CANCER DE L'OESOPHAGE

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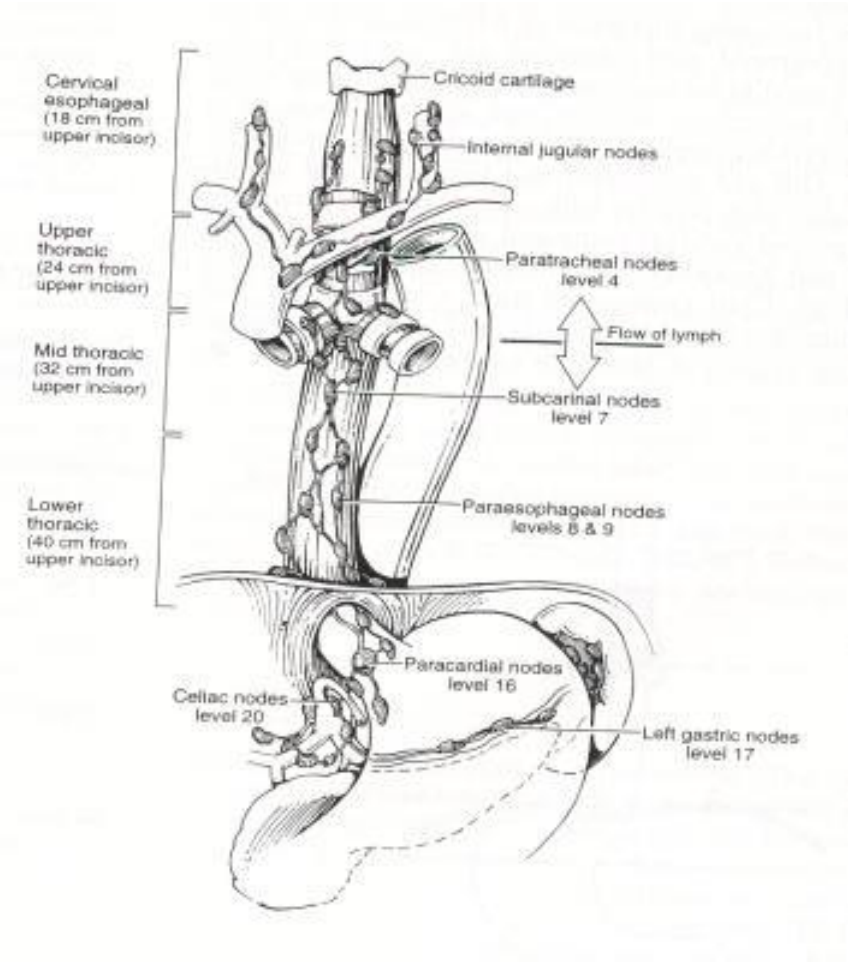
GENOLIER
Swiss Radio-Oncology Network

Introduction



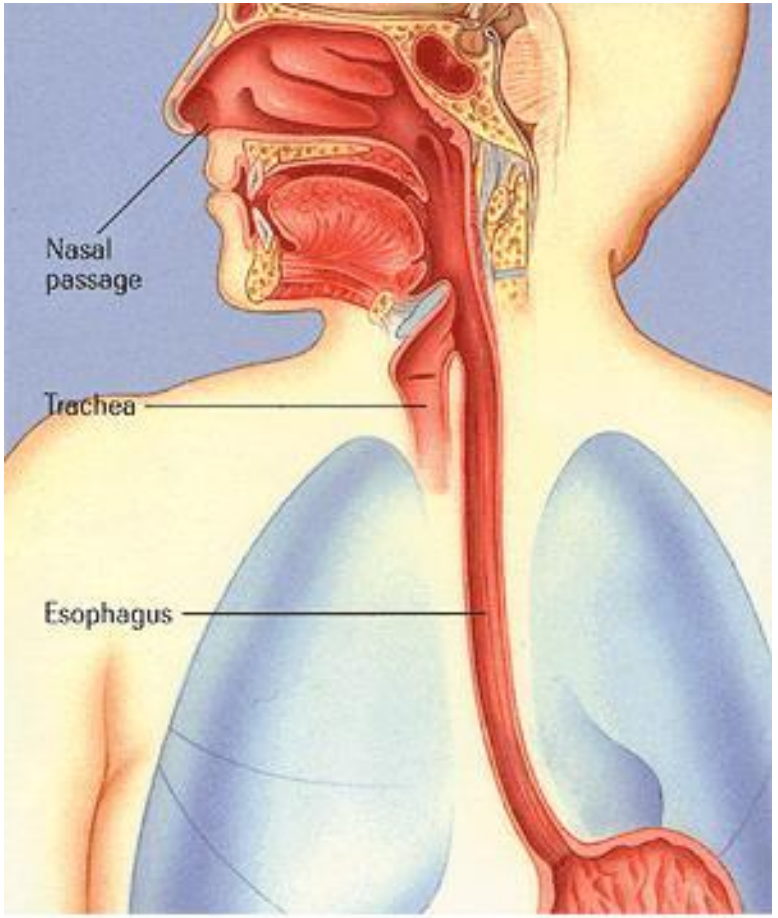


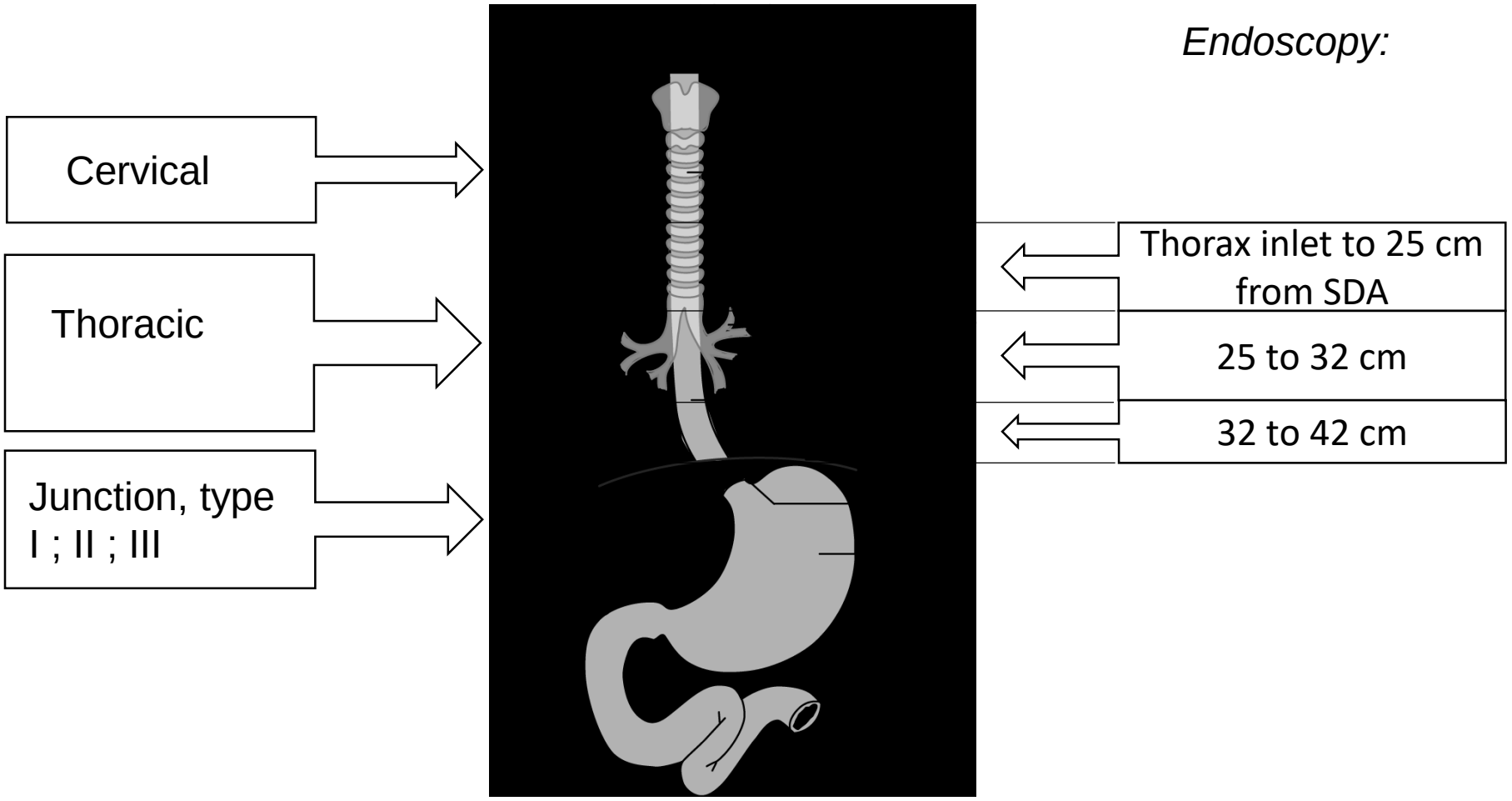
Image made available by a generous grant from Bristol-Myers Squibb

DEFINITION / ANATOMIE

Cancer pouvant affecter toute portion de l'œsophage:
-1/3 sup
-1/3 moy
-1/3 inf (jonction oeso-gastrique)

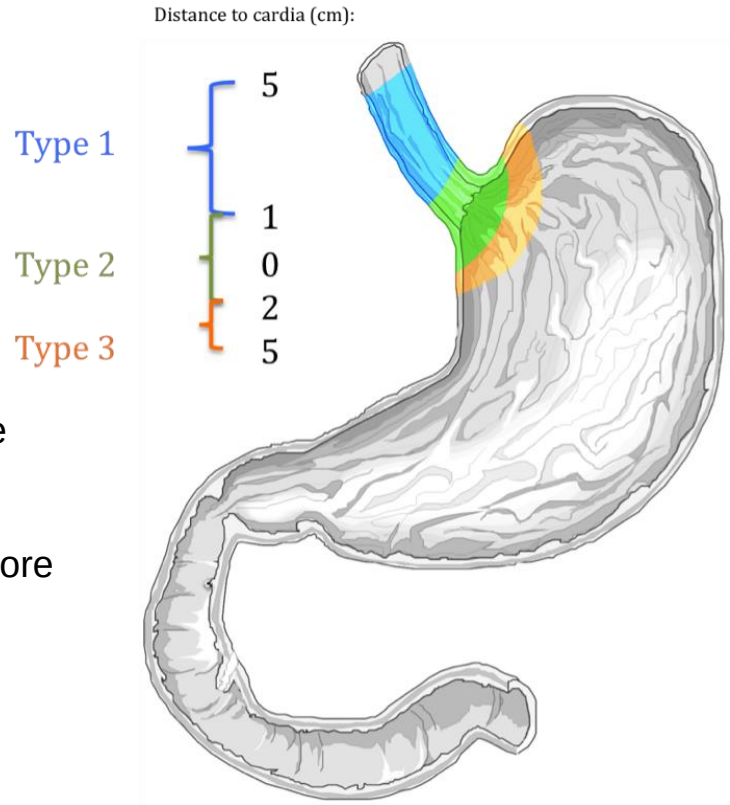
Evolution dépend de la localisation mais en général très mauvais pronostic.

Sub-site Anatomy Oesophagus



Gastroesophageal junction

Based on the anatomic location of the tumour centre three subtypes can be defined :



Type I tumours have their tumour centres more than 1 cm above the anatomical gastroesophageal junction.

Type II tumours are the true carcinomas of the cardia and have their tumour centres located within 1 cm oral and 2 cm aboral of the anatomical gastroesophageal junction.

Type III tumours have their tumour centre more than 2 cm but not more than 5 cm below the anatomical gastroesophageal junction.

Etiologie

- **Rôle de l'alcool, du tabac / Calvados.**
- **Probablement association avec mauvaise alimentation.**
- **Syndrome de Plummer-Vinson (déficiences multiples).**
- **Brûlures caustiques.**
- **Géographie : Région Caspienne ? Sols alcalins.**

EPIDEMIOLOGIE :

- **3 – 12 / 100’000/an (F/H)**

PATHOLOGIE :

Fréquents : **Ca épidermoïde : 60%**

Adénocarcinome (1/3 inférieur)

Rares : **Sarcomes**

Lymphomes

CLINIQUE

- Dysphagie, perte de poids (> 90 %)

- Odynophagie, toux, hématémèse

MODE D'EXTENSION

Locale :

Absence de barrière naturelle – pas de séreuse

- **Réseau lymphatique dense**

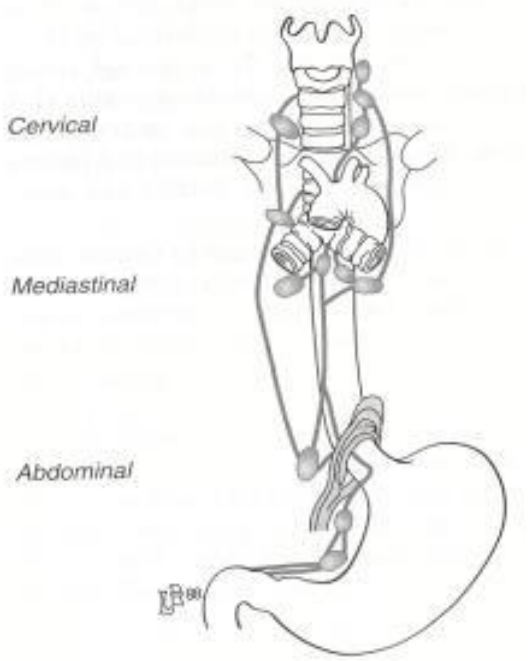
- **Extension axiale (« skip tumors »)**

- **Extension radiale (médiastin – fistules oeso-trachéales)**

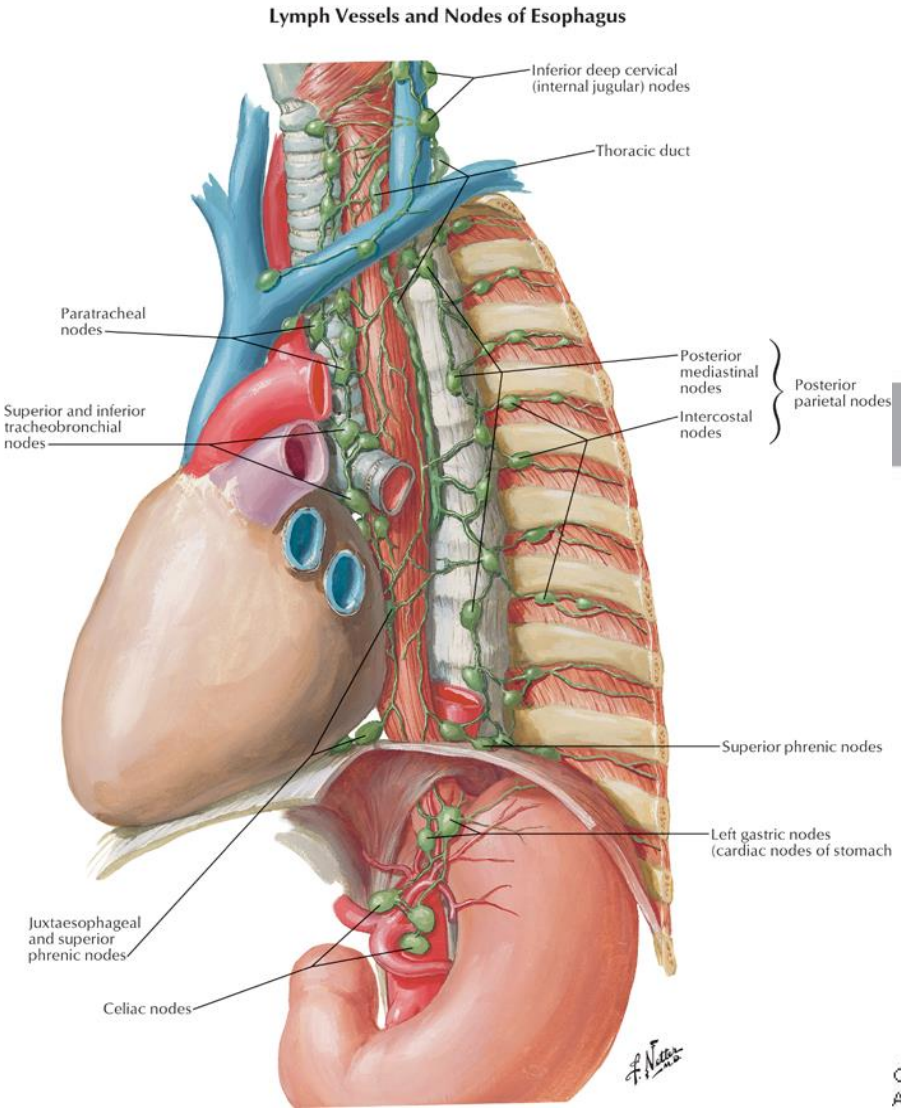
MODE D'EXTENSION

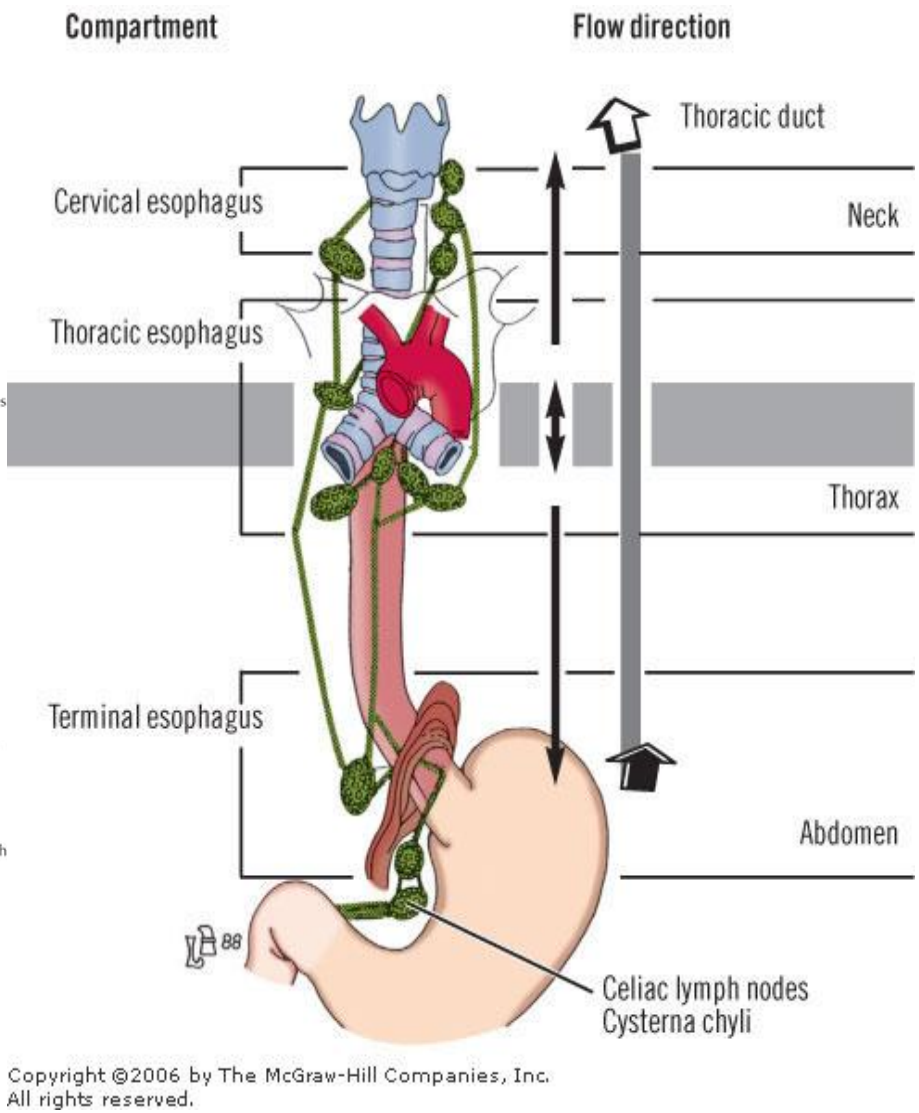
Régionale (ganglions) :

Fréquente, dépend de la localisation

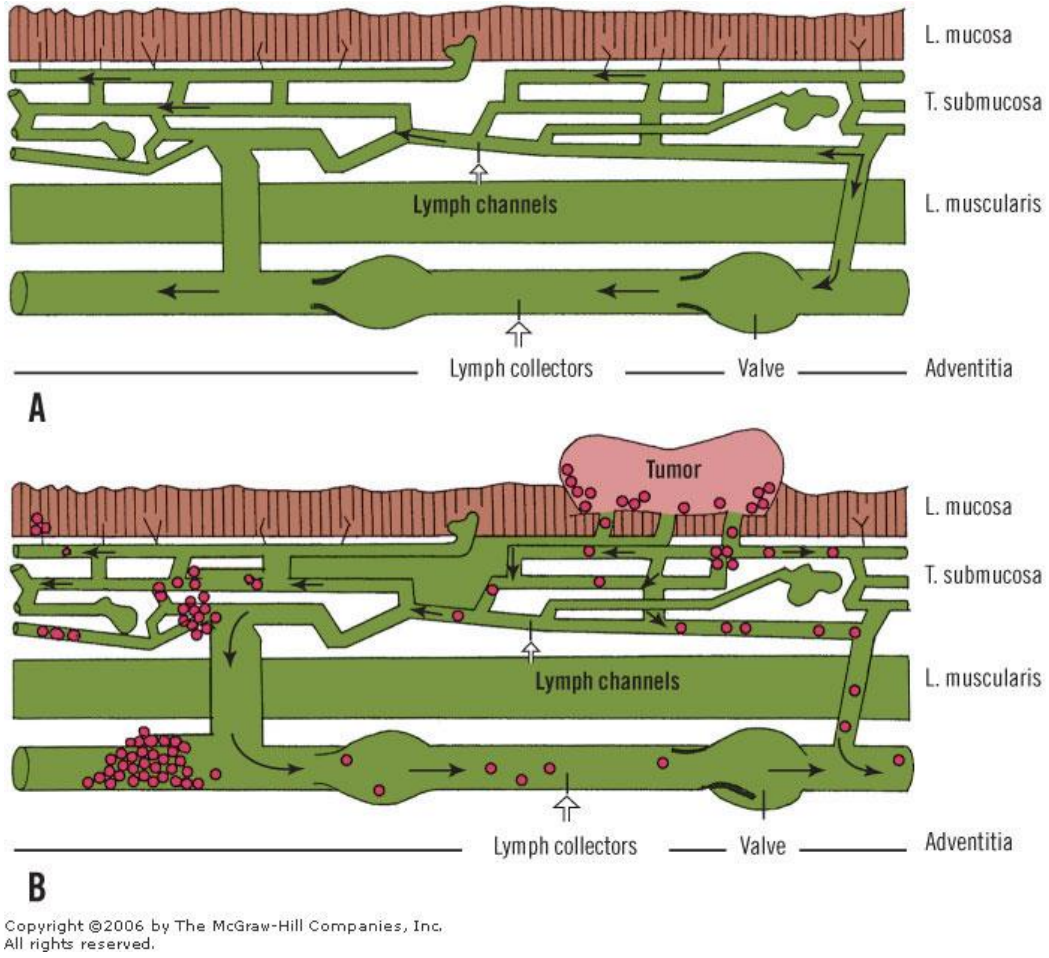


Lymphatic drainage





Lymphatic drainage (2)

