical College, Manipal

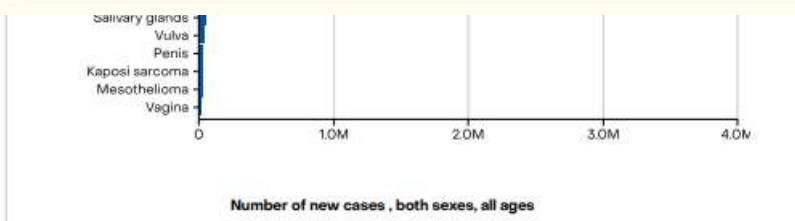
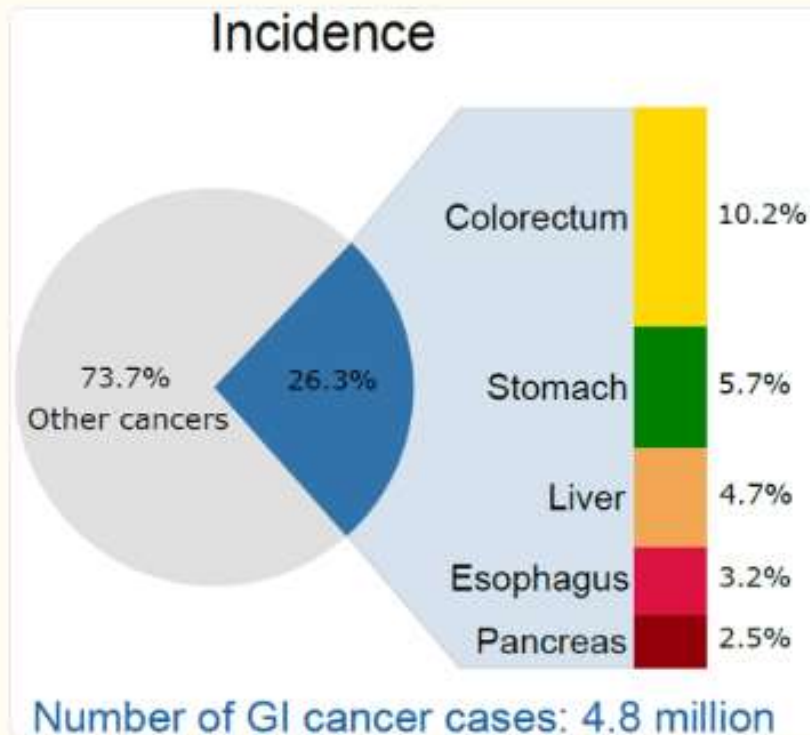
Panelists

- Dr Harni Natarajan - Yashoda Hospitals, Hyderabad. 2nd year
- Dr Sivaranjani P- AIIMS Bathinda. 1st year
- Dr Harsha Shaju -AJ Institute of Medical Science and Research centre. 2nd year
- Dr Chirantan Saha- Chittaranjan National Cancer Institute, Kolkata. 2nd year
- Dr Varsha V- Sri Shankara Cancer Hospital and Research centre. 1st year
- Dr Sharvani Y -Yashoda Hospitals, Hyderabad.1st year

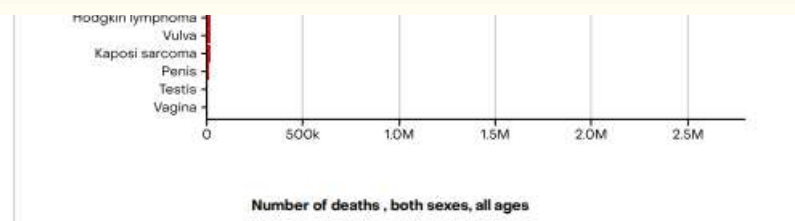
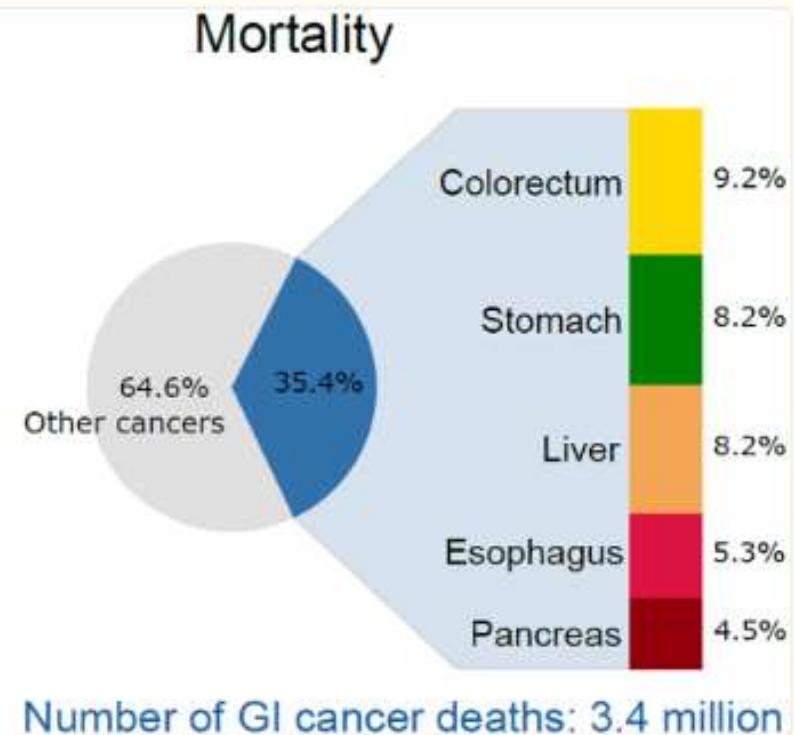


Esophageal cancer

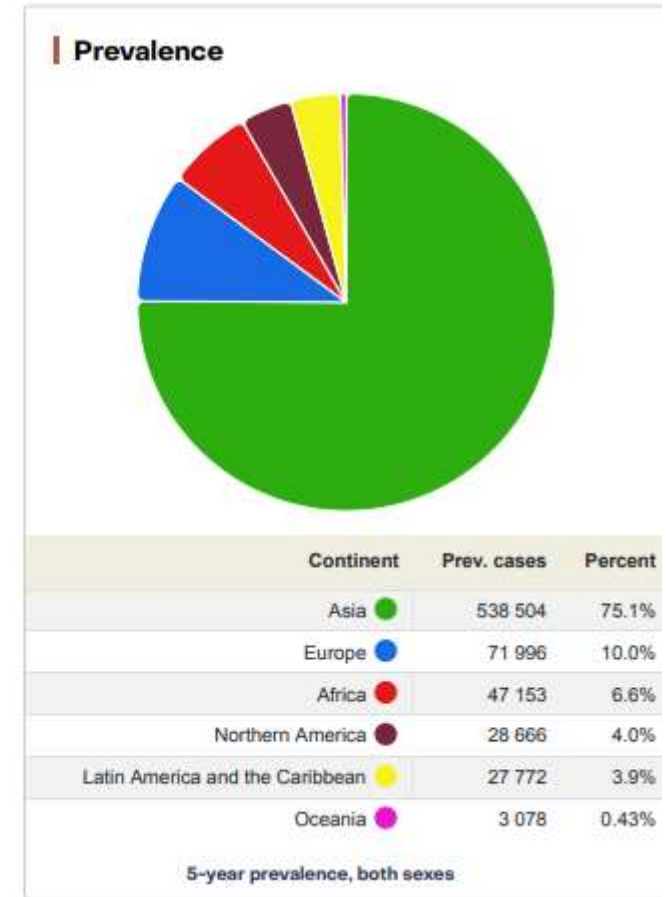
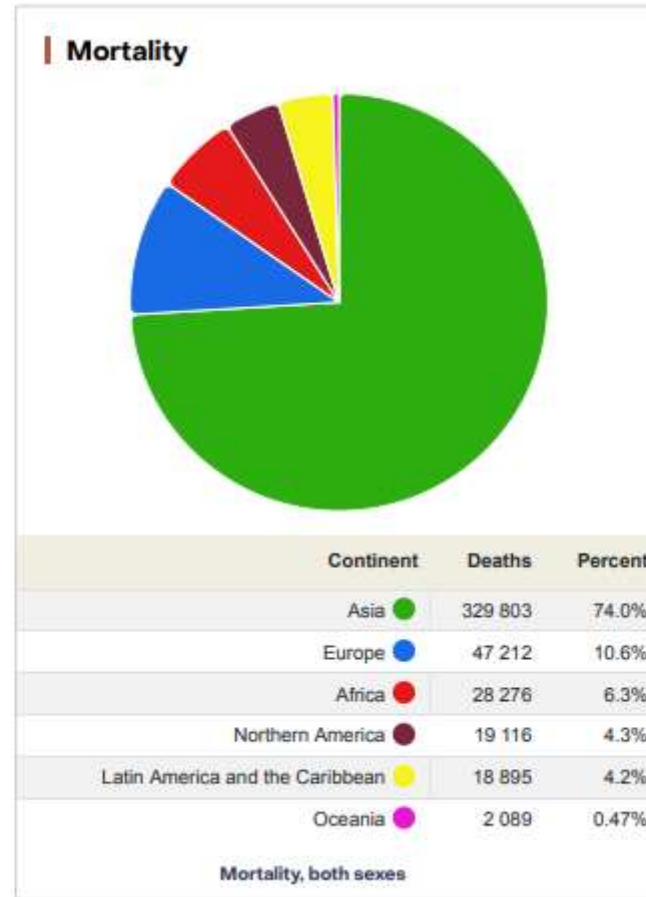
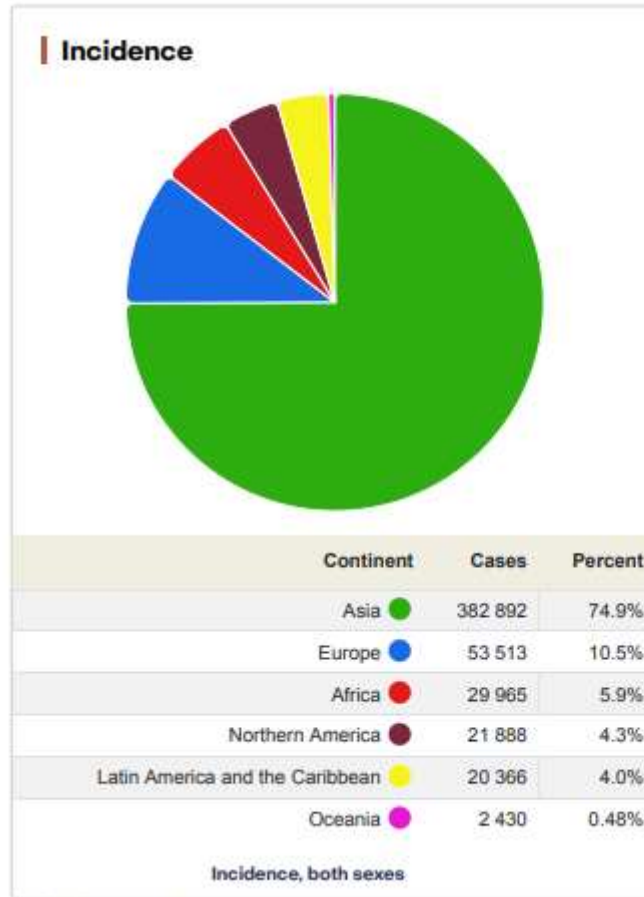
Incidence



Mortality

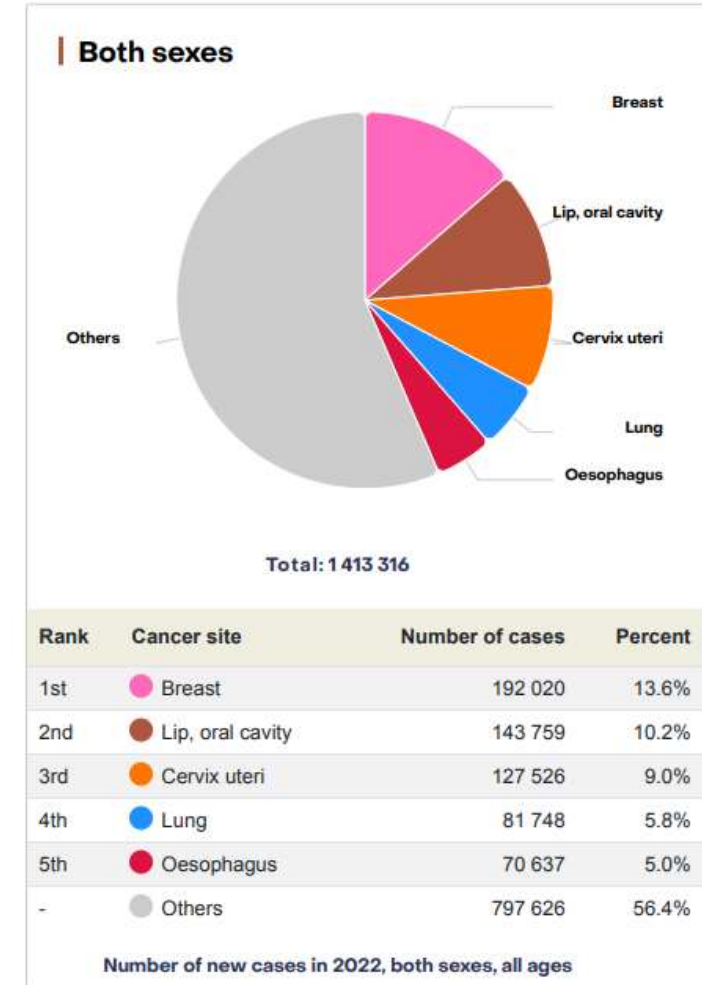
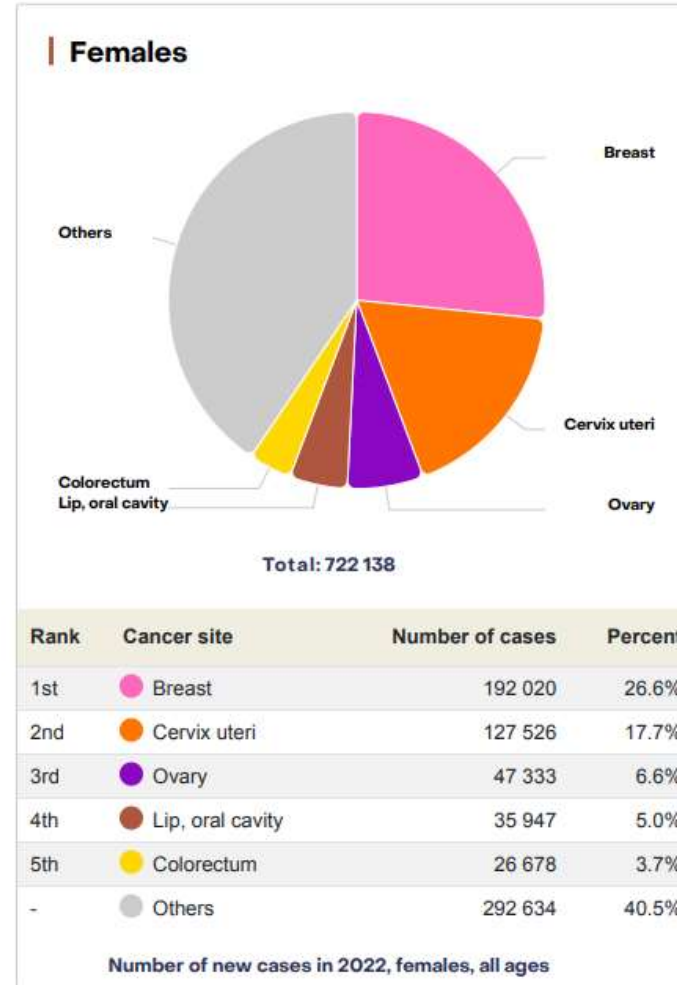
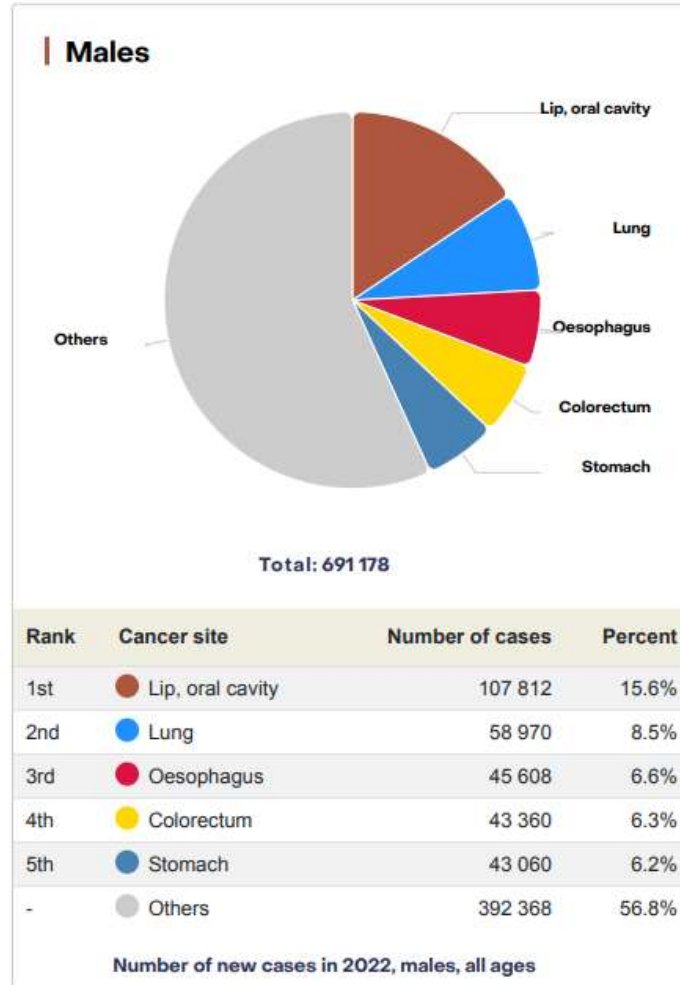


Geographic locations



India

Top 5 most frequent cancers**



Risk Factors?

