Non-small Cell Lung Cancer: Locally Advanced

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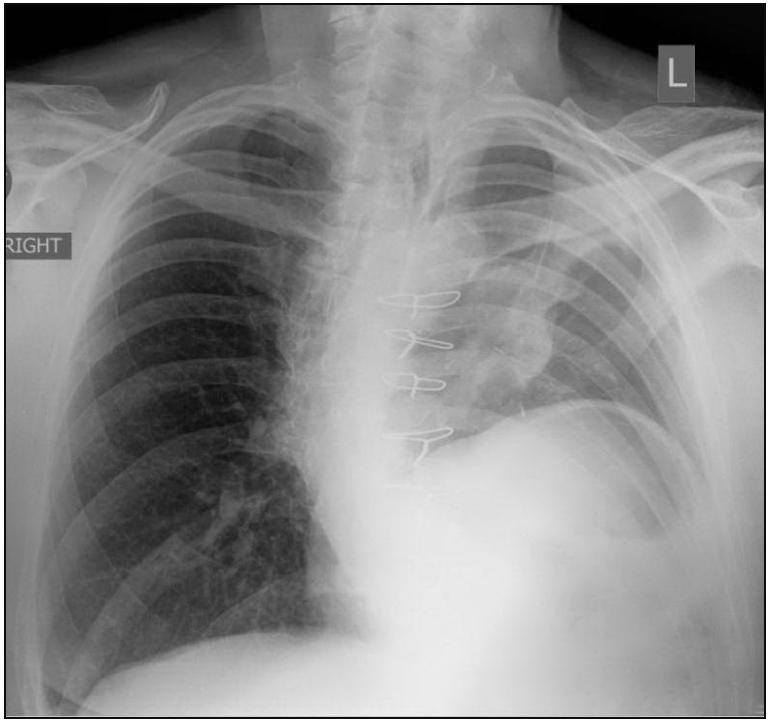
Clinical Presentation

- Presentation:
  - HPI: 66 year-old gentleman who presented with 1 week of hemoptysis. 15 pound weight loss over 6 months. Mild dyspnea on exertion. Denies chest pain or hoarseness.
  - Past medical: hypertension, CAD and MI s/p 4-vessel CABG, PVD, chronic renal insufficiency, GERD
  - Social history: Retired. Lives alone.
    - Smoking: 1-2 packs per day x40 years, quit 1 year before presentation
    - Alcohol: none
    - Illicits: none
  - Physical exam:
    - BP 114/66 HR 58 RR 20 T 35.8 C Wt 168 lbs
    - Well appearing, thin, comfortable.
    - No cervical or supraclavicular lymphadenopathy.
    - Lungs resonant to percussion, clear to auscultation bilaterally without rales, rhonchi or wheezing. No egophany.
    - Mild digital clubbing.
    - ECOG 1
  - Laboratories: Chemistries, CBC, liver enzymes all within normal limits

Chest X-ray

- Left upper lobe mass with elevated left hemidiaphragm suggesting phrenic nerve involvement

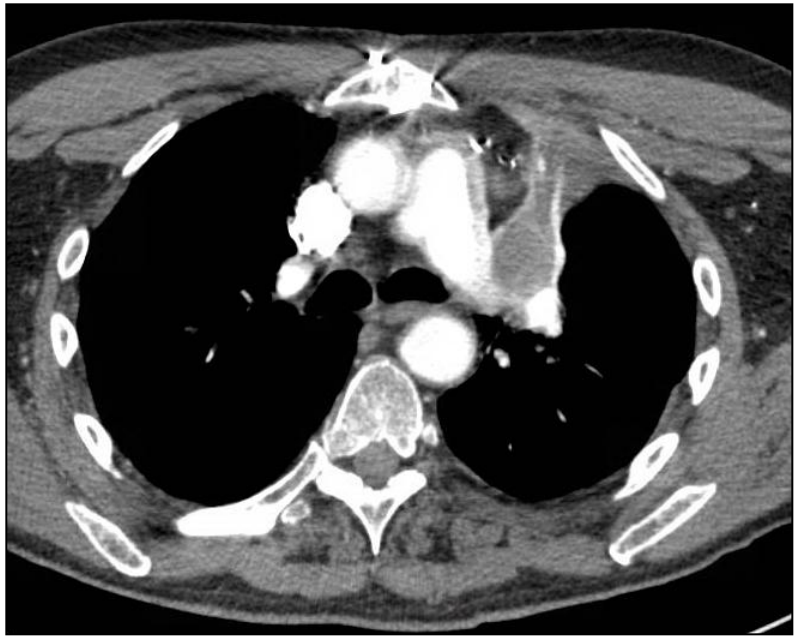


**Note: phrenic nerve involvement = T3 tumor

Diagnostic Work-up

Chest CT

- Left perihilar mass 2.6 cm in greatest dimension, elevation of the left diaphragm, and multiple enlarged bilateral mediastinal lymph nodes