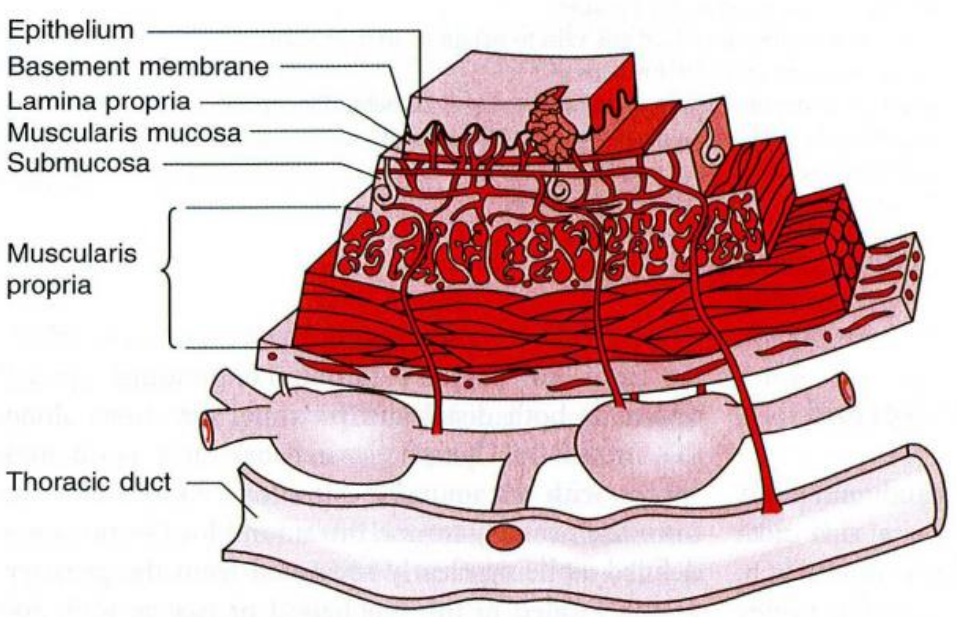


Regional lymph node involvement

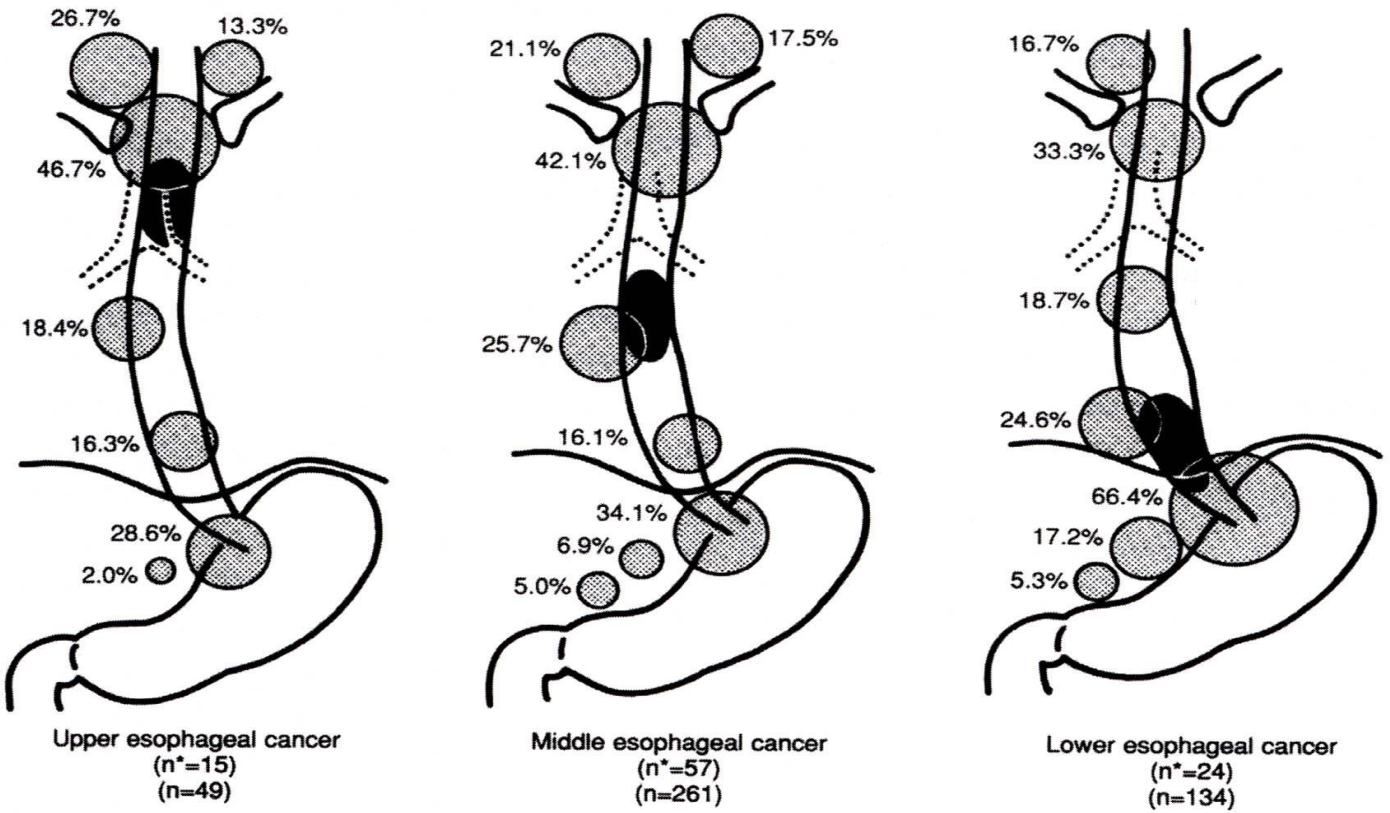
Distant lymph node metastasis:

'Skip metastasis'

- Tis 0%
- T1b 31-56%
- T2 58-78%
- T3 83-100%



A COMPLEX LYMPHATIC NETWORK



MODE D'EXTENSION

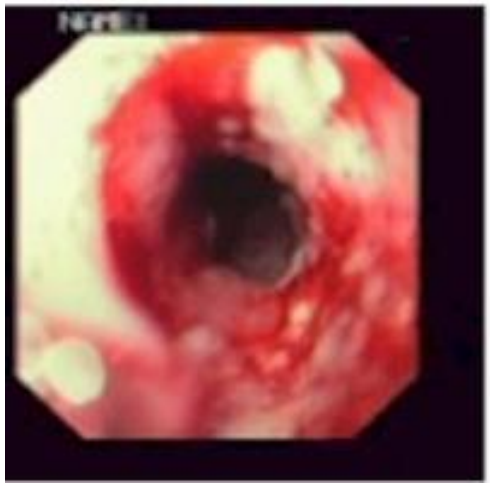
Hématogène :

Localisations métastatiques fréquentes :

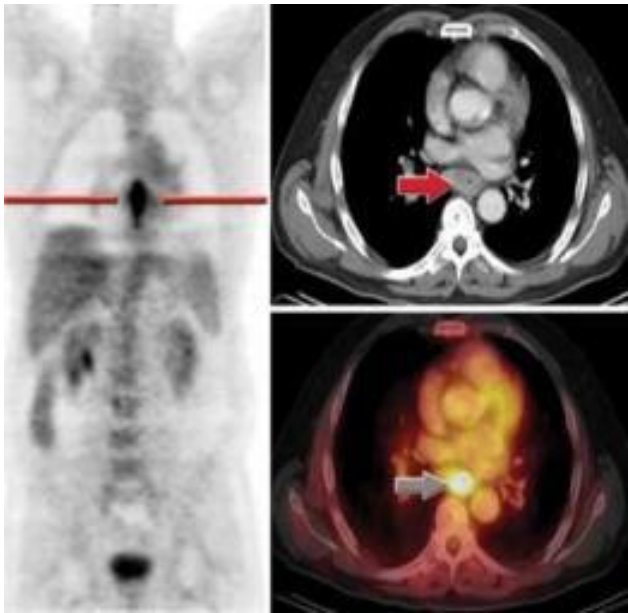
poumon / plèvres

foie / os

BILAN - INVESTIGATIONS



Anamnèse
Status, ex. ORL
RX thorax
Transit oesophagien
Endoscopie (oeso-gastroscopie)
US endo-oesophagien
CT thoraco-abdominal
PET-CT



PET - CT

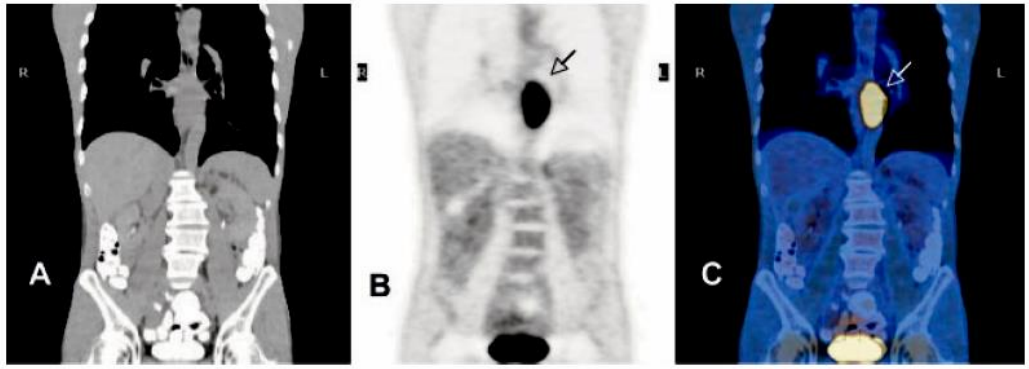


FIGURE 1. Integrated PET/CT of a patient showing NPA = 1 in the primary (arrow). (A) CT scan; (B) PET scan; (C) integrated image.

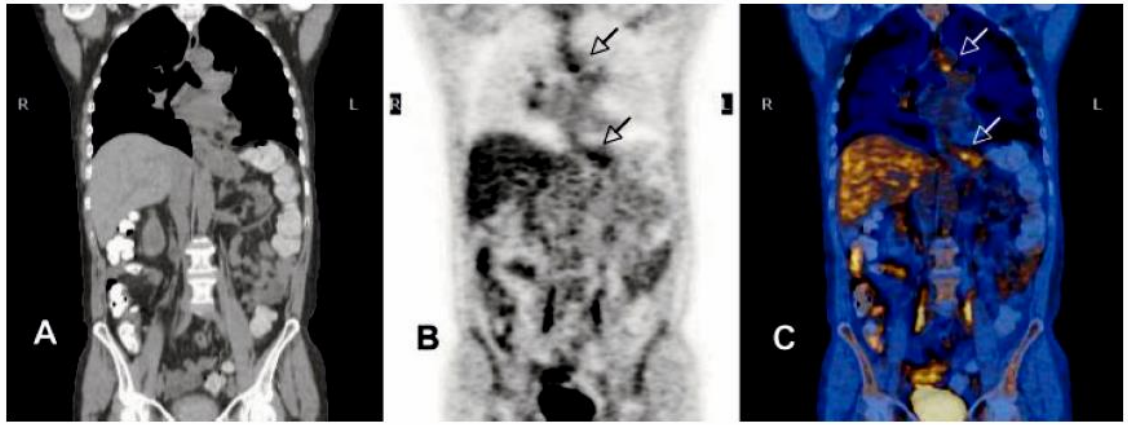


FIGURE 2. Integrated PET/CT of a patient showing NPA = 2 in the primary and mediastinum (arrows). (A) CT scan; (B) PET scan; (C) integrated image.

Hong D. Cancer 2005;104:1620-6

Resection versus PET scan

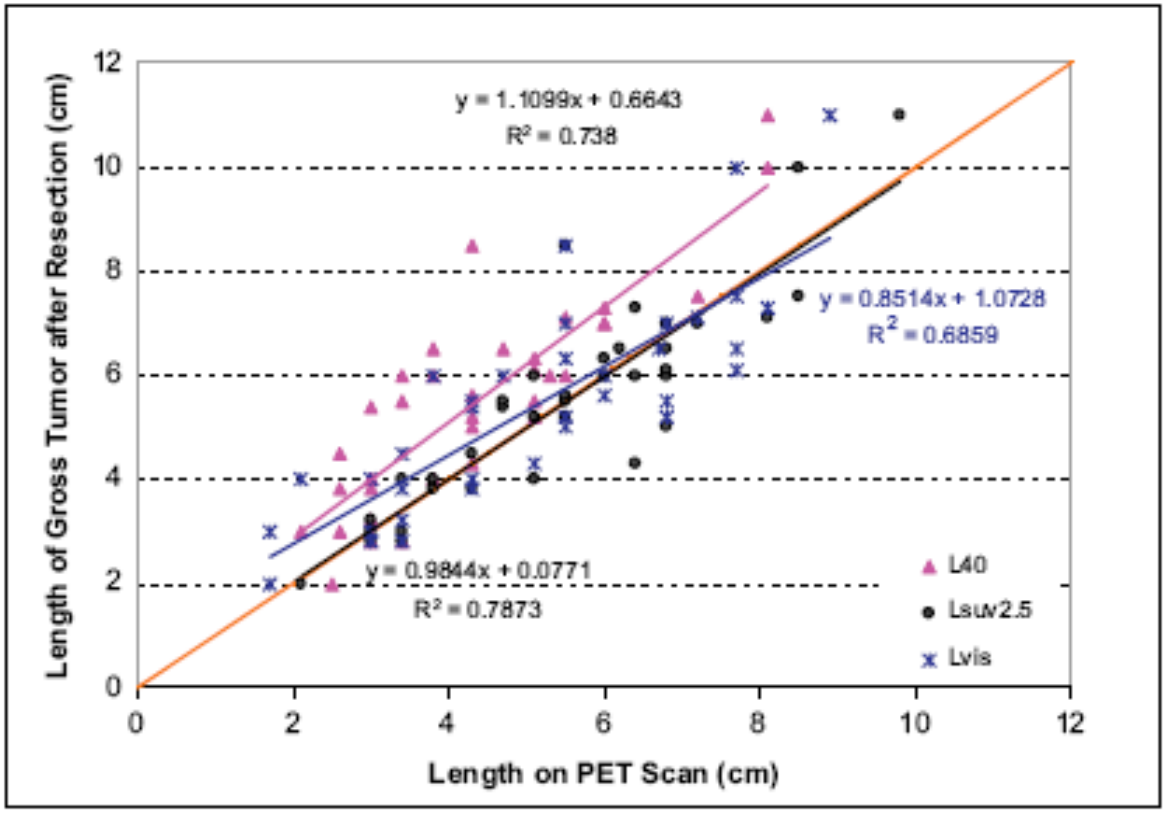


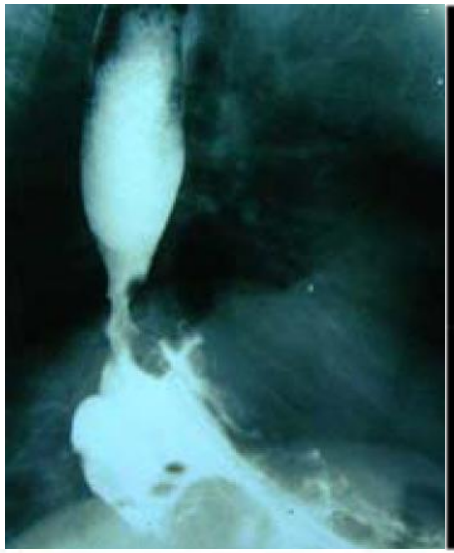
Fig. 2. Image–pathology correlations.

Xiaojun Zhong IJROBP 2009;73:136-141

CLASSIFICATION TNM SIMPLIFIEE

Tis:	cancer in situ
T1:	atteinte sous muqueuse
T2:	atteinte musculature
T3:	atteinte adventice
T4:	atteinte organes adjacents
N0:	pas de gg
N1:	gg atteints
M0:	absence de métastases
M1:	présence de métastases

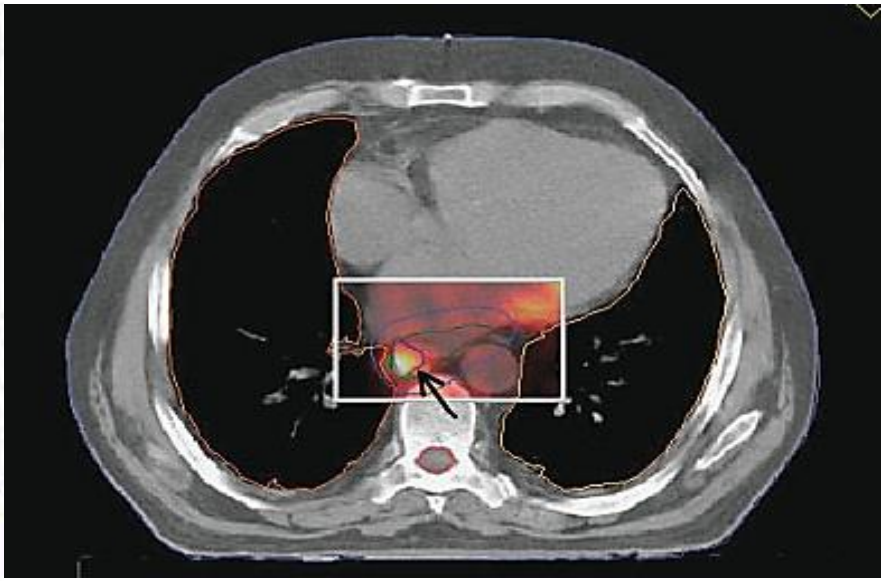
GTV



- Barium swallow
- CT-Scan
- Endoscopy
- EUS
- PET - CT

Circumferential esophageal cancer

EUS showing the cancer invading the inner layers of the esophagus



CTV

Generally applied margins for esophageal cancer

ICRU 50 Definitions: GTV plus areas at risk of microscopic extension

CTV: Gross tumor (GTV)
+ 3 to 5 cm margin craniocaudal
+ extension to involved nodes

+1 to 2 cm circumferential margin

CTV to PTV: 1 cm

i.e.: field border 5 cm craniocaudal from GTV

LNM distribution

TABLE 3. Rate of LNM to Different Regions According to the Location of the Primary Tumor

Location	Cervical	Um	Mm	Lm	Abdominal
Ut	12/82 (14.6)	24/82 (29.3)	7/82 (8.5)	8/82 (9.8)	6/82 (7.3)
Mt	55/1266 (4.3)	63/1266 (5.0)	417/1266 (32.9)	32/1266 (2.5)	189/1266 (14.9)
Lt	11/545 (2.0)	12/545 (2.2)	84/545 (15.4)	208/545 (38.1)	150/545 (27.5)
Total	78/1893 (4.1)	99/1893 (5.2)	508/1893 (26.8)	248/1893 (13.1)	345/1893 (18.2)

LNM, lymph node metastasis; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Um, upper mediastinal; Mm, middle mediastinal; Lm, lower mediastinal.

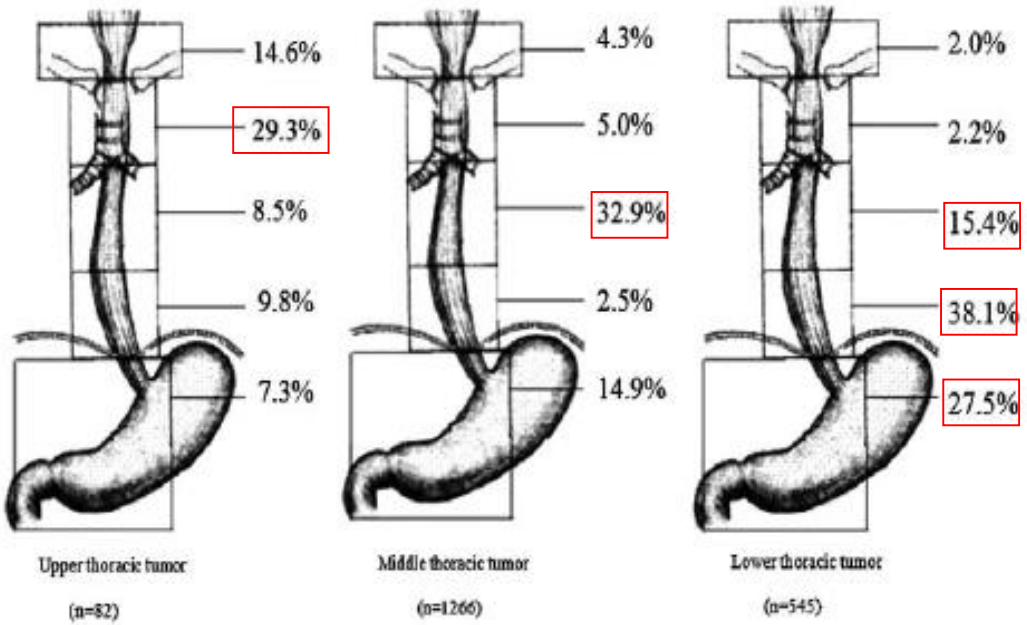


FIGURE 1. Rate of LNM in different regions according to the location of the primary tumor. LNM, lymph node metastasis.

J Thorac Oncol. 2013;8: 359-365

Control

- On surgical specimens: n= 34 SCC/32ADK

- **<u>Lateral (mean value) =</u>**
  - SCC : 10.5 ± 13.5 mm SUP et 10.6 ± 8.1 mm INF
  - ADK : 10.3 ± 7.2 mm SUP et 18.3 ± 16.3 mm INF