Table 1 Risk factors for squamous cell carcinoma and adenocarcinoma of the esophagus

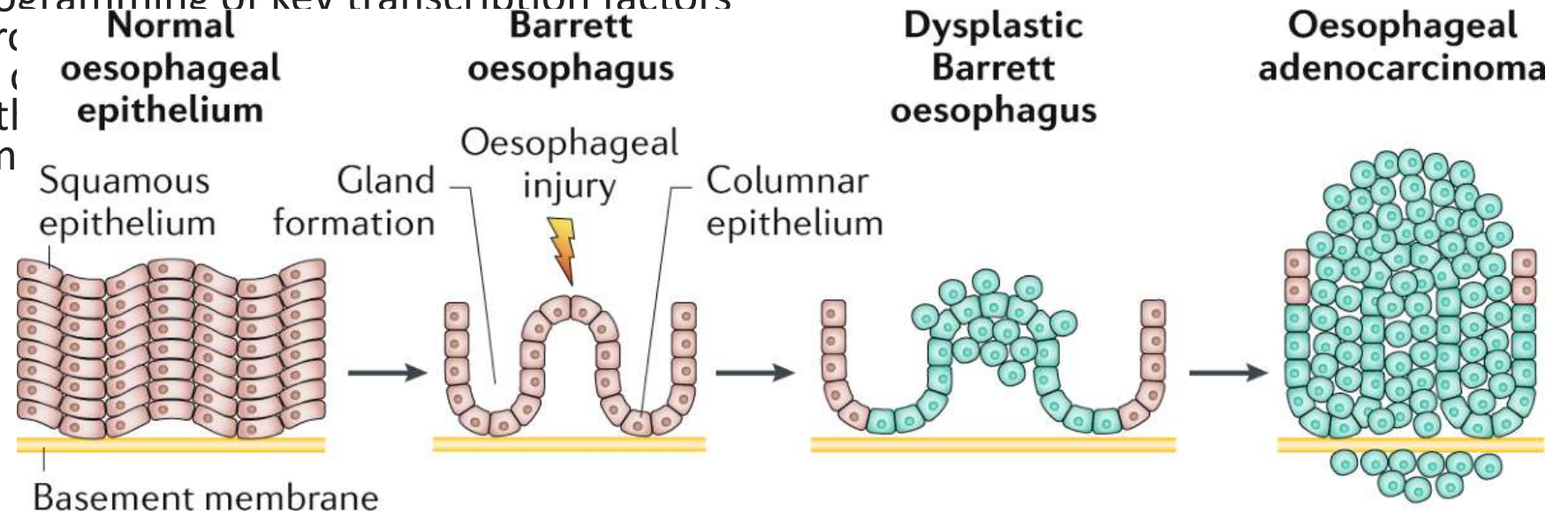
Risk factor			Adenocarcinoma
Geography	Nutritional deficiencies and nitrosamines.		North America (United States), Australia
Race	Betel quid chewing in the Indian subcontinent		Black
Gender	Consumption of pickled vegetables (e.g. in China) consumption		male
Alcohol	of food and beverages at very hot temperatures (e.g. in		
Tobacco	Uruguay, Iran and Tanzania)		
Obesity			
GERD	-		++++
Diet: Low fruits and vegetables	++		+
Socioeconomic conditions	++		-
Genetic aspects	++		+

Histology

- 2 main subtypes- SCC and Adnocarcinoma
- Overall SCC is most common worldwide
- HIC- Adenocarcinoma most common
- Excess body weight, gastroesophageal reflux disease and oesophageal intestinal metaplasia.

Barretts Esophagus

- Barrett oesophagus is defined conceptually as the condition in which a metaplastic mucosa that can predispose to cancer development lines a portion of the distal oesophagus.
- Potential cells of origin for Barrett metaplasia include basal cells of oesophageal squamous epithelium, oesophageal submucosal gland cells, transitional basal cells, residual embryonic cells, gastric gland cells and cells of compact mucous glands.
- GERD induces the reprogramming of key transcription factors in progenitor cells to promote metaplasia with goblet cell metaplasia to cardiac mucosa.

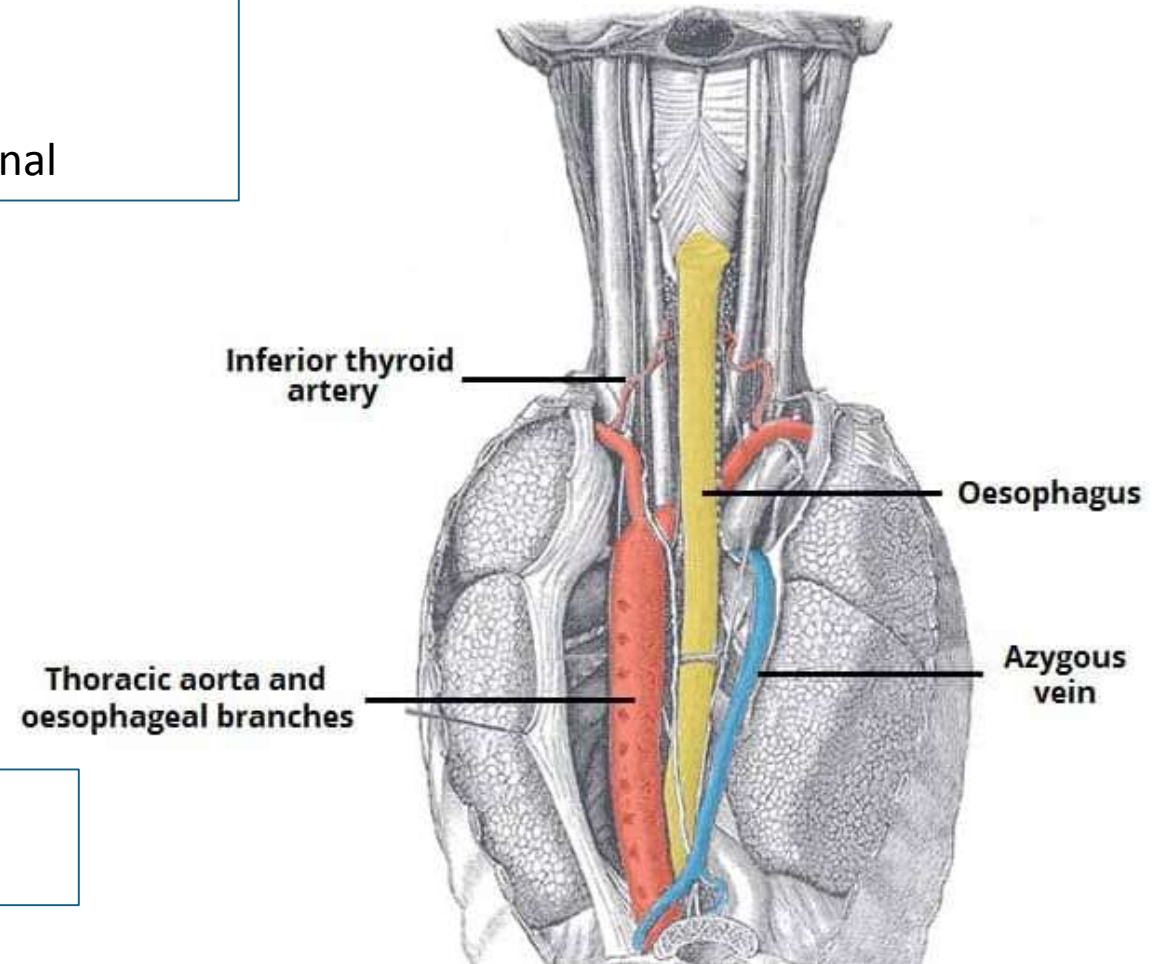


Anatomy of Esophagus

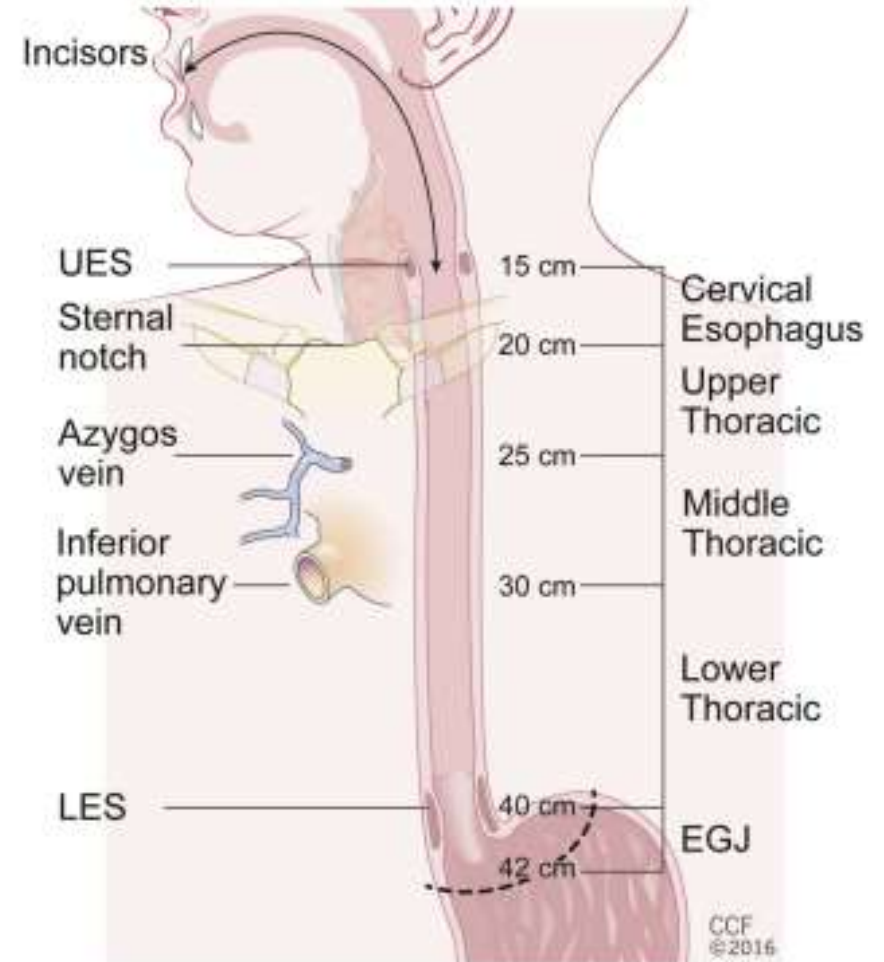
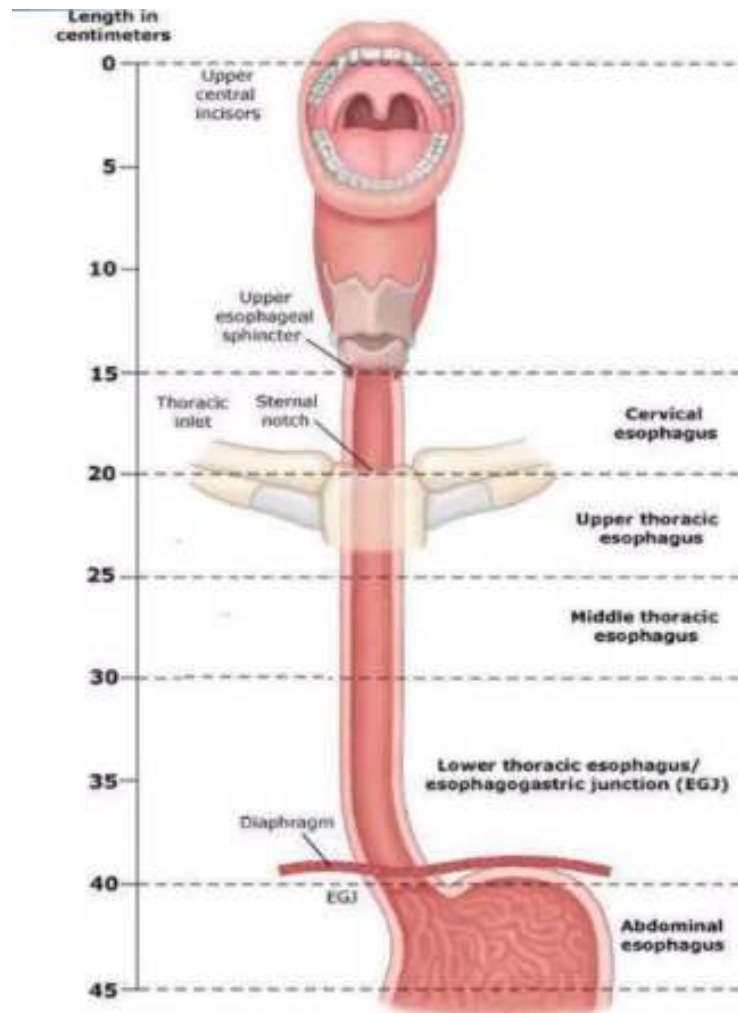
25 cm
Cricoid to stomach
C5-6 to T10-T11

3 parts
Cervical, Thoracic and abdominal

No serosal lining – adventitia

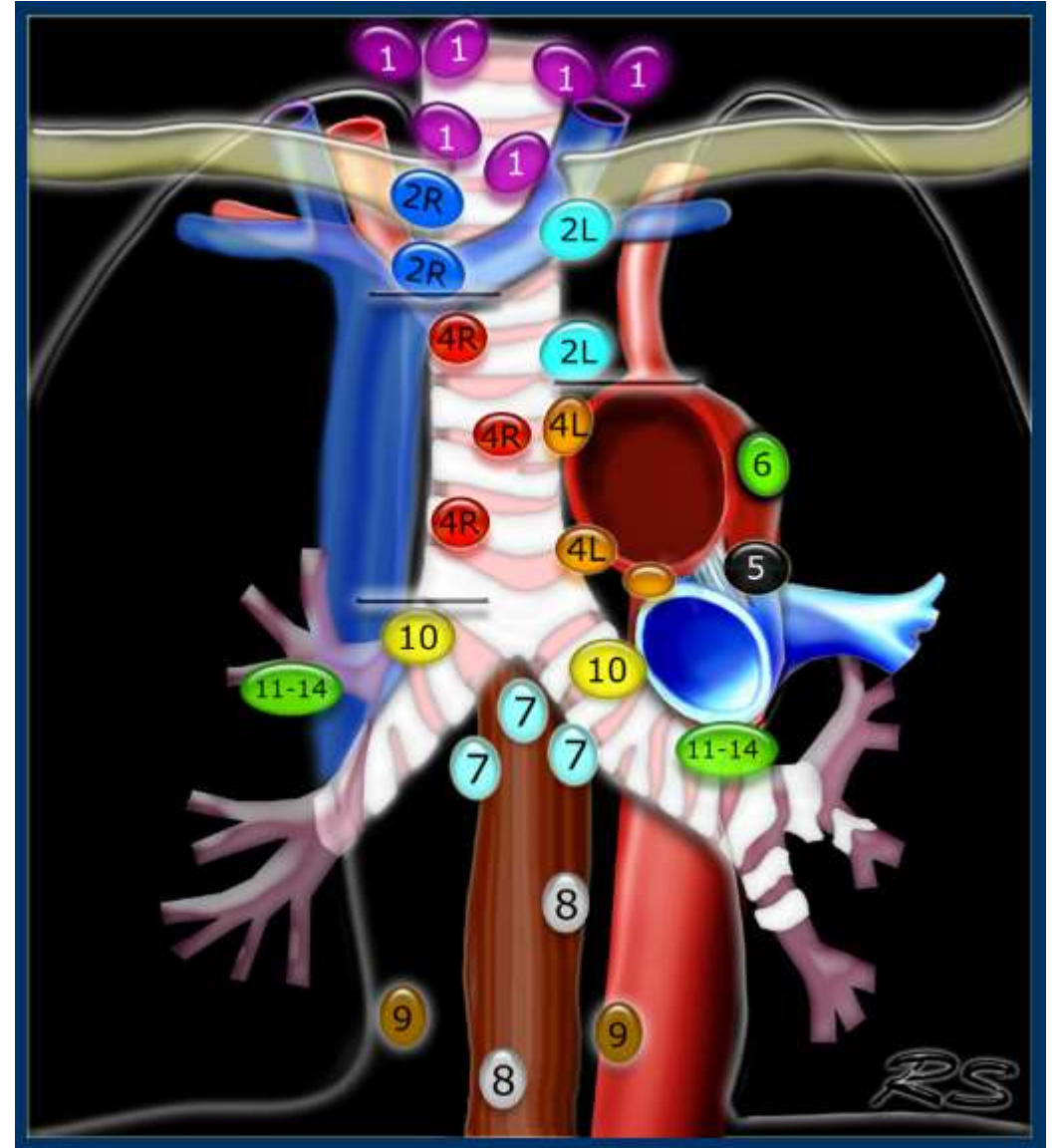


Esophagus- Regions

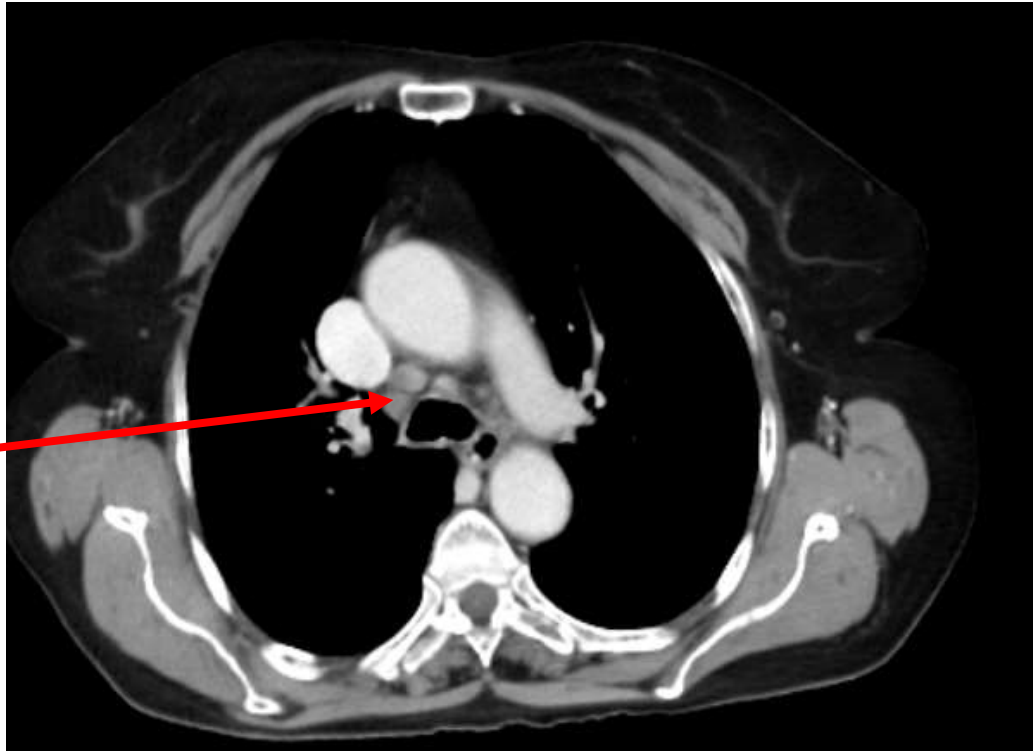


Lymphatics

- LN Map of mediastinum
- 1: Supraclavicular
- 2R,L: Upper Paratracheal
- 3 A,P- Prevascular and prevertebral
- 4R,L: Lower Paratracheal
- 5: subaortic
- 6: Paraaortic
- 7: Subcarinal
- 8: Paraesophageal
- 9: Pulmonary ligament



