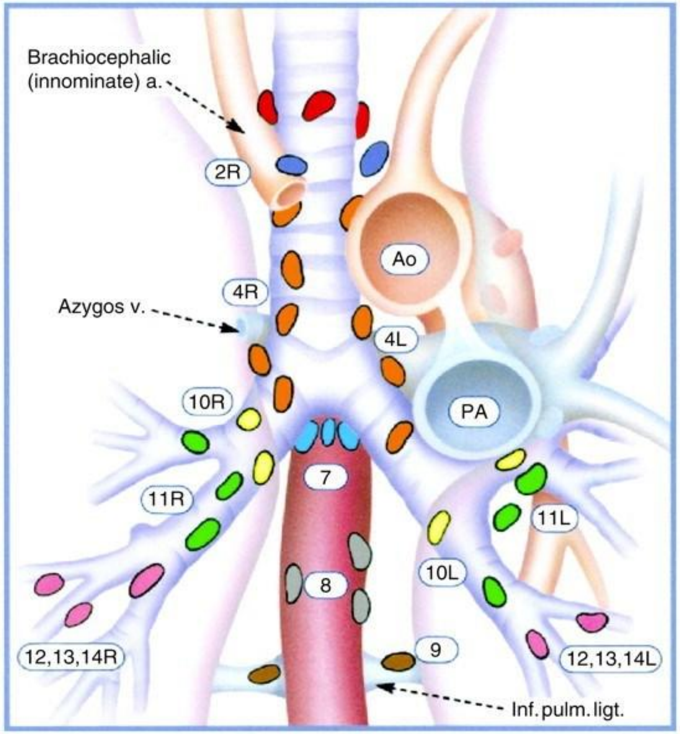
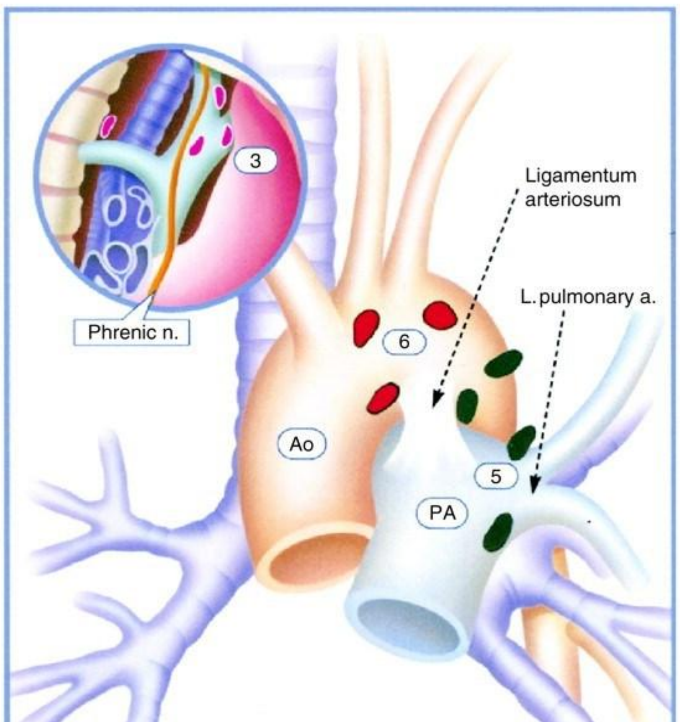
Radiotherapy in Lung

CancerAnatomy

- Oblique fissure in both lungs.
- Horizontal fissure in Right lung.
- Trachea bifurcates at the level of T5.
- Lymph nodes are divided into stations.
- Intrapulmonary, bronchopulmonary (hilar), mediastinal, supraclavicular(scalene) nodes.





Superior Mediastinal Nodes

- **1** Highest Mediastinal
- **2** Upper Paratracheal
- **3** Pre-vascular and Retrotracheal
- **4** Lower Paratracheal (including Azygos Nodes)

N_2= single digit, ipsilateral
N_3= single digit, contralateral or supraclavicular

Aortic Nodes

- **5** Subaortic (A-P window)
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- **7** Subcarinal
- **8** Paraesophageal (below carina)
- **9** Pulmonary Ligament

N_1 Nodes

- **10** Hilar
- **11** Interlobar
- **12** Lobar
- **13** Segmental
- **14** Subsegmental

Epidemiology

- Most common & Deadliest worldwide.
- Survival at 5 years in USA is 15%.
- Primary risk factor- SMOKING (~90%) ● Adenocarcinoma more than Small/Squamous.
  (Filtered cigarette, fine particles reach periphery)

Presentation

- Due to local tumor growth:
  - Centrally cough, haemoptysis, obstructive signs. – Peripherally silent, cough, pleuritic chest pain.

- Nerve entrapment (LRLN, phrenic), Vascular obstruction.
- Esophageal narrowing, obstruction, fistula.

- Due to metastasis:
  - 60% SCLC, 30% - 40% NSCLC.
  - CNS, Bones, Liver, Adrenal Glands.

Workup

- History:
  - Smoking, Weight loss, Performance status ● Examination ● Imaging:
  - CECT incl. adrenals, PET-CT preferred.(50% staging changed)
  - CECT (sens 75%, spec 66%) vs PET-CT (91%, 86%)
  - EBUS

- Tissue:
  - FNAC, TBFNA, Mediastinoscopy, VATS

TABLE 1: TNM staging of lung cancer[a]

Primary tumor (T)

Tx	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or any tumor that cannot be assessed, as in pretreatment staging
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3.0 cm in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	Tumor > 3.0 cm in greatest dimension; or tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina
T3	Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body; or tumor in the main bronchus within 2 cm of, but not involving, the carina
T4	Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body, or carina; or presence of

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region, including direct extension
N2	Metastasis to ipsilateral mediastinal and subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Overview of management in NSCLC

- Surgery is the main stay for resectable and operable non small cell lung cancer
- Radiation plays a role in the definitive and adjuvant management of NSCLC
- Chemotherapy is an important adjuvant treatment modality, often used with radiation
- Radiation along with chemotherapy are useful for palliation

RT in Lung Cancer: Issues

- NSCLC: A moderately radio-sensitive tumor: dose escalation needed
- Surrounded by organs which are dose limiting: heart, opp. lung, spinal cord, esophagus
- Respiratory motion: a pertinent factor necessitating motion management in radiation delivery

RT in NSCLC: Stage wise

- Stage: I : Surgery the mainstay; SBRT
- Stage II: Surgery the mainstay; SBRT
- Stage III: Surgery + RT, CT + RT
- Stage IV: Palliative RT
- Prophylactic cranial irradiation*

Adjuvant Radiation Therapy

- Indicated for insufficient margins* <1cm, mediastinal nodes(N2).
- 60-66Gy, 2Gy/# to the positive margin.
  50 Gy/25# to probable microscopic disease.
- PORT Meta analysis 21% more risk of death in post operative RT group.

- Studies since 1965, unpublished data included, Ill-defined surgical techniques,
  7 of 9 trials used Co-60 unit, Crude technology of radiation therapy

PORT meta-analysis group Lancet 1998; 352: 257–63

Early stage NSCLC

- Surgical resection: well established as the main curative treatment in stage I, II NSCLC
- 5-year overall survival for (p) stage I disease: 57% to 67%
- Poor PS, medical comorbidities & often preference preclude surgery in a large proportion (25%*)
- 5-year survival rates with unresectable stage I, II disease treated with radiotherapy range from 15% to 30%.
- 60% death due to distant metastasis

- Lancet Oncol 2009; 10: 885–94
- Better results with dose escalation.
- Difficult to achieve with conventional radiation delivery techniques
- Options now available:

(A) SBRT / Cyber knife

(B) Real time motion management: IGRT

(C) Brachytherapy: endoluminal and interstitial

Patient selection criteria for SBRT in early stage NSCLC

- Medically inoperable or don't want surgery
- PS 0-2
- Stage T1-3, N0 following PET-CT
- Maximum tumor size 5cm
- Not adjacent to major structures like vessels, heart, esophagus.
- Able to lie flat for at least one hour

SBRT vs Wedge resection in Stage I NSCLC

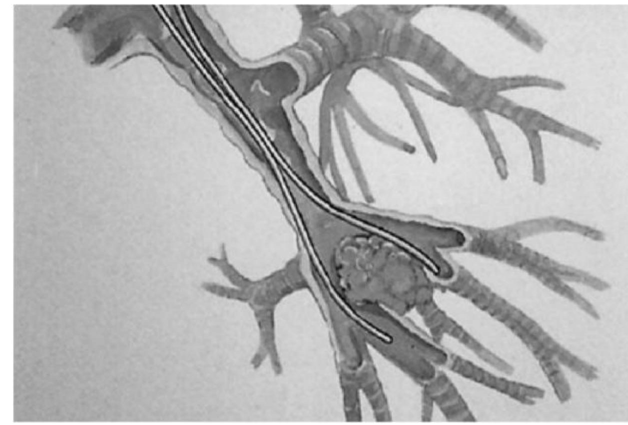
- 124 pts; T1-2N0MO
- 69 wedge resections, 58 SBRT

- SBRT prescribed as 48(T1) or 60(T2) Gy in 4 to 5 fractions
- Median follow up of 2.5 years
- No differences in DM, FFF, or CSS, but OS was higher with wedge resection at 30 months. (87% vs 72%)

(Distant Metastatis, Freedom from Failure, Case Specific Survival)

Journal of Clinical Oncology, Vol 28, No 6 , 2010: pp. 928-935

Brachytherapy for early stage NSCLC



- Endobronchial (endoluminal) brachytherapy

- Interstitial brachytherapy

NSCLC : Definitive RT

- Stage III:
  - Main bulk of the disease.
  - 60 – 75 Gy to the gross disease (RTOG 73-01)
  - 50 Gy to the microscopic disease – Hyperfractionation showed better roles.
  - 69.6 Gy . 1.2Gy/# , 2#/day.

  Best survival rates (20% at 3 years)
  - CHART (Continuous Hyperfractionated Acclerated Radiotherapy) : 1.5Gy/#. 3#/day. 36#. Total: 54Gy
  - RT vs CT/RT Benefit: 2 months (at 3 years)

Ann Intern Med. 1996;125:723-729.