  - **→ 50mm = 100% in field**
  - **→ 30mm = 94% in field**

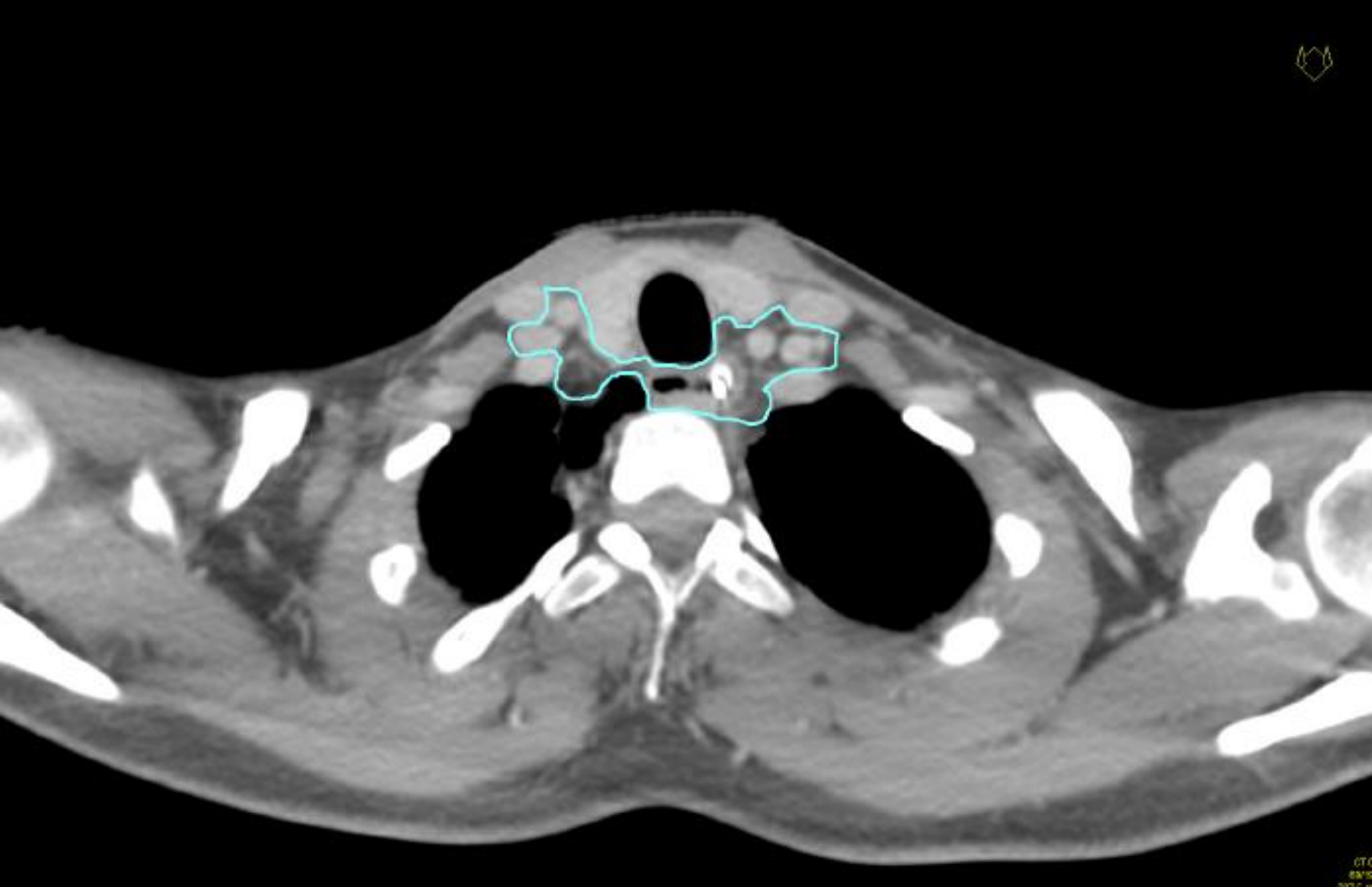
Gao S et al., IJROBP 2007

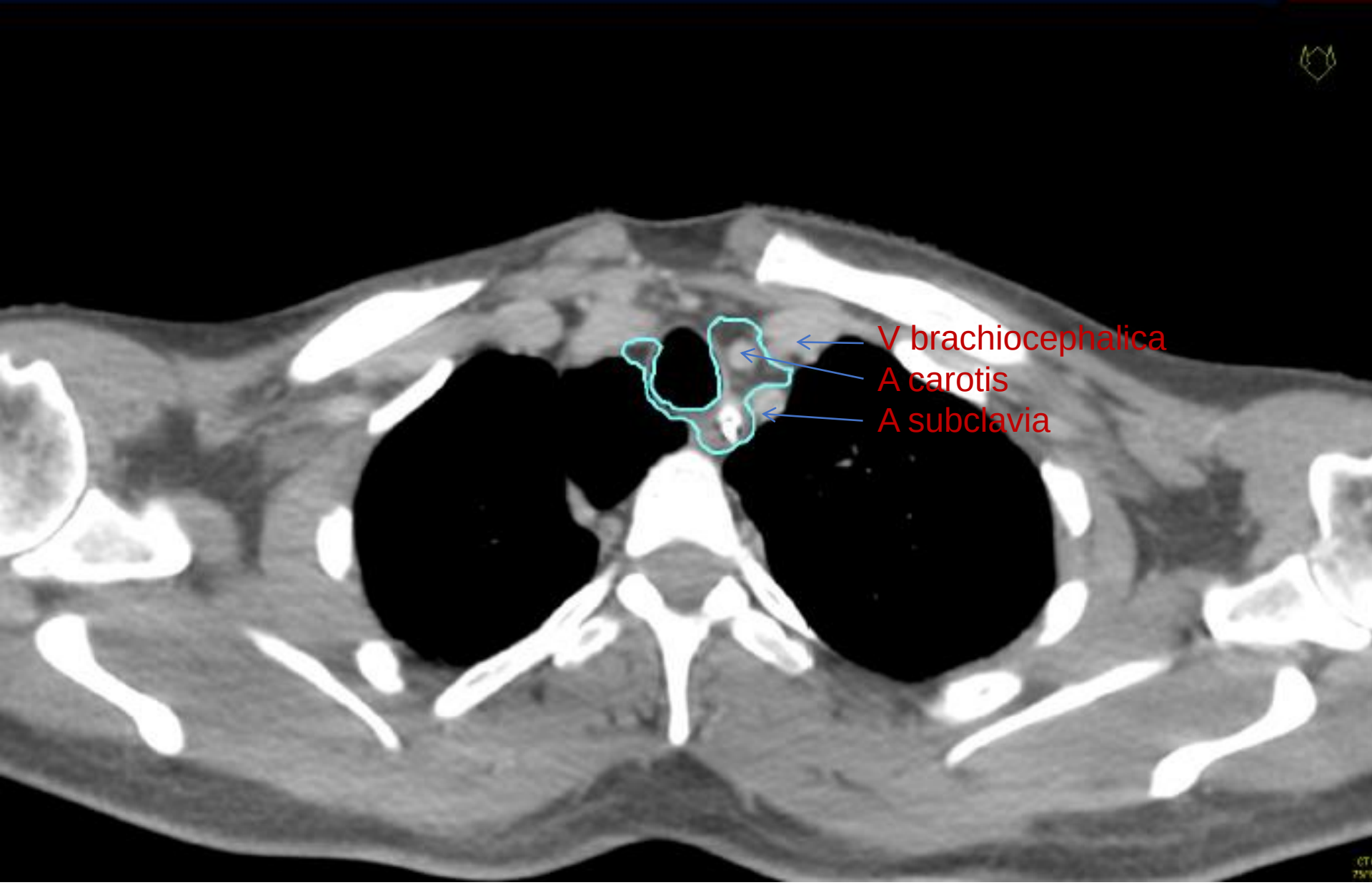
Elective CTV

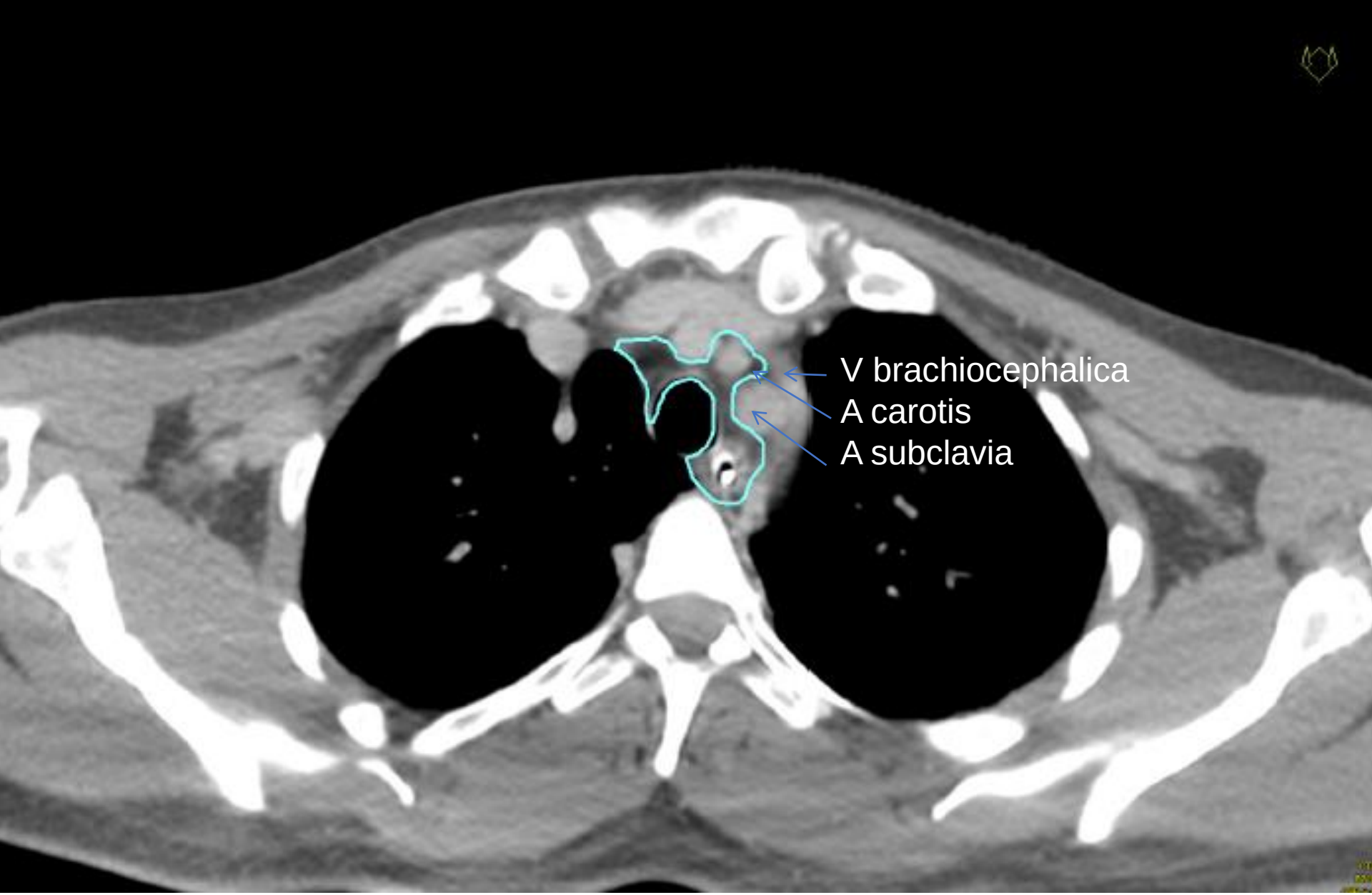
- ***For cervical tumors:***
- ➔ supraclavicular, para esophageal, pretracheal and a-p fenestra

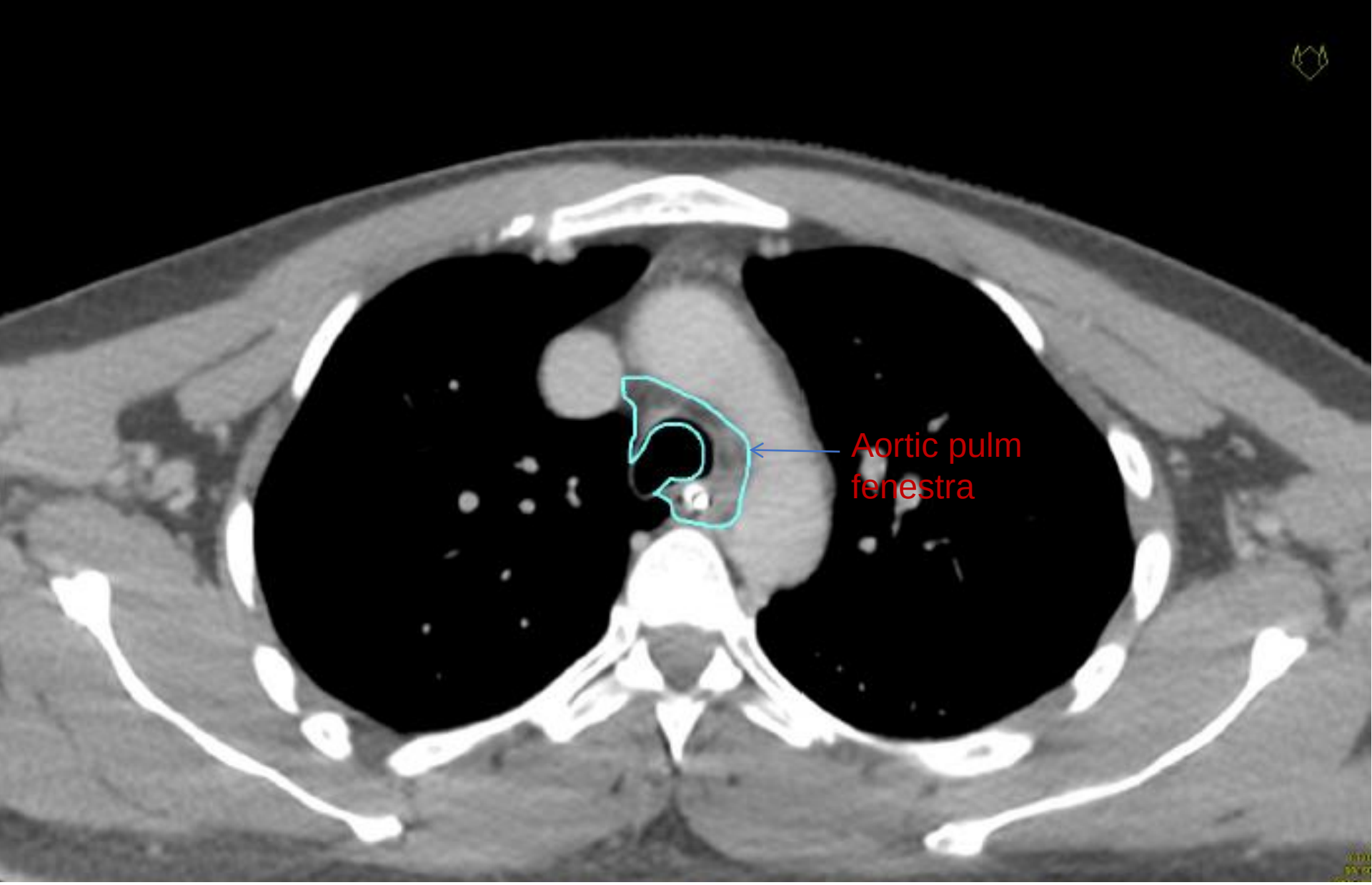
- ***For proximal tumors:***
- ➔ supraclavicular, para esophageal, pretracheal and a-p fenestra,(- pre and subcarinal)

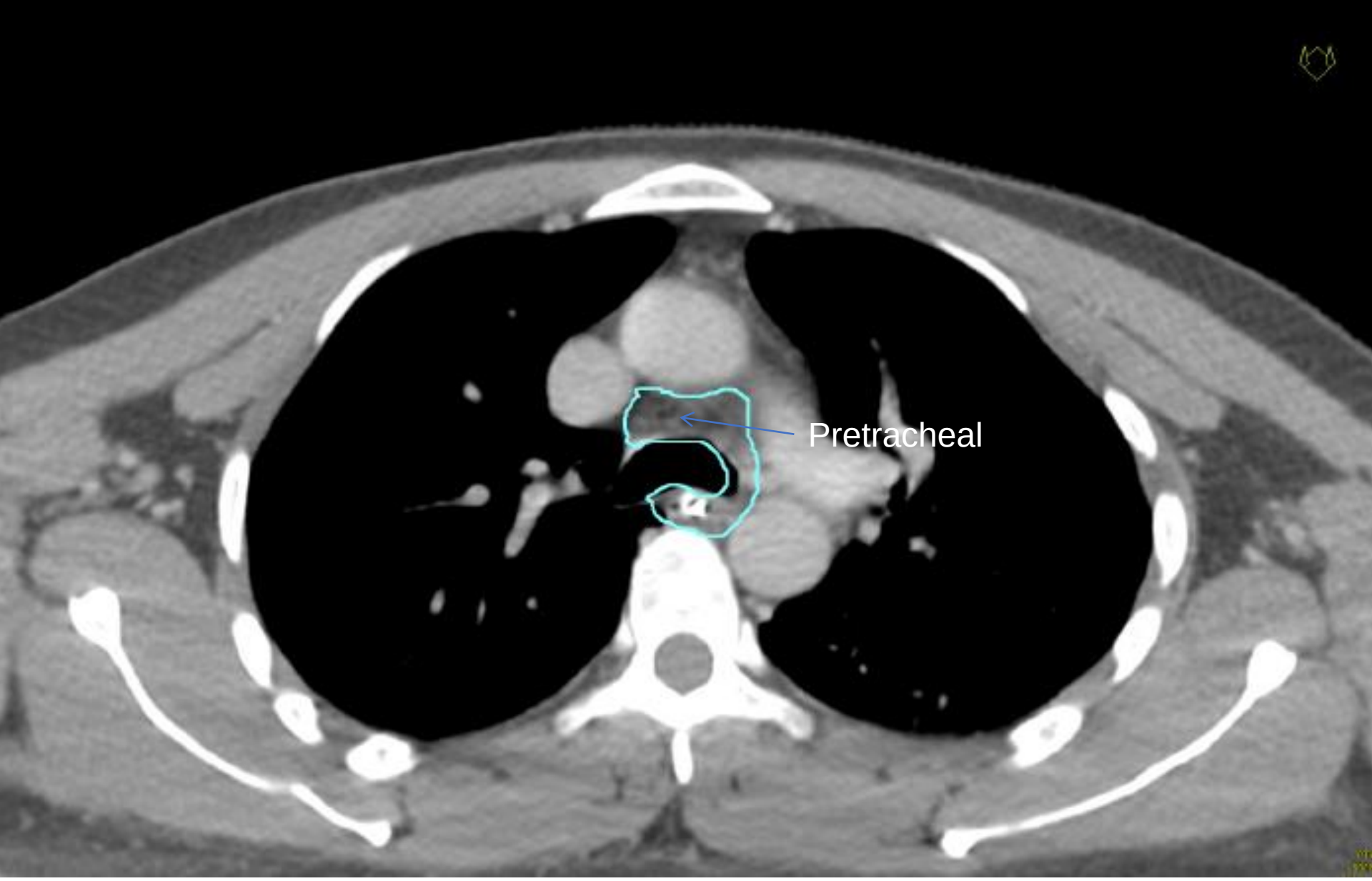
- ***For mid esophageal tumors:***
- ➔ para and pretracheal, a-p fenestra, pre and subcarinal and higher and lower para esophageal