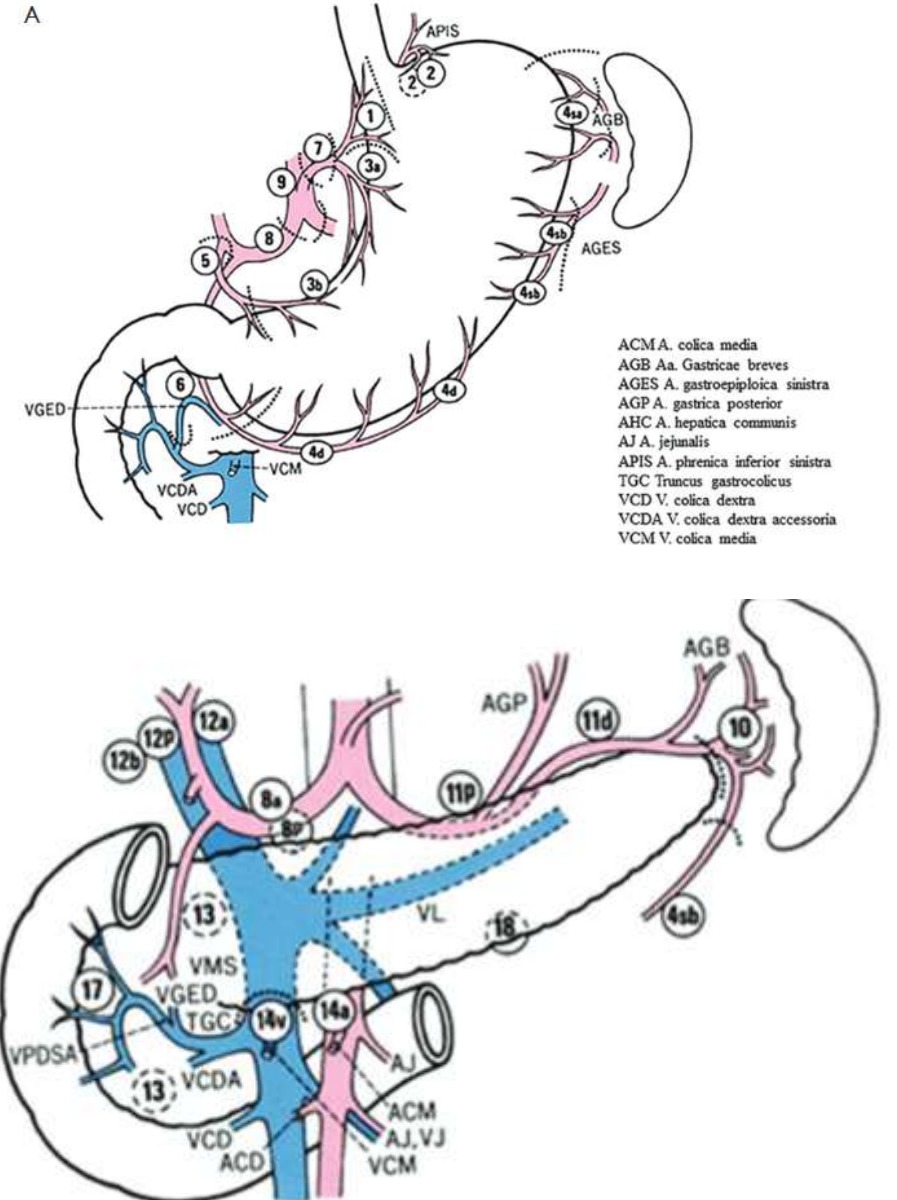
Identify the nodes



Abdominal lymph-nodal map

Table 1 Numbering of lymph nodes (LNs) according to the old classification of Japanese Research Society for Gastric Cancer (1)

Station nr	Lymph nodes
1	Right cardiac nodes
2	Left cardiac nodes
3	Nodes along the lesser curvature
4	Nodes along the greater curvature
5	Suprapyloric nodes
6	Infrapyloric nodes
7	Nodes along the left gastric artery
8	Nodes along the common hepatic artery
9	Nodes around the coeliac axis
10	Nodes at the splenic hilus
11	Nodes along the splenic artery
12	Nodes in the hepatoduodenal ligament
13	Nodes at the posterior aspect of the pancreas head
14	Nodes at the root of the mesentery
15	Nodes in the mesocolon of the transverse colon
16	Para-aortic lymph nodes



Case 1

- 55 year old gentleman, Nil Comorbid
- No past surgeries, Tobacco chewer- Reformed
- Wife treated for cervical cancer 1 year back

- Dysphagia for solids, Regurgitation- 3 months
- Loss of appetite and weight loss

- Clinically: PS 1, HN normal, No nodes wt: 50 kg
- Hopkins: B/L VC mobile

Clinical Presentation- Symptoms and signs

- Dysphagia- progressive 90%
- Odynophagia 50%
- Unintentional weight loss >5%
70%
- Chest Pain
- Hoarseness of voice- RLN
- Loss of appetite
- Regurgitation
- Vomiting
- Pain abdomen
- Advanced-cough

Cachexia/ Malnutrition

Anemia

Dehydration

Supraclavicular nodes

Vocal cord palsy

Abdominal mass/fullness

HN Exam vital- second primary 6.7%

What investigations?

Procedure	Purpose
FBC	Assess for iron-deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. PD-L1 and HER2 status (AC)
EUS	Accurate assessment of T and N stage in potentially resectable tumours
Bronchoscopy with endobronchial ultrasonography	Assess tumour growth towards central airways; complementary to EUS, especially when tumour stricture precludes EUS
CT of thorax + abdomen ± pelvis	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease
PET-CT, if available	Staging of tumour to detect local/distant lymphadenopathy and metastatic disease
Laparoscopy ± washings	Exclude occult metastatic disease involving peritoneum/diaphragm, especially in locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomical cardia

Investigations:

- Upper GI scopy: Obstructive growth at 30 cm
- Biopsy (Slide Block review): SCC Gr 2
- Labs: normal Hb: 13.8 Cr 0.95, Alb 3.8.
- Baseline nutritional assessment- Dietician consult.
- Cardiac evaluation, pulmonary evaluation

Imaging Investigations- CECT or PETCT

Staging investigations for oesophageal cancer: a meta-analysis

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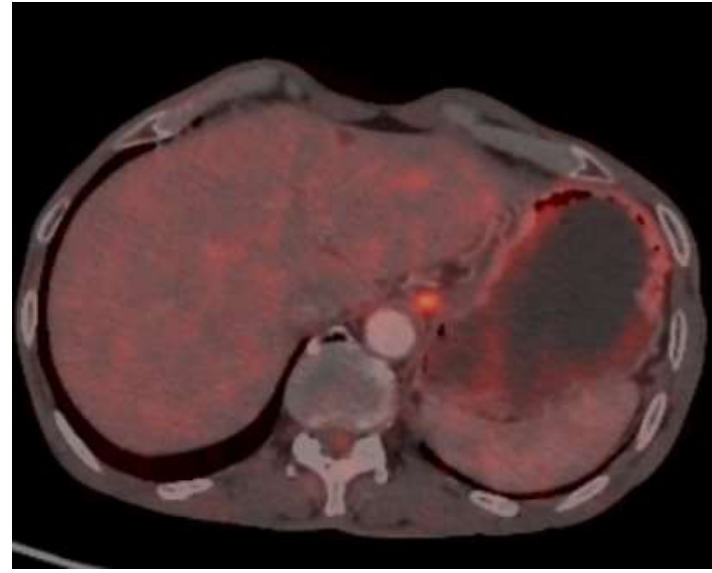
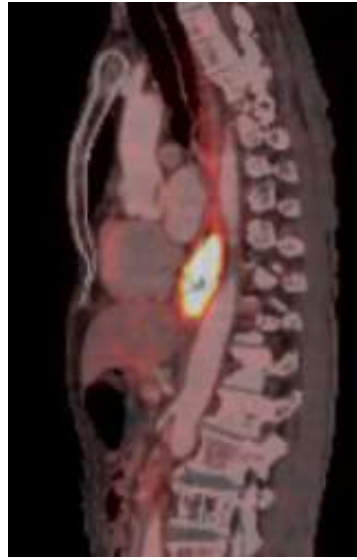
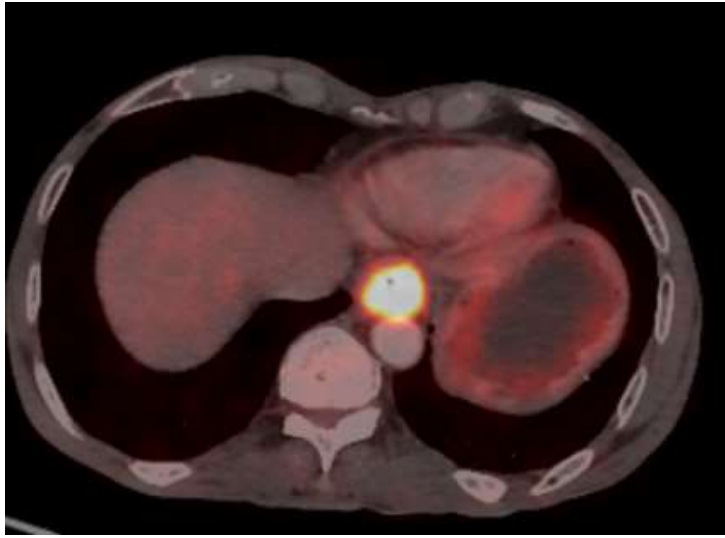
- PETCT - Valuable for distant metastases- higher sensitivity and specificity.
- Met yield 20%
- Prognostic

Disease	Investigation	Number of included studies	Total number of patients	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled log odds ratio (95% CI)
Regional lymph node metastases	EUS	31	1841	0.80 (0.75–0.84)	0.70 (0.65–0.75)	1.94 (1.71–2.17)
Regional lymph node metastases	CT	17	943	0.50 (0.41–0.60)	0.83 (0.77–0.89)	1.40 (1.08–1.72)
Regional lymph node metastases	FDG-PET	10	424	0.57 (0.43–0.70)	0.85 (0.76–0.95)	1.71 (1.22–2.20)
Celiac lymph node metastases	EUS	5	339	0.85 (0.72–0.99)	0.96 (0.92–1.00)	3.89 (2.67–5.11)
Abdominal lymph node metastases	CT	5	254	0.42 (0.28–0.54)	0.93 (0.86–1.00)	1.74 (0.45–3.04)
Distant metastases	CT	7	437	0.52 (0.33–0.71)	0.91 (0.86–0.96)	2.10 (1.59–2.62)
Distant metastases	FDG-PET	9	475	0.71 (0.62–0.79)	0.93 (0.89–0.97)	2.93 (2.41–3.45)

CI = confidence interval; EUS = endoscopic ultrasonography; CT = computed tomography; FDG = ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography.

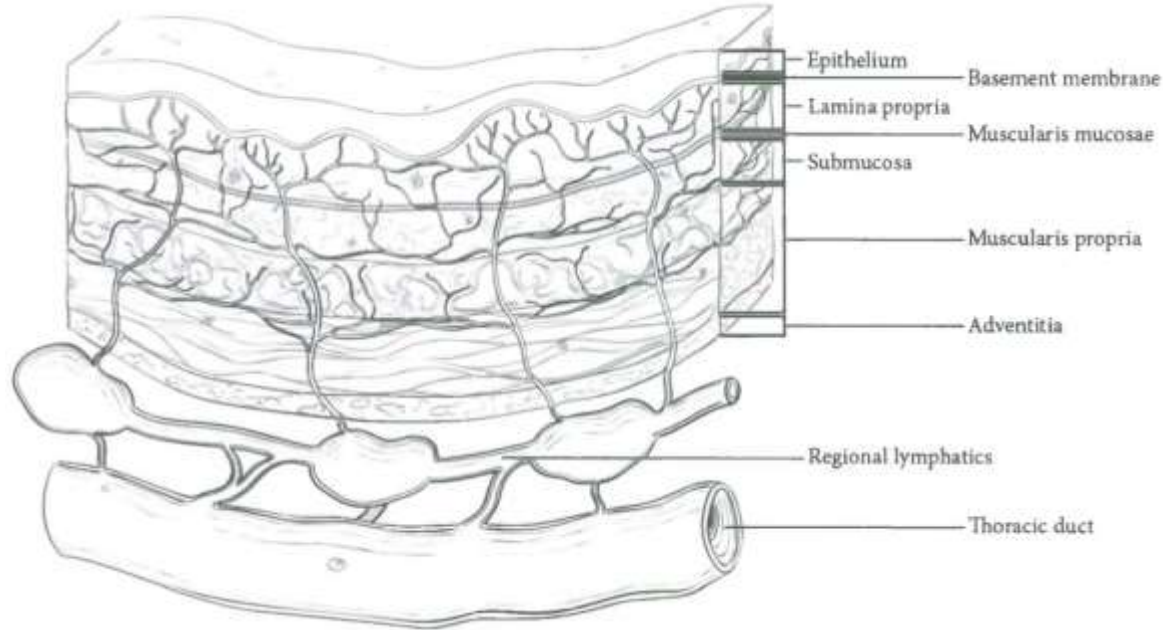
Optional investigations

- EUS- Very early upfront resectable cases to define T and N stage.
- EUS is particularly useful
 - (i) for assessment of T4b status with invasion towards the airways, pericardium or aorta
 - (ii) for identification and biopsy of suspected lymph node metastases outside the regular radiation field or beyond the planned resection limits
- Bronchoscopy: If suspected invasion to bronchus, tumour at or above carina
- Staging Lap:

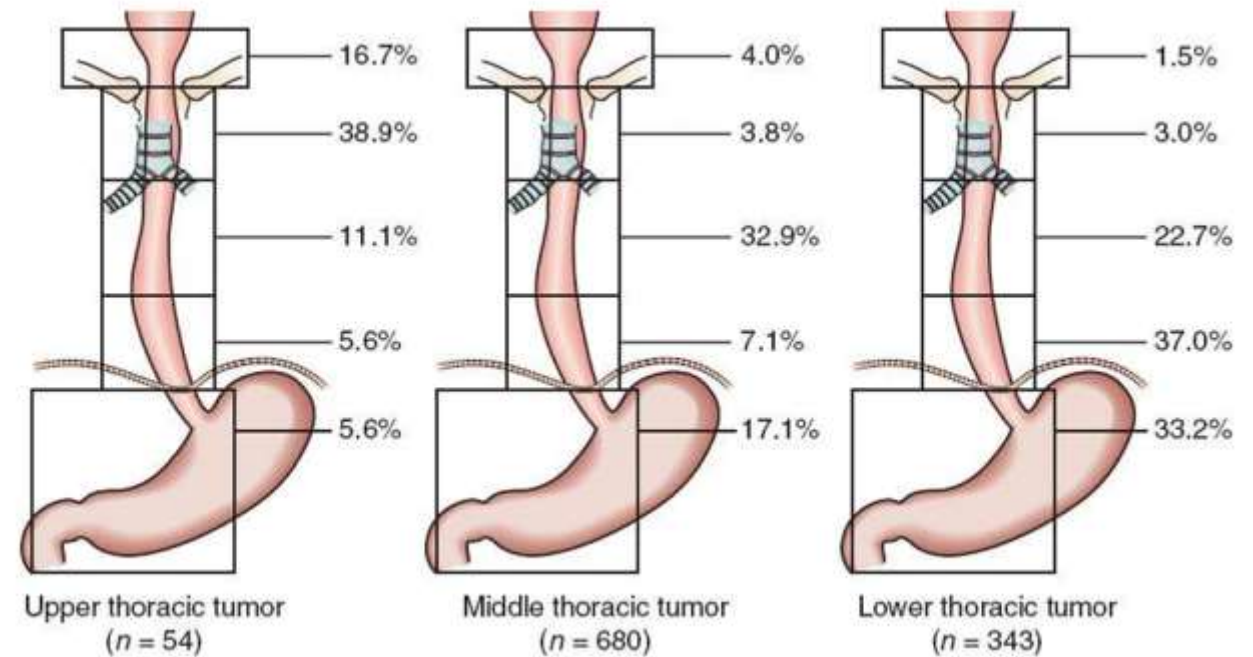


PETCECT: Lesion in lower esophagus, one left gastric node. Non avid small lung nodule in right lung.