Bronchoscopy with biopsy

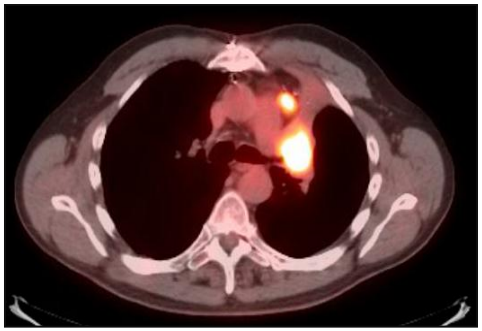
- Fungating mass with oozing blood obstructing the left upper lobe and 85% occlusion of left lower lobe.

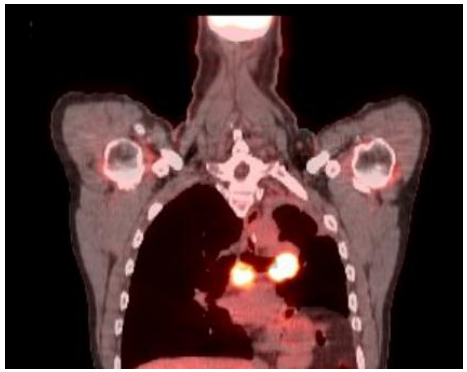
- Biopsies:
  - Distal left mainstem bronchus = squamous cell carcinoma, moderately differentiated
  - FNA of right subcarinal adenopathy = atypical cells, carcinoma cannot be excluded

Diagnostic Work-up

PET/CT

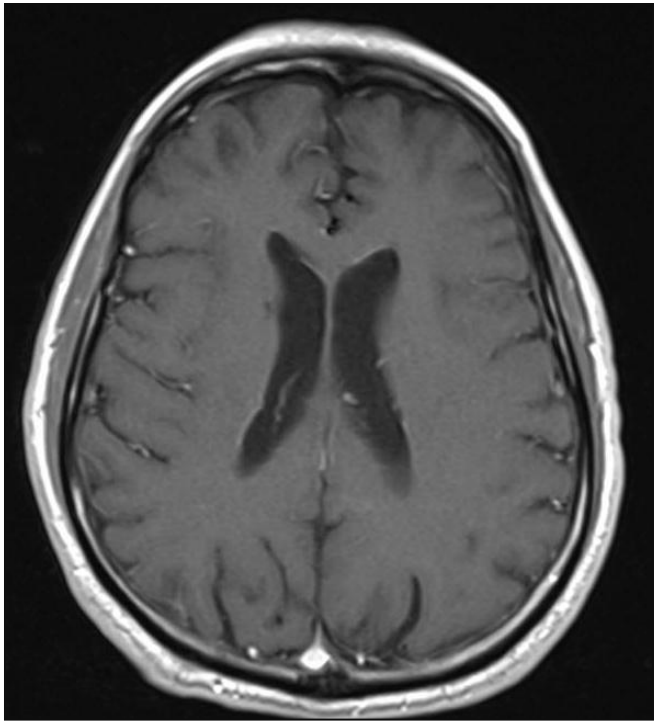
- Primary left upper lobe/hilar malignancy (SUV 14.0), enlarged paraaortic lymph node (SUV 10.1), and FDG avid subcarinal lymph node.





MRI brain

- No gross metastatic disease. Old ischemic changes and lacunar infarcts seen.



Work-up

Mediastinoscopy

- **Required to rule-in or rule-out N2 and/or N3 nodal disease.**
- Prominent lymph nodes were identified at 2R, 4R, 4L, and 7.
- Pathology demonstrated metastatic squamous cell carcinoma at all sampled levels.