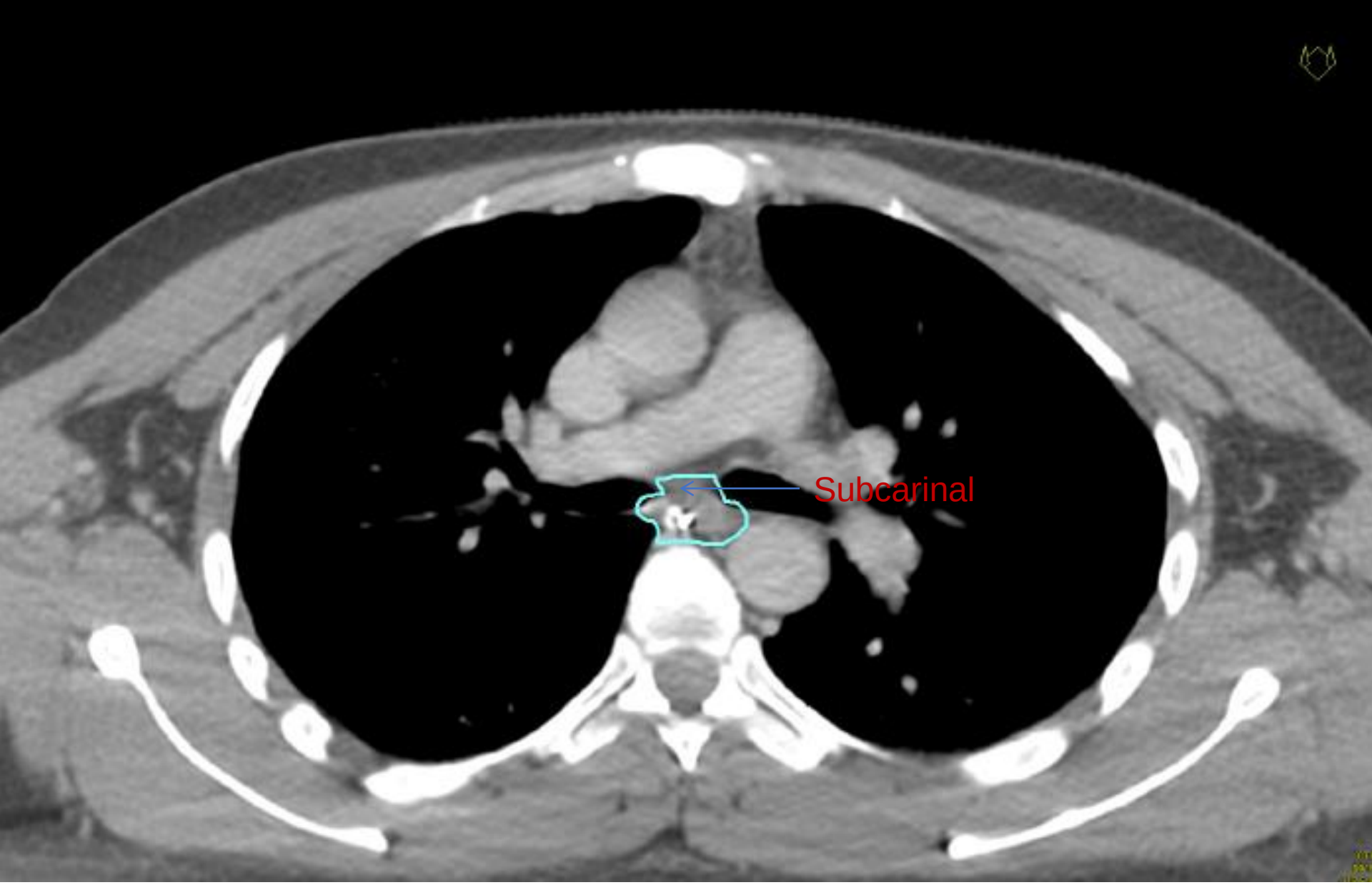


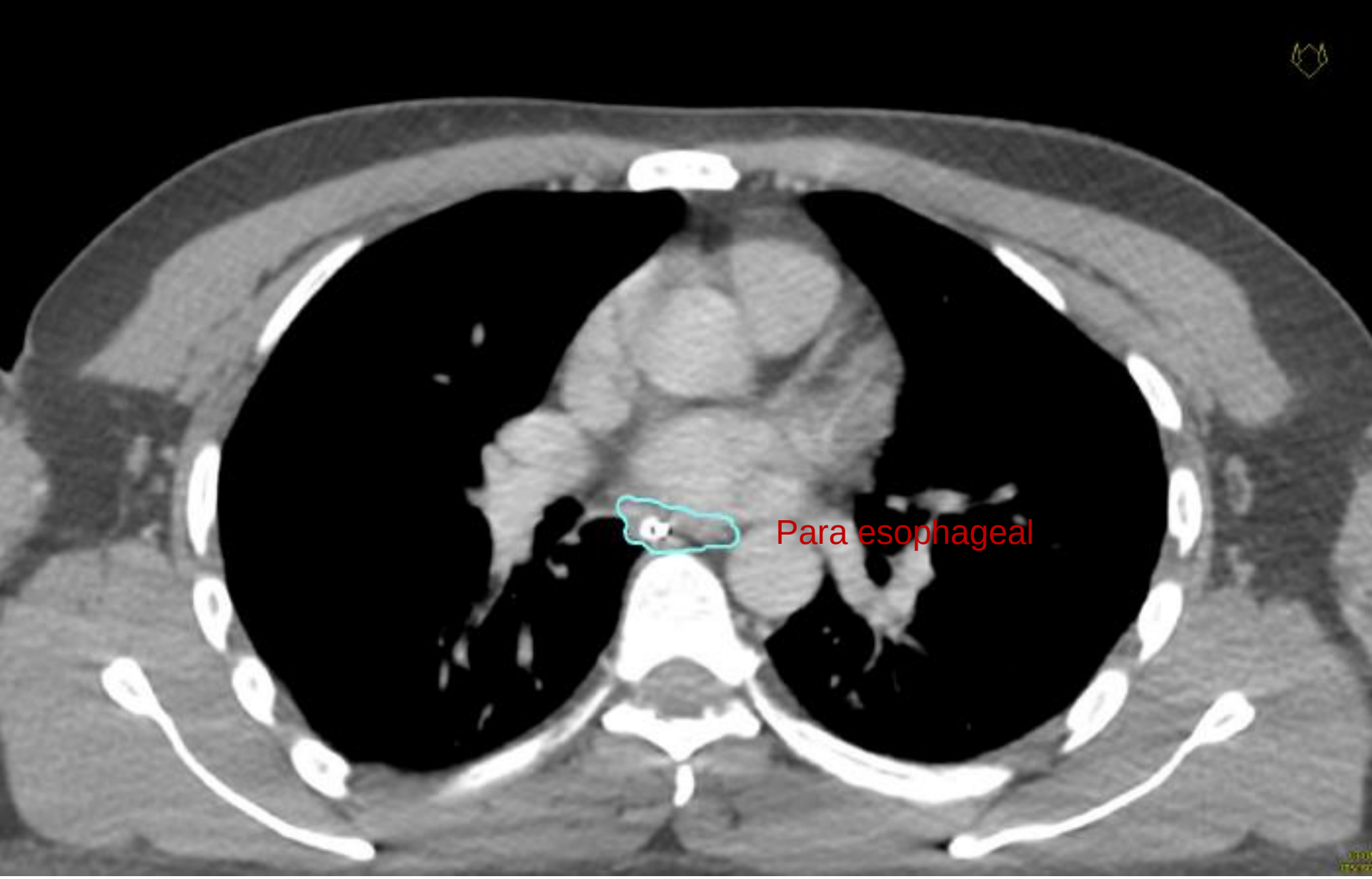

V brachiocephalica
A carotis
A subclavia

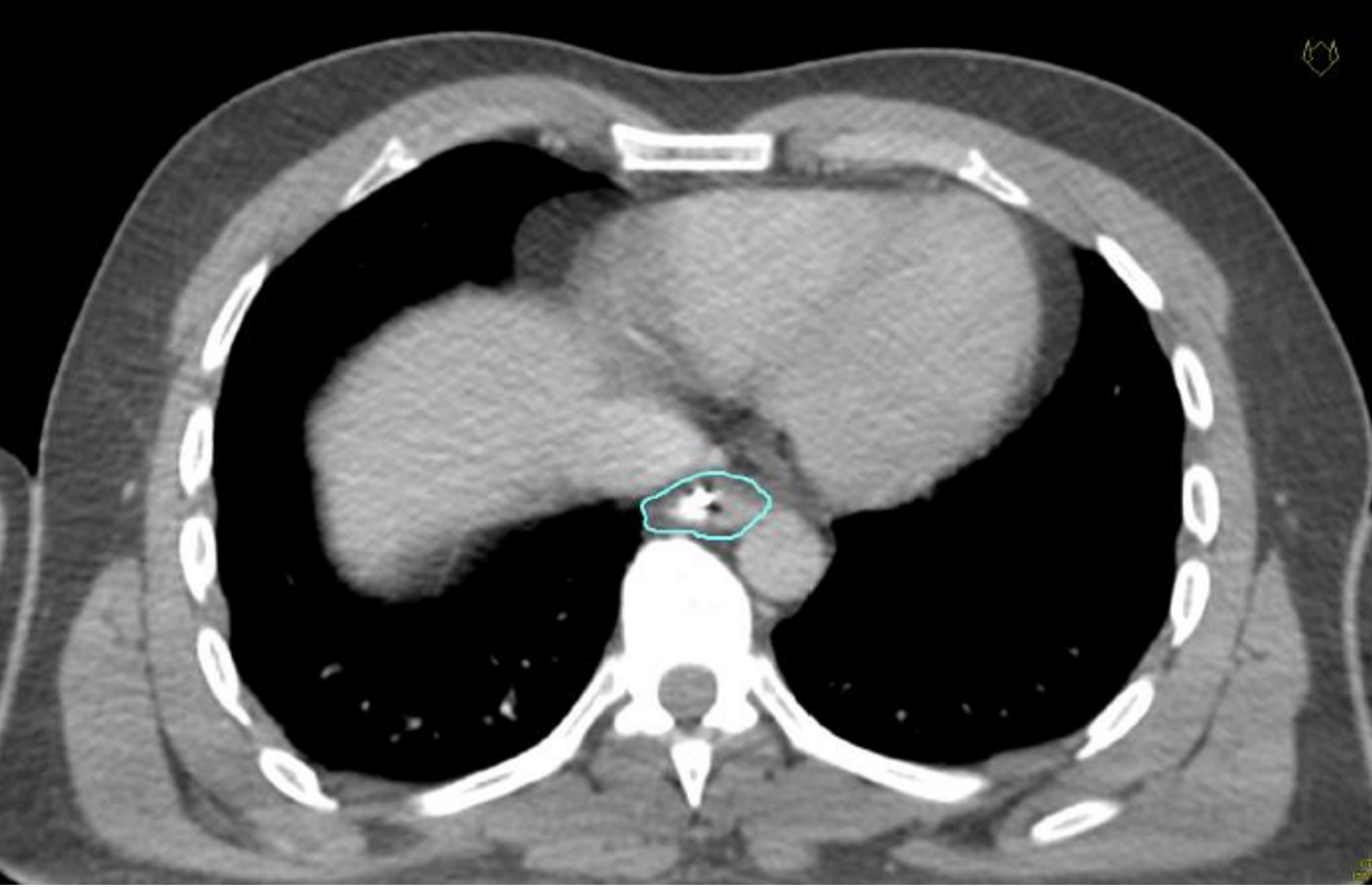

V brachiocephalica
A carotis
A subclavia


Aortic pulm
fenestra

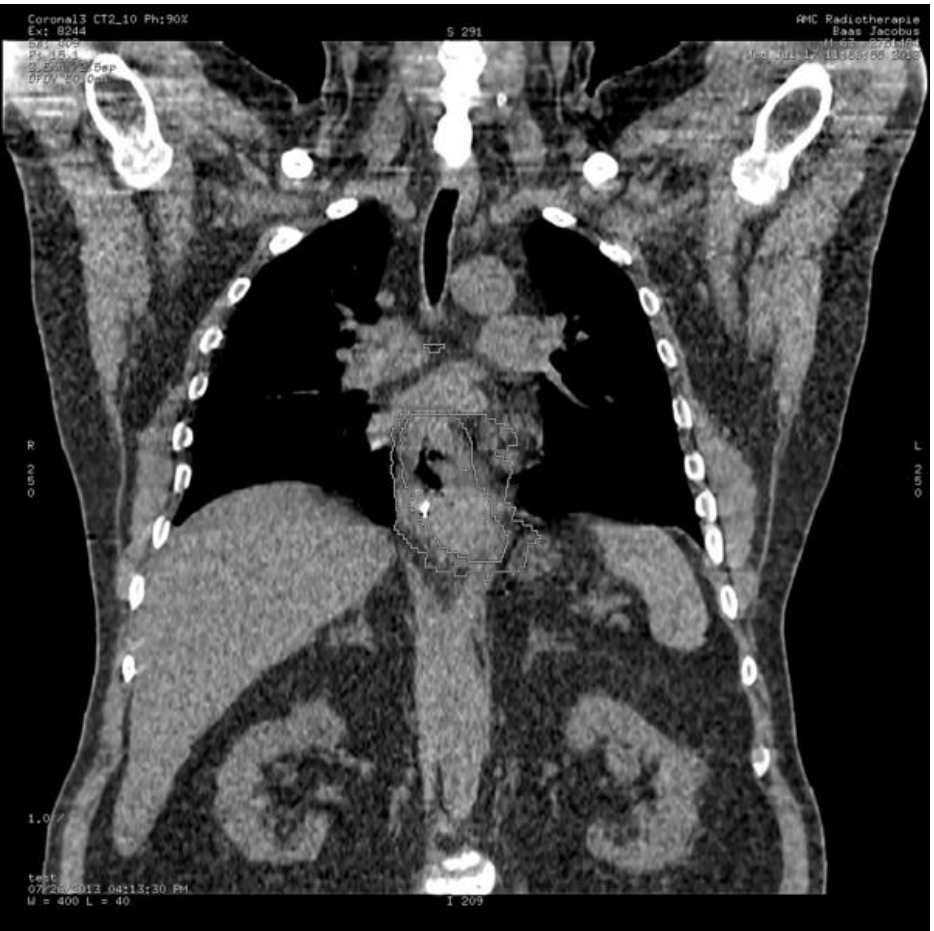

Pretracheal


Subcarinal


Para esophageal



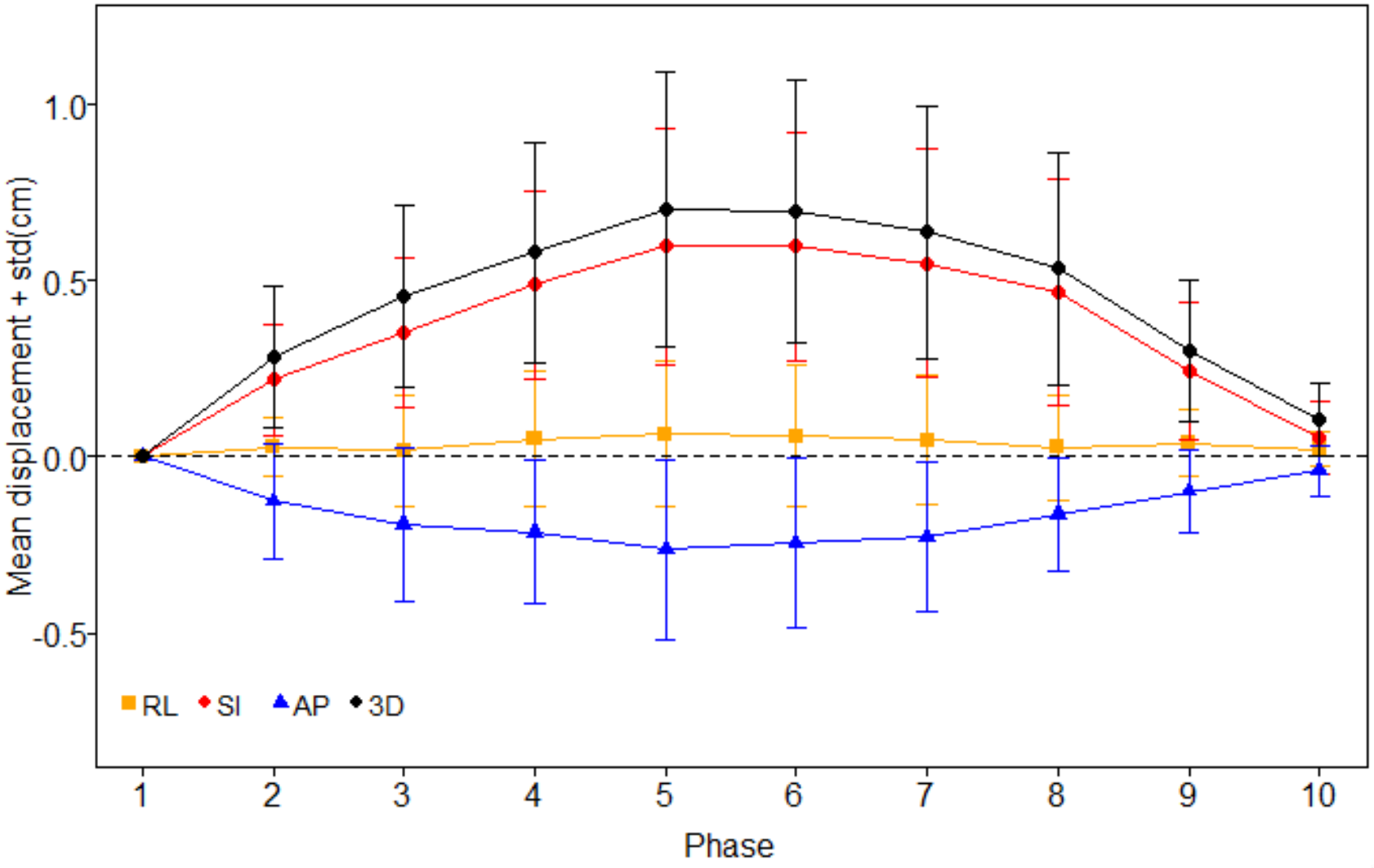
Mobility of oesophagus



Effect of breathing on oesophagus

	Thoracic part	Abdominal part
Yaremko 2008	8 mm	10 mm
Welch 1982	4 mm	6 mm
Dieleman 2007	7 mm	9 mm

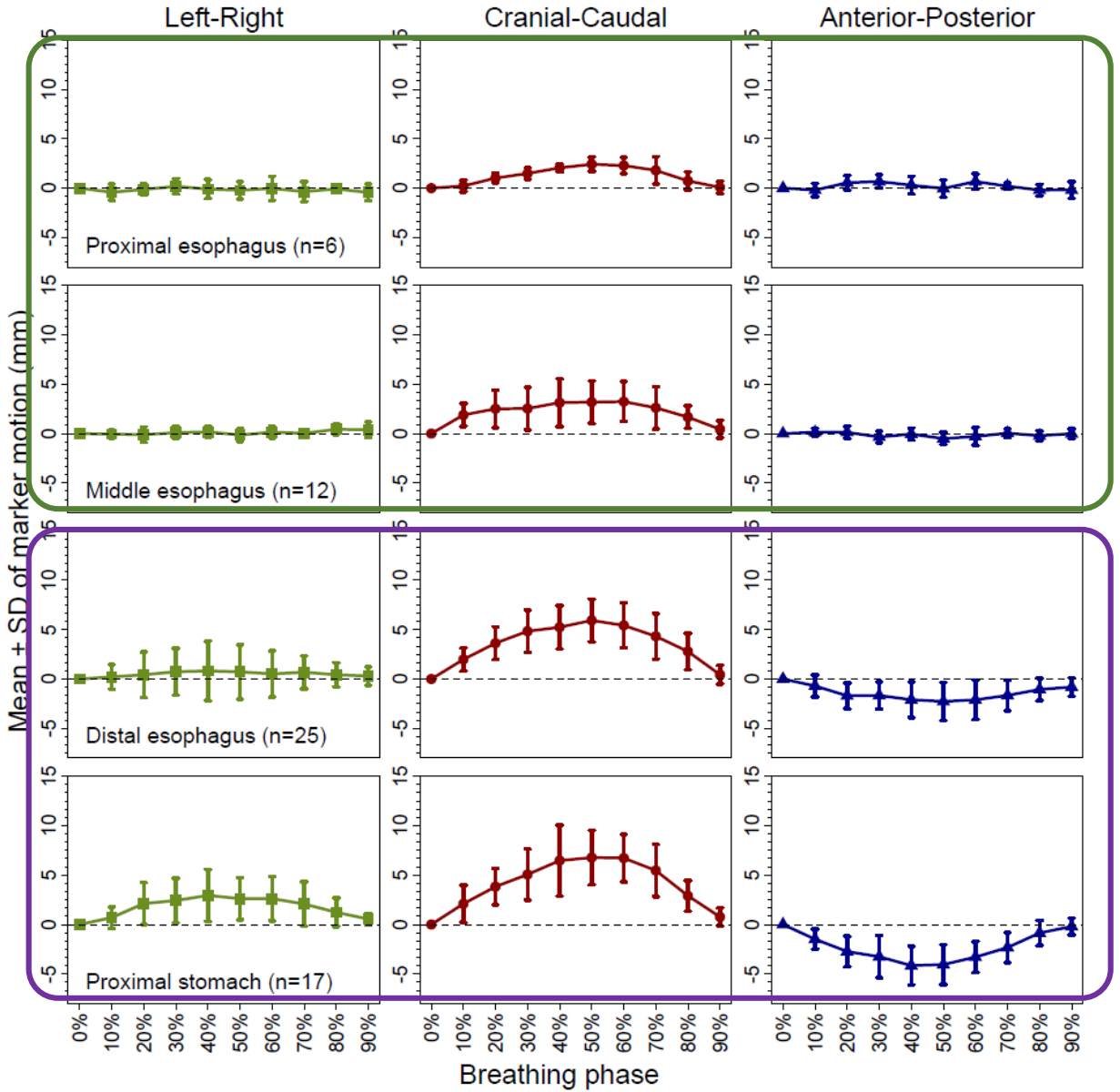
Relative marker displacement during breathing



Courtesy from Maarten C C M Hulshof

Motion in each phase

- CC > LR & AP
- Lower > Upper
- Exhalation
  - To left
  - To cranial
  - To posterior
- Induced by respiration



CTV-ITV margin proximal and mid- esophageal tumors

- APPA: 7-8 mm
- Lateral: 5-7 mm
- Craniocaudal: 10 mm

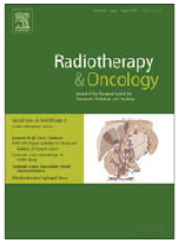
Target Volume definition oesogastric junction tumor

Radiotherapy and Oncology 92 (2009) 164–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger[a,b,*], Erich Gerber[c], Zvi Bernstein[d], Philippe Maingon[e], Karin Haustermans[f], Jean François Bosset[g], Akos Gulyban[a], Philip Poortmans[h], Laurence Collette[a], Abraham Kuten[d]

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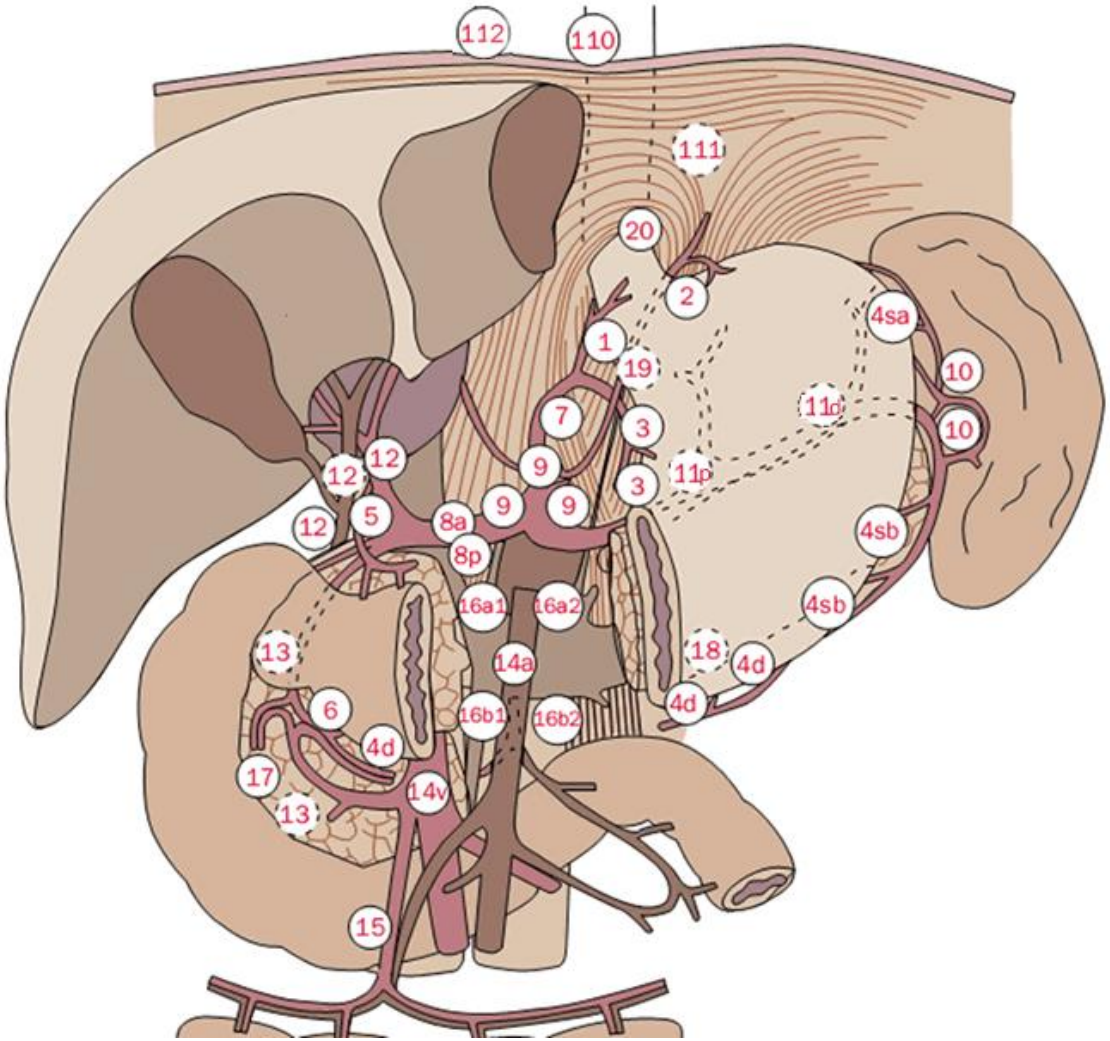
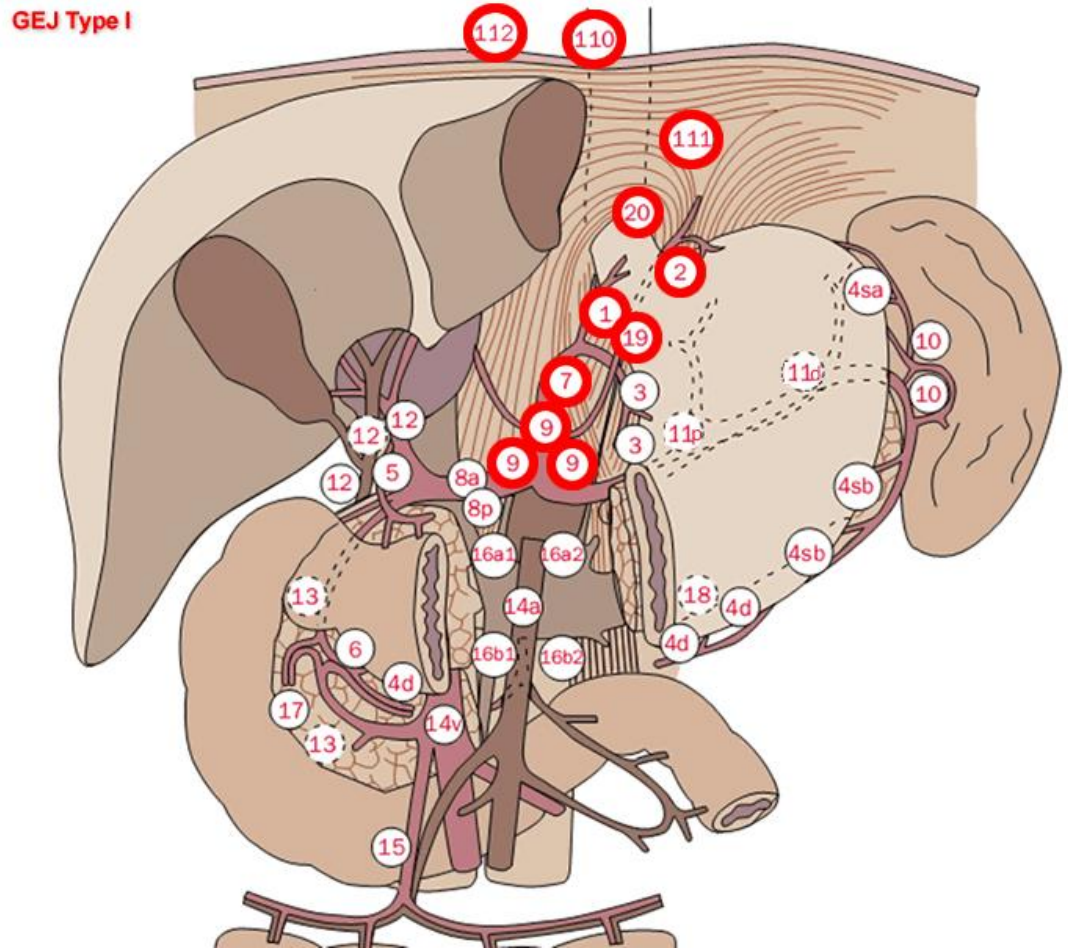
The classification of the lymph node stations of the stomach and the perigastric region according to the JGCA