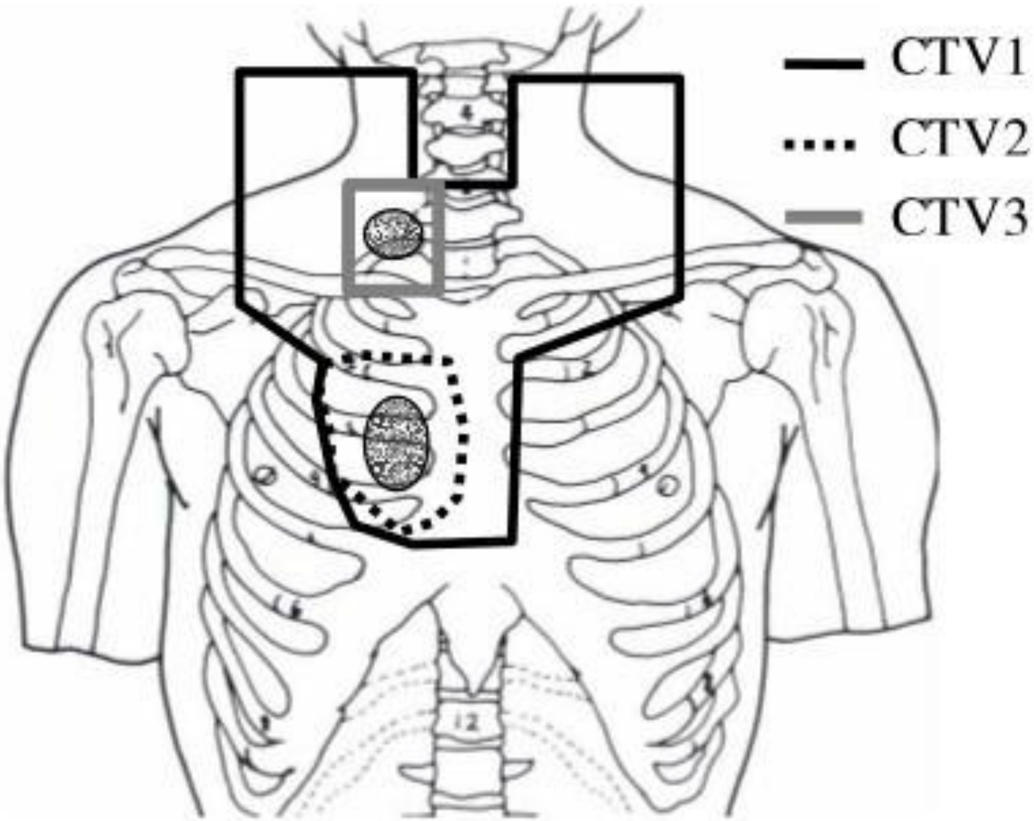
RT Techniques: 2D Planning

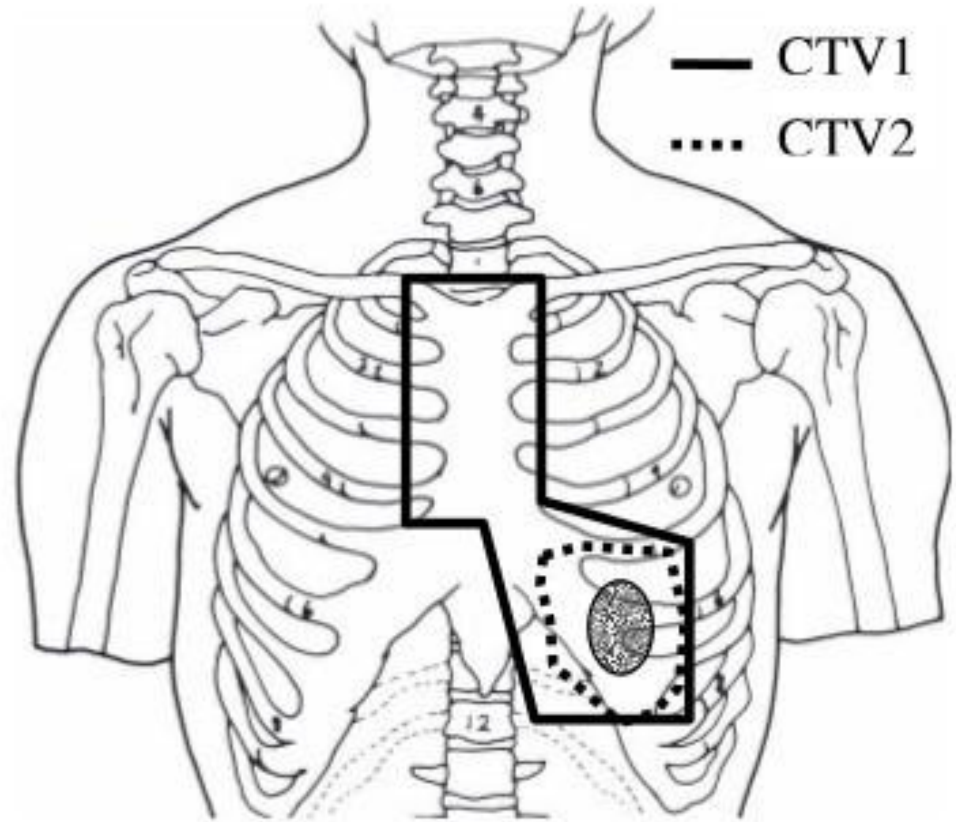
- 2 cm margin around any gross tumor.
- 1 cm margin around regional LN groups.

- Upper lobe tumor: B/L supraclav & subcarina.
- Middle lobe tumor: Entire mediastinum

(thoracic inlet to 8 cm below carina)

- Lower lobe tumor: Entire mediastinum from thoracic inlet to diaphragm.


CTV1
CTV2
CTV3
12


CTV1
CTV2
12

RT Techniques: 3DCRT

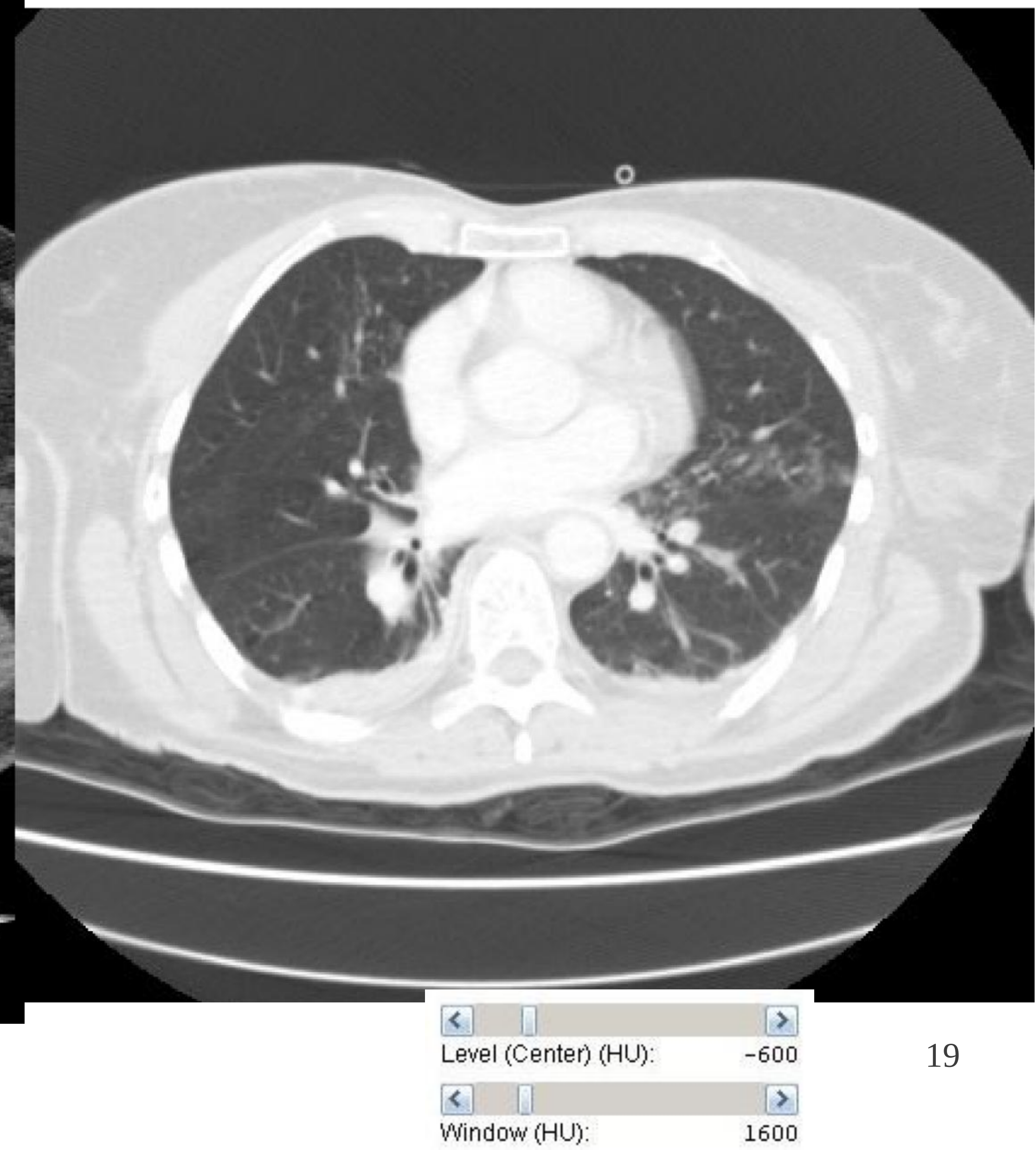
- CT Scan in treatment position. (optional Styrofoam)
- GTV : primary tumor & any gross lymph nodes.
- CTV : Area thought to harbor micrometastasis (hilar / mediastinal LN, Margin).
- PTV: Margin for physiologic organ motion during treatment and daily inaccuracies.

Bethesda, MD: ICRU; 1993:50

GTV

- Visible tumor by any imaging modality.
- Pulmonary extent: on pulmonary windows. ● Mediastinal extent: mediastinal windows.
- Lymph node >1 cm in shortest: +ve (15% chance)
- FDG-PET : quite important. (collapse vs tumor, LNs)


Level (Center) (HU): 40
Window (HU): 400


Level (Center) (HU): -600
Window (HU): 1600

CTV

- Contains gross and microscopic disease.
- GTV-to-CTV : 6 mm for squamous cancers 8 mm for adenocarcinomas to cover the gross tumor and microscopic disease with 95% accuracy. For others, 8mm.
- In the absence of radiographic proof of invasion, CTV of primary lesion should not extend into the chest wall or mediastinum.
- CTV expansions of lymph node disease should not extend into the major airways or lung.

Giraud P et al. Evaluation of microscopic tumor extension in NSCLC for 3D-CRT planning.
Int J Radiat Oncol Biol Phys 2000;48:1015-1024.

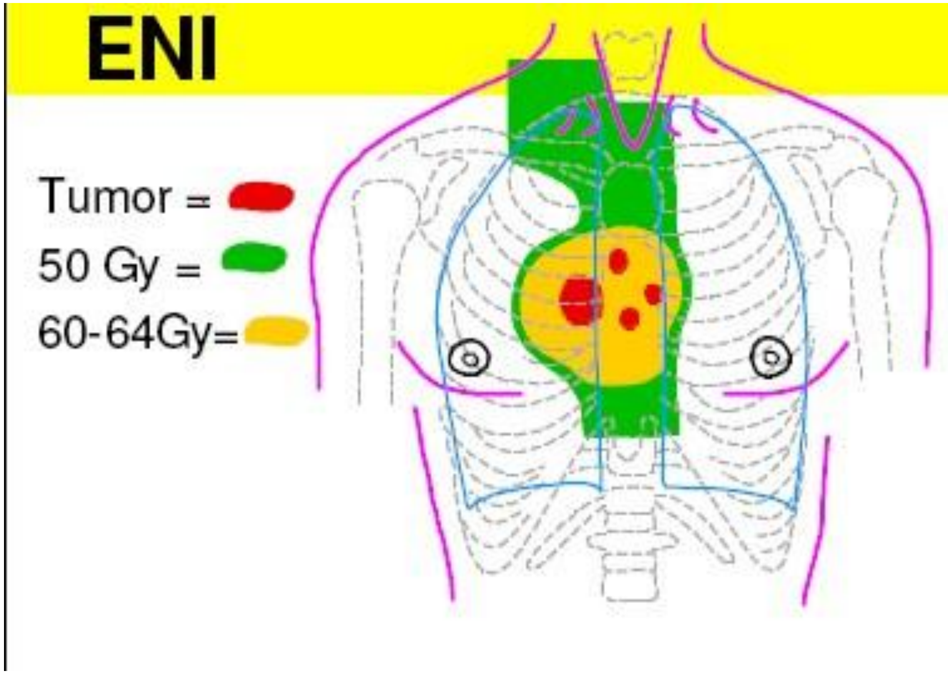
PTV

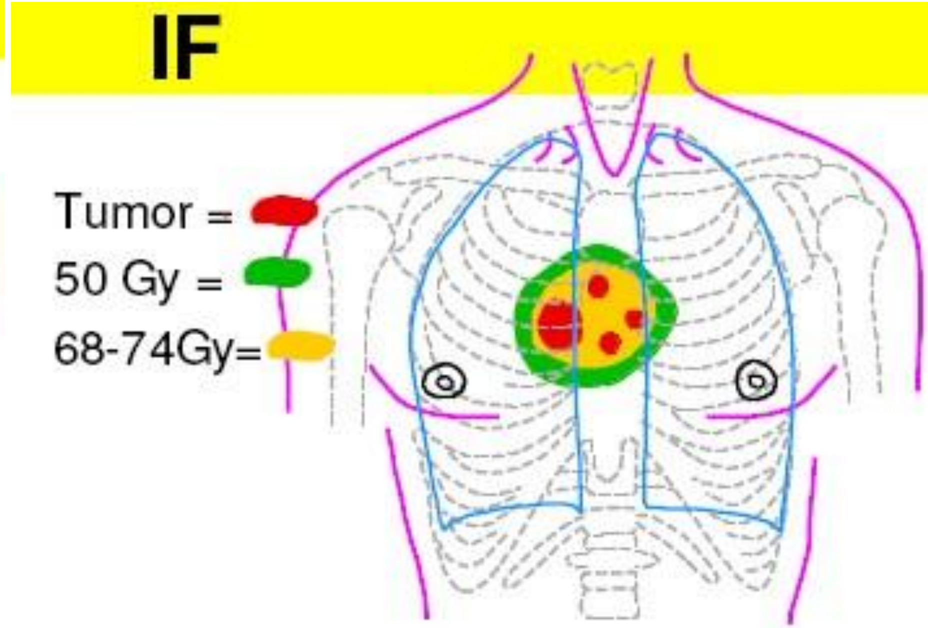
- CTV + margin for daily setup error and target motion.
- 4D CT study, 50% of the tumor moves > 5 mm 13% moves > 1 cm (more when near diaphragm)
- Individual assessment is recommended.
- Breath holding, Gated techniques.
- ITV : Only takes the organ movements.

ICRU 62

Dose and volume

- Gross disease i.e. primary and involved nodes: 65-70 Gy (+/- CT)
- Elective nodal irradiation not recommended





More radiation pneumonitis with ENI (29% vs.17%, P = 0.044).