Pulmonary function tests

- **Important in inoperable cases to evaluate post-treatment changes in lung function**
- FEV1 66% predicted
- DLCO 50% of predicted

**Rule of thumb:

Pneumonectomy: FEV1 >80%, DLCO >50%
Lobectomy: FEV1 >70%

Final Diagnosis

- **Non-small cell lung cancer (squamous cell carcinoma) of the left upper lobe**
  - T3 = involvement of phrenic nerve
  - N3 = contralateral mediastinal disease, pathologically proven with mediastinoscopy
  - Stage IIIB, unresectable

General Disease Site Principles

- Inoperable* = usually T4, N3, or “bulky” N2 disease
  - **T4**
    - Tumor invades mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or separate tumor nodules in a different ipsilateral lobe
  - **N3**
    - Contralateral mediastinum/hilum
    - Ipsilateral or contralateral scalene or supraclavicular
- Treat for cure if no distant metastases and no malignant pleural or pericardial effusion

*Exceptions may be made on an individual case basis when discussed with the surgeon.

General Disease Site Principles

- Concurrent chemoradiation is superior to sequential chemotherapy and radiation or radiation alone
- Radiation dose escalation to 74 Gy compared with 60 Gy failed to demonstrate a benefit in RTOG 0617
- Due to lack of heterogeneity corrections used in historical trials, standard dose remains 60 -70 Gy
- Observing lung metrics is critical to prevent severe radiation pneumonitis

General Management: Literature Review

Evidence for concurrent chemoradiation

- *RTOG 73-01 Perez Cancer 1982* demonstrated improved outcomes with 60 Gy continuous RT compared with 40 or 50 Gy.
- Three subsequent trials demonstrated sequential chemotherapy followed by radiation improved outcomes over radiation alone *(Dillman CALGB JNCI 1996, Sause RTOG/ECOG JNCI 1995/Chest 2000, LeChevalier JNCI 1991)*
- Multiple trials then demonstrated improved outcomes with concurrent CRT over sequential therapy
  - *Curran RTOG 9410, Furuse JCO 1999, Fournel JCO 2005*
- SWOG 9504 *Gandara Clin Lung Can 2006* 3-year overall survival of 37% using radiation + cisplatin/etoposide.
  - This protocol included consolidation docetaxel. Was this the reason for the good outcomes?
- HOG 0124 randomized concurrent CDDP/etoposide+RT +/- consolidation docetaxel and did not demonstrate a benefit to consolidation chemotherapy *Jalal Ann Onc 2012*.
- CALGB *Vokes JCO 2007* failed to show a benefit to induction chemotherapy.
- Current standard of care therefore = concurrent chemoradiation without induction or consolidation chemotherapy.

Therapy	**Median OS** (months)
Radiation alone	11
Chemotherapy → RT	14
Concurrent chemoradiation	17

General Management: Radiation Dose

Current standard of care is 60-70 Gy radiation with concurrent cisplatin/etoposide or carboplatin/paclitaxel

- Multiple phase I/II trials showed safety and efficacy of radiation dose escalation
- CALGB 30105 *Socinski JCO 2008* showed induction chemo followed by carboplatin/paclitaxel + 74 Gy had 3-year overall survival of 37%
- RTOG 0117 phase I/II *Bradley IJROBP 2010* found maximum tolerated dose of 74 Gy with carboplatin/paclitaxel, median overall survival 22 months
- RTOG 0617 randomized patients to concurrent carboplatin/paclitaxel + 60 versus 74 Gy radiation
  - Included 2x2 randomization +/- cetuximab
  - Closed early due to no benefit to increased dose
  - **Failed to show a benefit** (*Bradley, Proc. ASTRO 2011*)
  - Continuing to randomize cetuximab on 60 Gy arm

Treatment Regimen

- Radiation Dose:
  - 70 Gy prescribed to PTV
- Chemotherapy:
  - Cisplatin 50 mg/m^2 days 1, 8, 29, 36
  - Etoposide 50 mg/m^2 days 1-5, 29-33
  - 2 cycles, Q4 weeks

Radiation planning

- Simulation
  - Patient position: supine, chin up, arms behind head
  - Immobilization: upper and lower alpha cradles
  - CT scan: without and with IV contrast to help delineate nodal volumes and mediastinal vasculature. 3 mm slices.
  - Respiratory gating and 4-D CT: used to generate ITV