No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN



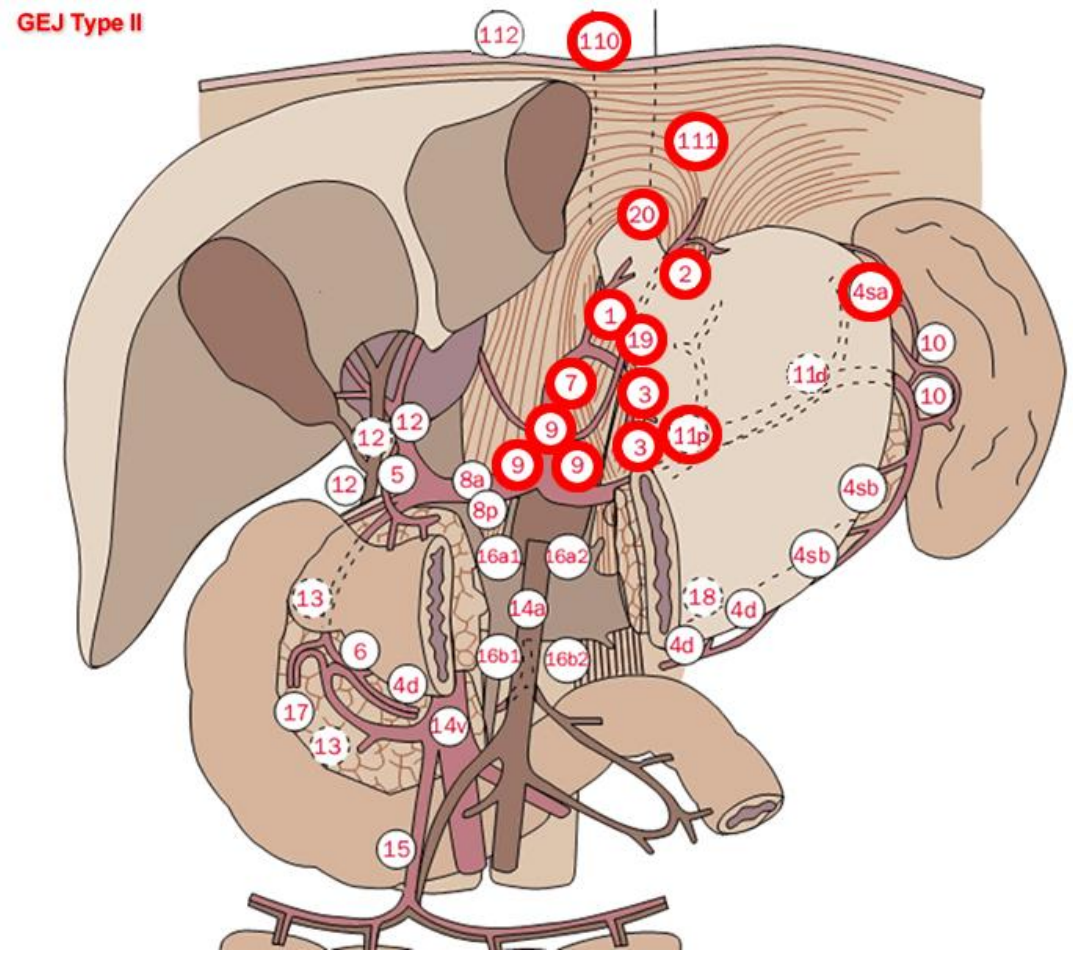
Lymph node stations of gastroesophageal junction tumors: Type I

1 Right paracardial LN
2 Left paracardial LN
7 LN along the left gastric artery
9 LN around the celiac artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN
112 Posterior mediastinal LN



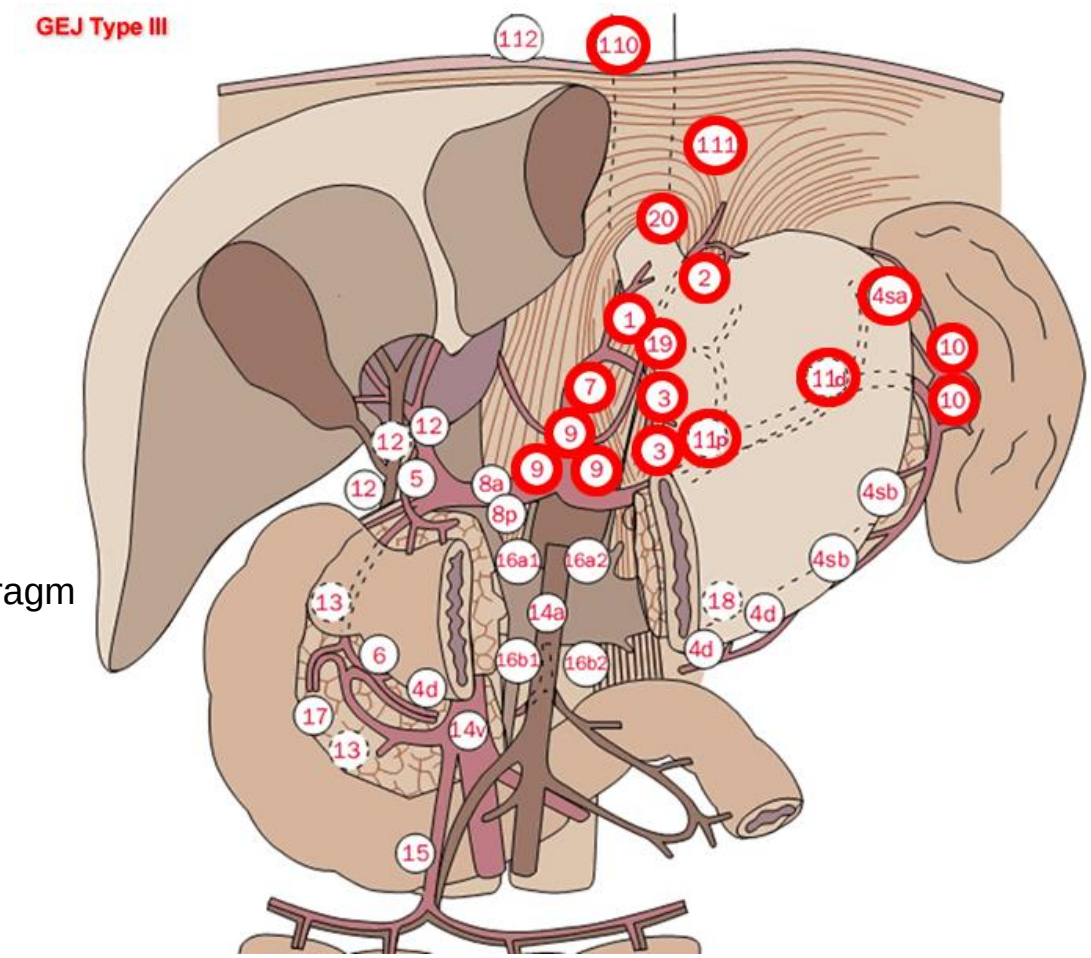
Lymph node stations of gastroesophageal junction tumors: Type II

1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
11p LN along the proximal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN



Lymph node stations of gastroesophageal junction tumors: Type III

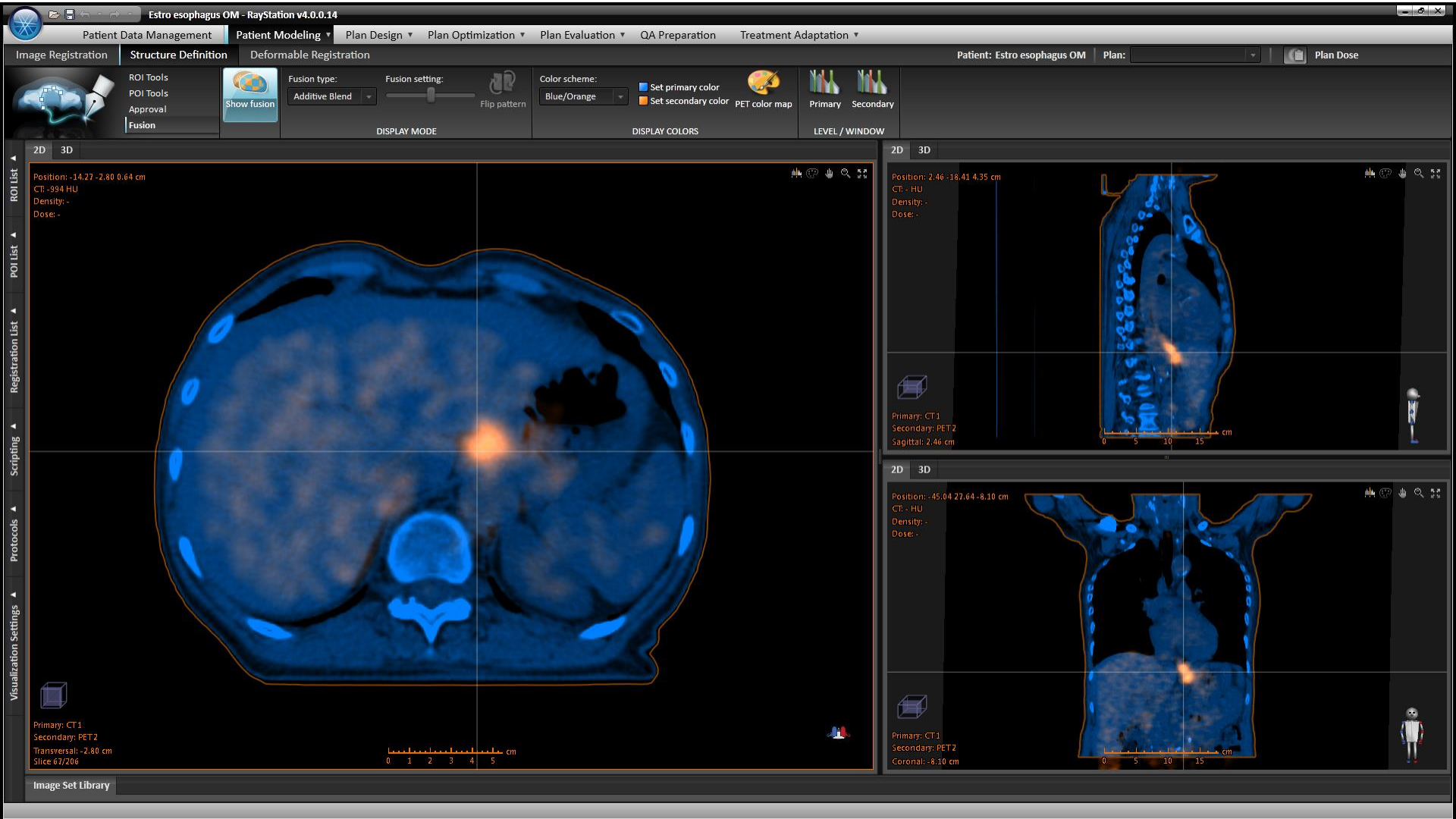
1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
10 LN at the splenic hilum
11p LN along the proximal splenic artery
11d LN along the distal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN



Clinical case

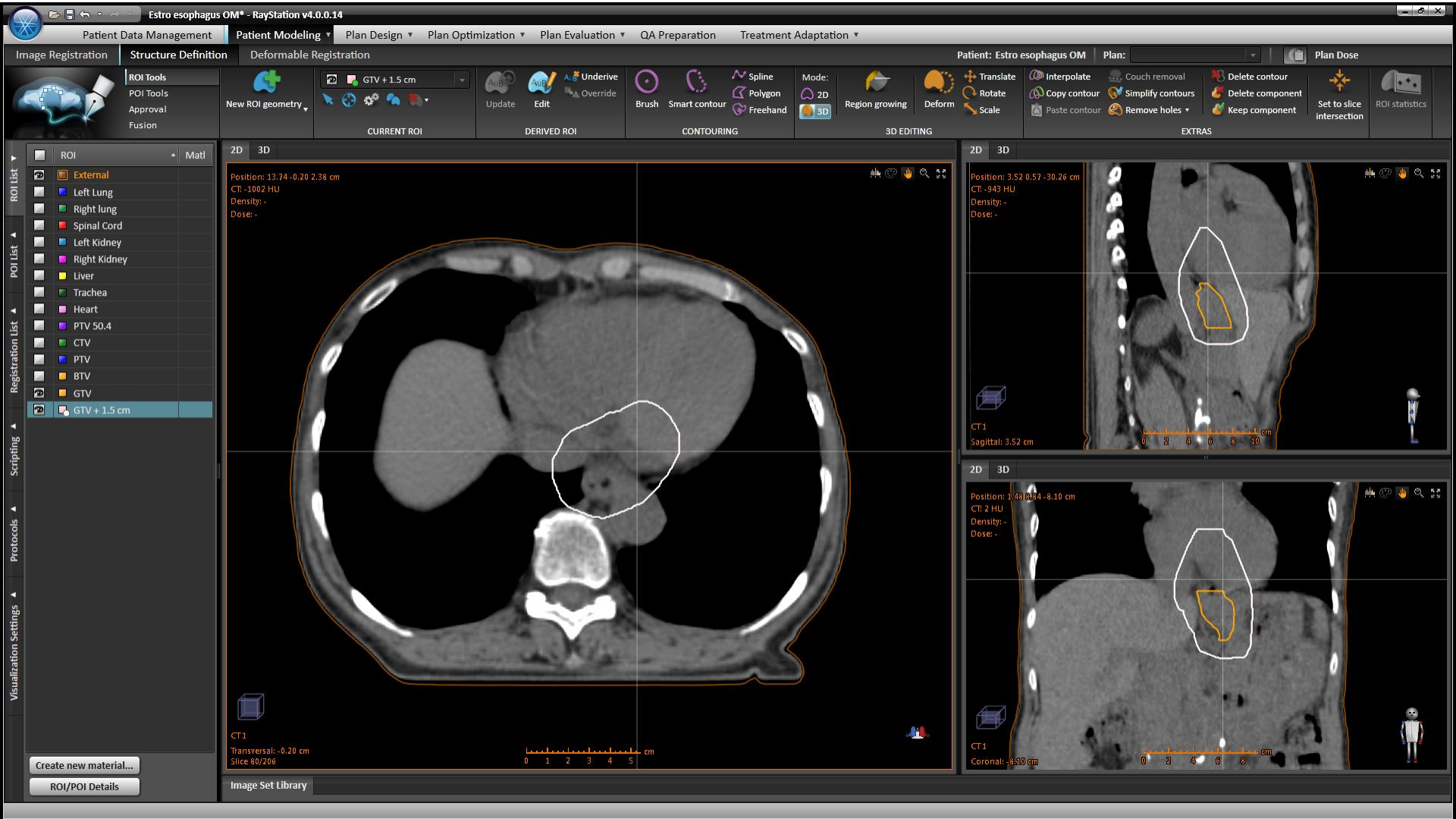
Clinical case: GTV?

BTV?

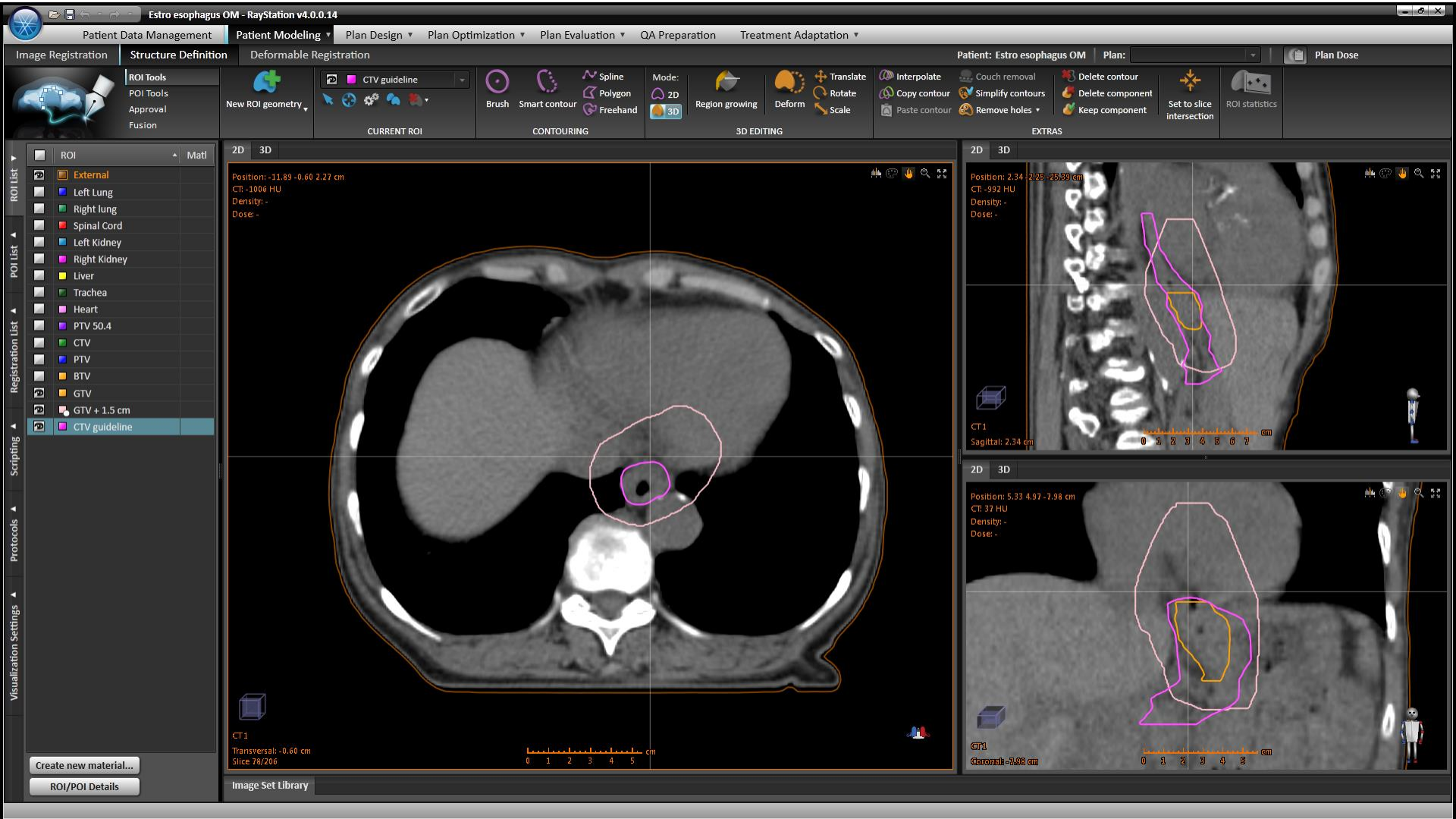

Estro esophagus OM - RayStation v4.0.0.14
Patient Data Management
Patient Modeling
Plan Design
Plan Optimization
Plan Evaluation
QA Preparation
Treatment Adaptation
Image Registration
Structure Definition
Deformable Registration
Patient: Estro esophagus OM
Plan:
Plan Dose
ROI Tools
POI Tools
Approval
Fusion
Show fusion
Fusion type:
Additive Blend
Fusion setting:
Flip pattern
DISPLAY MODE
Color scheme:
Blue/Orange
Set primary color
Set secondary color
PET color map
DISPLAY COLORS
Primary
Secondary
LEVEL / WINDOW
ROI List
POI List
Registration List
Scripting
Protocols
Visualization Settings
2D
3D
Position: -14.27 -2.80 0.64 cm
CT: -994 HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Transversal: -2.80 cm
Slice 67/206
Position: 2.46 -18.41 4.35 cm
CT: - HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Sagittal: 2.46 cm
Position: -45.04 27.64 -8.10 cm
CT: - HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Coronal: -8.10 cm
Image Set Library

BTV ? CAVEAT…
SUV & registration

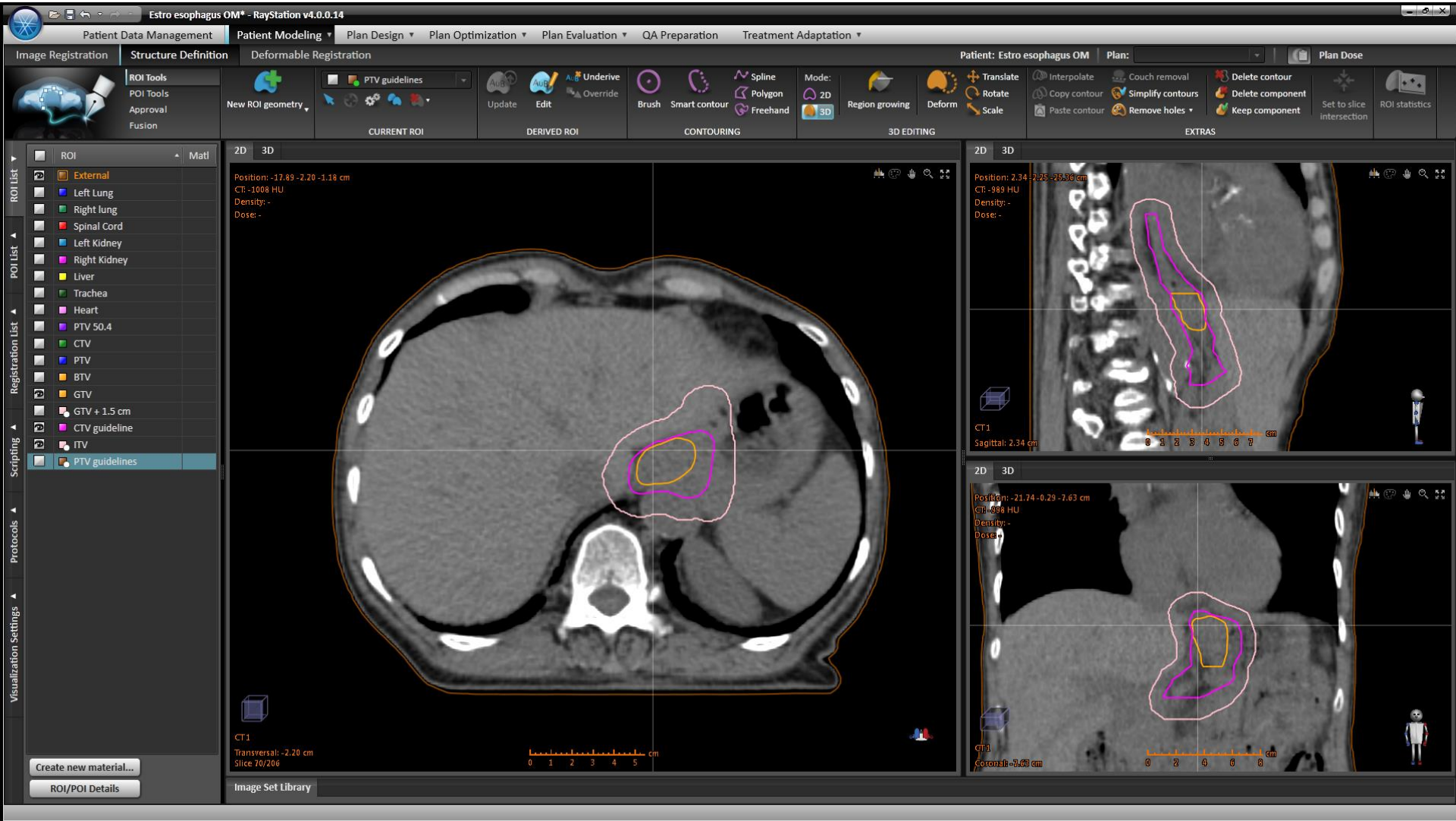
CTV margins: (1,5 cm; 5cm)?