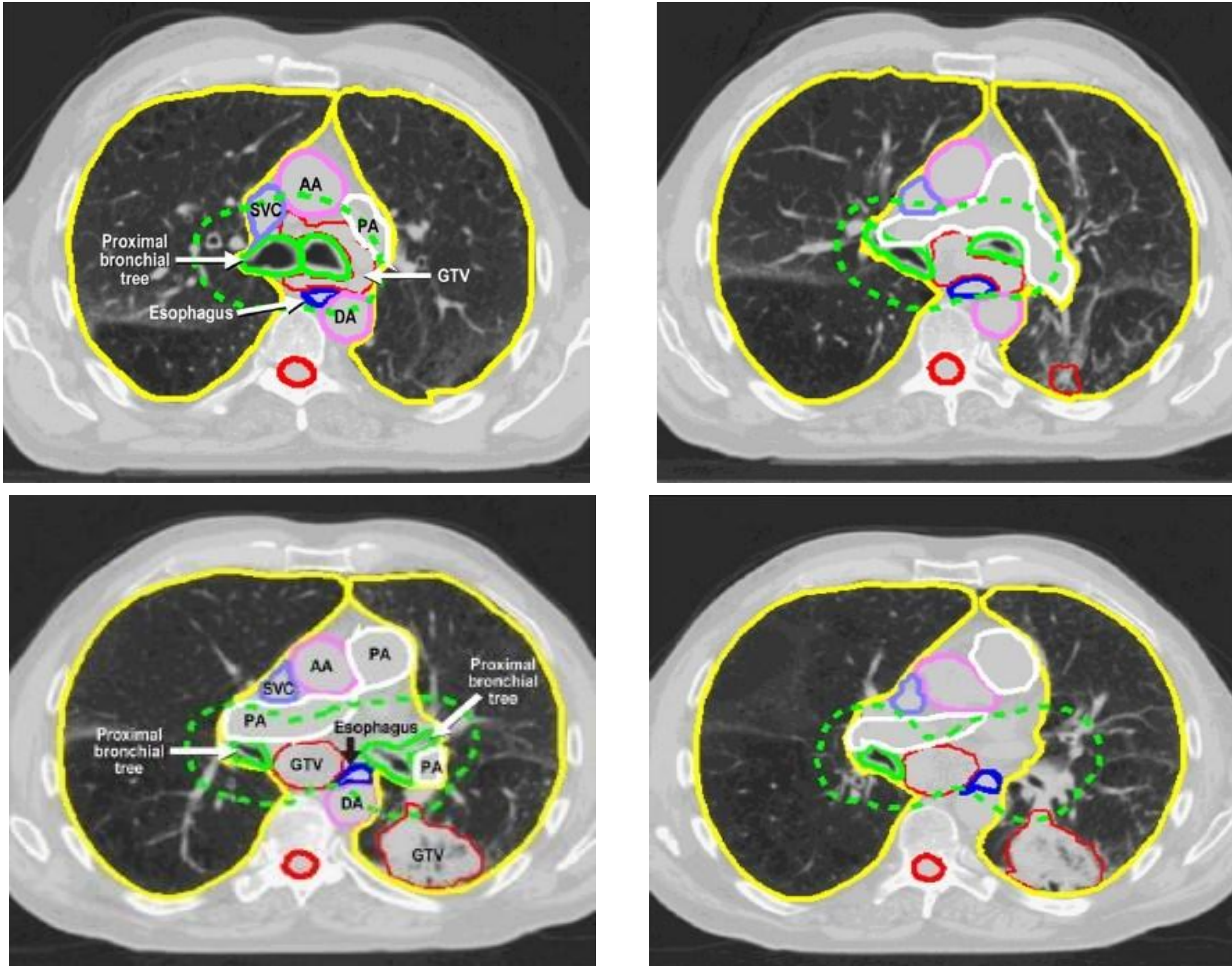
RTOG 1106 Required OARs

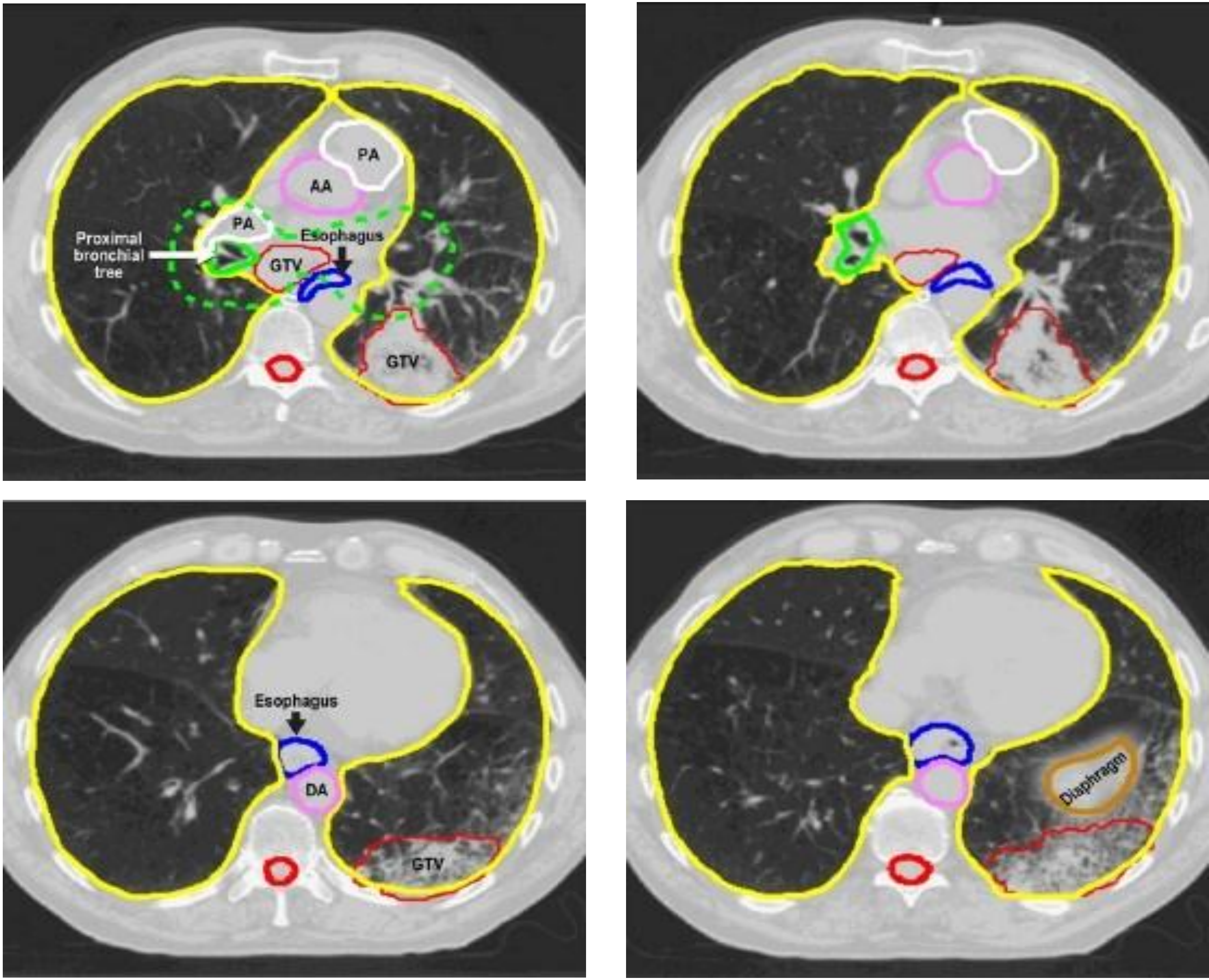
Structure	Instructions
Lung	Both lungs should be contoured using pulmonary windows. The right and left lungs can be contoured separately, but they should be considered as one structure for lung dosimetry. All inflated and collapsed, fibrotic and emphysematic lungs should be contoured, small vessels extending beyond the hilar regions should be included; however, GTV, hilars and trachea/main bronchus should not be included in this structure.

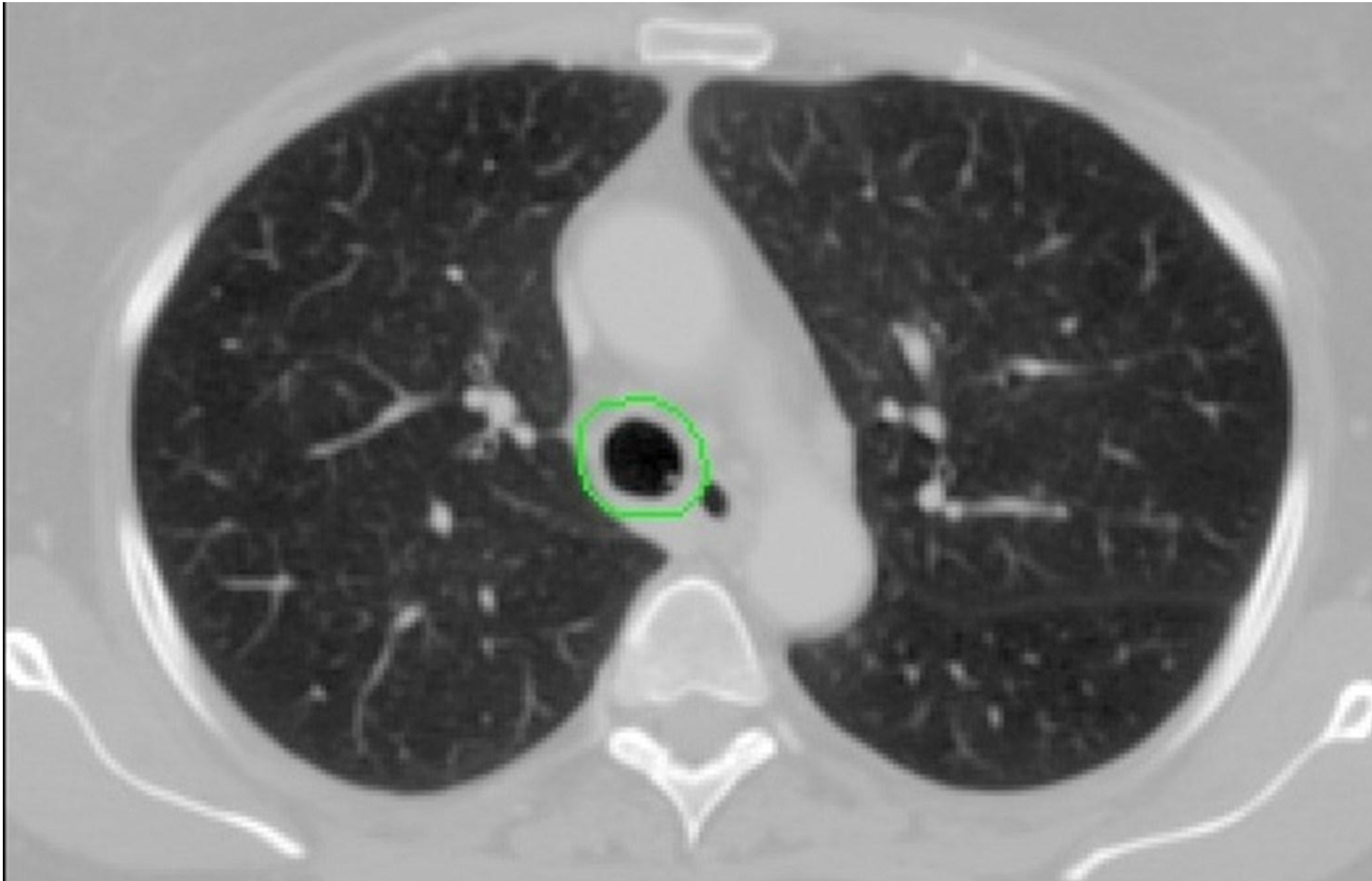
Heart	The heart will be contoured along with the pericardial sac. The superior aspect (or base) will begin at the level of the inferior aspect of the pulmonary artery passing the midline and extend inferiorly to the apex of the heart.

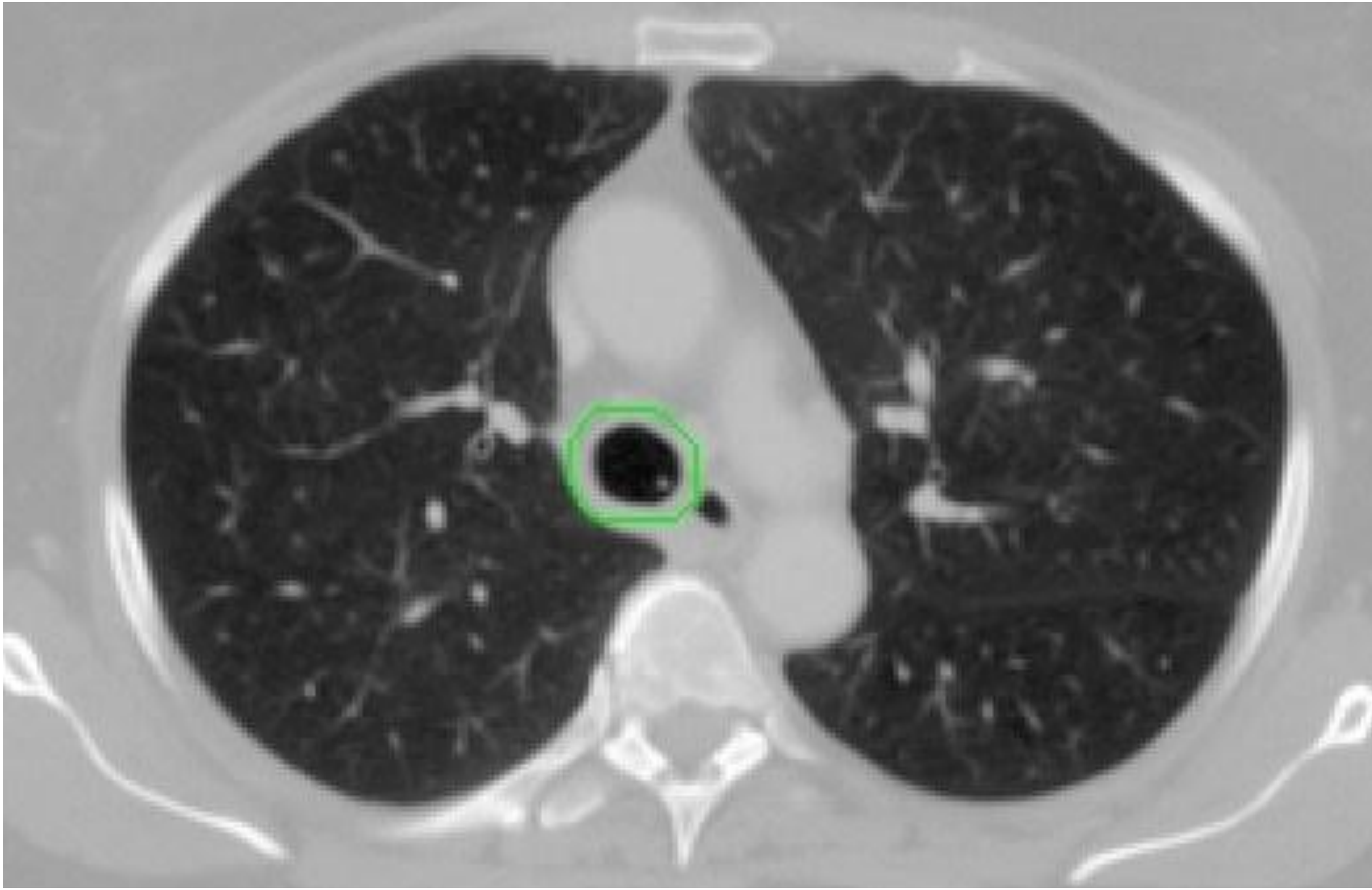
Esophagus	The esophagus should be contoured from the beginning at the level just below the cricoid to its entrance to the stomach at GE junction. The esophagus will be contoured using mediastinal window/level on CT to correspond to all muscular layers out to the fatty adventitia.