Regional lymph nodes for Esophagus

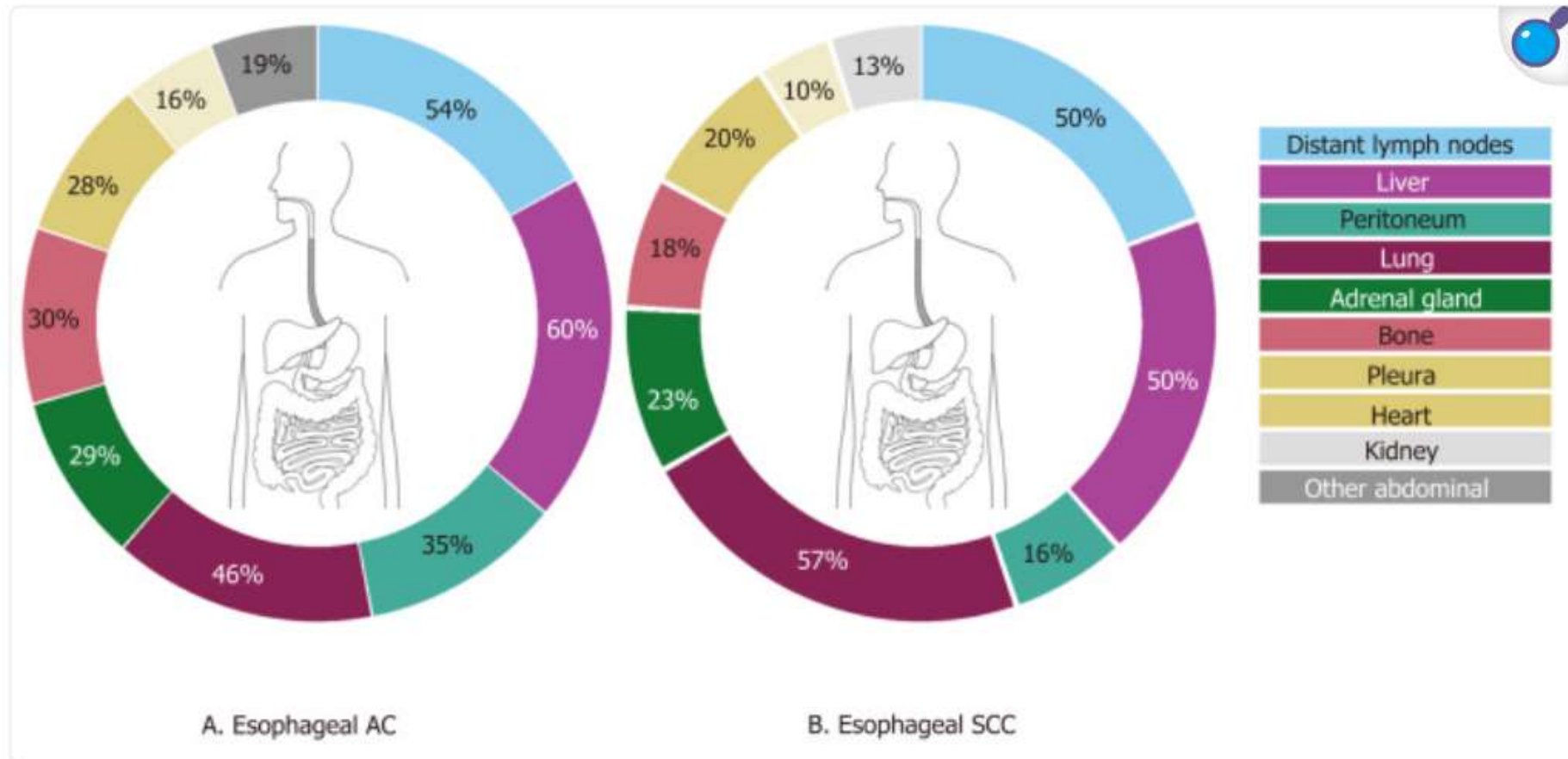


Esophageal lymphatic drainage is intramural and longitudinal

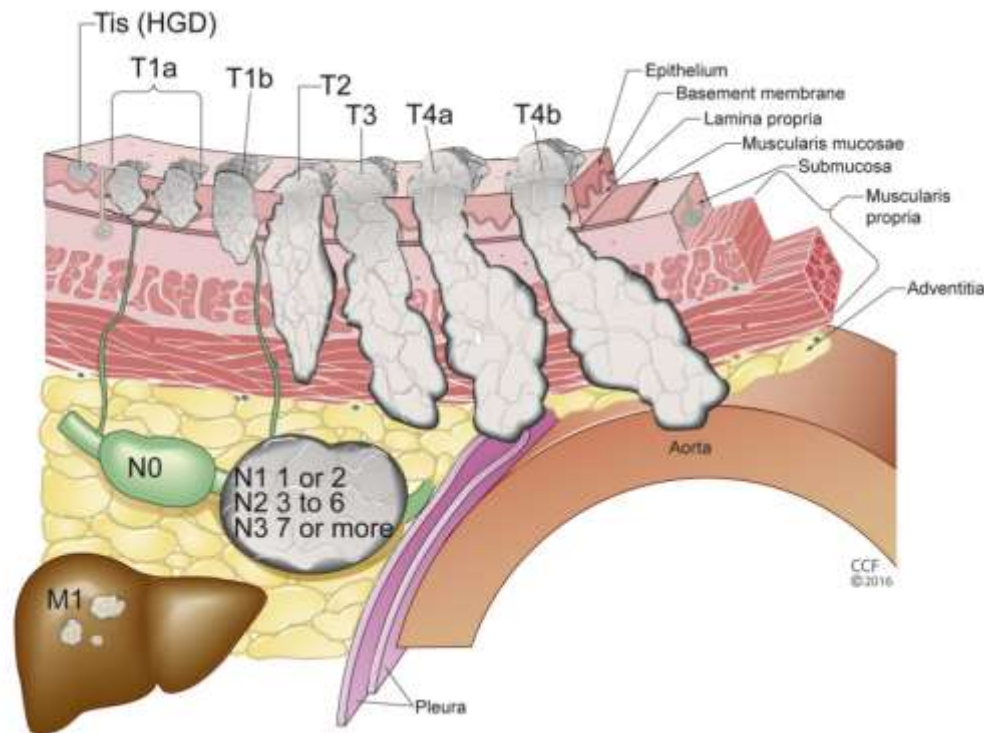


From AJCC and Perez

Metastatic sites



Staging TNM AJCC 8th edition



T category

TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a*	Tumor invades the lamina propria or muscularis mucosae
T1b*	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a*	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b*	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea

N category

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

Adenocarcinoma			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
III	T2	N1	M0
	T3-4a	N0-1	M0
IVA	T1-4a	N2	M0
	T4b	N0-2	M0
IVB	T1-4	N3	M0
	T1-4	N0-3	M1

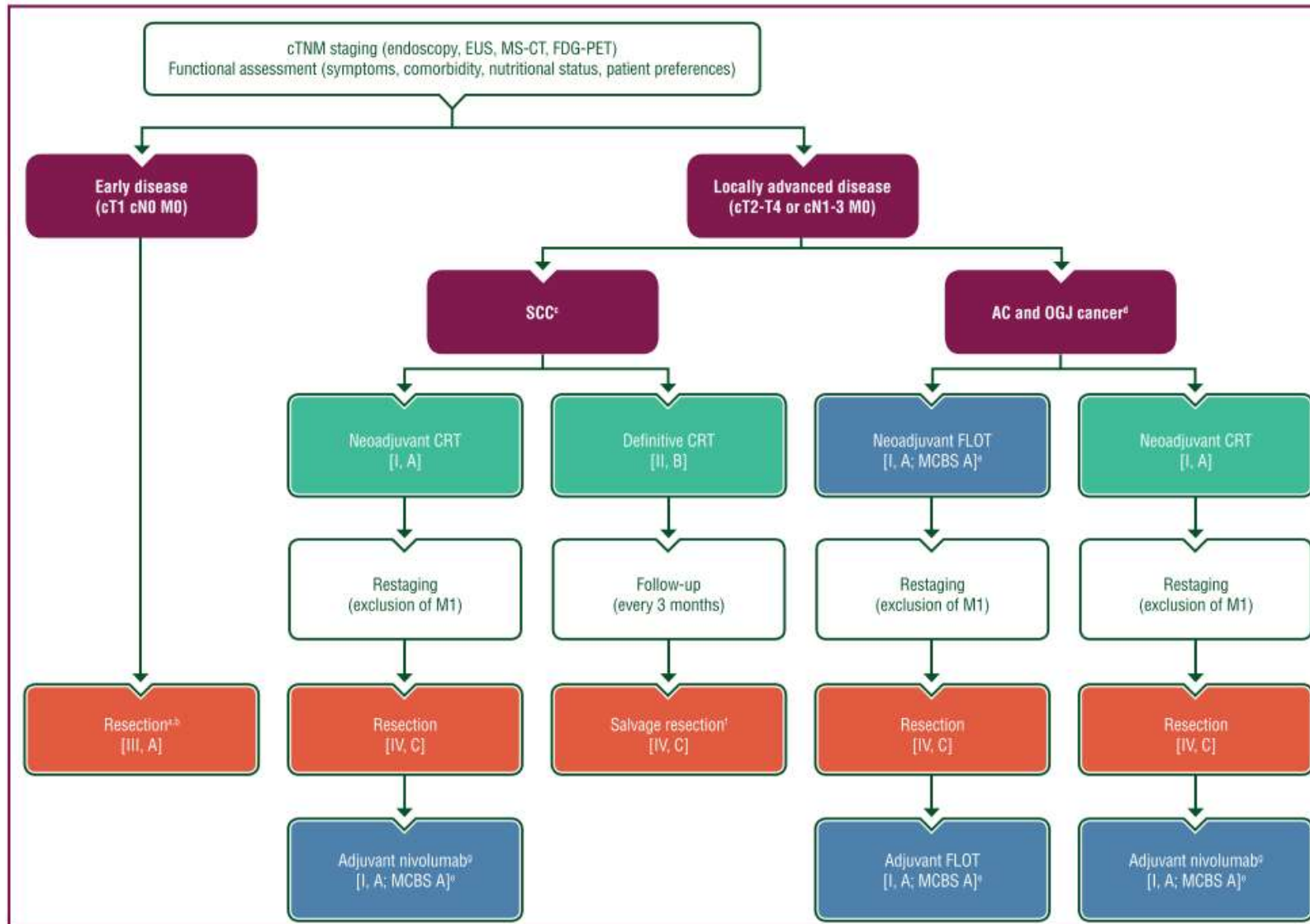
cStage group	cT	cN	cM
Squamous cell carcinoma			
0	Tis	N0	M0
I	T1	N0-1	M0
II	T2	N0-1	M0
	T3	N0	M0
III	T3	N1	M0
	T1-3	N2	M0
IVA	T4	N0-2	M0
	T1-4	N3	M0
IVB	T1-4	N0-3	M1

Clinical stage: Ca Esophagus Lower third SCC
cT3N1M0 III

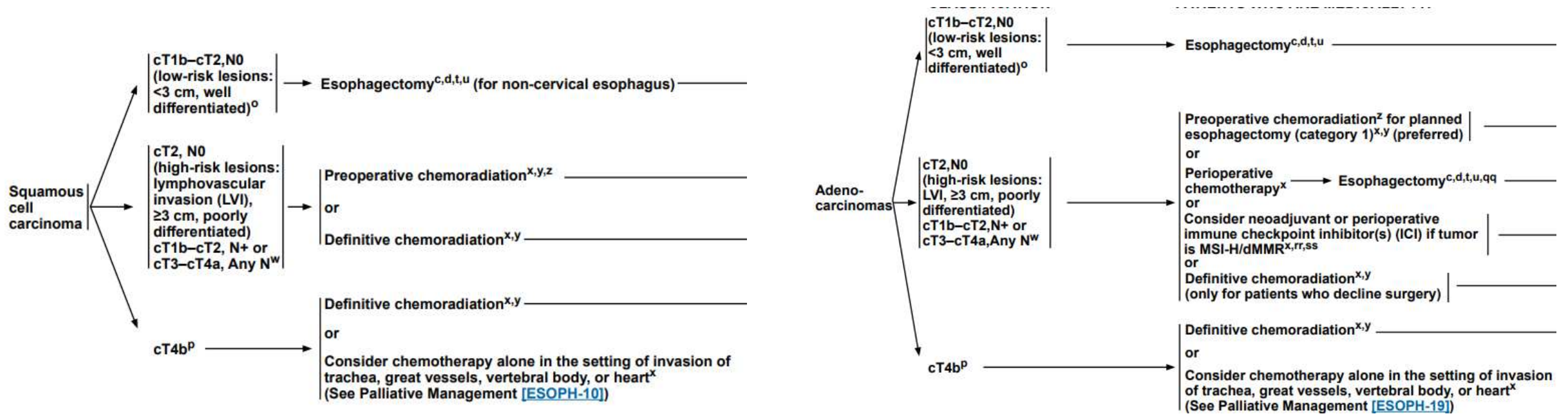
Plan for management

- Surgery f/b Adjuvant chemo
- NACTRT f/b Surgery
- NACT f/b Surgery
- Staging lap- NACT- Surgery
- Definitive RTCT

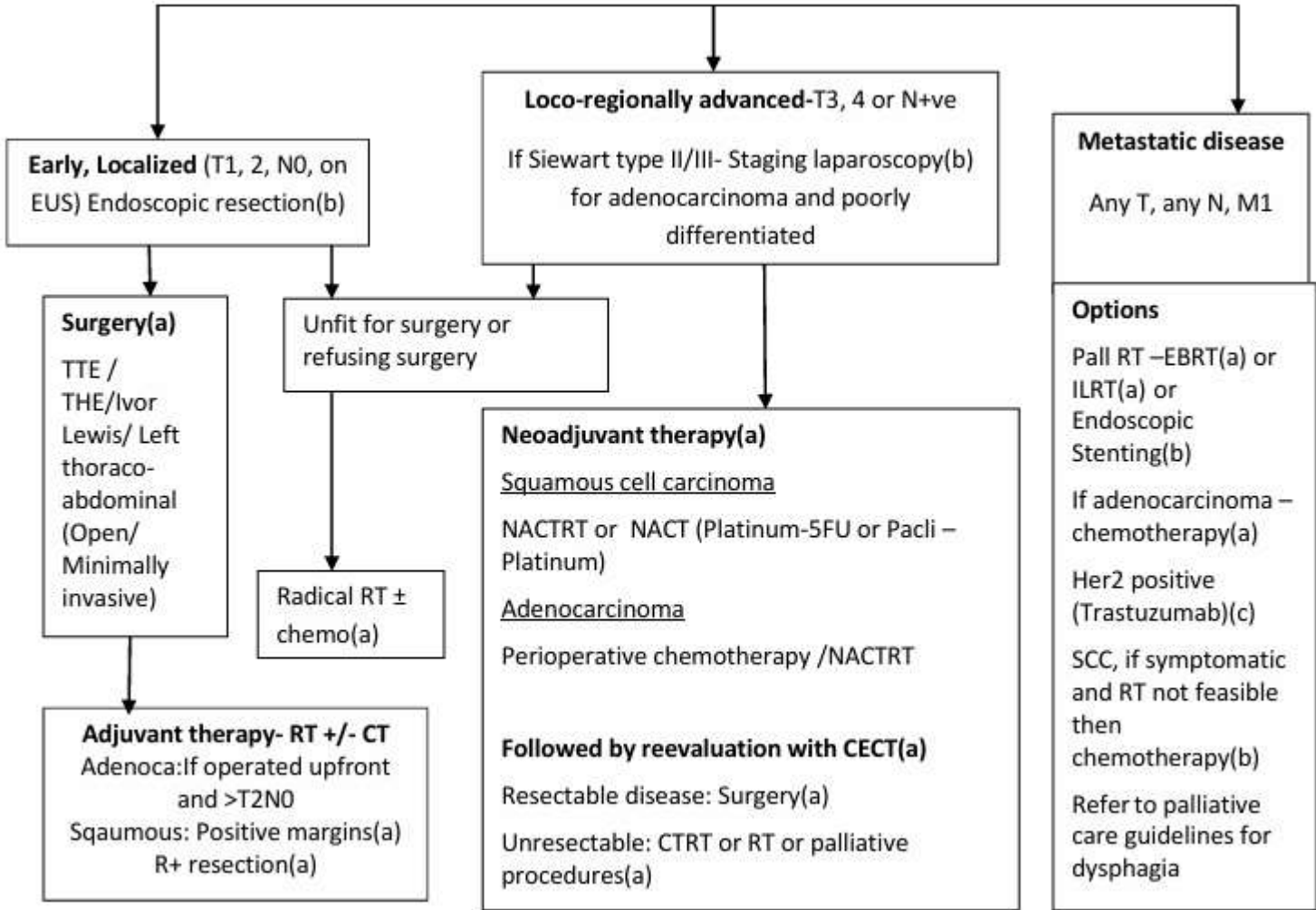




NCCN



NCG Guidelines



Early, Localized (T1, 2, N0, on EUS) Endoscopic resection(b)

Surgery(a)
TTE / THE/Ivor Lewis/ Left thoraco-abdominal (Open/ Minimally invasive)

Adjuvant therapy- RT +/- CT
Adenoca: If operated upfront and >T2N0
Squamous: Positive margins(a)
R+ resection(a)

Unfit for surgery or refusing surgery

Radical RT ± chemo(a)

Loco-regionally advanced-T3, 4 or N+ve
If Siewart type II/III- Staging laparoscopy(b)
for adenocarcinoma and poorly differentiated

Neoadjuvant therapy(a)
Squamous cell carcinoma
NACTRT or NACT (Platinum-5FU or Pacli – Platinum)
Adenocarcinoma
Perioperative chemotherapy /NACTRT

Followed by reevaluation with CECT(a)
Resectable disease: Surgery(a)
Unresectable: CTCT or RT or palliative procedures(a)

Metastatic disease
Any T, any N, M1

Options
Pall RT –EBRT(a) or ILRT(a) or Endoscopic Stenting(b)
If adenocarcinoma – chemotherapy(a)
Her2 positive (Trastuzumab)(c)
SCC, if symptomatic and RT not feasible then chemotherapy(b)
Refer to palliative care guidelines for dysphagia

Evidence- NACTRT f/b Surgery

What is the aim
of Neoadjuvant
therapy?

Can you tell one
trial supporting
this?