CTV margins: anatomic corrections



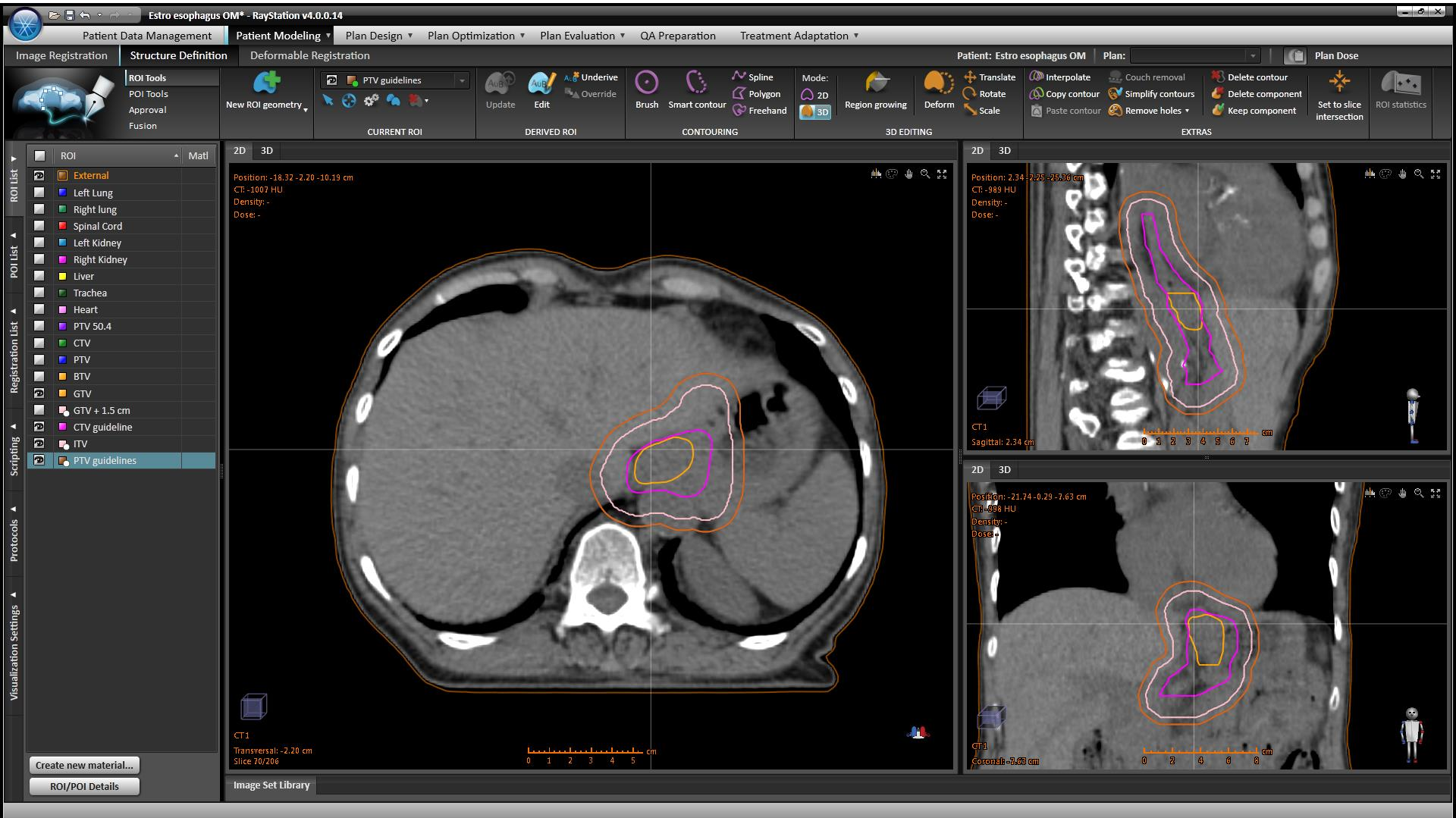
ITV


Estro esophagus OM* - RayStation v4.0.0.14
Patient Data Management
Patient Modeling
Plan Design
Plan Optimization
Plan Evaluation
QA Preparation
Treatment Adaptation
Image Registration
Structure Definition
Deformable Registration
Patient: Estro esophagus OM
Plan:
Plan Dose
ROI Tools
POI Tools
Approval
Fusion
New ROI geometry
PTV guidelines
CURRENT ROI
Update
Edit
Underive
Override
DERIVED ROI
Brush
Smart contour
Spline
Polygon
Freehand
CONTOURING
Mode:
2D
3D
Region growing
Deform
Translate
Rotate
Scale
3D EDITING
Interpolate
Copy contour
Paste contour
Couch removal
Simplify contours
Remove holes
Delete contour
Delete component
Keep component
EXTRAS
Set to slice intersection
ROI statistics
ROI
Matl
External
Left Lung
Right lung
Spinal Cord
Left Kidney
Right Kidney
Liver
Trachea
Heart
PTV 50.4
CTV
PTV
BTV
GTV
GTV + 1.5 cm
CTV guideline
ITV
PTV guidelines
Create new material...
ROI/POI Details
ROI List
POI List
Registration List
Scripting
Protocols
Visualization Settings
2D
3D
Position: -17.89 -2.20 -1.18 cm
CT: -1008 HU
Density: -
Dose: -
CT1
Transversal: -2.20 cm
Slice 70/206
Position: 2.34 -2.25 -25.36 cm
CT: -989 HU
Density: -
Dose: -
CT1
Sagittal: 2.34 cm
Position: -21.74 -0.29 -7.63 cm
CT: -998 HU
Density: -
Dose: -
CT1
Coronal: -7.63 cm
Image Set Library

Planning Target Volume (PTV)

- According to the ICRU 50 and 62 report
  - PTV will then be defined as the ITV-volume plus a 3-D margin of ***5 mm*** (except if the centre has defined its own measures of positioning inaccuracy).

PTV


Estro esophagus OM* - RayStation v4.0.0.14
Patient Data Management
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Interpolate
Copy contour
Paste contour
Couch removal
Simplify contours
Remove holes
Delete contour
Delete component
Keep component
EXTRAS
Set to slice intersection
ROI statistics
ROI
Matl
External
Left Lung
Right lung
Spinal Cord
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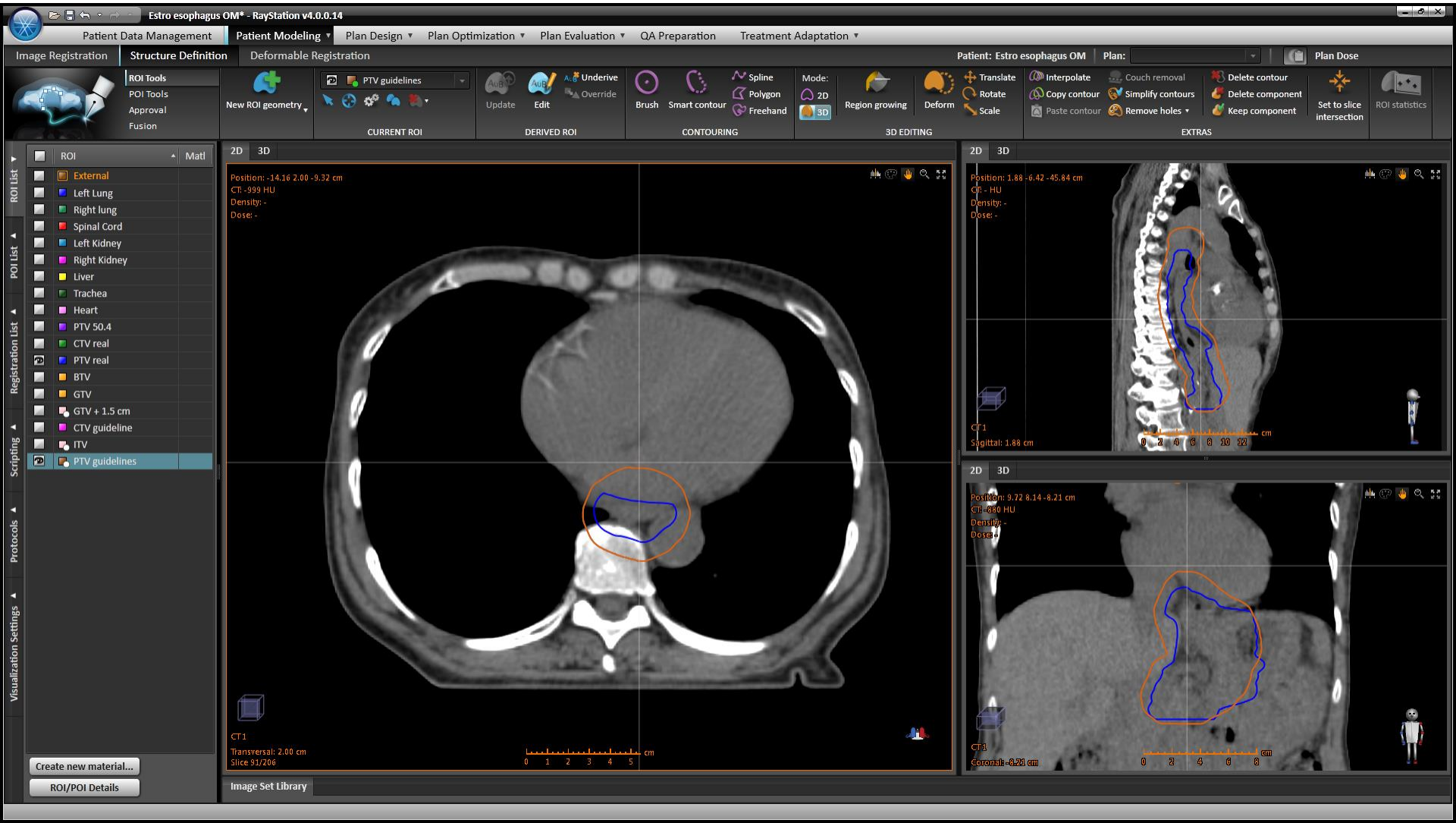
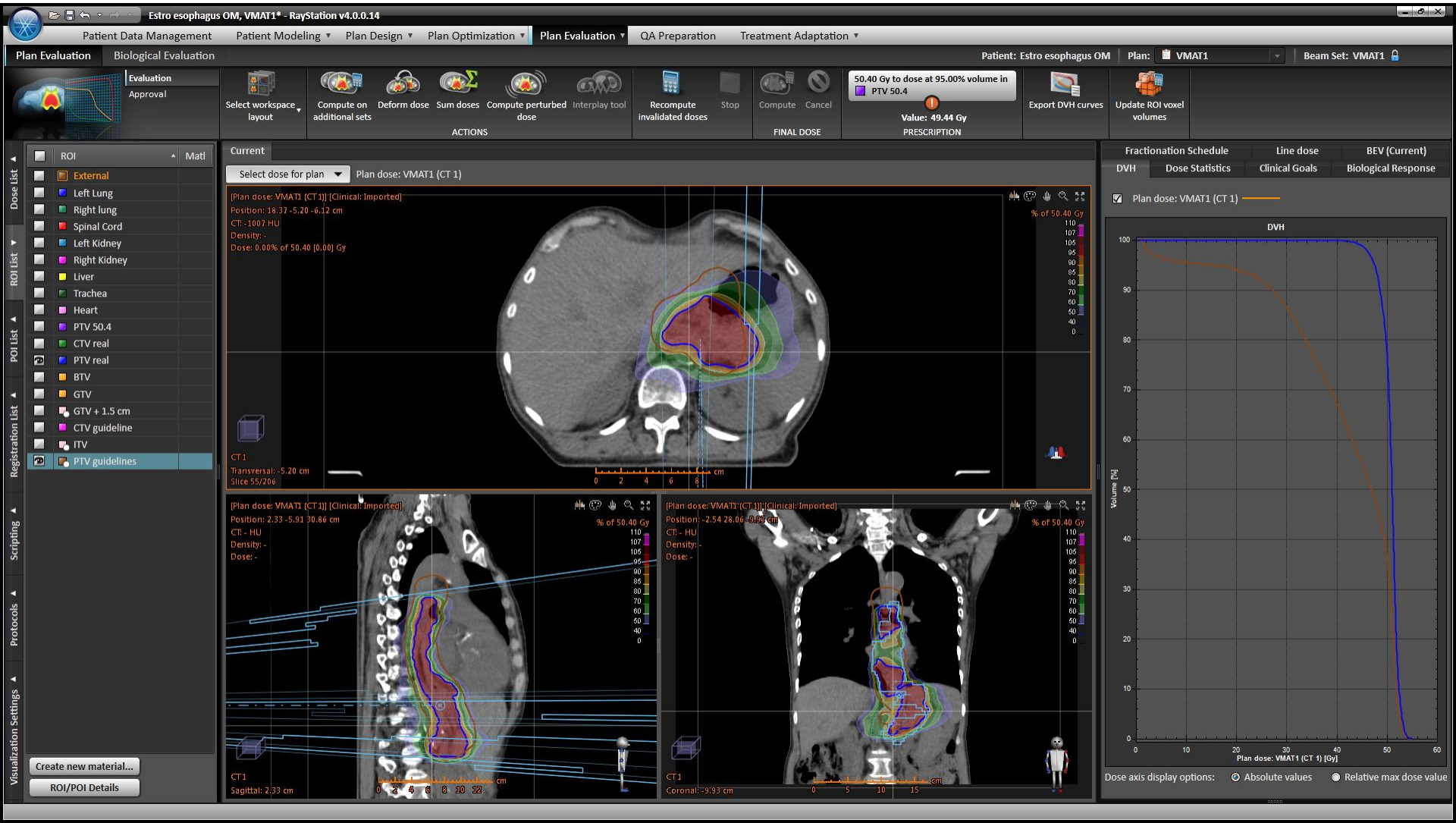
Right Kidney
Liver
Trachea
Heart
PTV 50.4
CTV
PTV
BTV
GTV
GTV + 1.5 cm
CTV guideline
ITV
PTV guidelines
Create new material...
ROI/POI Details
ROI List
POI List
Registration List
Scripting
Protocols
Visualization Settings
2D
3D
Position: -18.32 -2.20 -10.19 cm
CT: -1007 HU
Density: -
Dose: -
CT1
Transversal: -2.20 cm
Slice 70/206
Position: 2.34 -2.25 -25.36 cm
CT: -989 HU
Density: -
Dose: -
CT1
Sagittal: 2.34 cm
Position: -21.74 -0.29 -7.63 cm
CT: -998 HU
Density: -
Dose: -
CT1
Coronal: -7.63 cm
Image Set Library

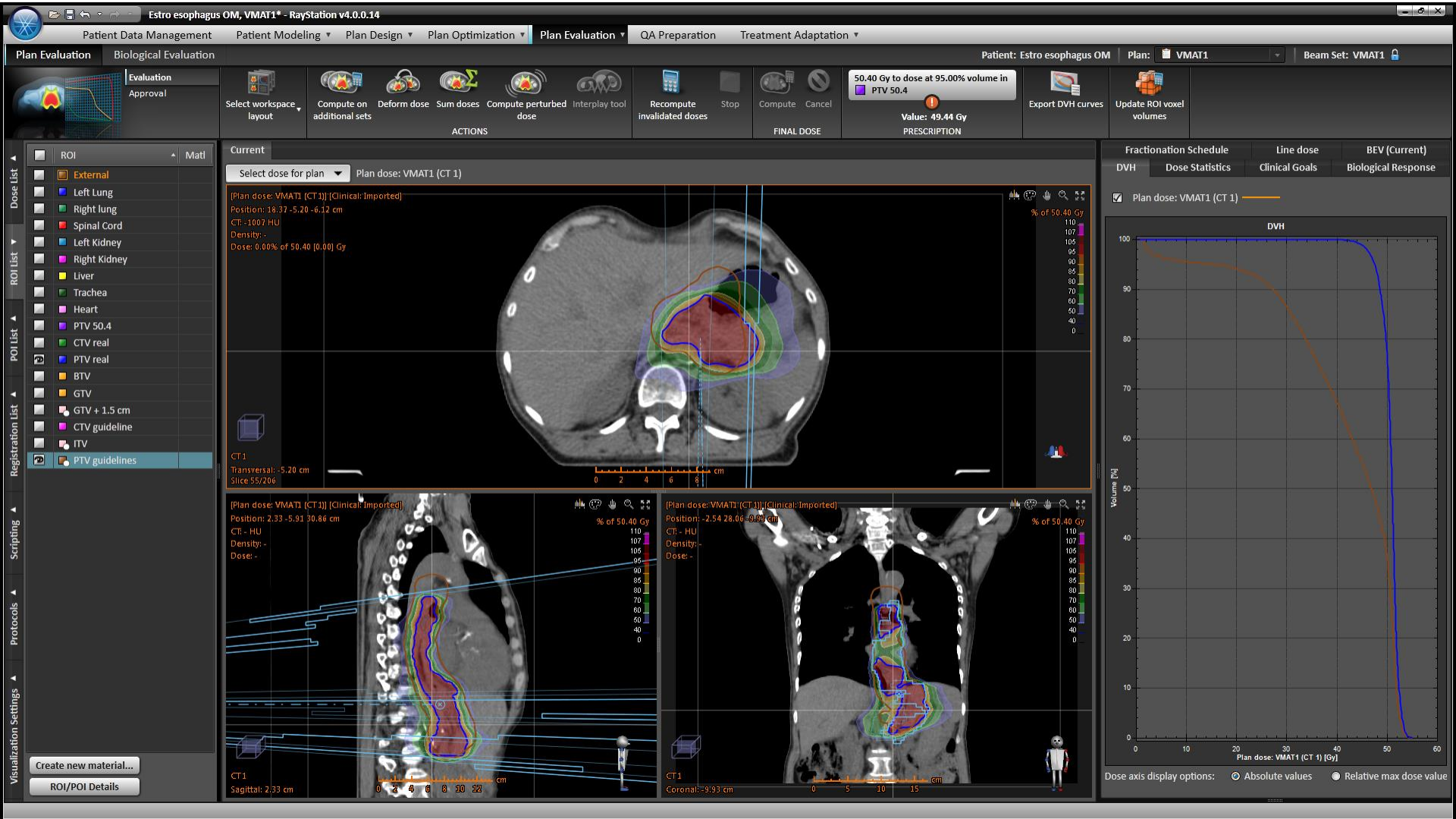
Reality vs guidelines (I)



Reality vs guidelines (II)



Reality vs guidelines (II)
does it matter?



APPROCHE MULTIDISCIPLINAIRE

<u>Approche curative</u> :

OPTIONS POSSIBLES :

- **Chirurgie seule (ex. ca précoce du tiers moyen).**
- **RT seule : ca précoce du tiers supérieur, curiethérapie.**
- **Associations:**
  - **RT + CT.**
  - **RT + CT + Chir. (tumeurs localement avancées)**

Radio-chimiothérapie Neo-adjuvante

Etude	*n*	*Histologie*	*neo RCTX*	*CHIR*	*p*
Walsh 1996	**113**	**AC**	**16 M**	**10 M**	**0.02**
Bosset 1997	**297**	**SCC**	**19 M**	**19 M**	**ns**
Urba 2001	**100**	**AC > SCC**	**17 M**	**18 M**	**ns**
Burmeister 2005	**256**	**AC > SCC**	**21 M**	**18 M**	**ns**
Tepper 2008	**56**	**AC > SCC**	**4.5 a**	**1.8 a**	**0.02**

Etude CROSS, ASCO 2010:
Radio-chimiothérapie neo-adjuvante

N=363

Stade II & III

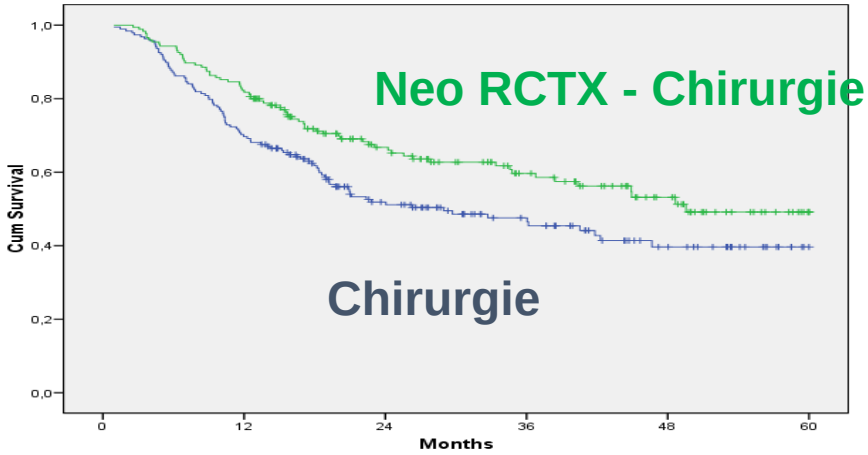
AC (n=273)
SCC (n=86)
other (N=4)

RANDOM

Neoadj. RCTX: + Chirurgie

Chirurgie

Survie



Van Gaast et al. ASCO 2010, abstract 4004

Tendances actuelles :

Tumeurs potentiellement opérables :

Protocoles « néo-adjuvants »

RT (45-50 Gy) +
CT
suivi d'une résection.

Avantages : « downstaging », parfois (20 %) disparition de la tumeur sur la pièce opératoire.

Inconvénients : morbidité et mortalité significative

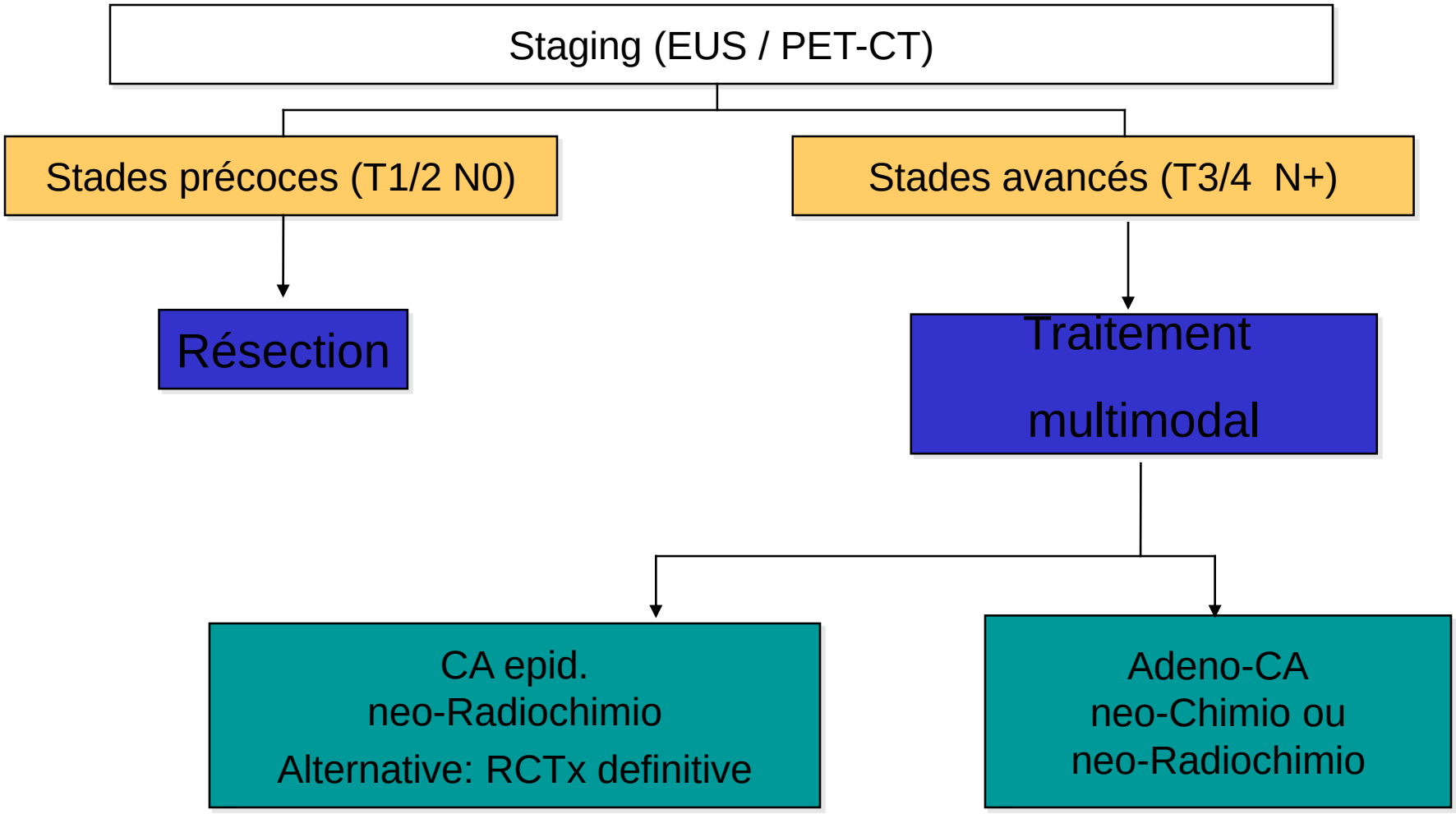
Tendances actuelles :

Tumeurs potentiellement inopérables, mais M0 :

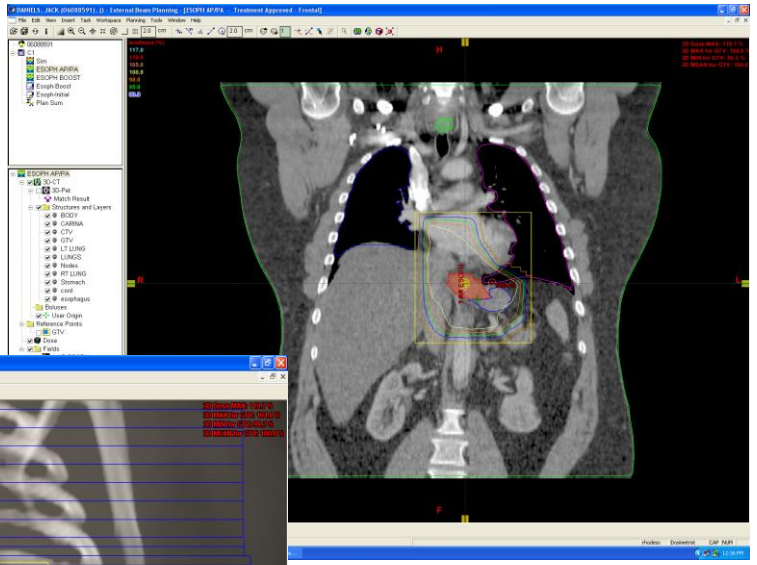
protocoles d'association radio-chimiothérapeutique

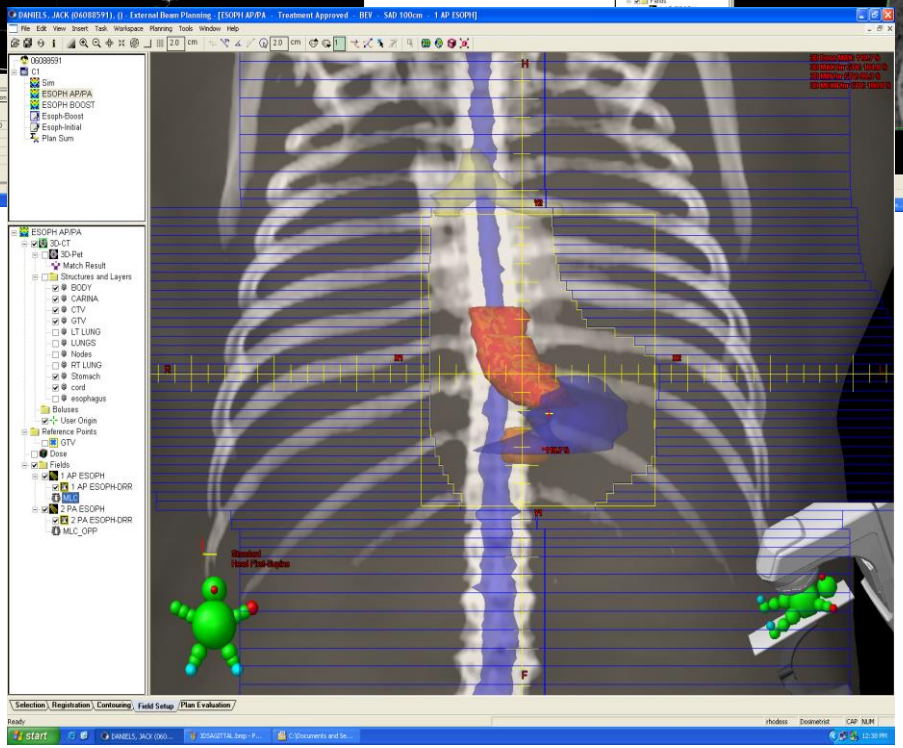
RT (50 Gy) + CT.