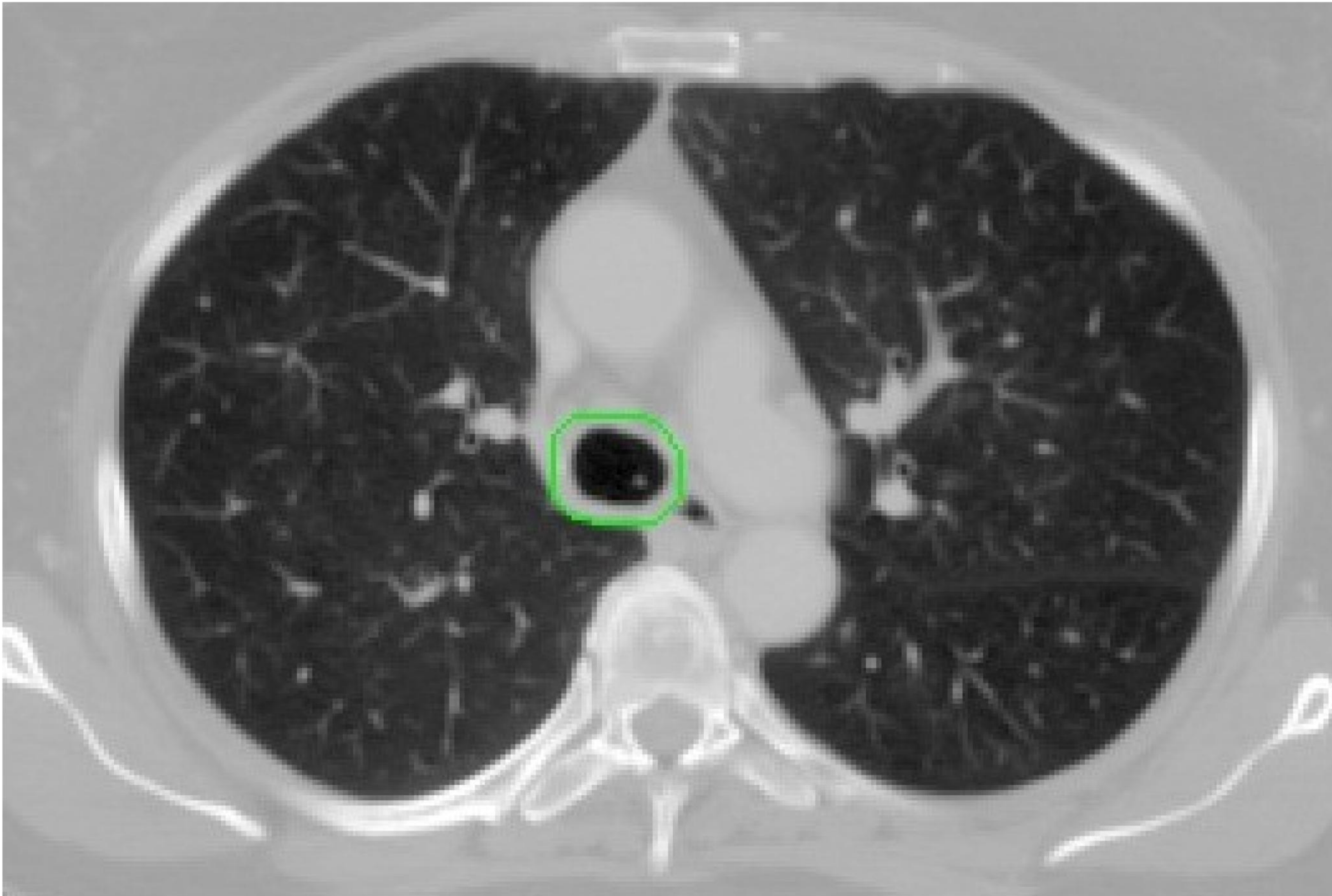
Spinalcord	The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at the level just below cricoid (base of skull for apex tumors) and continuing on every CT slice to the bottom of L2. Neuro formanines should not be included.
Brachial plexus	This is only required for patients with tumors of upper lobes. Only the ipsilateral brachialplex is required. This will include the spinal nerves exiting the neuro foramine from top of C5 to top of T2.. 27

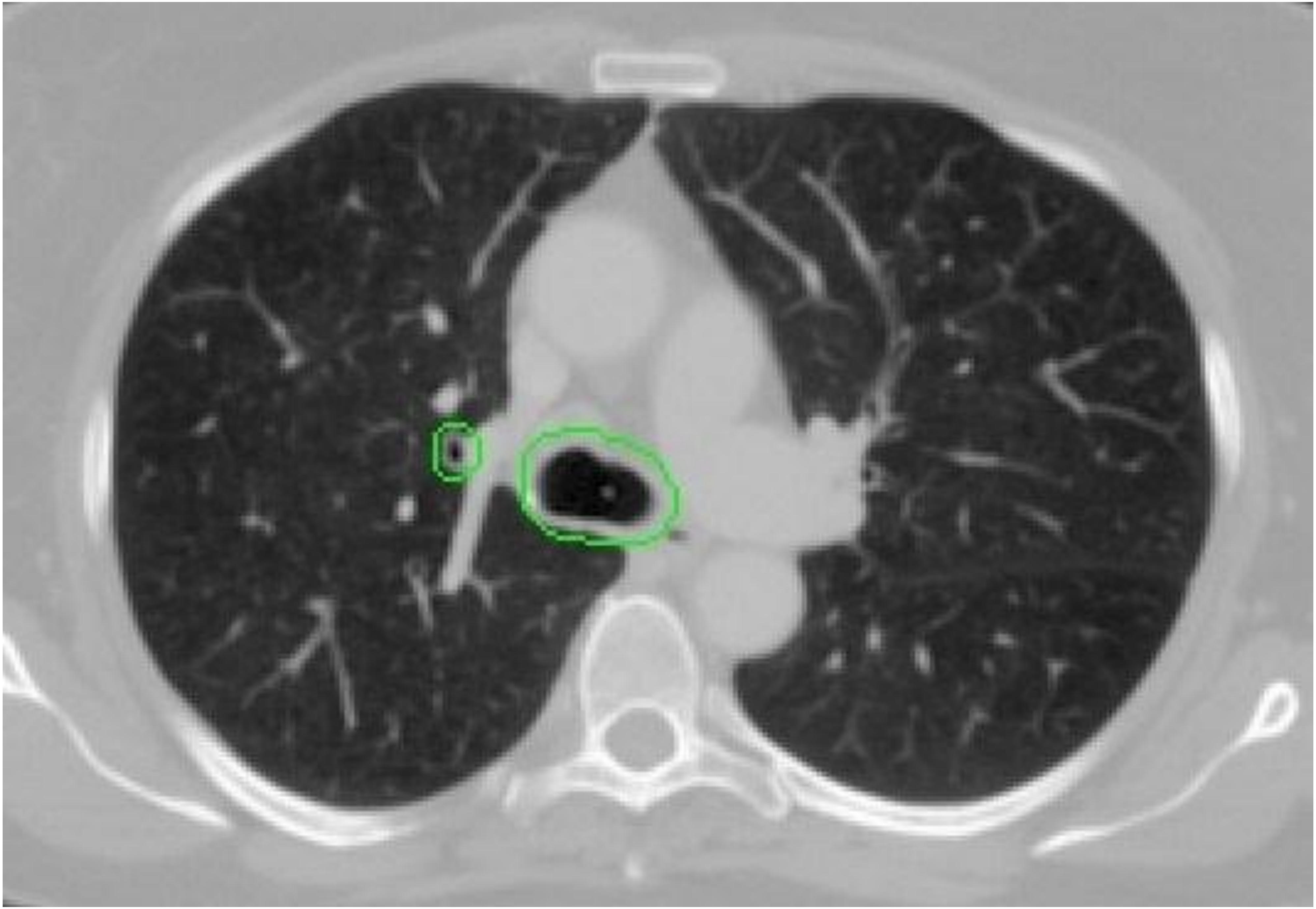

AA
SVC
PA
Proximal bronchial tree
GTV
Esophagus
DA
AA
PA
SVC
PA
Proximal bronchial tree
Esophagus
Proximal bronchial tree
GTV
PA
DA
GTV