Neoadjuvant Therapy

- LA ESCC recurrences with surgery alone-35-50% and 5 yr OS 15-30%.
- Neoadjuvant strategies (NART, NACTRT, NACT) aimed to improve outcomes.
- Advantage:
 - Early treatment of micrometastases
 - Downsizing of the primary tumor and improved locoregional control
 - Sterilizing resection margins resulting in enhanced complete (R0) resection

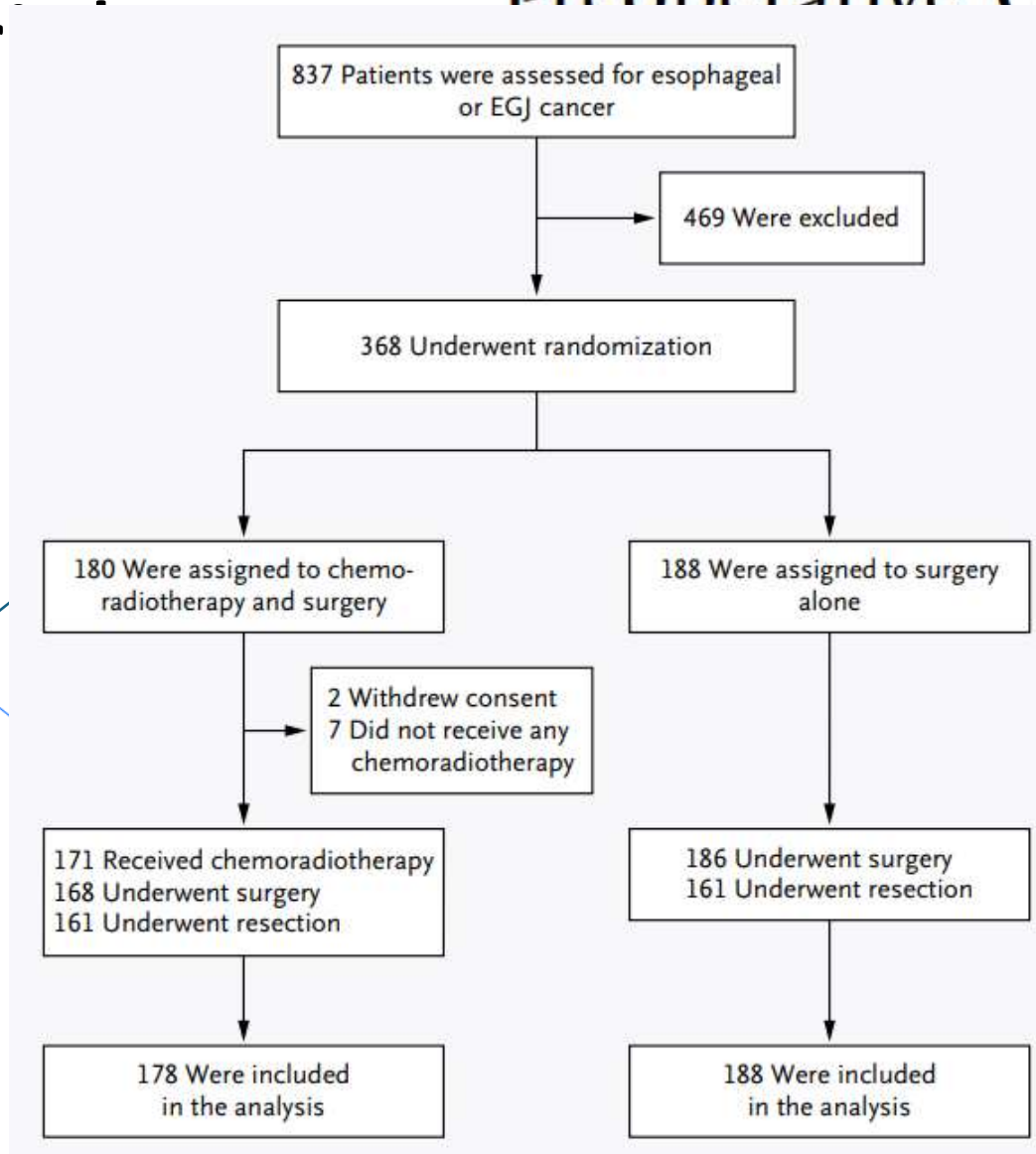
NACTRT followed by Sx vs Sx alone

Table 1 Clinical trials of neoadjuvant chemoradiotherapy followed by surgery vs surgery alone in resectable esophageal cancer							
Author and year	Patient Number	Histology	Radiation (Gy) and Chemotherapy Regimen	R0 Rates (%)	pCR (%)	Survival (%)	Postoperative Mortality (%)
Walsh et al, ²⁷ 1996	nCRT-S: 58 S: 55	Adenocarcinoma	RT: 40/15 CT: 2 cycles CF	NA	25 NA	3y: 32 3y: 6	3 2
Tepper et al, ²⁸ 2008	nCRT-S: 30 S: 26	Adenocarcinoma and squamous	RT: 50.4/28 CT: 2 cycles CF	NA	40 NA	5y: 39 5y: 16	0 4.2
Mariette et al, ²⁹ FFCD 9901, 2014	nCRT-S: 98 S: 97	Adenocarcinoma and squamous	RT: 45/25 CT: 2 cycles CF	93.8 92.1	NA	5y: 41.1 5y: 33.8	11.1 3.4
CROSS, VanHagen et al, ^{12,30} 2012	nCRT-S: 178 S: 188	Adenocarcinoma and squamous	RT: 41.4/23 CT: 5 weekly TC	92 69	29 NA	5y: 47 5y: 34	4 4
NEOCRTEC ²⁶	nCRT-S: 224 S: 227	Squamous	RT: 40/20 CT: 2 cycles Cisplatin Vinorelbine	98.4 91.2	43.2 NA	5y: 59.9 5y: 49.1	2.2 0.4

CROSS trial

Preoperative Chemoradiotherapy for Junctional Cancer

Esophagus/GEJ tumours (n=368) 2004-2008



Eligibility:

Adeno Esophagus
(5 cm below UES)
5 cm length and 5 cm width
T1N1 or T2-3N0-1, M0
18-75 years
ECOG ≤ 2
Weight loss of $< 10\%$

Imaging with CECT TAP

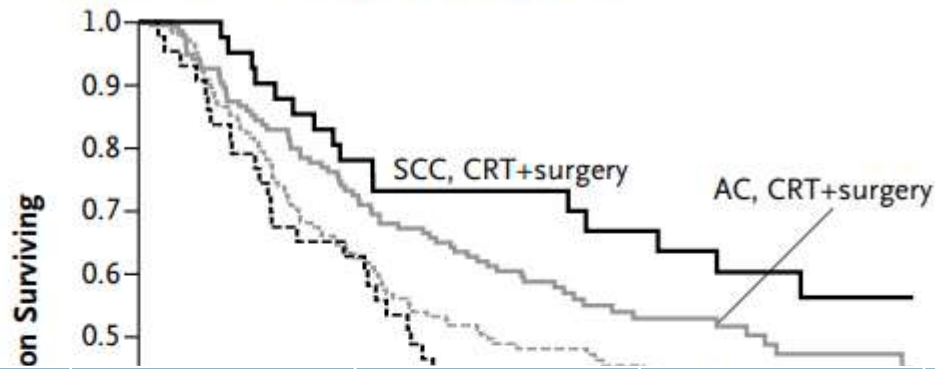
Superiority Design:
Med OS 6 month (22 vs 16m)

Tumor type — no. (%)		
Adenocarcinoma	134 (75)	141 (75)
Squamous-cell carcinoma	41 (23)	43 (23)
Other	3 (2)	4 (2)
Tumor length — cm†		
Median	4	4
Interquartile range	3–6	3–6
Tumor location — no. (%)‡		
Esophagus		
Proximal third	4 (2)	4 (2)
Middle third	25 (14)	24 (13)
Distal third	104 (58)	107 (57)
Esophagogastric junction	39 (22)	49 (26)
Missing data	6 (3)	4 (2)
Clinical T stage — no. (%)‡		
cT1	1 (1)	1 (1)
cT2	26 (15)	35 (19)
cT3	150 (84)	147 (78)
cT4	0	1 (1)
Could not be determined§	1 (1)	4 (2)
Clinical N stage — no. (%)¶		
N0	59 (33)	58 (31)
N1	116 (65)	120 (64)
Could not be determined§	3 (2)	10 (5)

R0 resection rates:
 NACTRT-SX: 92%
 SX: 69% (p=<0.001)

pCR:
 29% overall
 SCC: 49%
 Adeno: 23%

B Survival According to Tumor Type and Treatment Group



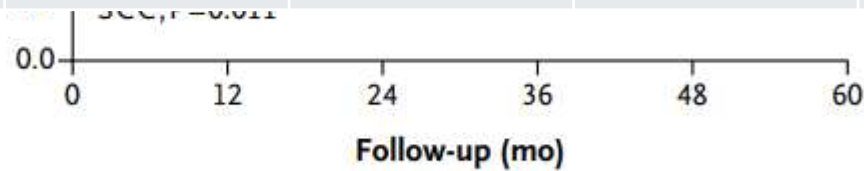
Median follow-up: 45.4 months
(range, 25.5 to 80.9)

Median OS:
NACTRT-Sx: 49.4 m

Arm	1 yr OS	2 yr OS	3 yr OS	5 y OS
NACTRT-Sx	82%	67%	58%	47%
Sx	70%	50%	44%	34%

h DFS:

NACTRT-Sx: NR
Sx: 24.2 m

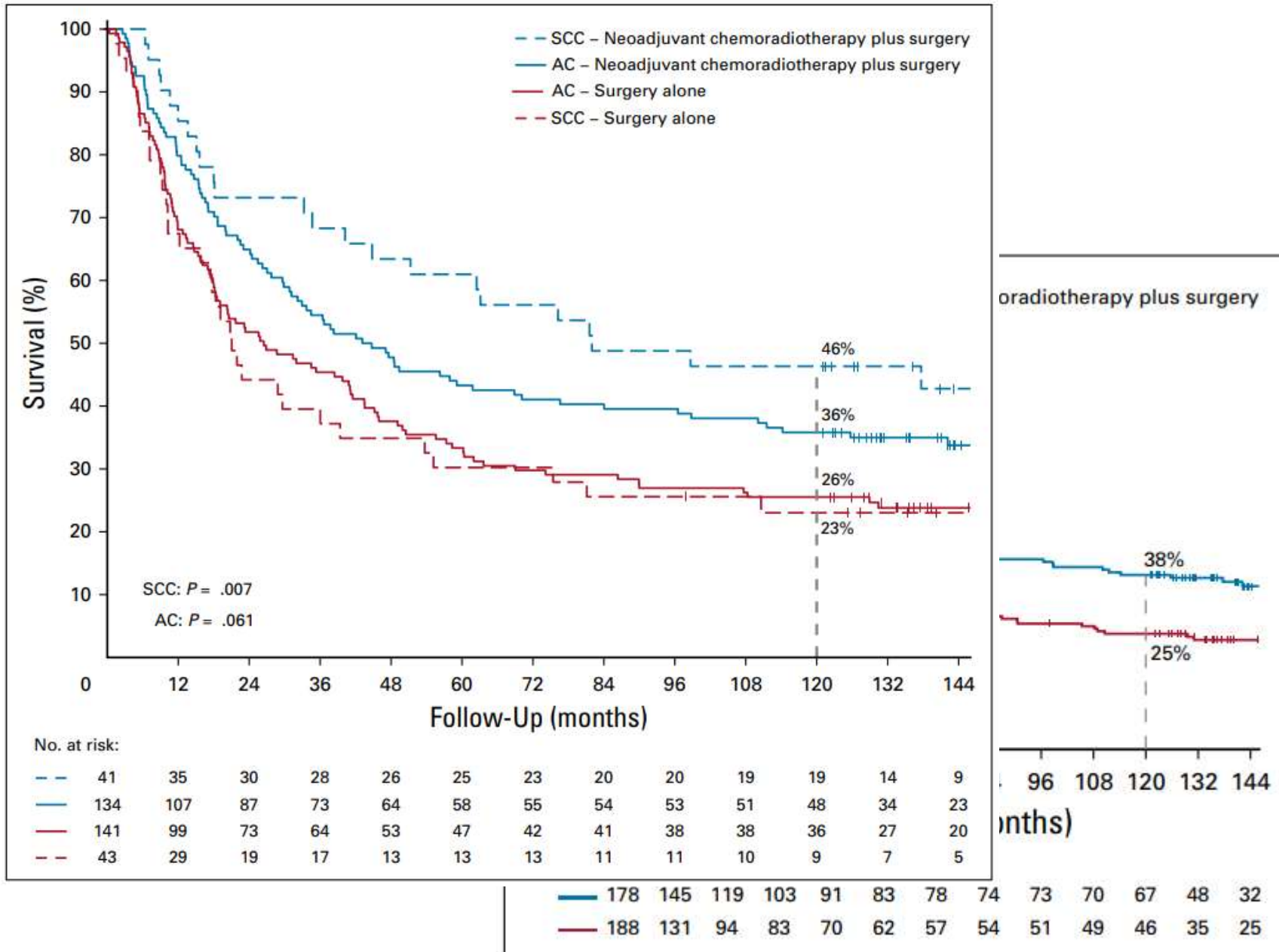


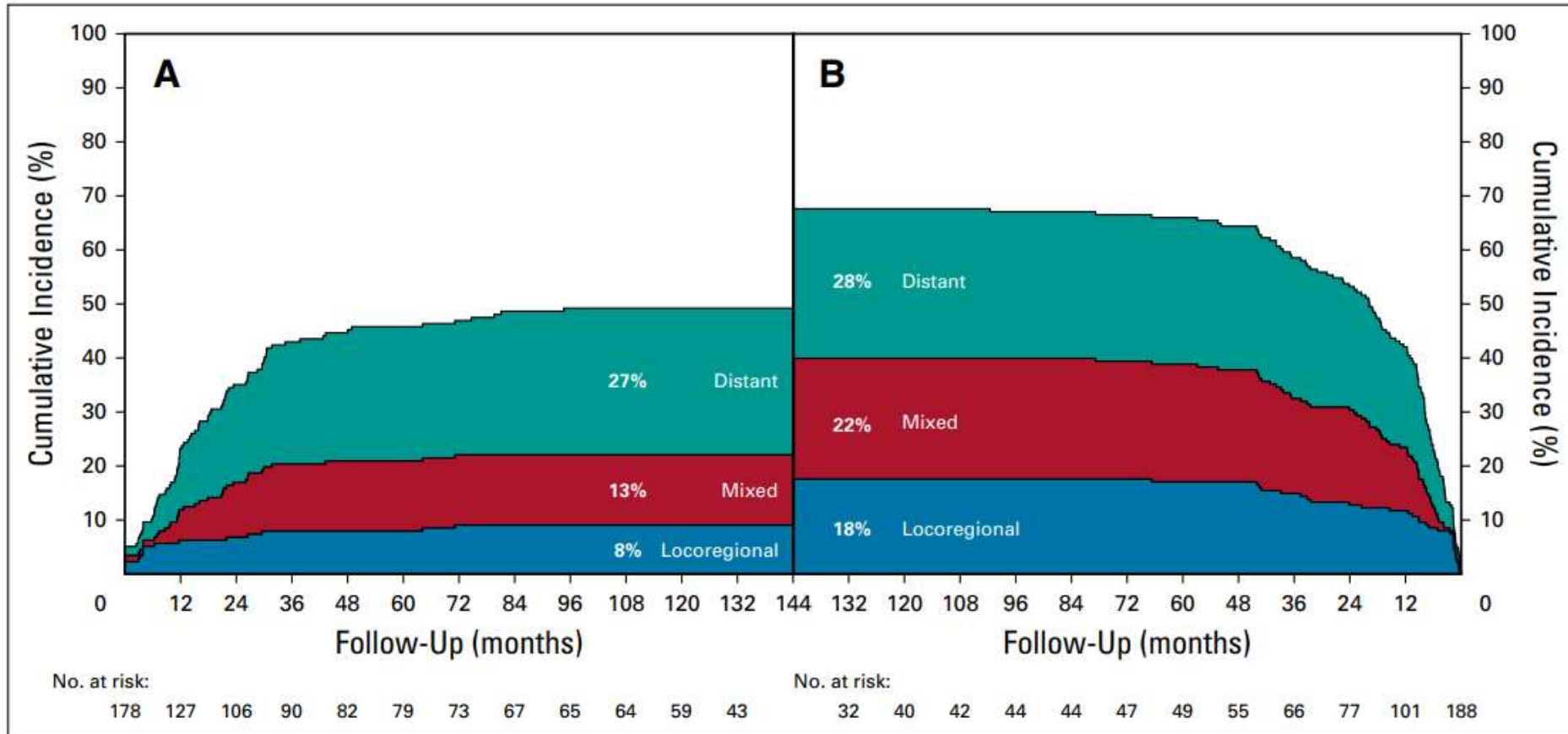
No. at Risk

AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

CR(

- Me
- 14
- 13





Radiation planning- Dose

Dose and Fractionation

Neo-adjuvant

- 41.4Gy in 23# with weekly concurrent carboplatin and paclitaxel

Definitive

- 50Gy in 25# with induction and concurrent cisplatin and Capecitabine
- 55Gy in 20# No chemo
- 50Gy in 25# with concurrent weekly carboplatin and paclitaxel for patients unable to tolerate cisplatin and capecitabine
- Consider 65 - 66Gy in 30-33# dose escalation with chemotherapy for cervical oesophageal carcinoma

Simulation

- CT slice thickness: 2-3mm
- Patients should be scanned in the treatment position:
 - i) For cervical and upper 1/3 oesophageal tumours: patients will be scanned supine with arms down by their side with knee support and immobilisation using a 5 point shell or equivalent.
 - ii) For middle 1/3, lower 1/3 and GOJ tumours: patients will be scanned supine with arms above head with knee support and immobilisation with thermoplastic device or vacuum cushion as per local protocols.
- For distal (lower 1/3 and GOJ tumours): 4DCT planning scans should be considered.
- The extent of the scan : 1cm superior to the apices of the lungs or 5-6cm superior to the proximal disease- to the bottom of the L4 vertebra in order to ensure inclusion of all OARs (lungs, liver, kidneys and stomach).

Stomach filling protocol- L/3 GEJ

- Fasting with empty stomach
- Patients should be asked to fast for 2 hours and then drink 200mls of liquid 30 minutes prior to CT planning and treatment in an attempt to reproduce the same anatomical position of the stomach due to filling throughout treatment.