Tendances actuelles : algorithme



Planning - 3D





COMPLICATIONS POTENTIELLES DE LA RADIOTHERAPIE

- **Sténose oesophagienne (> 50-60 Gy).**
- **Pneumonie actinique / fibrose pulmonaire (> 25 Gy).**
- **Atteintes cardiaques (rares) (> 40 Gy).**
- **Myélite actinique (rare) (> 45 Gy).**

Planning - 3D DVH

[redacted]

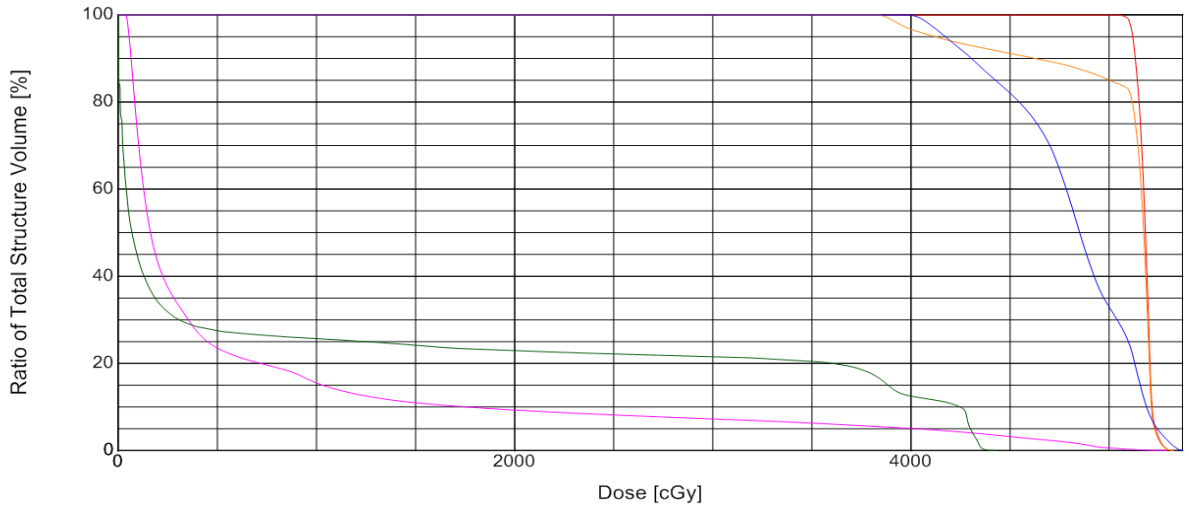
Print... | Next Page | Prev Page | Two Page | Zoom In | Zoom Out | Close

Eclipse

External Beam Planning 7.5.51 — Oregon Health & Science University, Portland, OR

Patient: DANIELS, JACK
Patient IDs: 06088591
Comment:

Cumulative Dose Volume Histogram



Structure	Plan Sum	Plan Sum Status	Course	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose
GTV	Plan Sum (Plan Sum)	-	C1	100.0 / 100.0	56.1 [cm³]	5032.8 cGy	5325.8 cGy	5179.9 cGy	5205.8 cGy	5183.0 cGy
CTV	Plan Sum (Plan Sum)	-	C1	100.0 / 100.0	67.1 [cm³]	3829.5 cGy	5325.8 cGy	5059.6 cGy	5205.8 cGy	5174.5 cGy
cord	Plan Sum (Plan Sum)	-	C1	100.0 / 99.8	86.0 [cm³]	0.0 cGy	4431.7 cGy	1010.6 cGy	0.0 cGy	68.9 cGy
Stomach	Plan Sum (Plan Sum)	-	C1	100.0 / 100.0	139.9 [cm³]	3963.3 cGy	5372.7 cGy	4815.9 cGy	5124.3 cGy	4851.2 cGy
LUNGS	Plan Sum (Plan Sum)	-	C1	100.0 / 100.0	2888.0 [cm³]	35.9 cGy	5294.1 cGy	627.6 cGy	72.5 cGy	162.1 cGy

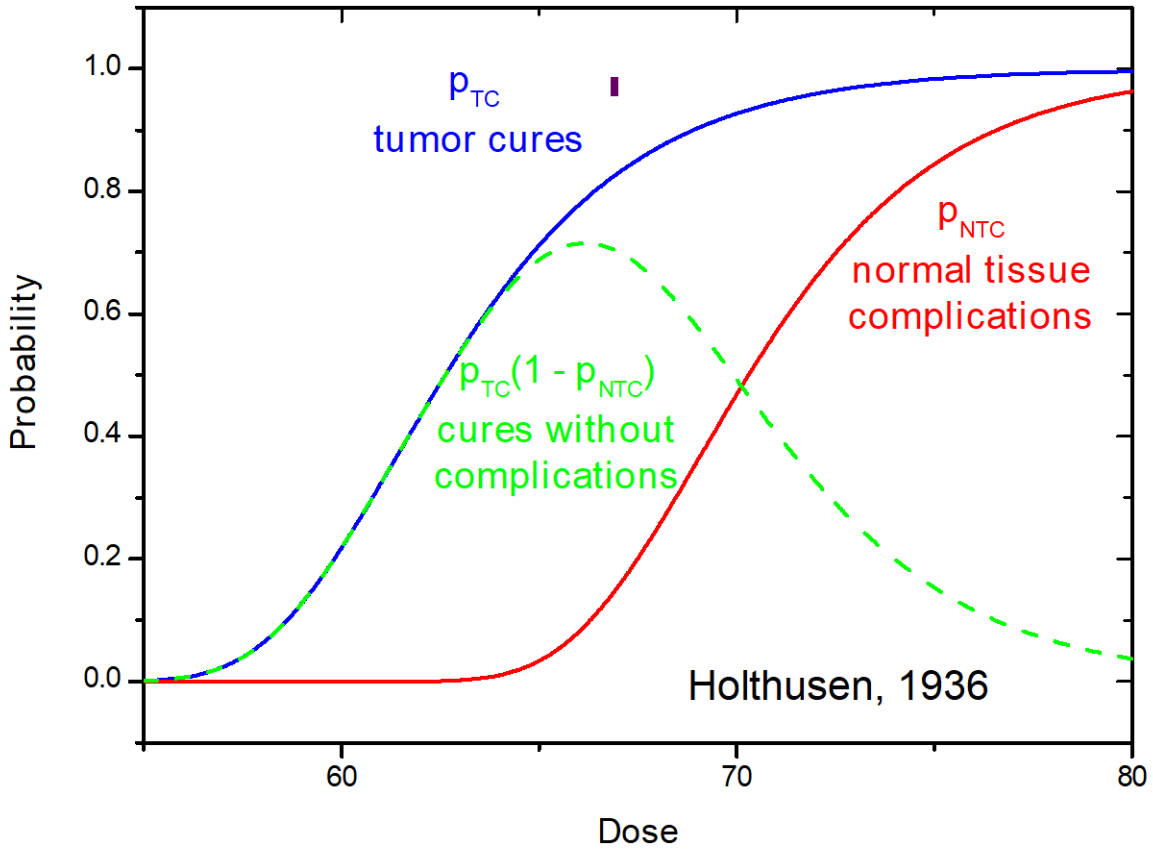
Patient: DANIELS, JACK (06088591)

Printed 9/11/2007 12:45 PM by rhodess
Page: 1/1

Page 1 | rhodess | Dosimetrist | CAP | NUM

start | DANIELS, JACK (060... | JDAPBST.bmp - Paint | C:\Documents and Se... | 12:45 PM

- Radiation therapy affects both tumor cells and uninvolved normal cells



Introduction

1972: First formal attempt to address normal tissue tolerance to radiation

Rubin P, Cassarett G. A direction for clinical radiation pathology. In: Vaeth JM, et al., eds. Frontiers of radiation therapy and oncology VI. Baltimore, MD: University Park Press, 1972:1–16.

1991: A committee reviewed available published data

➔ but much of the data was nonexistent

➔ rely on experience of 8 clinicians from major institutions in the US

CAVE:

Literature review up to 1991.
Pre-dated the 3D-CRT, IMRT- IGRT era.
Dose-volume histograms were not in routine clinical use.
Arbitrary decision: organs be divided into one-third, two-thirds, and whole organ volumes
It was only for external beam radiation with conventional fractionation.
Only one severe complication was chosen as an endpoint

Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–122.

ELSEVIER

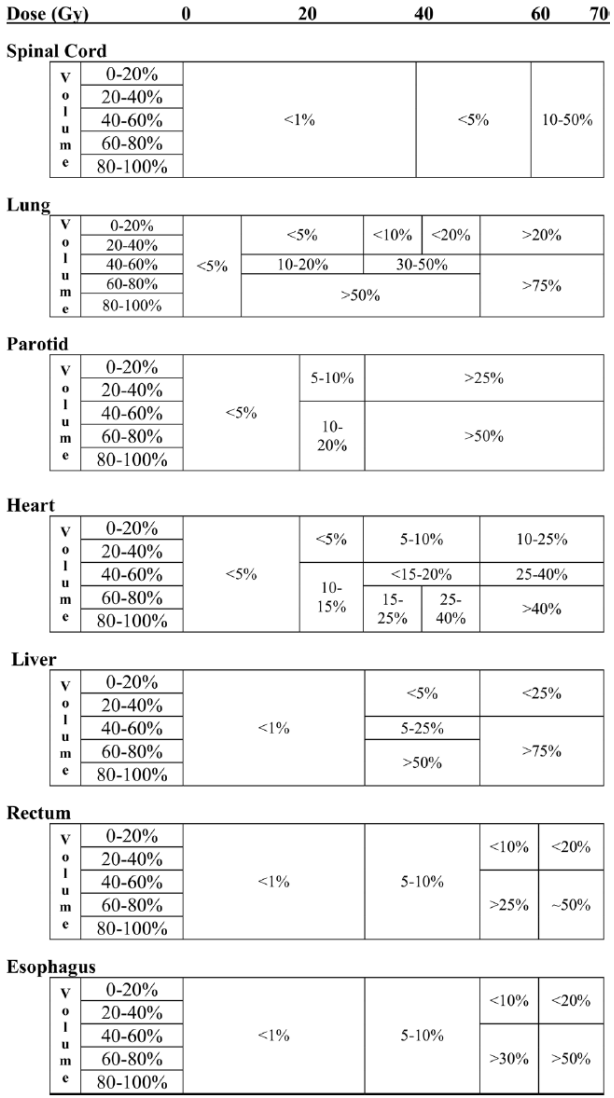
Seminars in
RADIATION
ONCOLOGY

Normal Tissue Tolerance Dose Metrics for Radiation Therapy of Major Organs

Michael T. Milano, MD, PhD, Louis S. Constine, MD, and Paul Okunieff, MD

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema



2010: Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10–S19, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.07.1754

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-C				
	Whole organ	3D-C				
	Whole organ	3D-C				
	Whole organ	SRS				
Spinal cord	Partial organ	3D-C				
	Partial organ	3D-C				
	Partial organ	3D-C				
	Partial organ	SRS				
	Partial organ	SRS				
Cochlea	Whole organ	3D-C				
	Whole organ	SRS				
Parotid	Bilateral whole parotid glands	3D-C				
	Unilateral whole parotid gland	3D-C				

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function redu pre-RT level	Mean dose <39	<50	For combined parotid glands (see
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic aspiration			
Larynx	Whole organ	3D-CRT	Vocal dysfun			
	Whole organ	3D-CRT	Aspiration			
	Whole organ	3D-CRT	Edema			
	Whole organ	3D-CRT	Edema			
Lung	Whole organ	3D-CRT	Symptomatic			
	Whole organ	3D-CRT	Symptomatic			
	Whole organ	3D-CRT	Symptomatic			
	Whole organ	3D-CRT	Symptomatic			
	Whole organ	3D-CRT	Symptomatic			
Esophagus	Whole organ	3D-CRT	Grade ≥3 acu			
	Whole organ	3D-CRT	Grade ≥2 acu			
	Whole organ	3D-CRT	Grade ≥2 acu			
	Whole organ	3D-CRT	Grade ≥2 acu			
Heart	Pericardium	3D-CRT	Pericarditis			
	Pericardium	3D-CRT	Pericarditis			
	Whole organ	3D-CRT	Long-term ca			

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

LAWRENCE B. MARKS, M.D.,* ELLEN D. YORKE, PH.D.,† ANDREW JACKSON, PH.D.,†
RANDALL K. TEN HAKEN, PH.D.,† LOUIS S. CONSTINE, M.D.,§ AVRAHAM EISBRUCH, M.D.,‡
SØREN M. BENTZEN, PH.D.,‖ JIHO NAM, M.D.,* AND JOSEPH O. DEASY, PH.D.¶

...versity of North Carolina, Chapel Hill, NC; †Department of Medical Physics, Memorial Sloan
‡Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; §Department of
...chester Cancer Center, Rochester, NY; ‖Department of Human Oncology, University of
..., WI; and ¶Department of Radiation Oncology, Alvin J. Siteman Cancer Center, Washington
University School of Medicine, St. Louis, MO

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD††	Mean dose <30–32	<5	Excluding patients with pre-existing liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <42	<50	
	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD	Mean dose <28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <36	<50	as an endpoint
	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13	<5	3 fractions, for primary liver cancer
				<18	<5	6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15	<5	3 fractions, for liver metastases
				<20	<5	6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions
Kidney	Bilateral whole kidney‡	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5	
	Bilateral whole kidney‡	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50	
	Bilateral whole kidney‡	3D-CRT	Clinically relevant renal dysfuntction	V12 <55% V20 <32% V23 <30% V28 <20%	<5	For combined kidney
Stomach	Whole organ	Whole organ	Ulceration	D100§ <45	<7	
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity§	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity§	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

(*Continued*)

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Milano MT, Semin Radiat Oncol 2007:17;131-40

Oesophagus: OAR…

- Heart
- Lungs
- Spinal cord
- Vertebrae
- Thyroïd
- Brachial plexus
- Stomach
- Liver
- Biliary tract
- Pancreas
- Spleen
- Kidneys

- Vessels, pericarde, coronary arteries
- Esophagus

- Patient at risk

OAR: Spinal cord

- Spinal cord injury rare but extremely debilitating

➔paralysis, sensory, deficits, pain, and bowel/bladder incontinence (10,30)

•Schultheiss review:

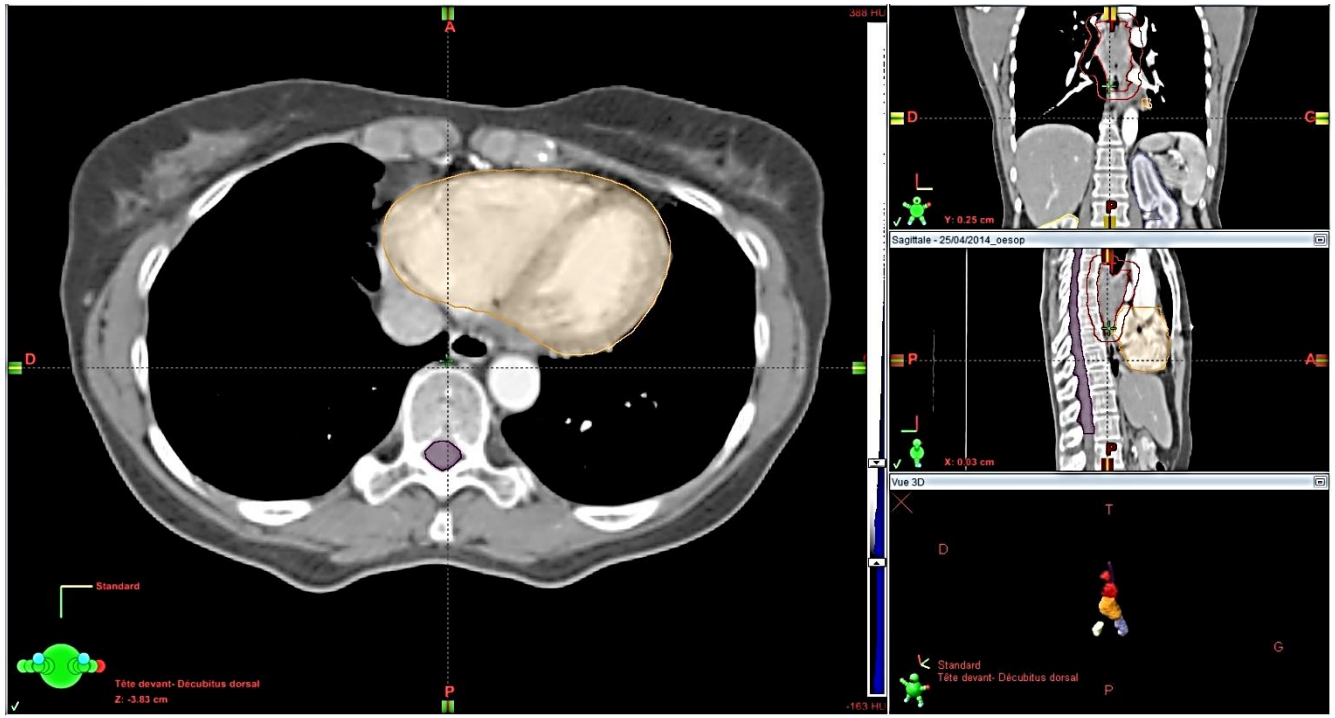
- •risk of myelopathy to be 0.2% at 50 Gy and 5% at 59.3 Gy

•Similar conclusions published by QUANTEC

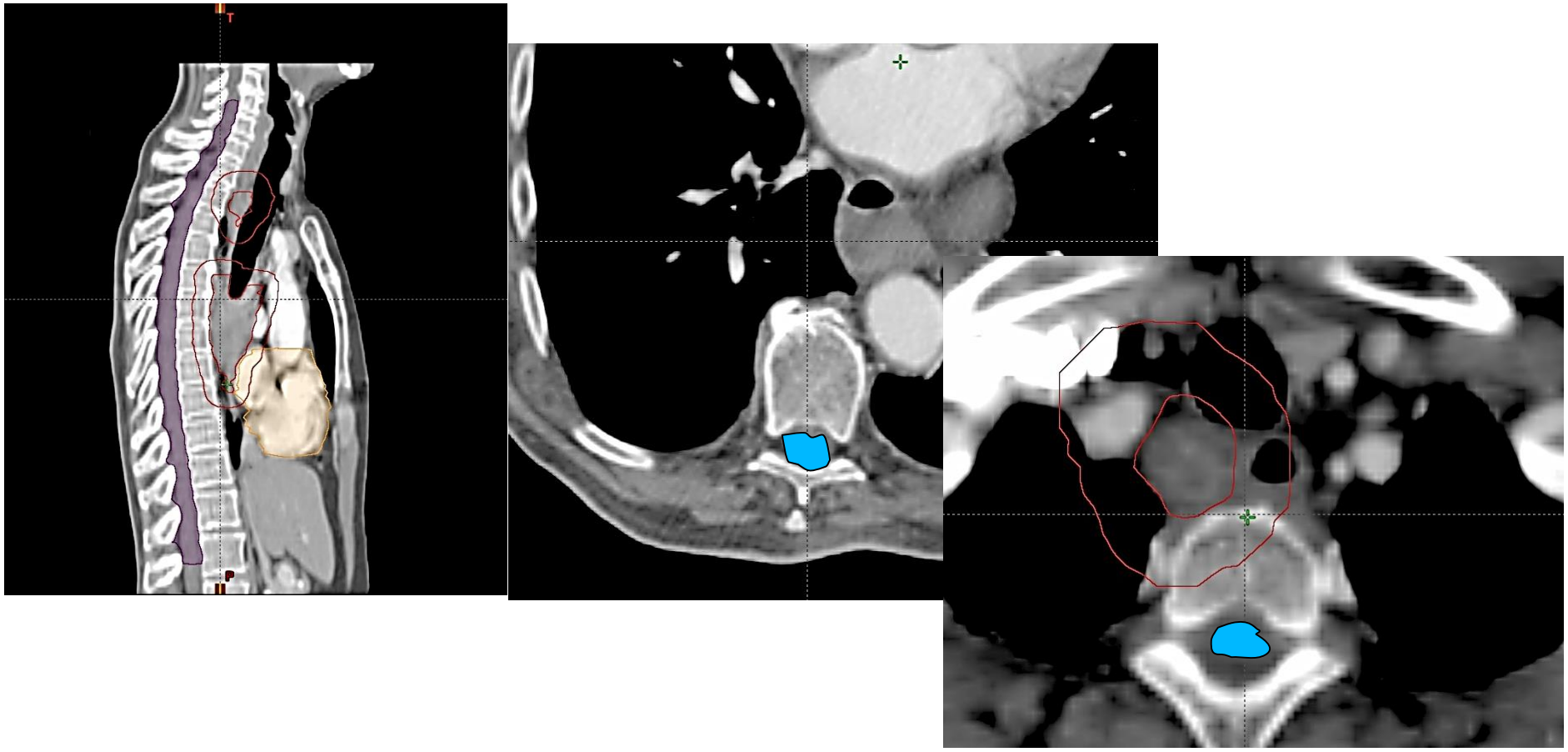
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	

Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31:1093–1112.

Spinal cord …


A
D
P
Standard
Tête devant- Décubitus dorsal
Z: -3.83 cm
D
C
P
Y: 0.25 cm
Sagittale - 25/04/2014_oesop
P
A
P
X: 0.03 cm
Vue 3D
T
D
G
Standard
Tête devant- Décubitus dorsal
P

Spinal cord … Which one ?