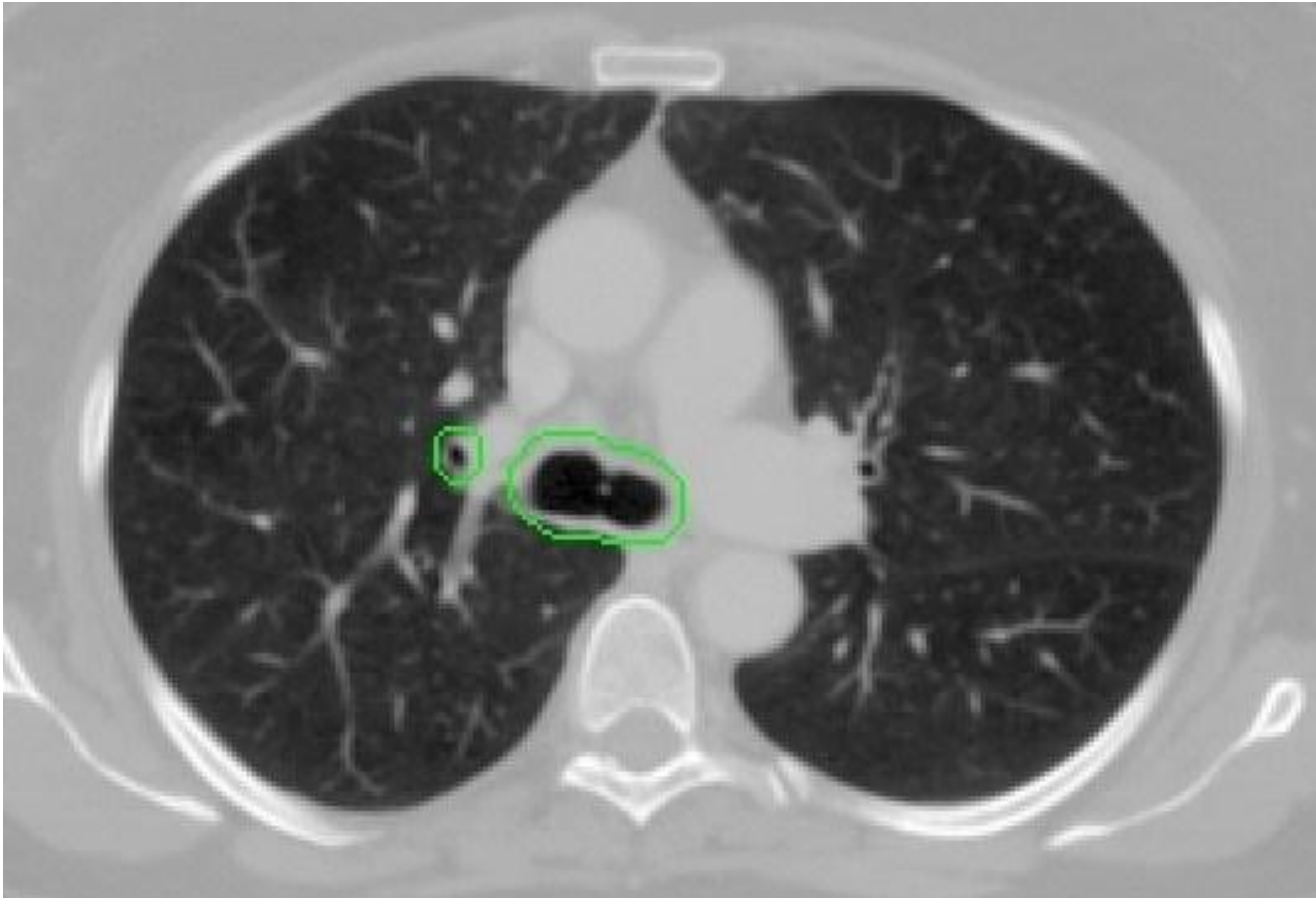

PA
AA
PA
Proximal bronchial tree
Esophagus
GTV
GTV
Esophagus
DA
GTV
Diaphragm

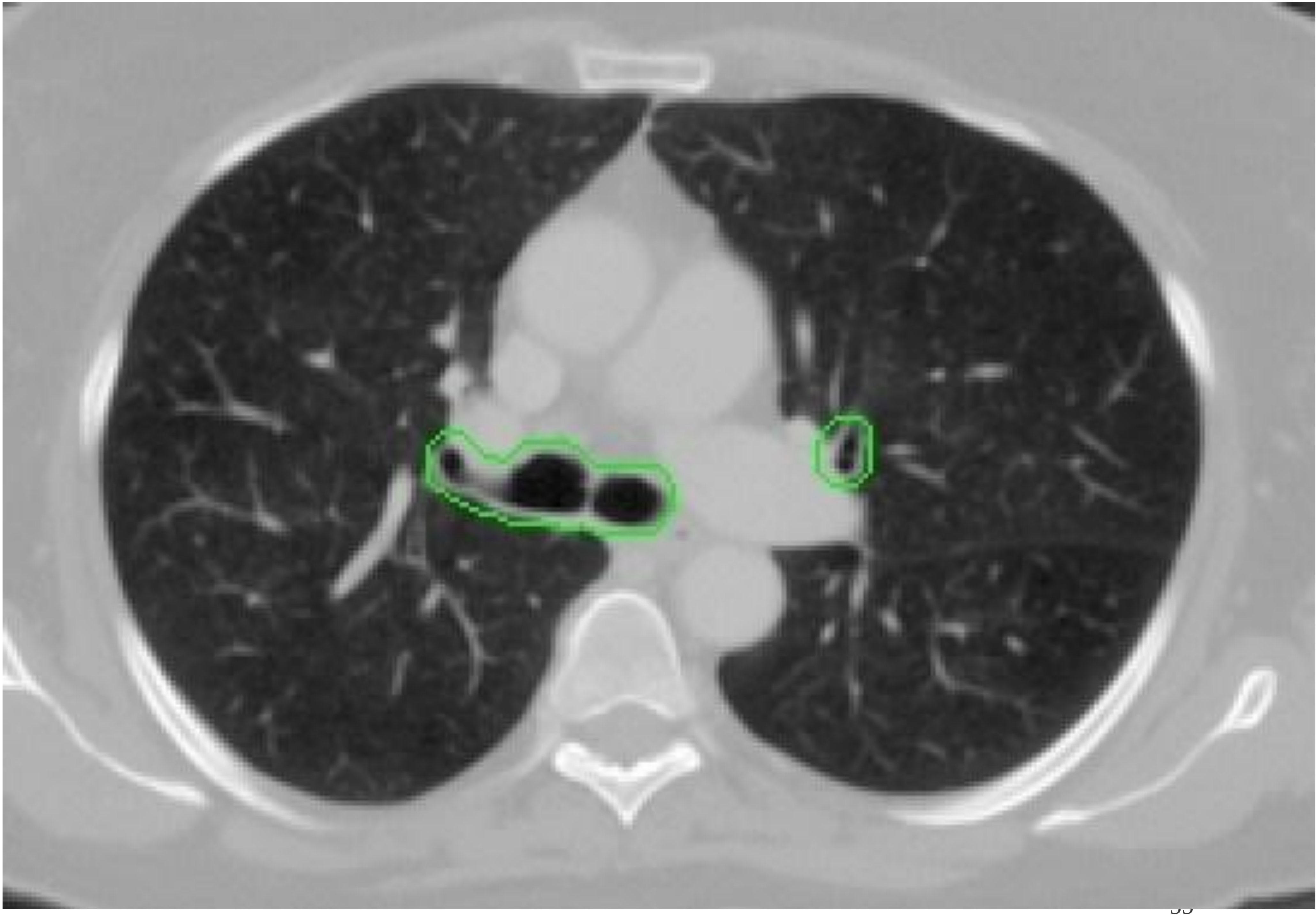


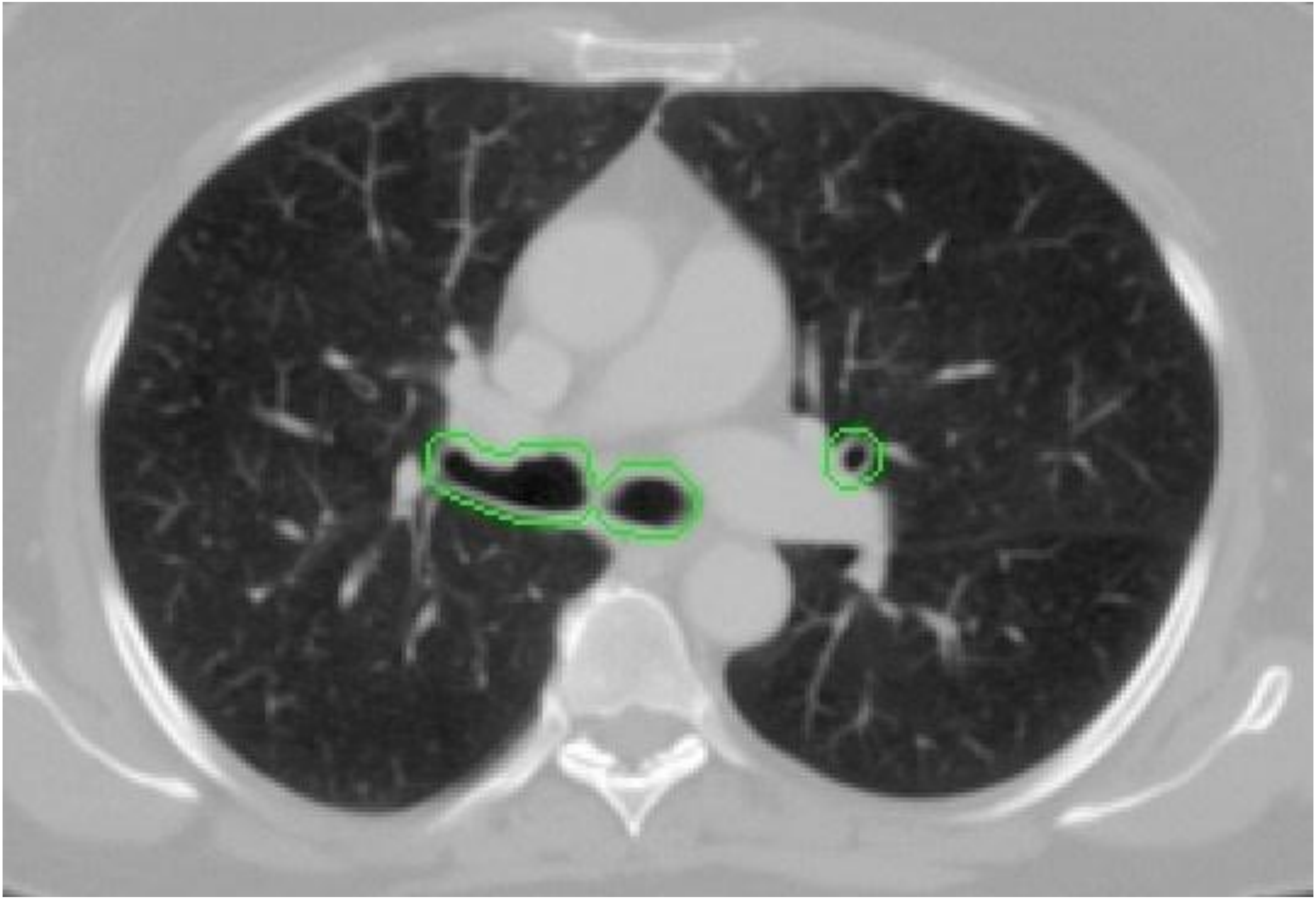


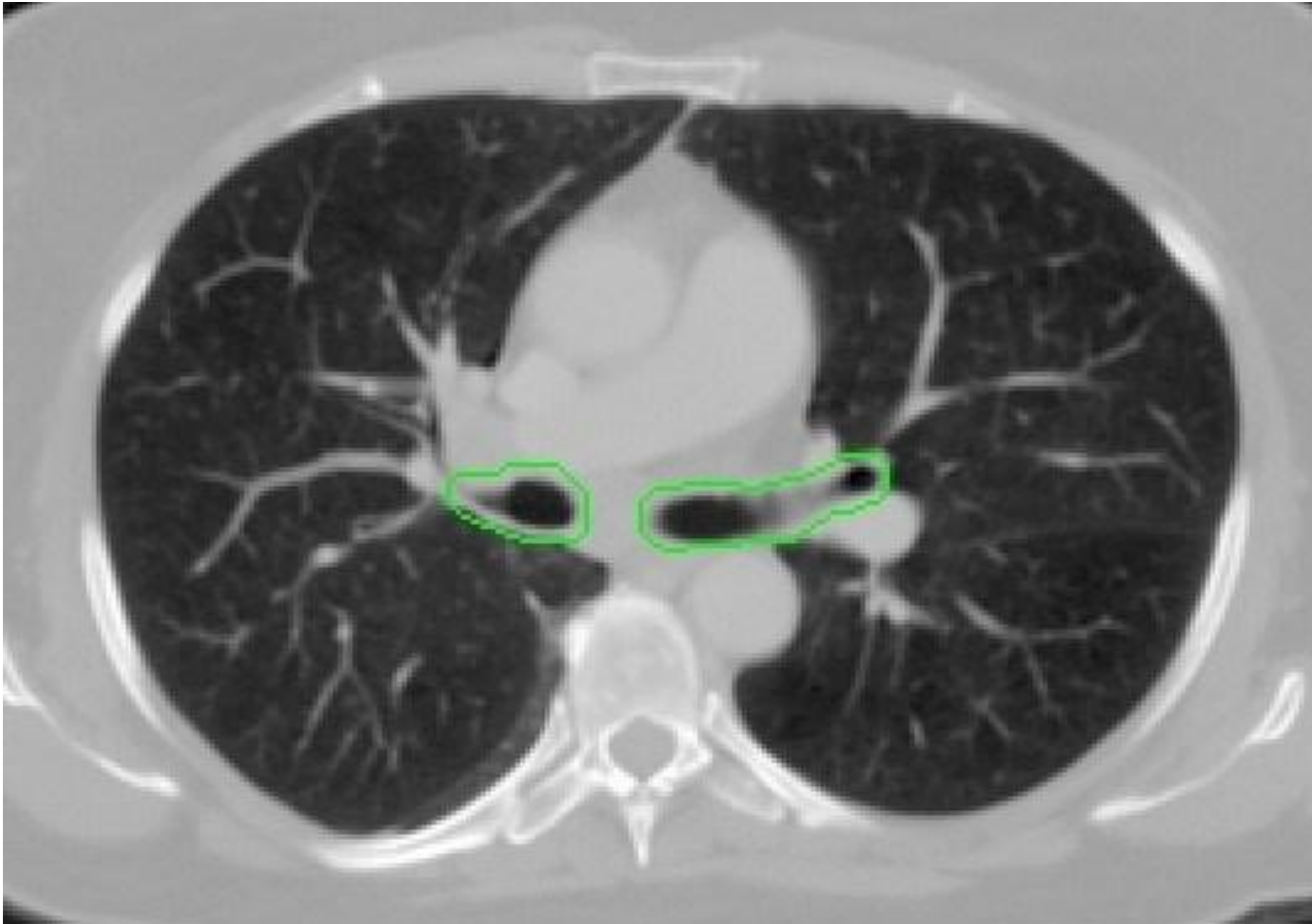


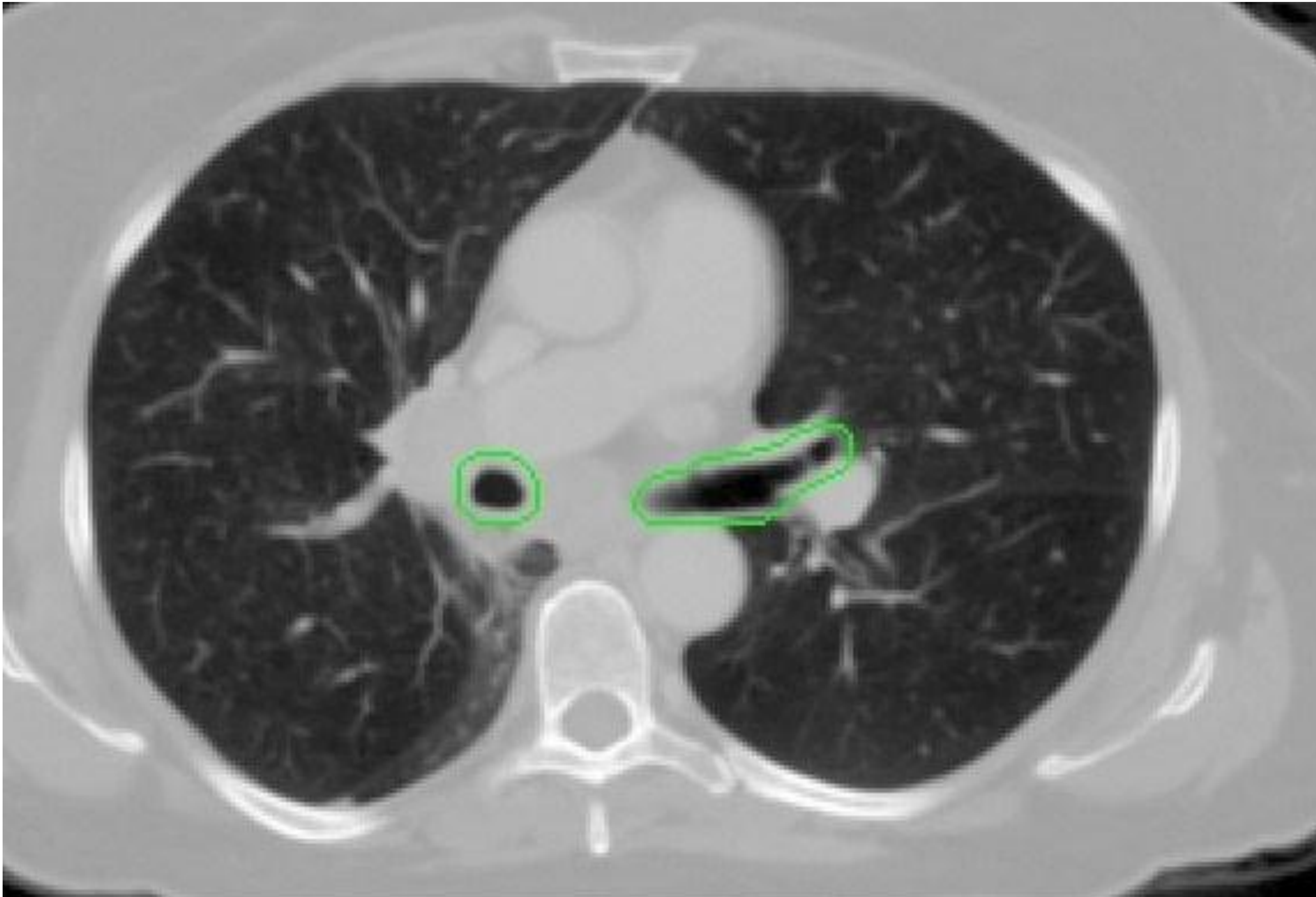


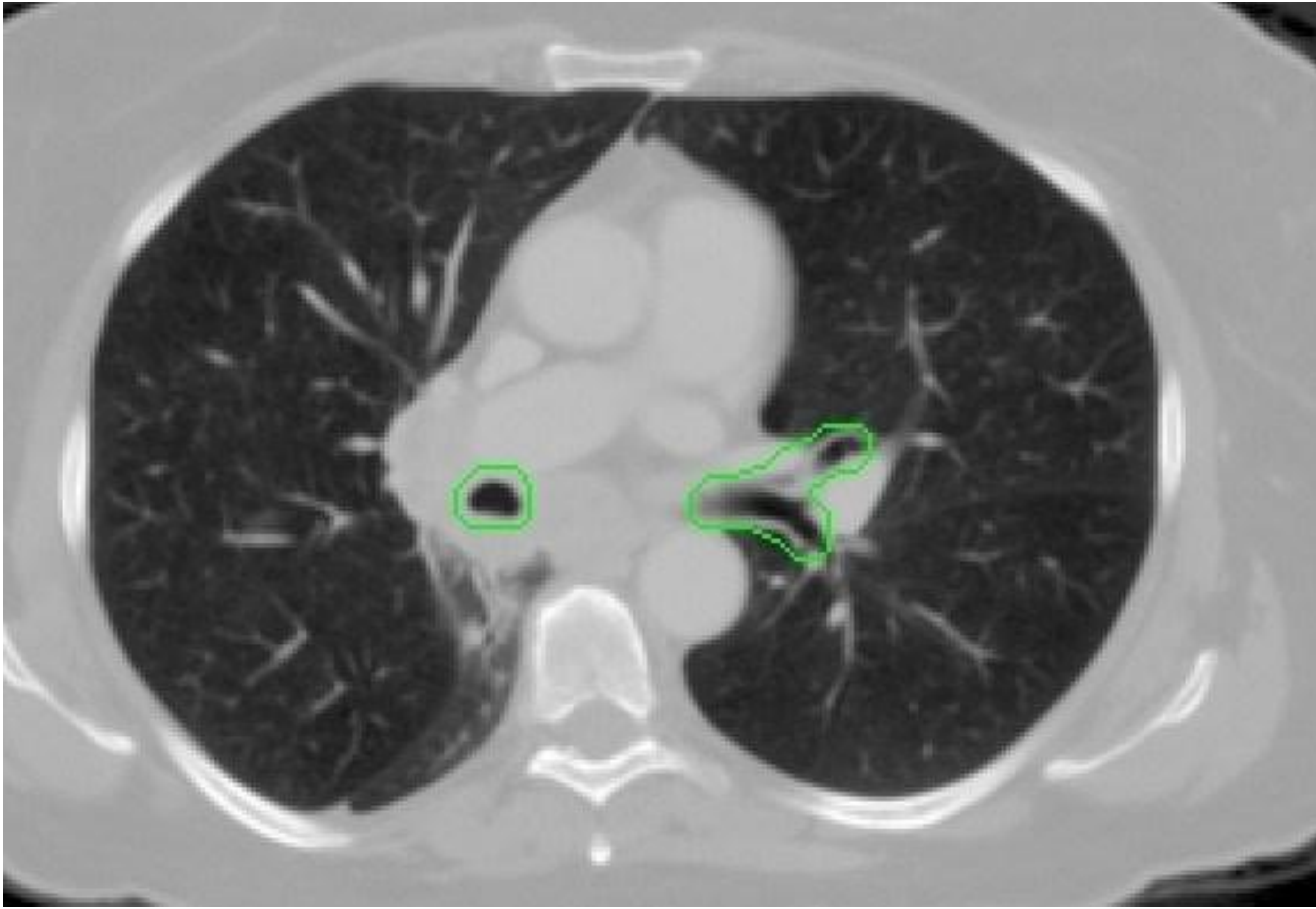


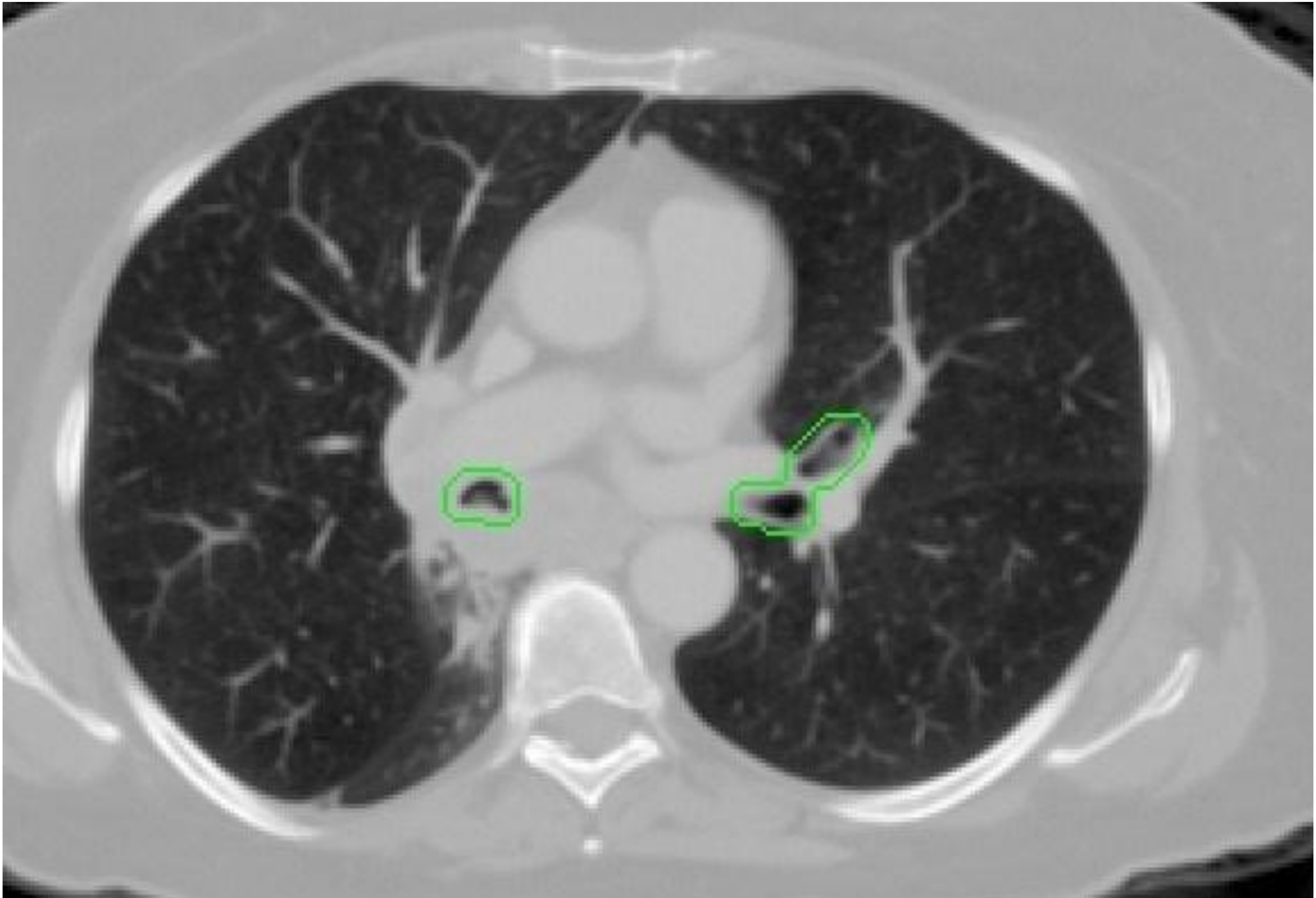


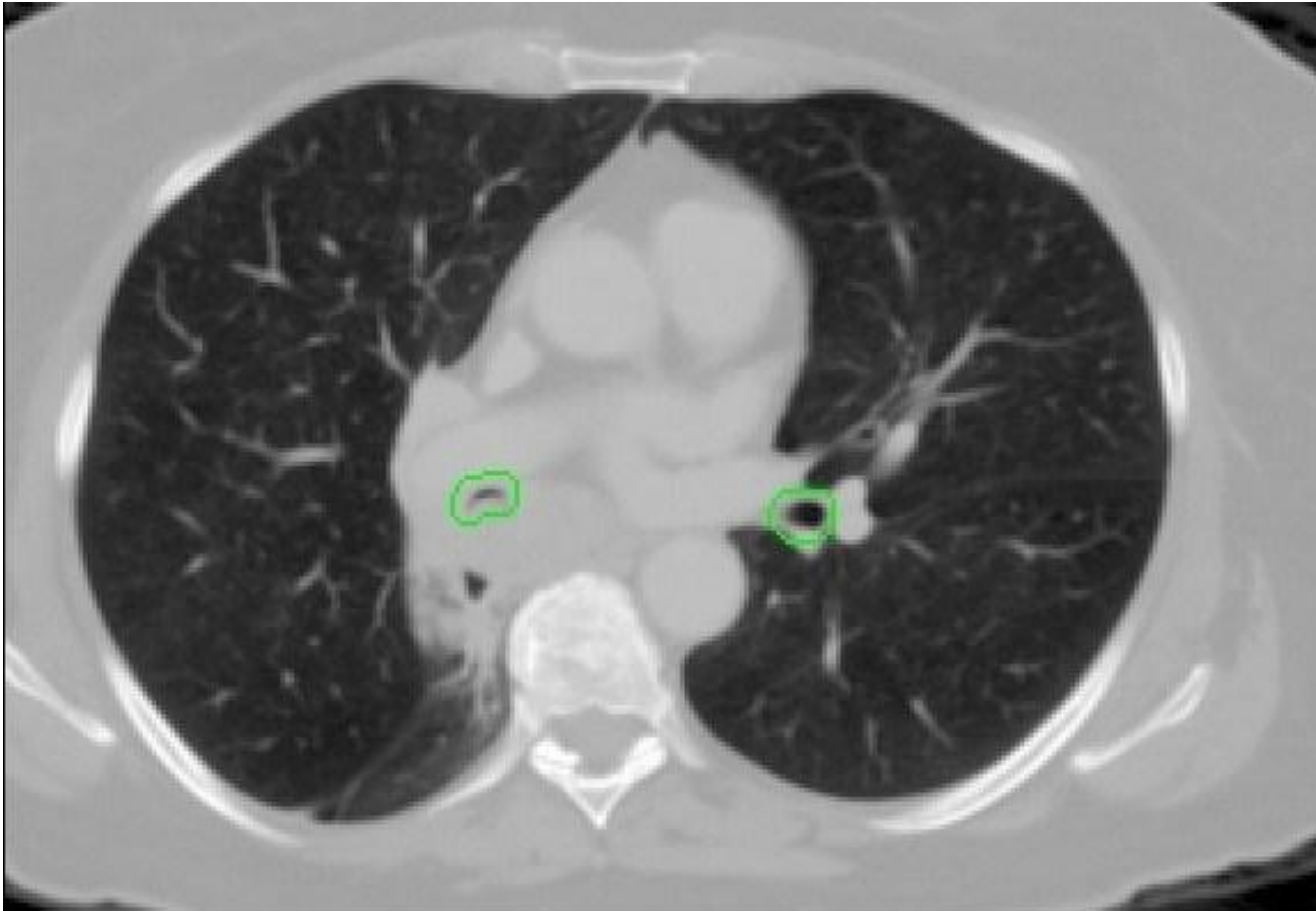


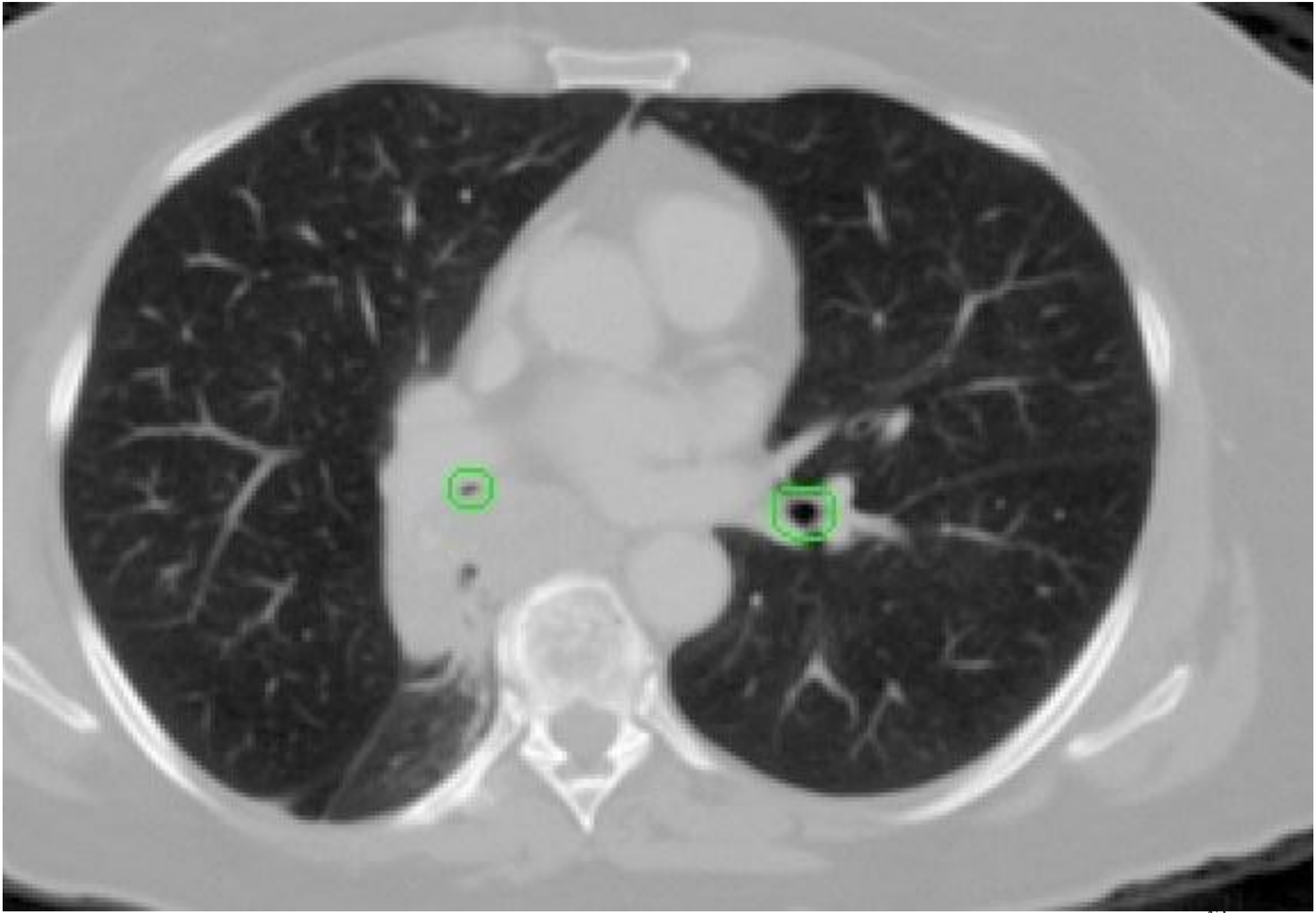


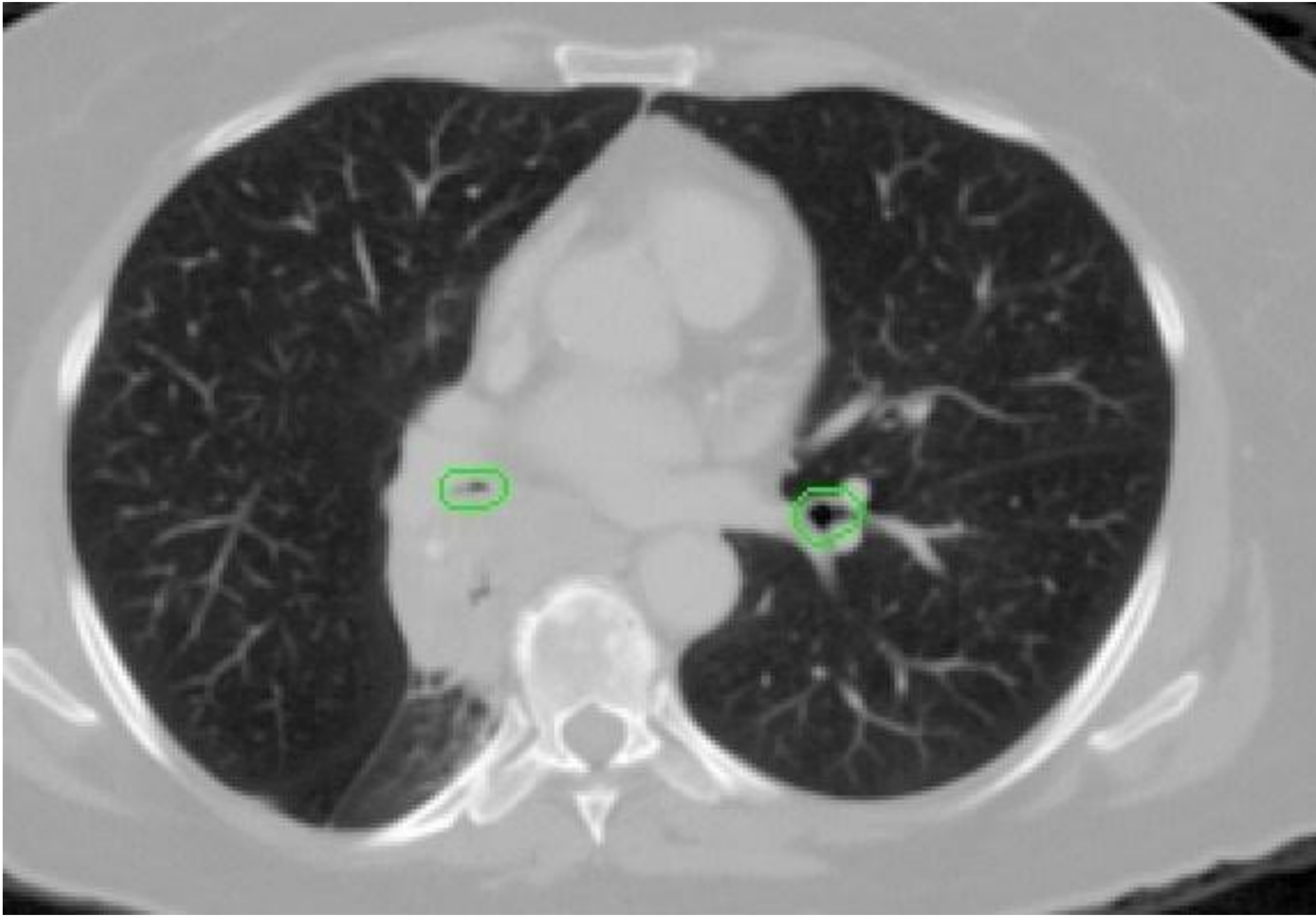