Localisation	Notes	
Position	Upper 1/3:	Supine
	Lower 2/3:	Supine
Arm/ leg/ head/ thorax position	Upper 1/3:	Arms down
	Lower 2/3:	Arms up
Immobilisation and supports	Upper 1/3:	Thermoplastic immobilisation head and neck shell
	Lower 2/3:	Upper body immobilisation as per local protocol
Organ pre-requisites	Upper 1/3:	No fasting required
	Lower 2/3:	Consider 2 hours fast and then drink 200mls of liquid 30 mins prior to CT.**
Contrast	Upper 1/3	IV contrast *** +/- oral contrast**
	Lower 2/3	IV contrast *** +/- oral contrast**
CT acquisition	Slice thickness:	Maximum of 3mm
	Scanning limits Upper 1/3:	Base of skull to L4 (ensure lung bases is covered)
	Scanning limits lower 2/3:	Lung apex to L4

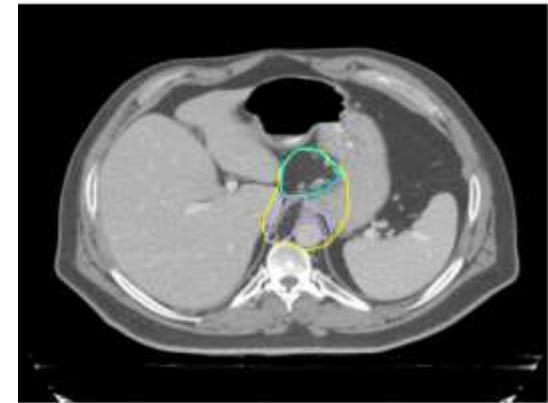
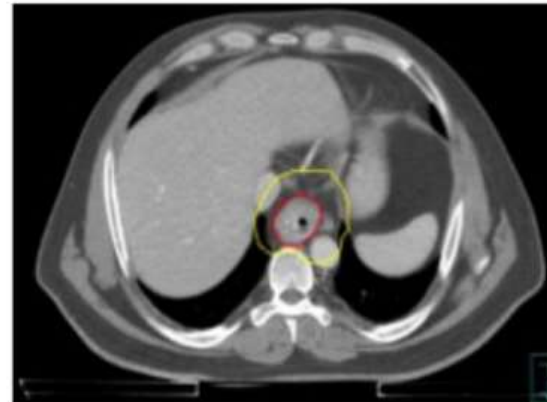
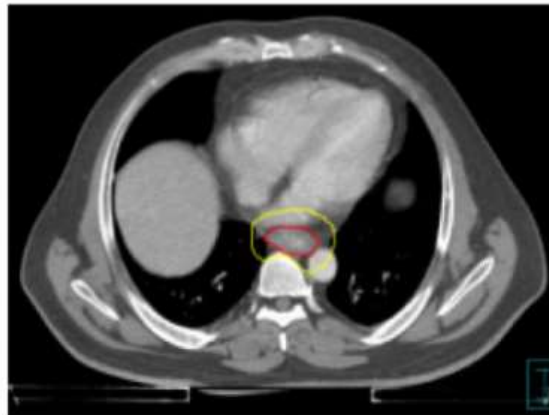
Target volumes

- CROSS
- NEOSCOPE/NEOAEGIS
- SCOPE
- NEEDS study
- Wu et al

GTVT: the entire circumference of the esophagus at the level of the tumor.

CTV T: 3 cm margin in the cranio-caudal direction and 0.5-1 cm radial margin from GTVT with corrections for natural anatomic boundaries (such as heart, lungs, skeletal structures, kidneys, and liver) and oriented along the esophageal mucosa (not a simple geometric expansion). For tumors located in the gastro-esophageal junction a 2-cm distal margin of clinically uninvolved gastric mucosa

Thoracic: No elective nodal irradiation.
Lower third- Gastrohepatic, Celiac, PA



4D and ITV

Table 3 4DCT acquisition options in the NeoSCOPE trial

	4DCT method 1	4DCT method 2
Pre-delineation	From the 4DCT data sets, identify the extreme phases of motion (MaxIn and MaxEx). Also identify the phase that best represents the time-weighted average (Mid).	From the 4DCT data sets, identify the extreme phases of motion (MaxIn and MaxEx).
GTV	Contour as per the 3D protocol on each of the three phases as defined above, giving: GTV_{MaxIn} , GTV_{Mid} and GTV_{MaxEx} .	Contour as per the 3D protocol on the 3D contrast enhanced CT scan and label it GTV_{3D} . Also contour the GTV in the extreme phases of the 4D scan, giving GTV_{MaxIn} and GTV_{MaxEx} . Combine these three to obtain a composite structure, label GTV_{motion} . Review GTV_{motion} on all 4DCT phases and manually increase the contour for any areas not covered.
CTVA	Contour as per the 3D protocol on each of the three phases, giving: $CTVA_{MaxIn}$, $CTVA_{Mid}$ and $CTVA_{MaxEx}$.	Contour as per the 3D protocol on the 3D contrast enhanced CT scan using GTV_{motion} as the starting point. Label $CTVA_{3D}$.
CTVB	Contour as per the 3D protocol on each of the three phases, giving: $CTVB_{MaxIn}$, $CTVB_{Mid}$ and $CTVB_{MaxEx}$.	Create $CTVB_{3D}$ from $CTVA_{3D}$ as per the 3D protocol on the 3D contrast enhanced CT. Make two copies of $CTVB_{3D}$, labelled $CTVB_{MaxIn}$ and $CTVB_{MaxEx}$ then proceed to manually increase these on their respective respiration phases for any areas not covered.
ITV	The ITV is defined as the composite CTVB volumes. Review the ITV on all 4DCT phases and manually increase the contour for any areas not covered.	The ITV is made by combining $CTVB_{MaxIn}$ and $CTVB_{MaxEx}$. Check that this volume covers any unusual motion patterns noted in the respiratory phases above.
PTV	Apply the margin to the ITV	Apply the PTV margin to the ITV
Planning	The mid phase CT is used for planning the dose distribution	The 3D CT is used for planning the dose distribution

Contours



Dose constraints

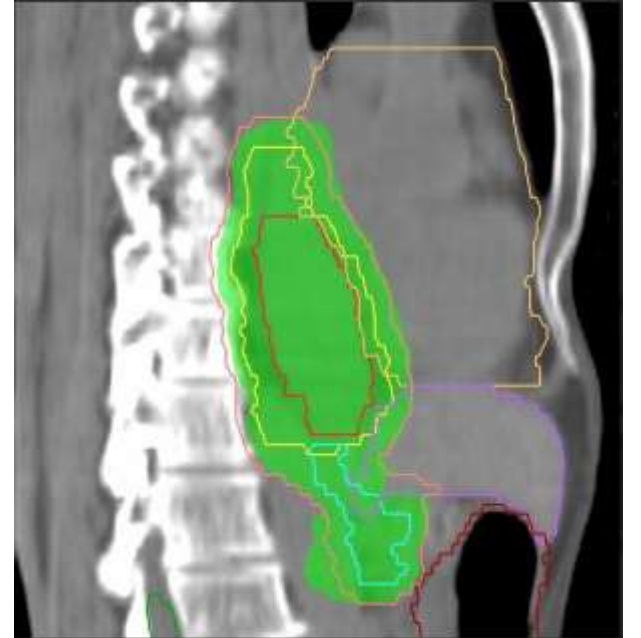
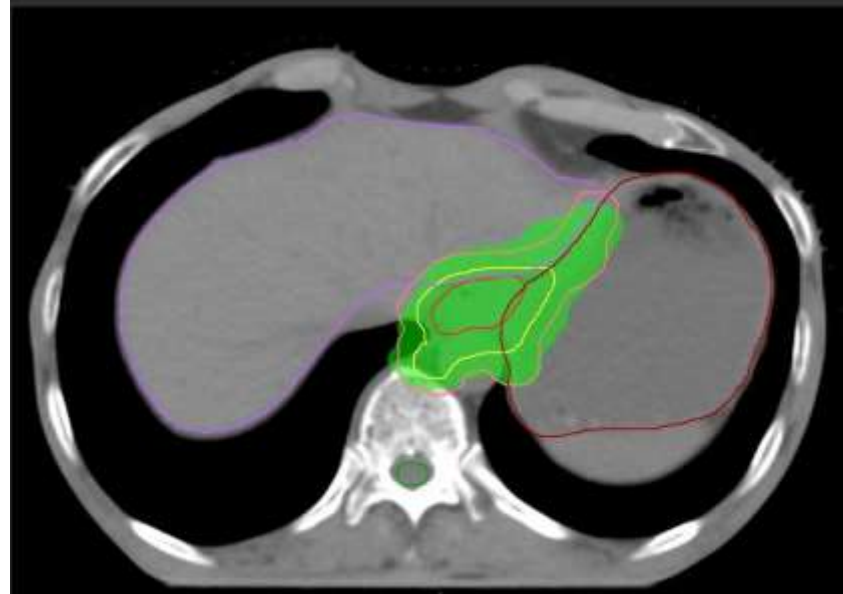
Organs at Risk

	41.4Gy in 23# (Neo-Agis)	50Gy in 25# (SCOPE2)		
Structure name		Constraint	Optimal	Mandatory
External	D1.8cc <107% of highest prescribed dose	D1.8cc	<107% of highest prescribed dose	
Spinal Cord	D0.1cc < 45Gy			
SpinalCord_PRV	D1cc <40Gy clinician may allow a discretionally point maximum dose up to 45Gy	D0.1cc	< 40Gy	< 42Gy
Heart	V40 < 30% V25 < 50%	Dmean V30Gy	< 25Gy < 45%	<30Gy -
Lungs (Combined lungs)	V20 < 25%	Dmean V20Gy	< 17Gy < 20%	<19Gy ≤25%
Stomach_excl_PTV (Stomach excluding	Not defined	V50Gy	< 16cc	< 25cc
Kidney_L and Kidney_R (Individual kidneys)	V20 < 70% with contralateral kidney V20 <30% Combined V20 < 50%	V20Gy	< 25%	≤30%

Planning

- 3DCRT

- VMAT



Structure	Volume (cm ³)	Min. Dose (cGy)	Max. Dose (cGy)	Mean Dose (cGy)	Cold Ref. (cGy)	Volume < (cm ³)	Volume < (%)	Hot Ref. (cGy)	Volume > (cm ³)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
PTV_41.4Gy/23Fr	289.245	3251.9	4381.2	4101.6				3933.0	276.435	95.57	100.00	yes	1.07	0.31
SPINAL CORD	32.892	3.0	1380.6	455.0							99.78	no	162.31	
LUNG_L	1806.855	11.4	4280.2	713.4				2000.0	99.321	5.50	100.00	yes	81.72	
LUNG_R	2344.071	10.8	4299.8	725.5				2000.0	121.108	5.17	100.00	yes	82.57	
HEART	533.676	106.3	4299.0	2897.3				4000.0	43.690	8.19	100.00	yes	12.72	
STOMACH	588.114	0.0	4282.3	1572.4							100.00	yes	35.57	0.02
DUODENUM	93.330	29.9	3478.6	518.7				4000.0	0.000	0.00	100.00	yes	56.80	0.00
patient(Unsp.Tiss.)	11209.062	0.9	4221.3	296.4							99.46	no	247.08	
KIDNEY_L	113.628	20.8	1287.1	225.2							100.00	yes	29.08	
KIDNEY_R	97.551	24.5	1803.5	250.6							100.00	yes	29.31	
LIVER	949.158	17.3	4299.3	1016.9				3000.0	47.053	4.95	100.00	yes	69.73	

Print OK

Toxicities and Revaluation

Skin

GI: Dysphagia,
Odynophagia

Pain management

Dietician, Tube
feeding where
needed.

Persistent cough

Response
evaluation: 4
weeks after
NACTRT

Checkmate 577- Adjuvant Nivolumab

- 1 year of anti-PD-1 antibody nivolumab.
- OGJ cancer, evidence of residual pathological disease in the resection specimen (ypT1 and/or ypN1) after NACTRT.
- Improvement in disease-free survival : 22.4 months vs 11.0 months ((CI) 0.56-0.86; P < 0.001).

Case 2:

- 72 year gentleman, Farmer, no comorbs
- Smoker 50 years
- Presented with Odynophagia, Dysphagia for solids for 2 months

- No voice change, weightloss or loss of appetite

- Clinically: SCF: No nodes wt: 52 kg
- P/A: Soft no organomegaly

Investigations:

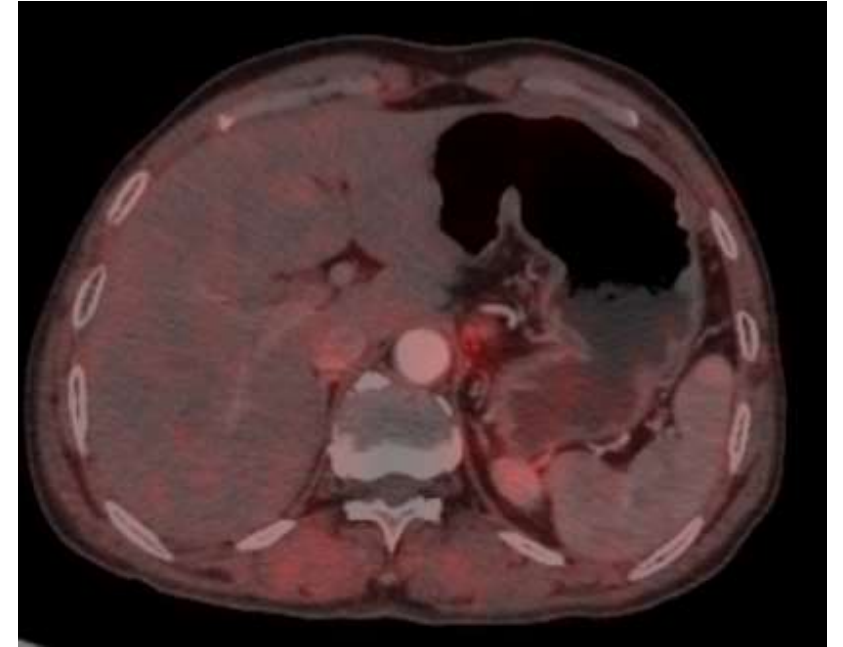
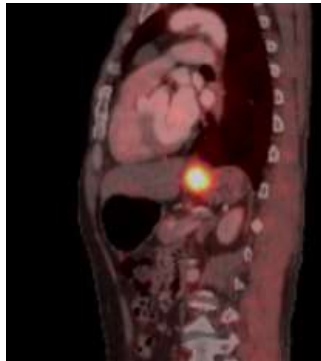
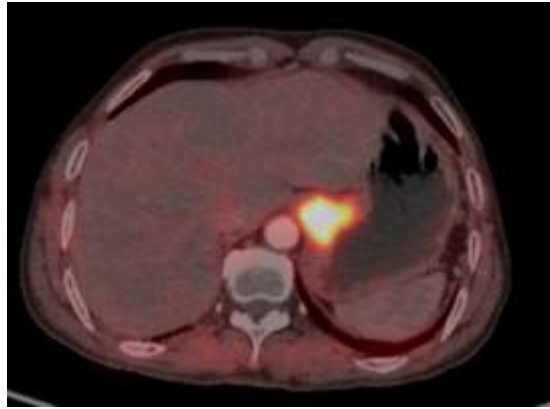
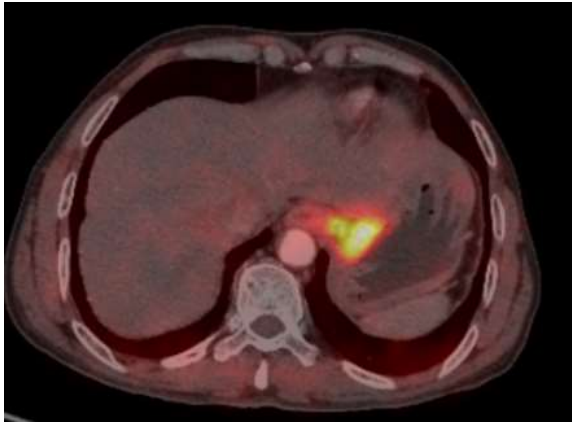
- Upper GI scopy: Ulcerated mucosa at GEJ, growth at fundus, extending to cardia.
- Biopsy (outside): SCC
- Labs: normal Hb: 14.2 Cr 1.07, Alb 4.2.
- Baseline nutritional assessment done



What next?



Imaging



- PET/CT: Primary lesion in GEJ. Subcm avid left gastric nodes. no distant metastases.

Slide Block review

SLIDE AND BLOCK REVIEW- GE JUNCTION BIOPSY

Microscopy:

Deeper sections studied shows gastroesophageal mucosa with foci of adenocarcinoma, grade 2(40%) arranged predominantly in tubular pattern.

Additionally, there is a distinct component of atypical squamous cells forming sheets and nests, along with occasional dyskeratotic cells (20%).

FINAL DIAGNOSIS:

SLIDE AND BLOCK REVIEW-GE JUNCTION BIOPSY: PRESENCE OF DISTINCT COMPONENTS OF ADENOCARCINOMA, GRADE 2(40%) AND SQUAMOUS CELL CARCINOMA, GRADE 2/3 (20%), SUGGESTS THE POSSIBILITY OF ADENOSQUAMOUS CARCINOMA INVOLVING THE GE JUNCTION.