Dose volume effect in the heart

Most relevant cardiac toxicities

- Clinical pericarditis
- Long-term cardiac mortality

Long-term cardiac mortality

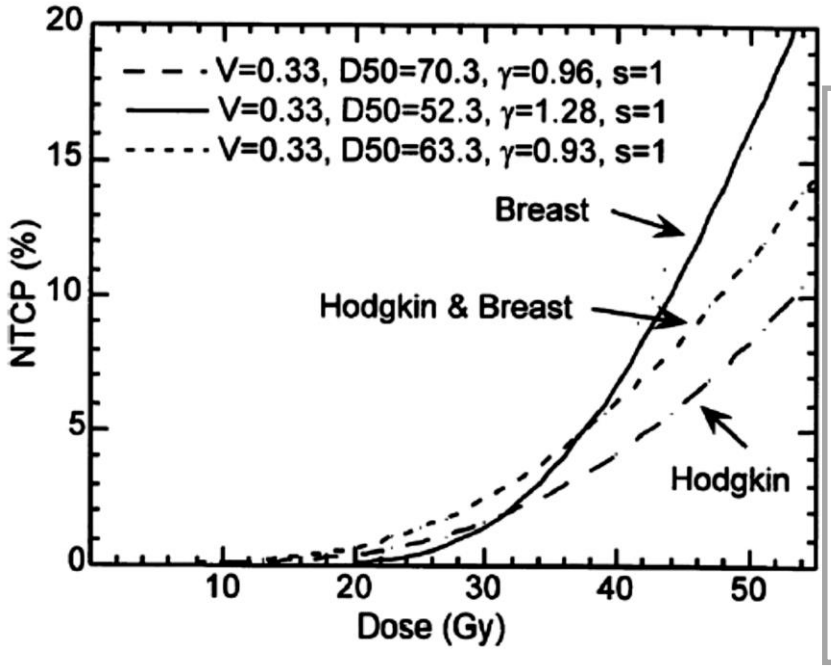


Table 2. Pericarditis/pericardial effusion: Dose–volume predictors and NTCP parameters

Authors, Year, Reference	Diagnosis, No. of patients, Years of treatment	OAR	Fractionation schedule, dose data	Predictive parameters	NTCP parameters
Carmel and Kaplan* 1976 (3)	Hodgkin's 377 Patients 1964–1972	Pericardium		$D_{pericardium} > 30$ Gy 50% pericarditis, 36% requiring treatment	
Cosset *et al.* 1991 (65)	Hodgkin's 499 Patients 1971–1984		35–43 Gy/ 2.5–3.3 Gy/fraction pre-3D dose data	$D_{Mediastinum} \geq 41$ Gy d/ fraction ≥ 3 Gy (marginal significance)	
Burman *et al.* 1991 (66)	Historical data				LKB† *TD50* = 48 Gy $m = 0.10$ $n = 0.35$
Martel *et al.* 1998 (26)	Esophagus 57 Patients 1985–1991	Pericardium	37.5–49 Gy/ 1.5–3.5 Gy / fraction 3D data	$D_{mean} > 27.1$ Gy‡ $D_{max} > 47$ Gy‡ d/ fraction 3.5 Gy	LKB (95% CI) *TD50* = 50.6 Gy (–9; 23.1) $m = 0.13$ (–0.07; 0.13) $n = 0.64$ (–0.58; 3)
Wei *et al.* 2008 (27)	Esophagus 101 Patients 2000–2003	Pericardium	45–50.4 Gy 1.8–2.0 Gy/fraction 3D data	D_{mean}pericardium > 26.1 Gy $V_{30} < 46\%$	

Gagliardi G. IJROBP 2010

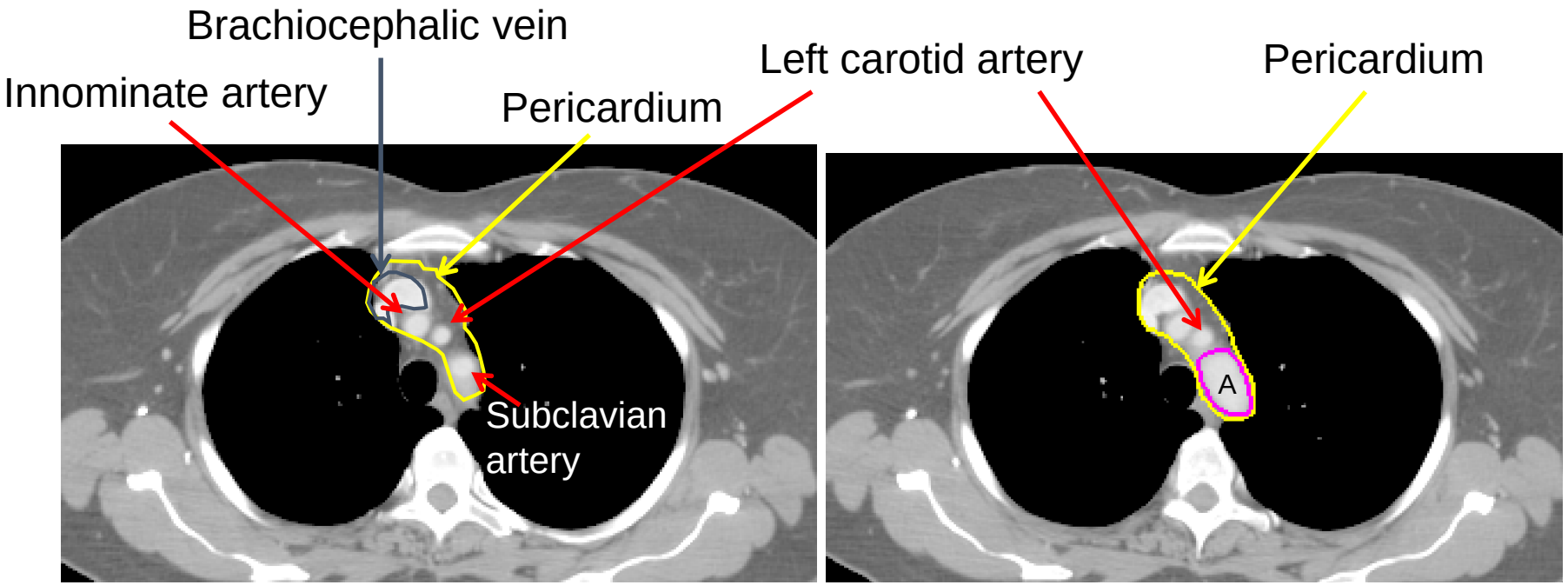
Dose volume effect in the heart

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Heart	Pericarditis	<15	V30 <46%		<26
	Long-term cardiac mortality	<1	V25 <10%		

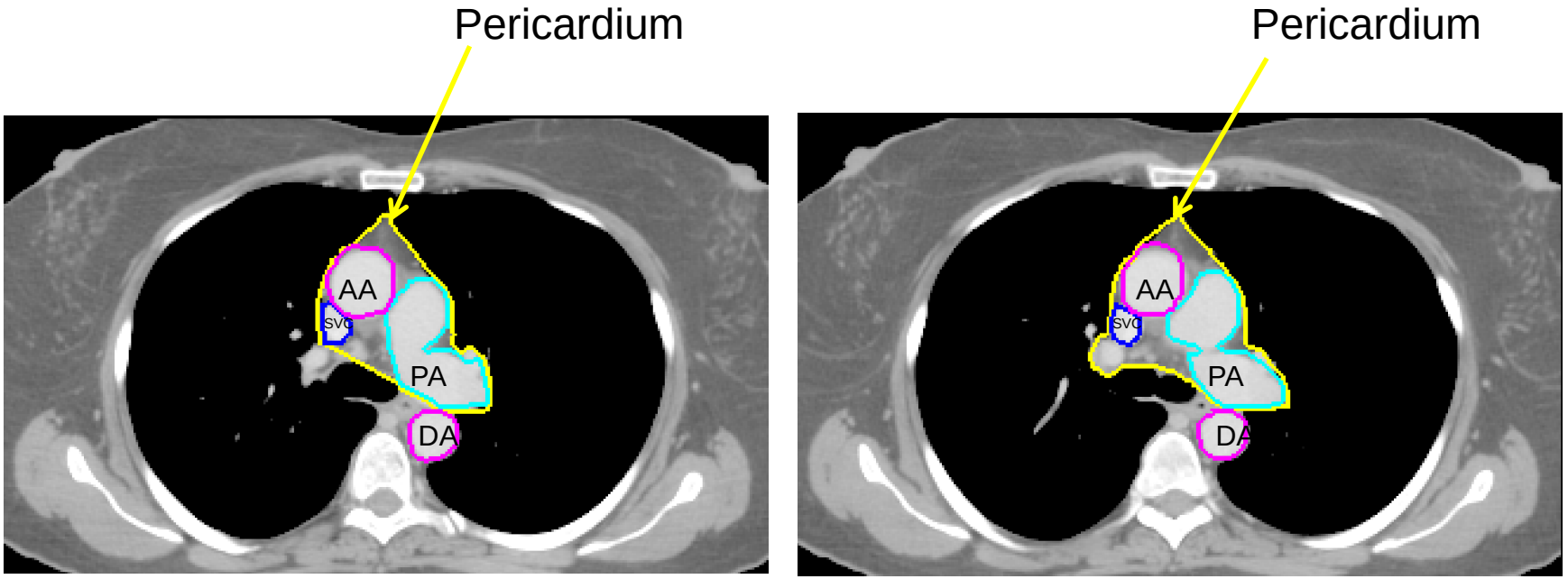
CAVE: ALARA left ventricule

Pericardium starts …



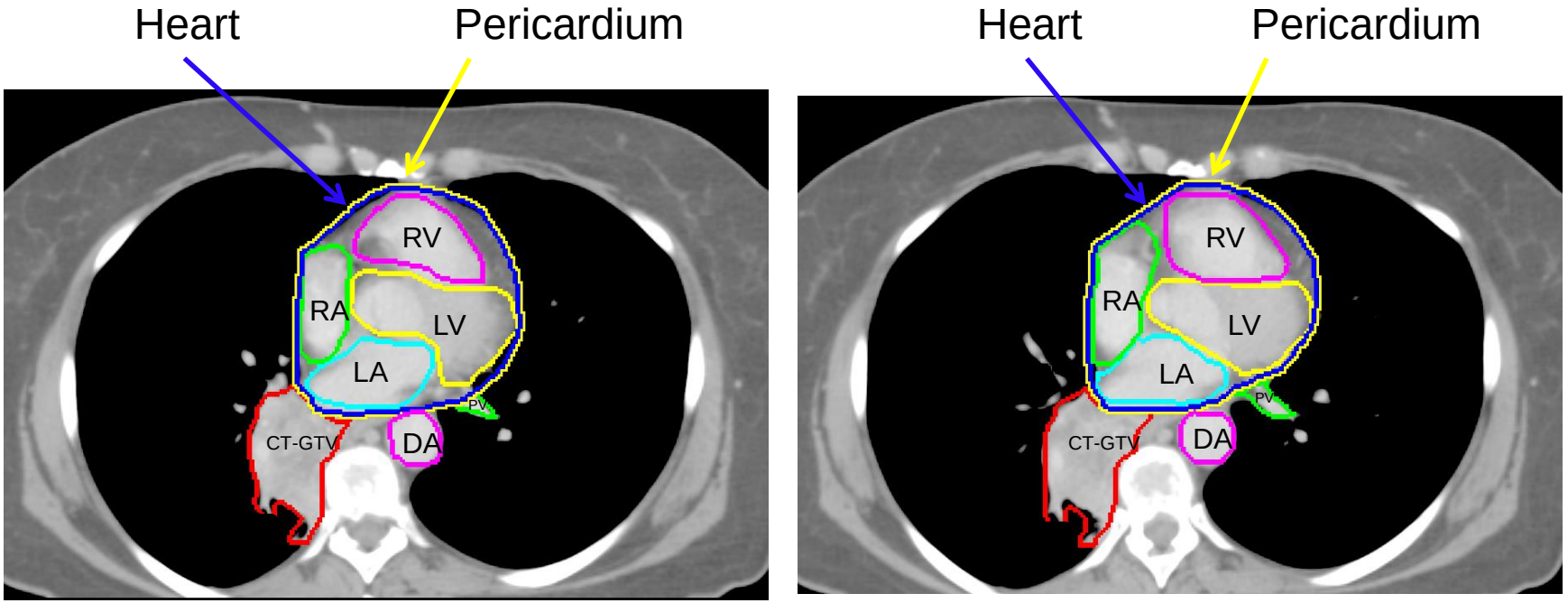
Pericardium starts at 1-2 slices (5-6 mm) above the superior end of the aortic arch

Pericardium Continues…



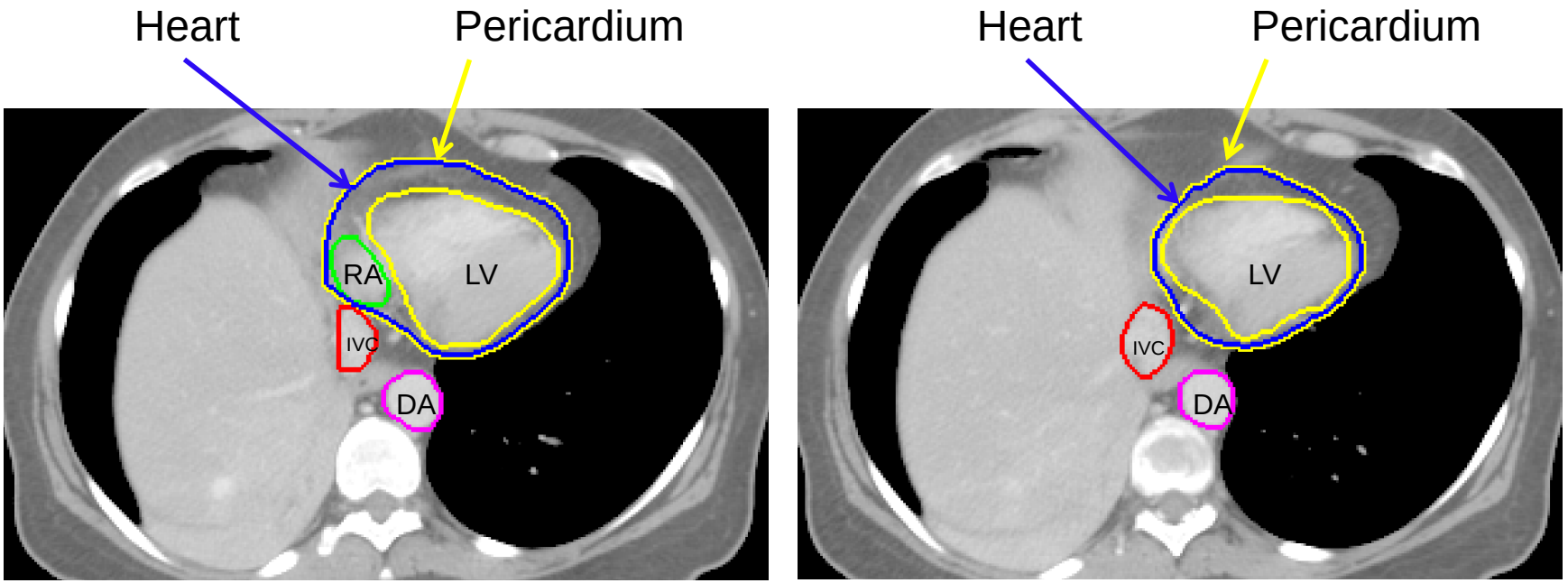
SVC=Superior vena cava
PA=Pulmonary artery
AA=Ascending aorta
DA=Descending aorta

Heart and pericardium continue…



RA=right atrium, RV=right ventricle
LV=left ventricle, LA=Left atrium
DA=descending aorta

Heart and pericardium continue…



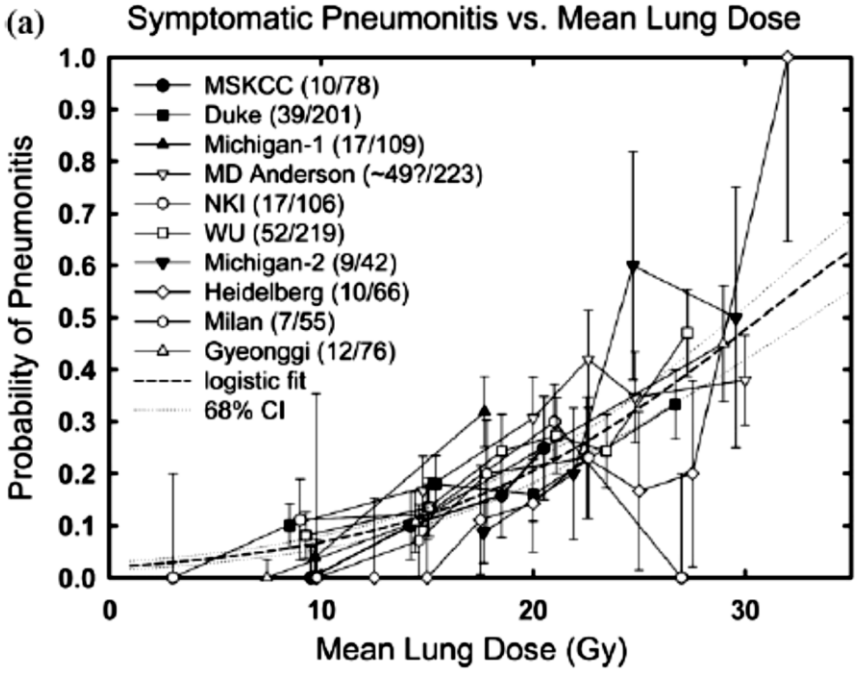
IVC=inferior vena cava
RA=right ventricle
LV=left ventricle
DA=descending aorta

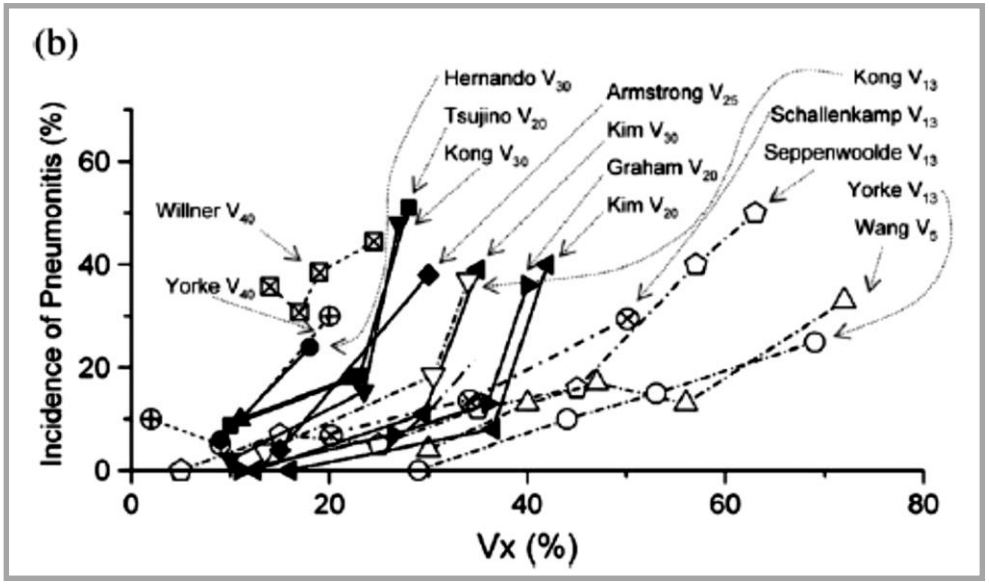
Radiation Dose-Volume effect in the lung

QUANTEC review >70 articles: mean lung doses & Vx parameters

➔ no clear threshold dose

➔ 20% risk of pneumonitis for a **mean lung dose** of 20 Gy
➔ **V20** most useful parameter





Marks L. IJROBP 2010

OAR: lung

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Lung	Symptomatic pneumonitis	5	V5 <42%, V20 <22%		7
		10	V20 <31%		13
		20	V20 <40%		20
		30			24
		40			27

NCCN guidelines

Spinal cord	Dmax = 45Gy
Heart	1/3 < 40Gy, ALARA left ventricule
Lungs	D max normal lung (2 cm outside PTV) < 40 Gy
	•V 20 Gy < 25%; V5 Gy < 50 %

- Liver — V60% < 30Gy; 25 Gy mean
- Kidney — 2/3 ≤ 20Gy

National Comprehensive Cancer Network guidelines, Clinical practice guidelines in oncology, Esophageal cancer, 02.2016.

http:// www.nccn.org

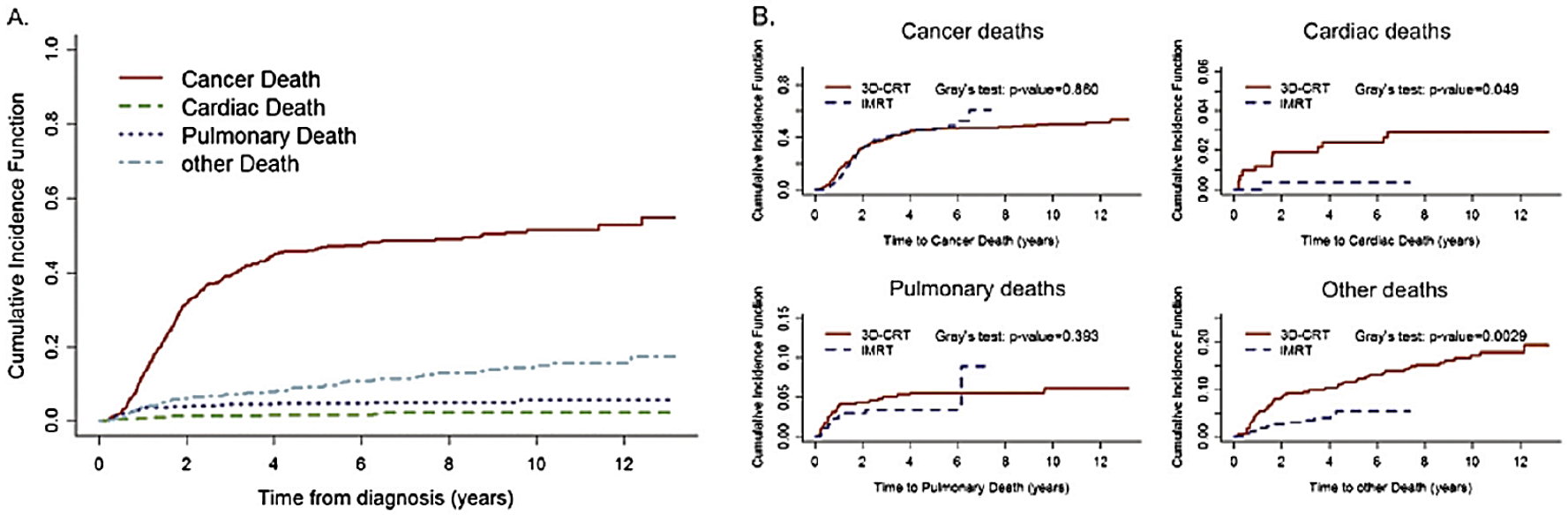
Last, but … Esophagus

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Esophagus	Grade ≥2 esophagitis	<30	V35 <50% V50 <40% V70 <20%	<74 Point	
	Grade ≥3 esophagitis	≤10	V60 <30%		<34

- Dose limit = 50 Gy Mean dose > 34 Gy *Sing IJROBP 2003*
- Lenght of esophagus receiving more than 55 Gy *Maguire IJROBP 1999*
- Acute esophageal toxicity is the greatest predictor of late toxicity

IMRT : Evolution or Revolution?

Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer.



Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1078-85. doi: 10.1016/j.ijrobp.2012.02.015.

Approche palliative (M+) :

- **RT palliative pour désobstruction de l'œsophage.**
  ex: 10 * 3Gy
- **Curiethérapie**
- **Pose de prothèses "stent".**
- **Photothérapie, laserthérapie.**
- **Chirurgie palliative**
- **Chimiothérapie palliative**