Dose-Volume Constraint

Organ	RT Alone	Chemo/RT
Cord	50 Gy	45 Gy
Lung	MLD <20 Gy	MLD <20 Gy
	V20<40%	V20 <35%
		V10 <45%
		V5 <65%
Heart	V40 <50%	V40 <50%
Esophagus	Dmax <75 Gy	Dmax <75 Gy
	V60 <50%	V55 <50%

Kidney	20 Gy (<50% of combined both kidneys or <75% of one side of kidney if another kidney is not functional)	Same as RT
Liver	30 Gy (<40%)	Same as RT

M.D. Anderson

IMRT

- Dose escalation without big dose to surrounding tissue.
- Benefits in Prostate and Head & Neck.
- Scientists were skeptical about IMRT in Lungs due to assumption that IMRT may deliver low yet

damaging doses to a larger volume of normal lung tissue.

- Movement of a tumor because of respiration introduces another level of complexity to both the IMRT dosimetry and the technique used.

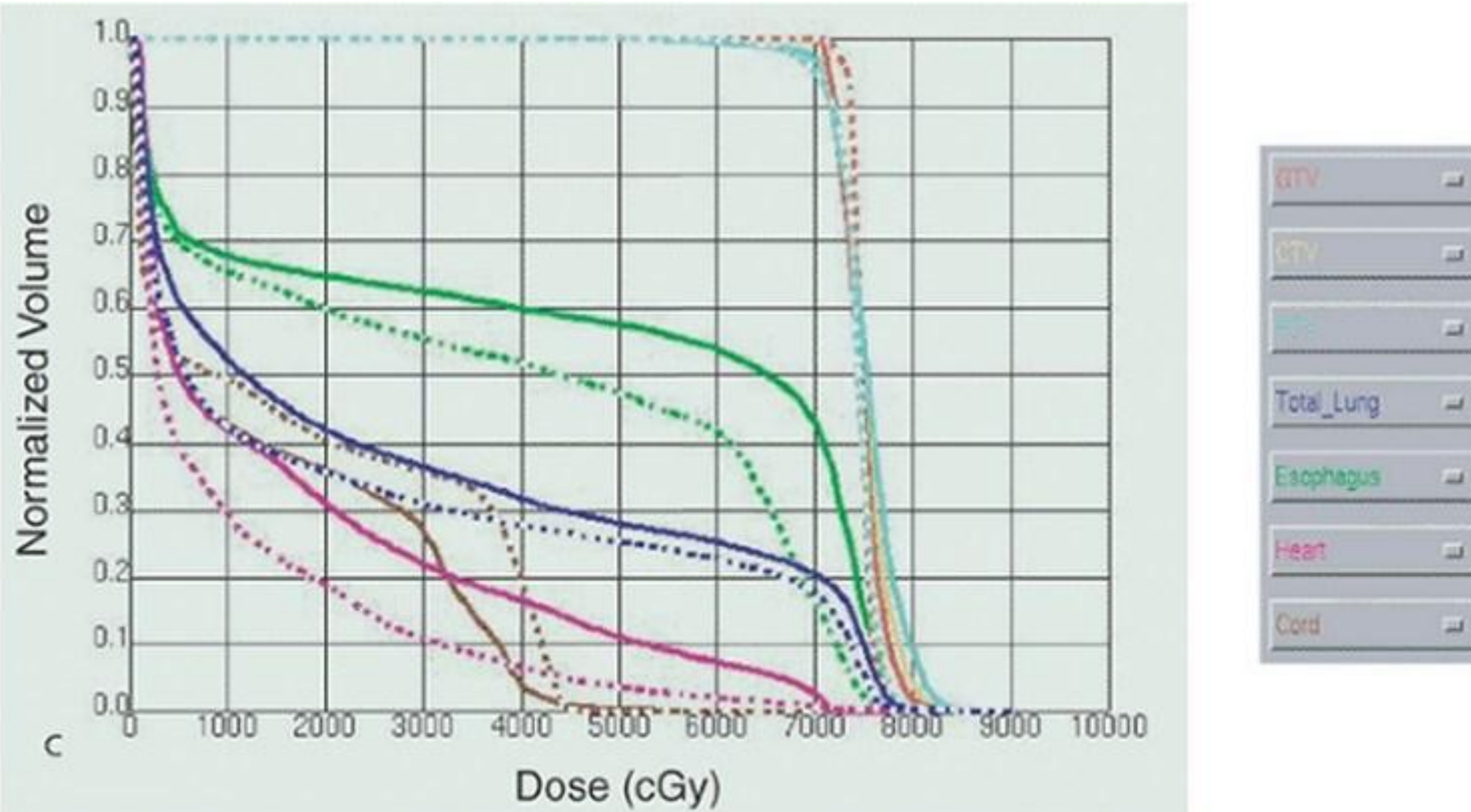
IMRT

- Found that IMRT may be more suitable than 3D CT treatment planning for cases of advanced-stage disease with a larger GTV.
- Median absolute reduction of lung volume irradiated above 10 and 20 Gy were 7% and 10%, respectively.