Histologies

Epithelial Tumors

Squamous cell carcinoma

Variants of squamous cell carcinoma

Basaloid squamous cell carcinoma

Squamous cell carcinoma with sarcomatoid features

Undifferentiated carcinoma

Spindle cell carcinoma

Pseudosarcoma and carcinosarcoma

Verrucous carcinoma

In situ carcinoma

Adenocarcinoma

Adenoacanthoma

Adenoid cystic carcinoma (cylindroma)

Mucoepidermoid carcinoma

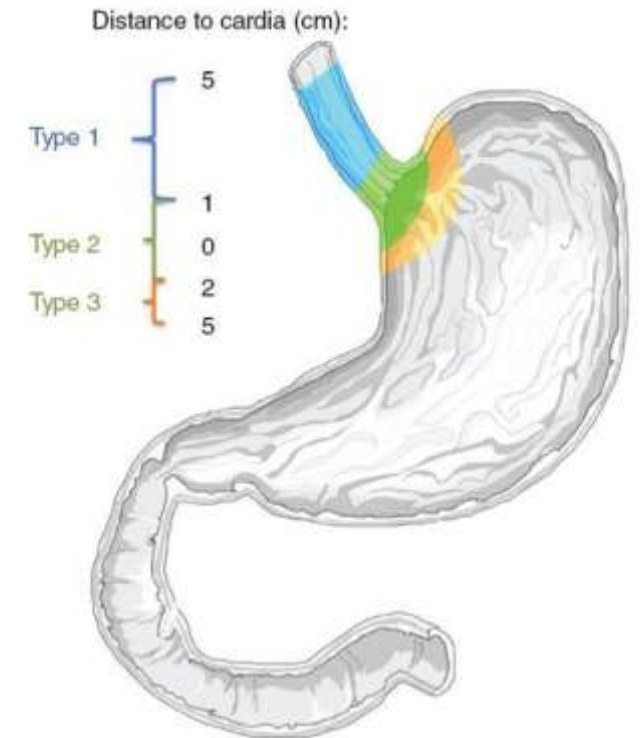
Adenosquamous carcinoma

Carcinoid

Small cell carcinoma

GEJ -Seiwert Classification

Anatomic boundary between esophagus and stomach: tumors involving the esophagogastric junction (EGJ) with epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancers; tumors with epicenter located greater than 2 cm into the proximal stomach are staged as stomach cancers even if EGJ involved.



Ca Esophagus- Adenocarcinoma

Stage: cT2/3N0/1M0

What treatment options?

Surgery

NACT- SX

NACTRT-SX

Adeno- NACTRT or CT?

Criteria	CROSS	MAGIC	FLOT-AIO
Patients	177 vs 188	250 vs 253	360 vs 356
Arms	CTRT f/b surgery vs Surgery alone	Peri-op chemo f/b surgery vs Surgery alone	ECF/ECX f/b surgery vs FLOT f/b surgery
Stage	cT1/T2N1M0	Stage II	CT2N+ or
Histology	SCC/AdenoCa	AdenoCa	AdenoCa
Site	Whole esophagus and GEJ	Stomach, lower esophagus, GEJ	Stomach, GEJ GEJ
Median fu	147 months	48 months	43 months
OS	48 vs 24 months 5 yr OS: 47% 46% SCC, 36% AdenoCa (At 10 years)	24 vs 19 mth 5 yr OS: 36%	50 vs 35 months (Median) 3 yr OS 72%
DFS	LRR 8% vs 18%	PFS 31% vs 21%	30 vs 18 (Median)

NEOAEGIS

in
the
:

Esophagus
tumours
(n=377)
2013-2020

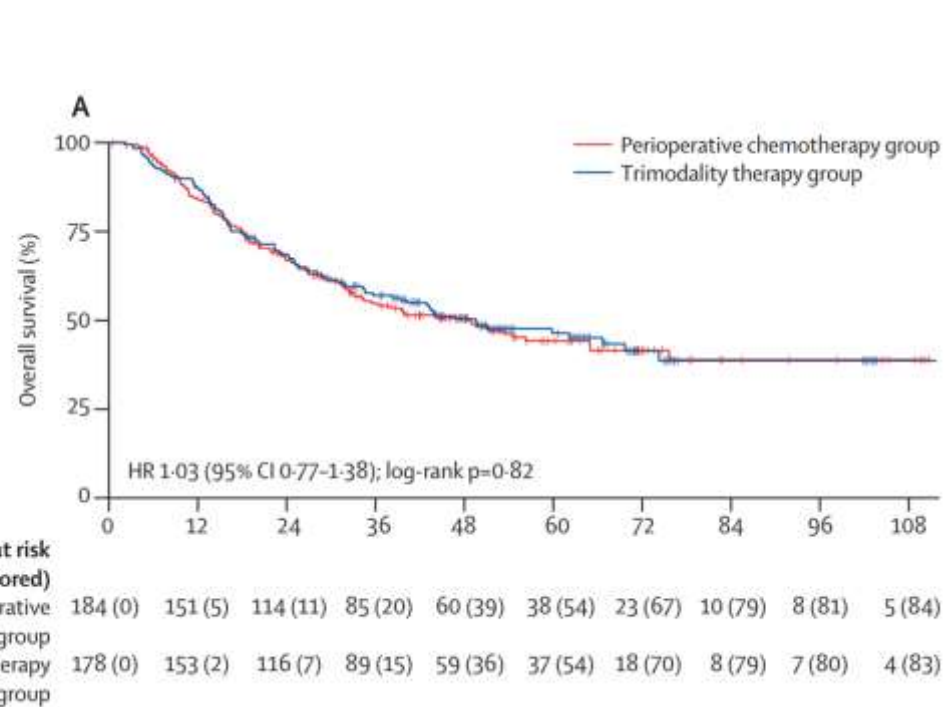
R

Multicentric-24 centres
Superiority Design (10-15%)
- Non inferiority- 5% (3 yr OS
57%)

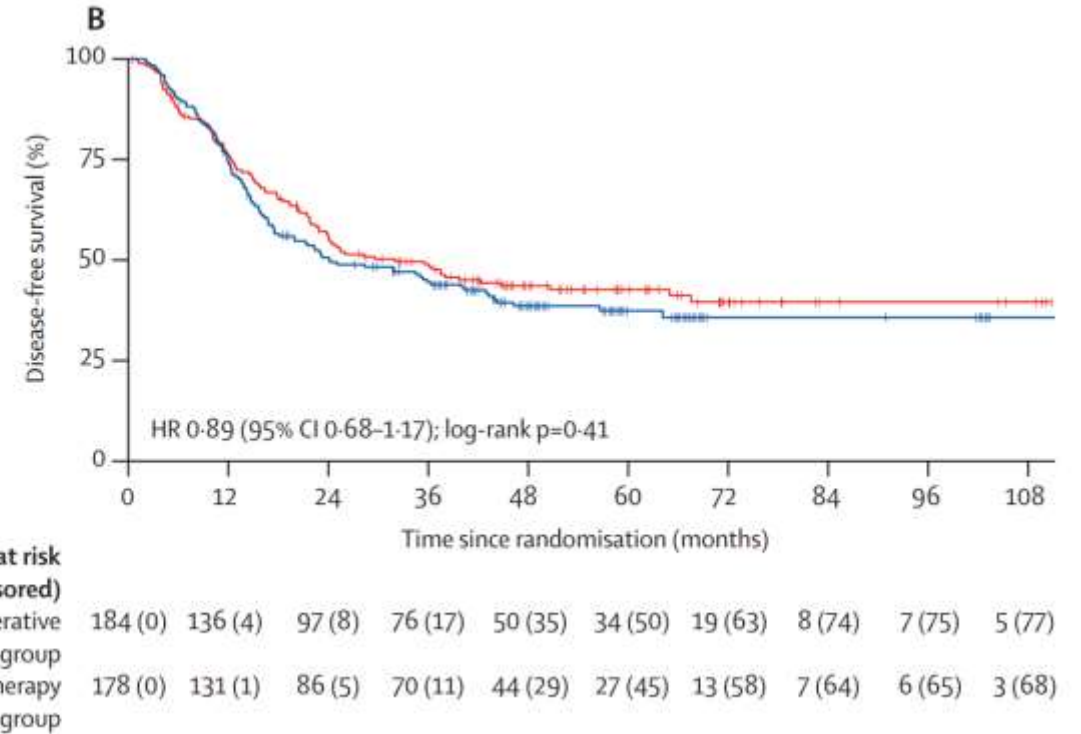


	Perioperative chemotherapy group (n=184)	Trimodality therapy group (n=178)		
Age, years	63.8 (8.8)	63.8 (7.9)		
Sex				
Male	169 (92%)	158 (89%)		
Female	15 (8%)			
Race			Clinical nodal stage	
White	183 (99%)		N0	73 (40%) 78 (44%)
Other	1 (1%)		N1	83 (45%) 73 (41%)
BMI, kg/m ²	27.5 (3.9)		N2	23 (13%) 27 (15%)
Diabetes	15 (8%)		N3	5 (3%) 0
Hypertension	68 (37%)		Surgery type	
Current smoker	23 (13%)		En-bloc two-stage transthoracic resection	115/162 (80%) 130/167 (78%)
ECOG performance status			Minimally invasive en-bloc	30/162 (19%) 17/167 (10%)
0	155 (84%)		En-bloc three-stage transthoracic resection	7/162 (4%) 4/167 (2%)
1	27 (15%)		Extended total gastrectomy and mediastinal anastomosis	6/162 (4%) 6/167 (4%)
2	2 (1%)		Extended total gastrectomy and thoracic anastomosis	2/162 (1%) 3/167 (2%)
Tumour location			Trans-hiatal oesophagectomy	2/162 (1%) 7/167 (4%)
Lower oesophagus or AEG type I	123 (67%)			
AEG type II	46 (25%)	38 (21%)		
AEG type III	15 (8%)	14 (8%)		
Clinical tumour stage				
T2	29 (16%)	28 (16%)		
T3	155 (84%)	150 (84%)		

- Median follow-up was 38.8 months (IQR 16.3–55.1)



Med OS 48 vs 49.2m (p=0.82)



Med DFS 32.4 vs 24 m (p=0.41)

Arm	1 yr OS	2 yr OS	3 yr OS
NACTRT-Sx	87%	69%	57%
Periop-Sx	84%	67%	55%

	Perioperative chemotherapy group (n=162)	Trimodality therapy group (n=167)	p value
Tumour pathology	0.020
ypT0	7 (4%)	23 (14%)	..
ypT1a	6 (4%)	8 (5%)	..
ypT1b	19 (12%)	26 (16%)	..
ypT2	24 (15%)	22 (13%)	..
ypT3	97 (60%)	84 (50%)	..
ypT4	9 (6%)	4 (2%)	..
Nodal pathology	0.0035
ypN0	71 (44%)	100 (60%)	..
ypN1	50 (31%)	35 (21%)	..
ypN2	16 (10%)	21 (13%)	..
ypN3	25 (15%)	11 (7%)	..
Tumour regression grade	<0.0001
1	8 (5%)	23 (14%)	..
2	11 (7%)	41 (25%)	..
3	38 (23%)	53 (32%)	..
4	65 (40%)	39 (23%)	..
5	35 (22%)	7 (4%)	..
Not evaluable	5 (3%)	4 (2%)	..
Pathological complete response	7 (4%)	20 (12%)	0.012
Circumferential margin R0	119/145 (82%)	131/137 (96%)	0.0003

Number of nodes analysed	27 (22-37)	22 (16-31)	0.0002
Number of nodes involved	1 (0-3)	0 (0-2)	0.0025
Response to therapy by endoscopy	0.020
Complete response	23/130 (18%)	28/138 (20%)	..
Partial response	62/130 (48%)	83/138 (60%)	..
No response	45/130 (35%)	27/138 (20%)	..
Site of treatment failure (multiple sites possible per patient)			
Systemic	49/184 (27%)	58/178 (33%)	..
Liver	11/184 (6%)	22/178 (12%)	0.035
Lung	13/184 (7%)	24/178 (13%)	0.044
Bone	12/184 (7%)	17/178 (10%)	..
Multiple sites	22/184 (12%)	26/178 (15%)	..
Nodal non-regional	14/184 (8%)	20/178 (11%)	..
Locoregional	27/184 (15%)	34/178 (19%)	..
Anastomosis and oesophageal	17/184 (9%)	21/178 (12%)	..
Stomach	6/184 (3%)	2/178 (1%)	..
Regional nodes	15/184 (8%)	17/178 (10%)	..
Missing	1/184 (1%)	1/178 (1%)	..

Toxicities

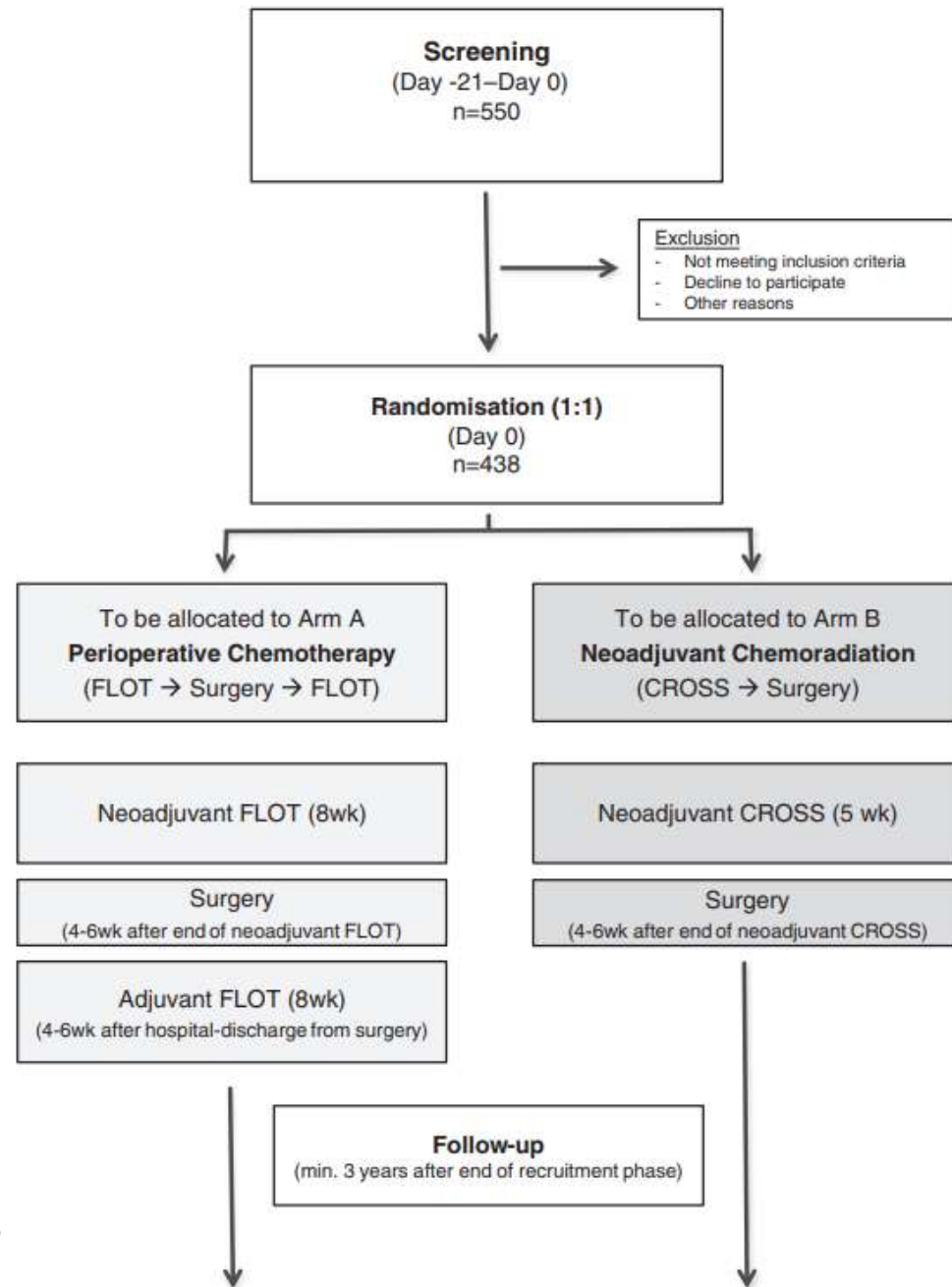
Periop chemotherapy group more likely to have a **dose reduction** vs Trimodality therapy group (75 [41%] vs 16 [9%]; $p < 0.0001$).

Fewer patients in the trimodality therapy group **withdrew from treatment due to toxicity** vs peri-op chemotherapy group (25 [14%] vs 14 [8%]; OR 0.54 [95% CI 0.27–1.08], $p = 0.077$).