- >2 Gy less mean total lung dose and 10% decrease in the risk of radiation pneumonitis.
- Heart, Esophagus, thoracic tissue dose decreased.

Liu H, Wang X, Dong L, et al. Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;58:1268-1279.

Murshed H, Liu H, Liao Z, et al. Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage nonsmall-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;58:1258-1267.


Normalized Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Dose (cGy)
c
Total_Lung
Esophagus
Heart
Cord

IMRT

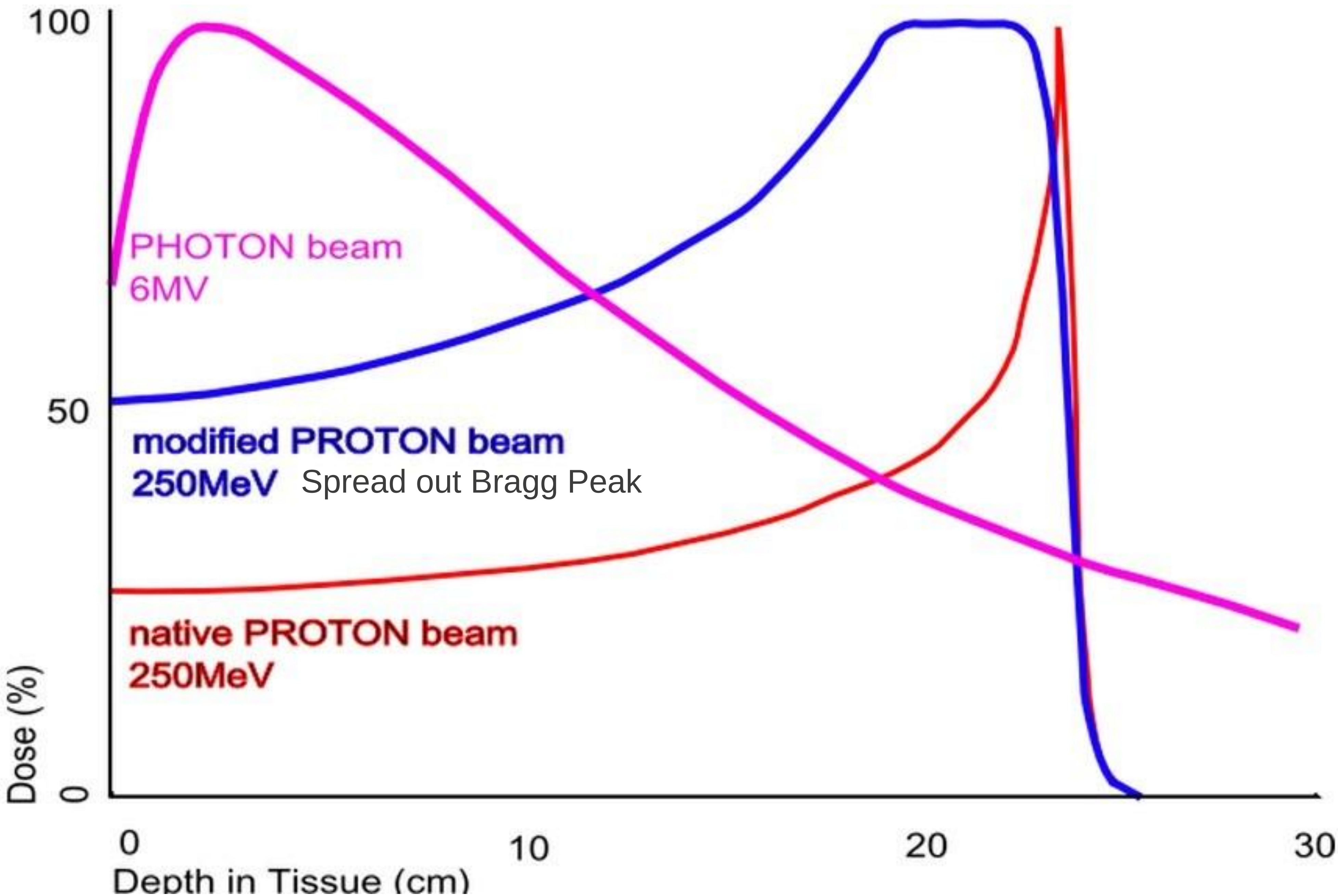
- Tumors in the superior sulcus or close to the esophagus or spinal cord or patients with positive lymph nodes may benefit more.
- Earlier-stage, small mobile tumors may not be good candidates for IMRT

Chang J, Liu H, Komaki R. Intensity modulated radiation therapy and proton radiotherapy for non-small cell lung cancer. Curr Oncol Rep 2005;7:255-259.

Proton Beam

- Well-defined range of penetration.
- By modulating the Bragg peak across the target volume, proton beams can deliver a full, localized, uniform dose of energy to the treatment site while sparing the surrounding normal tissues.
- In combination with IGRT.
- Results comparable to surgery in stage IA.

Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;56:7-13.


100
50
0
Dose (%)
PHOTON beam
6MV
modified PROTON beam
250MeV
Spread out Bragg Peak
native PROTON beam
250MeV
0
10
20
30
Depth in Tissue (cm)

Palliative Radiotherapy

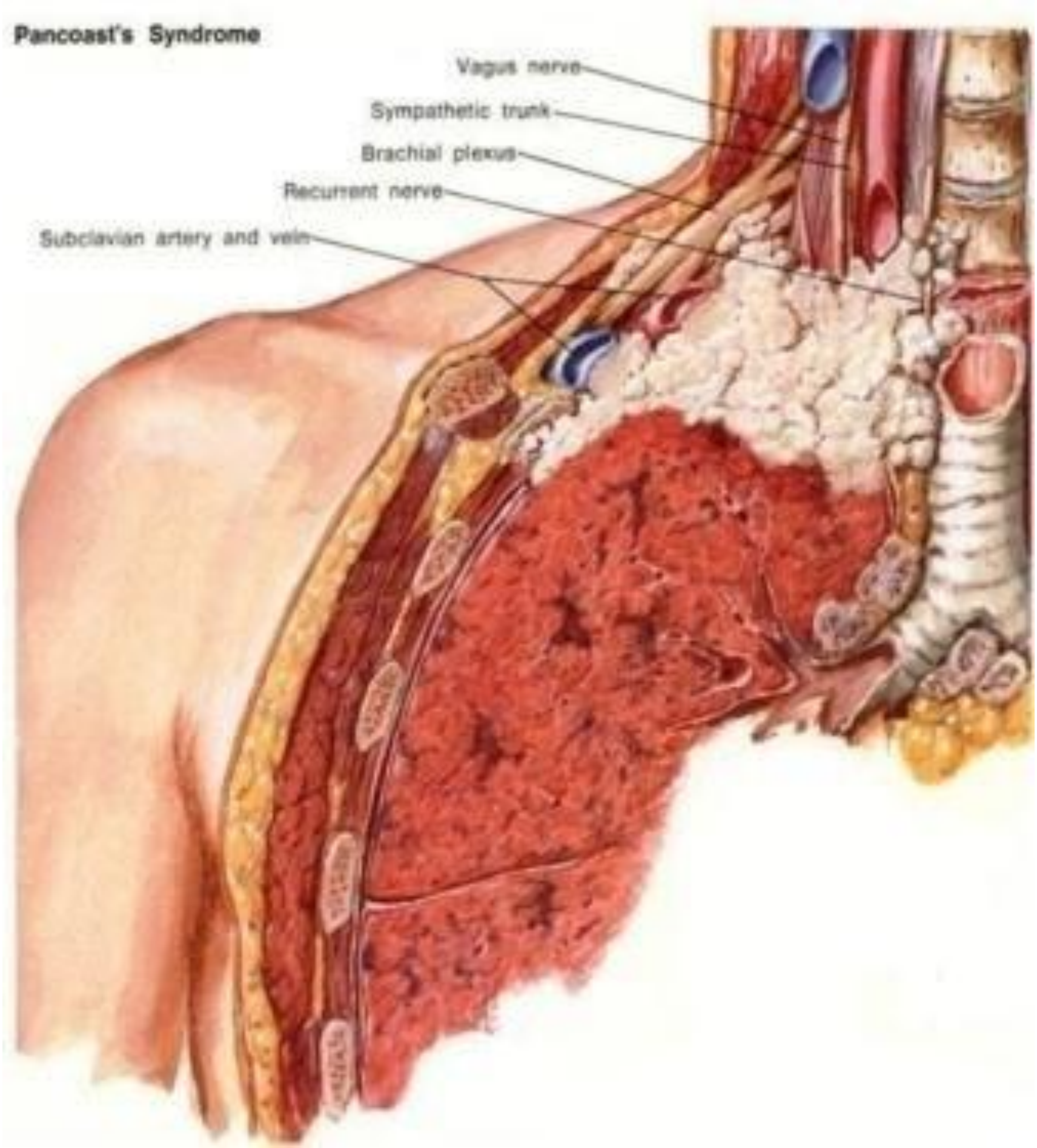
- Stage IIIB/IV
- 40Gy/20# vs 30Gy/10# → No difference.
- 20Gy/10# for short term palliation.

TABLE 2
Prospective Trials That Compared Fractionation Schemes in Patients with Nonsmall Cell Lung Cancer

Reference	No. of patients	Stage/Performance	Dose, Gy	Fractions	Survival, Months	Symptom response/comment
Simpson et al, 1985[23]	409	Inoperable, stage IIIB	30	10	6	Overall 69%/No difference between the 3 arms
			40	20	6	
			20	20 (Split)	6	
Teo et al, 1988[24]	291	Inoperable	45	18	5	71% ($P = .02$)
		Mostly stage IIIA or IIIB	31.2	4	5	54%
MRC, 1991[25]	369	Inoperable/Good performance	17	2	6	65–81%
			27 or 30	6 or 10	6	56–86%
MRC, 1992[26]	235	Inoperable/Poor performance	17	2	3	48–75%
			10	1	4	55–72%
Abratt et al, 1995[27]	84	Unresectable/WHO 0-1	35	10	8.5	68% ($P = .07$)/More esophagitis in 45-Gy arm
			45	15	8.5	76%
Macbeth et al, 1995[28]	509	Inoperable, nonmetastatic/ Good performance	17	2	7	More rapid palliative effect
			39	13	9	
Rees et al, 1997[29]	216	Poor performance	17	2	6	No difference between treatment arms
			22.5	5	6	
Plataniotis et al, 2002[30]	92	Poor performance	17	2	5.8	39%
			21.25	5	5.8	36%
Bezjak et al, 2003[31]	230	Mostly locally advanced	10	1	4.2	Better symptom control and QOL in 20-Gy arm
			20	5	6	
Sundstrom et al, 2004[32]	421	Stage III, IV/Mostly KPS 70–80	17	2	8.2	No difference in symptom response or toxicity
			42	15	7	
			50	25	6.8	
Kramer et al, 2005[33]	297	Stage IIIA, IIIB, IV/Mostly ECOG 3–4	16	2	10.9% at 1 y	30 Gy in 10 fractions/Better 22 wk posttreatment
			30	10	19.6% at 1 y	$P = .03$
Senkus-Konefka et al, 2005[34]	100	Inoperable/Median ECOG of 2	20	5	5.3	No difference in symptom control
			16	2	8	$P = .02$

Gy indicates grays; MRC, Medical Research Council; WHO; World Health Organization performance status score; QOL, quality of life; KPS, Karnofsky performance status score; ECOG, Eastern Cooperative Oncology Group performance status score.

Superior Sulcus Tumor


Pancoast's Syndrome
Vagus nerve
Sympathetic trunk
Brachial plexus
Recurrent nerve
Subclavian artery and vein

Superior sulcus tumors

- Preoperative RT f/b extended surgical resection: most common treatment.
- Radiotherapy: a primary treatment, for inoperable superior sulcus tumors
- Palliation of pain in up to 90 percent of the patients.
- Doses of 20 to 80 Gy have been used
- A dose of at least 60 Gy is recommended for primary radiotherapy.

NEJM, 1997, 337(19): 1370-76

Small Cell Lung Cancer

- Limited disease: confined to the hemithorax. • Extensive : extends beyond the hemithorax.
- Most of the improvement in outcome was attributed to more effective combination chemotherapy regimens.
- Locoregional therapy alone, either surgery or RT, improved the short-term survival only slightly.

- Role of RT proven once distant metastasis was controlled & local failure was apparent.

Small Cell Lung Cancer

- Thoracic RT and Prophylactic Cranial Irradiation.
- TRT concurrent with chemotherapy.
- Early TRT showed better outcome than late.
- Accelerated hyperfractionation better than daily fractions (5yr survival 28% vs 21%)
- No significant difference in local tumor control or survival with treatment between 45 Gy and 65 Gy when effective chemotherapy was given.

Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung
 cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;11:336-344.

Prophylactic Cranial Irradiation

- Brain metastases -10% at presentation
  - 80% at 2 yrs*
- Irradiation of entire intracranial contents
- Lower border at C2-3 vertebra
- Doses 24 – 30 Gy @ 3 Gy/#
- Increased the 3 year survival from 18% to 26%#

*Cancer 1979:44;1885-1893

#Ann Oncol 2002;13:748-54

Thank you