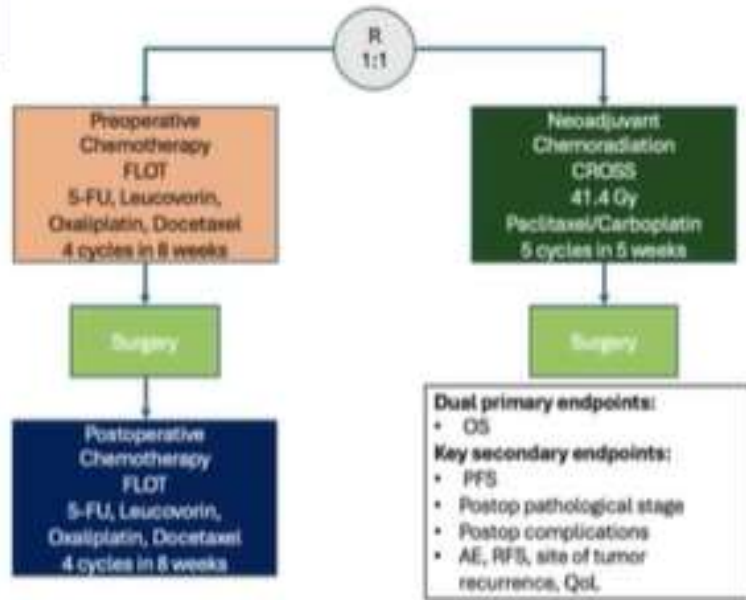
165 (46%) of 362 patients had at least one serious adverse event

Regimen	Peri-op chemotherapy-Sx	NACRT-Sx
Serious adverse events	91(50%)	74(42%)
Gr 3/ 4 Neutropenia	49(27%)	11(6%)
Deaths due to adverse events	1(1%)	3(2%)

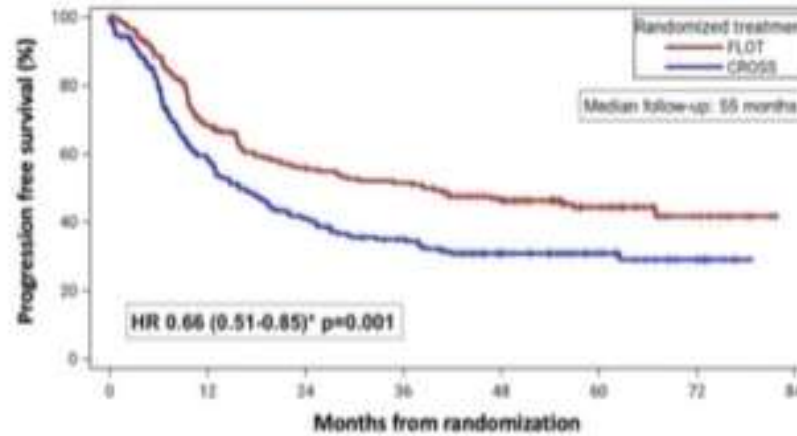
ESOPEC



ESOPEC: Comparing periop FLOT to neoadj CRT CROSS in Esoph Adeno

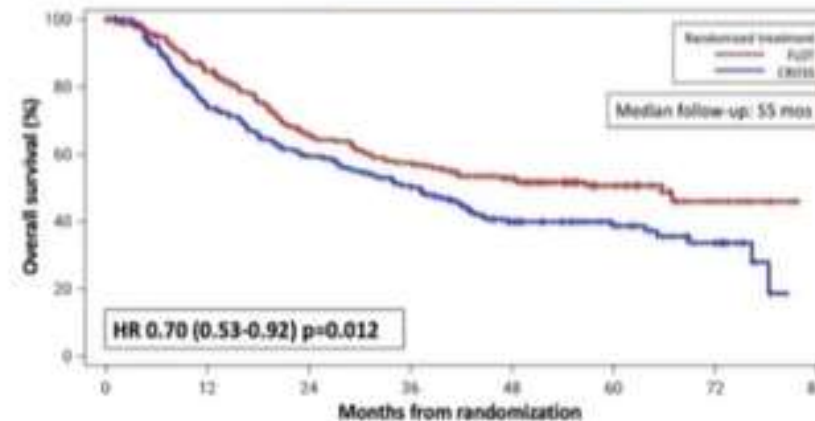


Progression Free Survival



	FLOT	CROSS
Events	107	137
Median PFS time (months)	38	37
95% CI (months)	21 - n.e.	12 - 22
3 yr PFS rate	51.6 %	35.0%
5 yr PFS rate	44.4 %	30.9%

Overall Survival

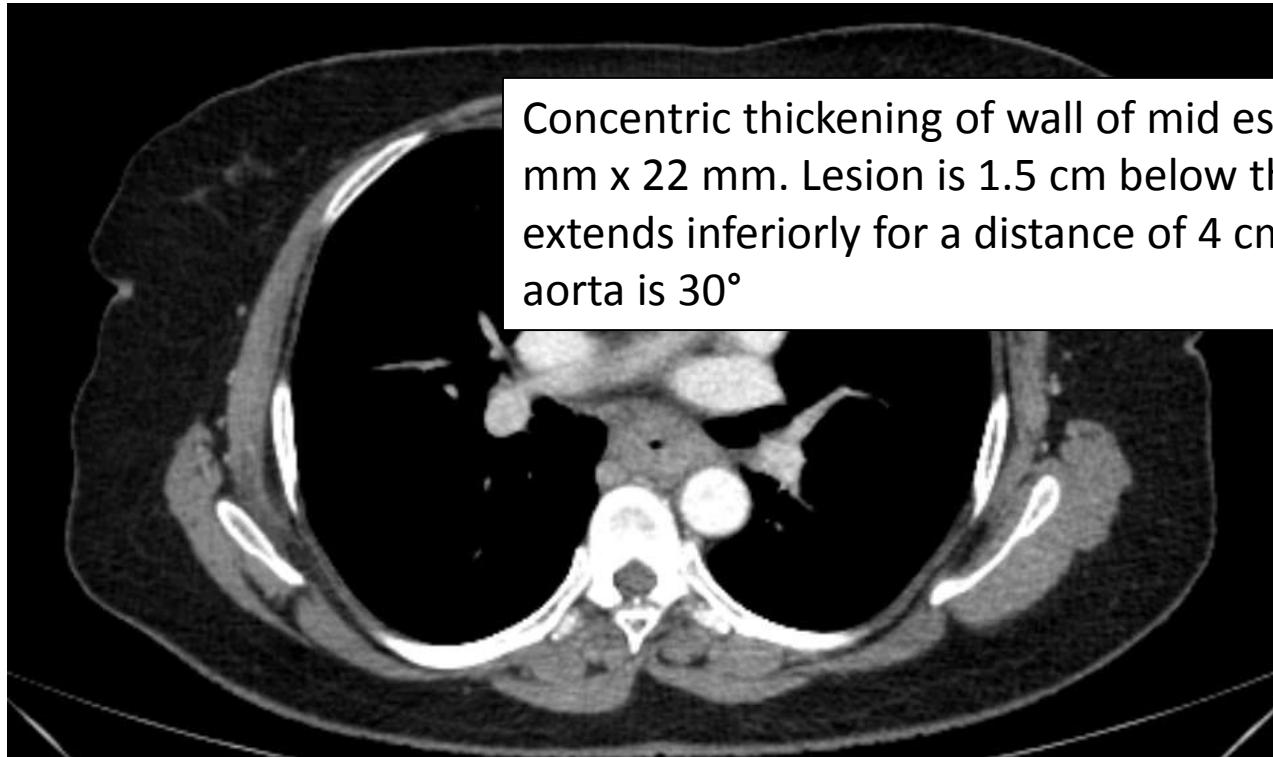


	FLOT	CROSS
Events	97	121
Median OS time (months)	66	37
95% CI (months)	36 - n.e.	28 - 43
3 yr OS rate	57.4 %	50.7%
5 yr OS rate	50.6 %	38.7%

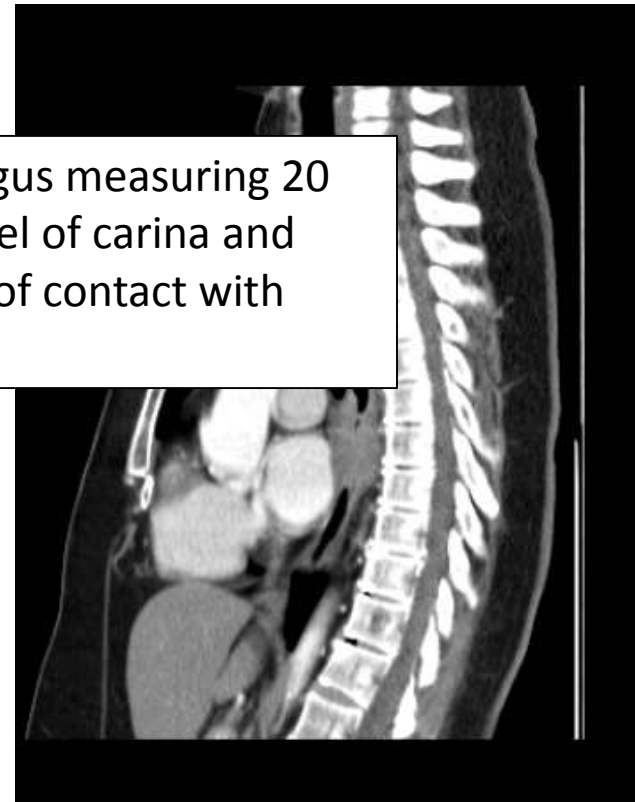
Case 3:

- 54 year old lady Hypertensive
- Dysphagia- solids, Odynophagia 1 months
- Neck : no nodes palpable RS : B/L NVBS
- Wt: 65 kg
- Inv:
- UGI scopy: Growth in mid third starting at 30 cm
- Biopsy: SCC

Imaging: CECT TAP



Concentric thickening of wall of mid esophagus measuring 20 mm x 22 mm. Lesion is 1.5 cm below the level of carina and extends inferiorly for a distance of 4 cm Arc of contact with aorta is 30°



Ca Esophagus- Mid Third squamous

Stage: cT3N0M0

What treatment options?

Surgery

NACT- SX

NACTRT-SX

Def RTCT

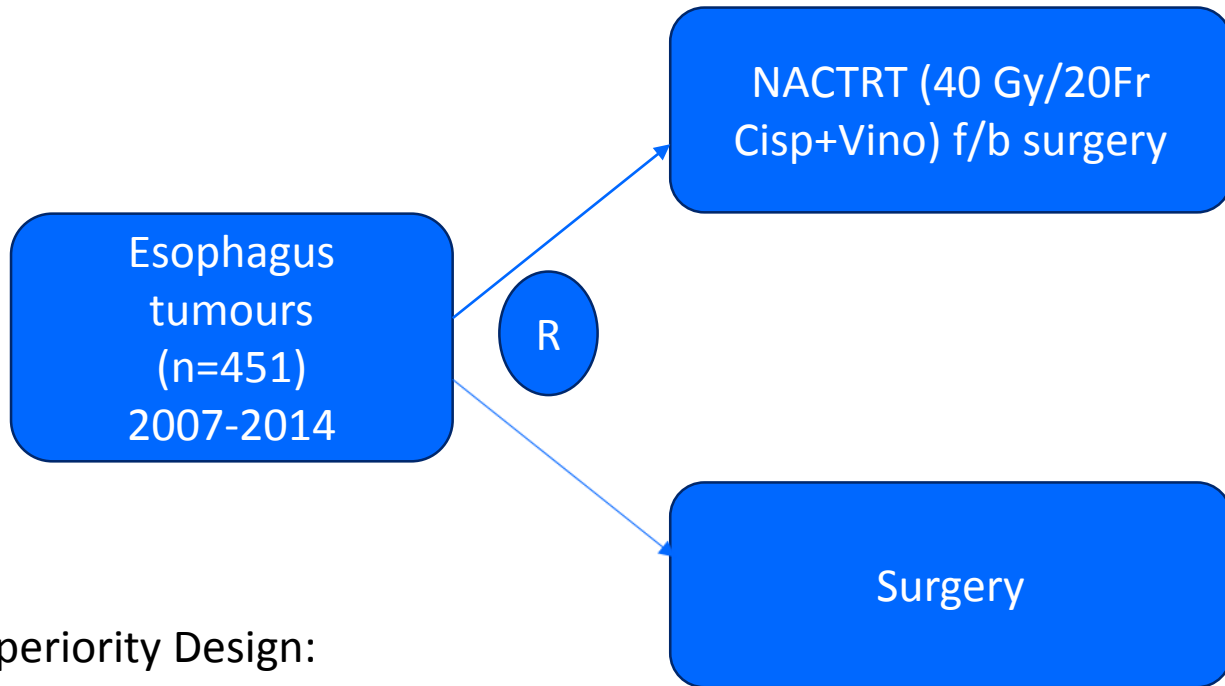
NACT vs NACTRT for SCC

NEOCRETEC

NEXT

NEOCRTEC 5010

Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial



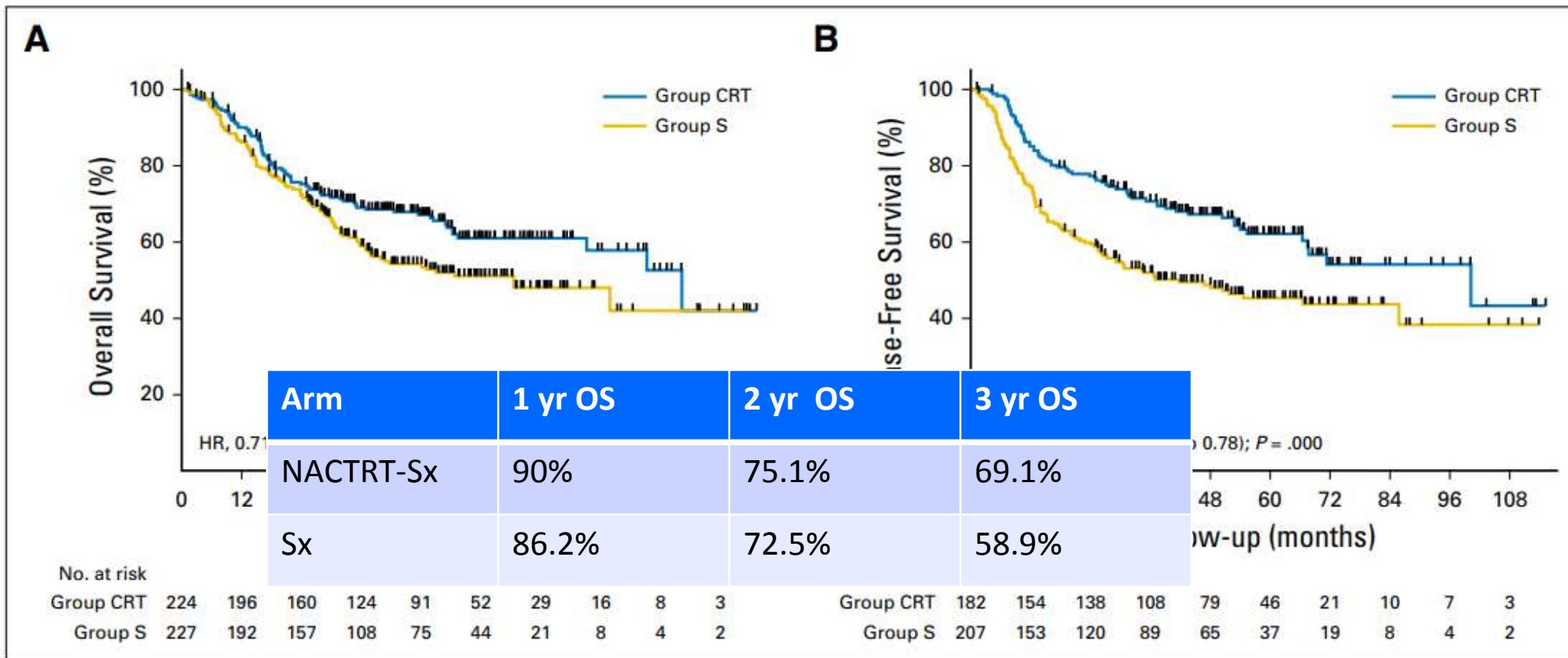
Eligibility:

- Thoracic SCC
- T1-4N1M0/T4N0M0
- 18-70 years
- KPS >90

Staged with CECT TAP

Superiority Design:
Med OS 17 month (56 vs 39 m)





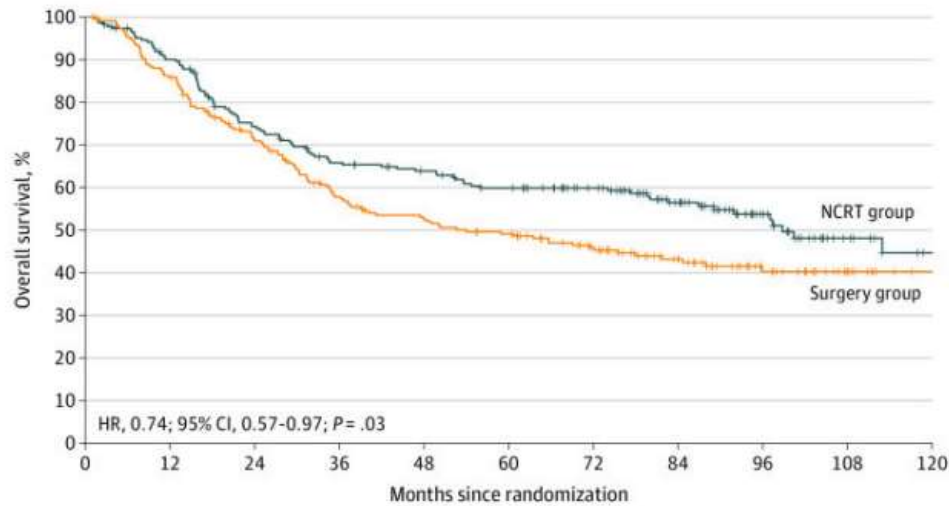
Median OS was 100.1 months versus 66.5 months

Median DFS was 100.1 months vs 41.7 months



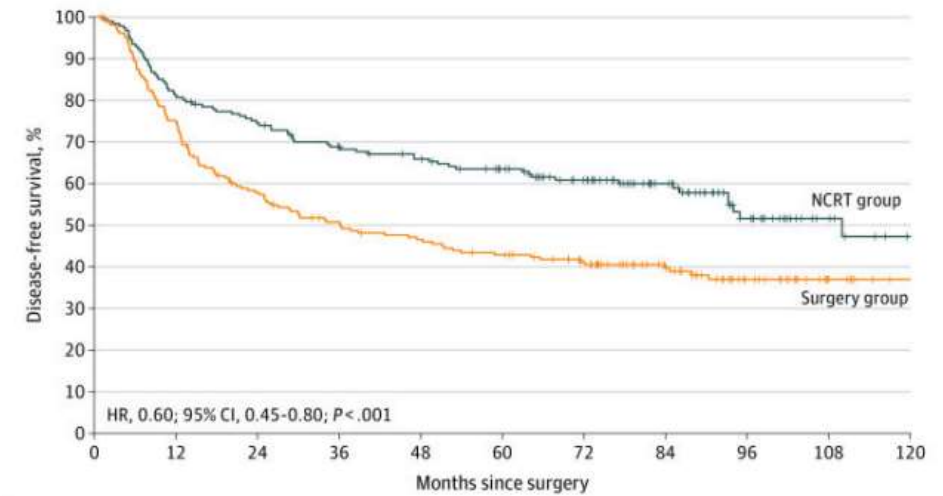
NEOCRTEC-Update

Median follow-up time of all surviving patients was **53.5 months (IQR, 18.2-87.4 months)**.



No. at risk	0	12	24	36	48	60	72	84	96	108	120
NCRT group	224	197	159	138	129	118	102	73	42	19	10
Surgery group	227	193	154	122	108	99	78	54	33	15	6

Absolute OS benefit at 5 years was 10.8%



No. at risk	0	12	24	36	48	60	72	84	96	108	120
NCRT group	182	154	137	117	123	114	85	64	37	16	8
Surgery group	207	154	117	98	89	81	68	48	28	13	6

DFS benefit at 5 years was 20.6%



NEXT trial-JCOG 1109

Triplet chemotherapy vs Doublet vs NEOCF RT

Triplet improved survival

Similar rates of survival with Doublet vs NEO CFRT



Take home message

Esophageal cancer is common in India especially SCC.

Radiation plays an important role in treatment- Neoadjuvant Definitive and palliative.

Management paradigm is evolving and multidisciplinary approach is vital.



Thank You!