Treatment Planning

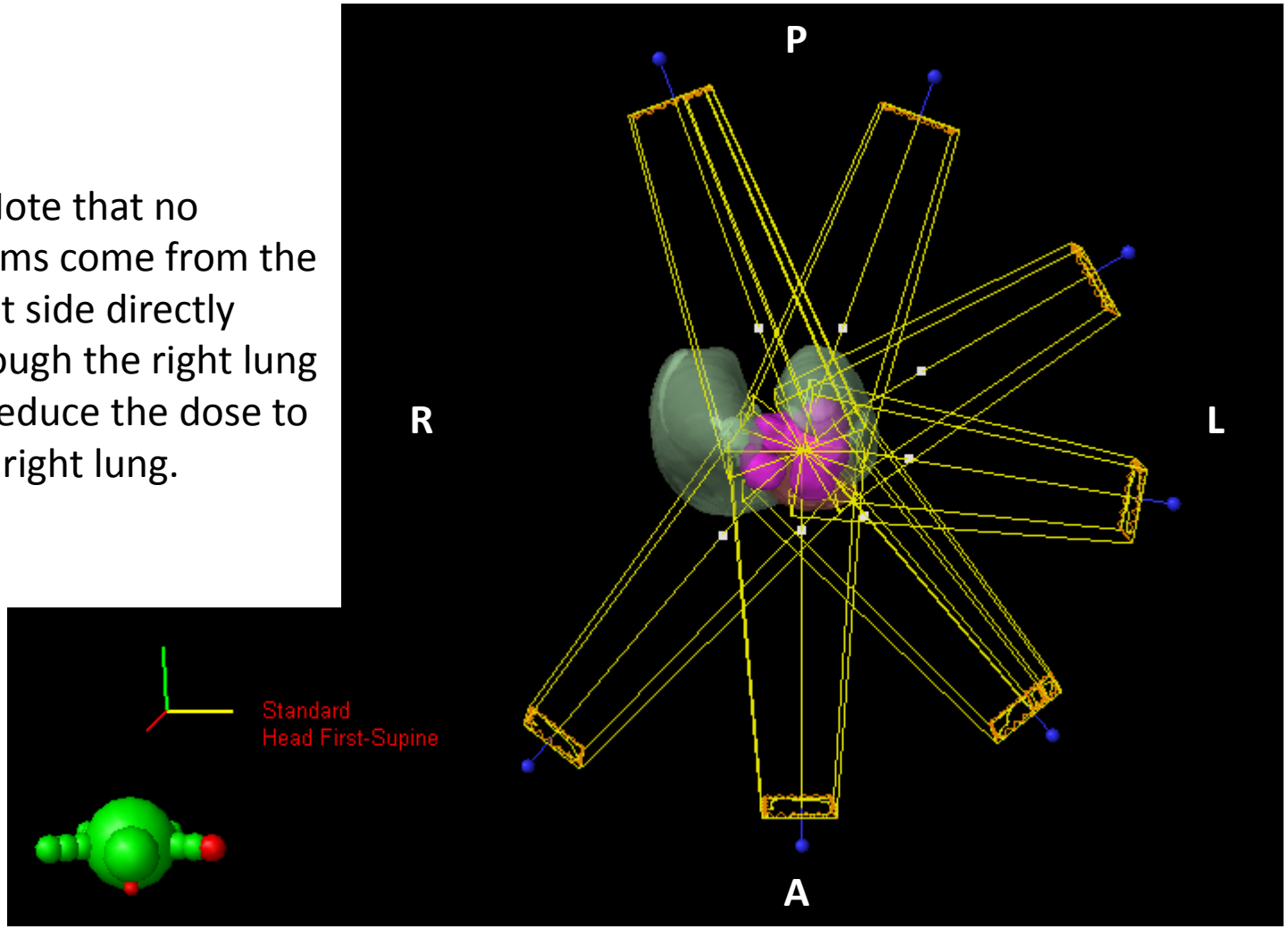
- **GTV**
  - Fuse PET to planning CT to assist with delineation of primary tumor and nodal volumes
  - PET can be used to determine areas of active tumor versus post-obstructive atelectasis
- **ITV**
  - Generated using MIP (maximal intensity projection) of primary tumor throughout respiratory cycle
  - No respiratory gating used if tumor motion <1 cm on 4D-cine
- **CTV**
  - Primary tumor expanded 6-8 mm based on pathologic review (*Giraud IJROBP 2000*)
    - Adenocarcinoma extends 8 mm
    - Squamous cell carcinoma extends 6 mm
- **PTV**
  - 5 mm uniform margin (symmetric expansion since using ITV)

Treatment Planning

- Nodal stations
  - Contour only gross nodes.
  - Do not treat “elective nodal” volumes
    - Increased dose to lungs, no evidence for benefit
  - Nodal level atlases
    - *Chapet IJROBP 2005*
    - *Lynch PRO 2013*

IMRT beam arrangement

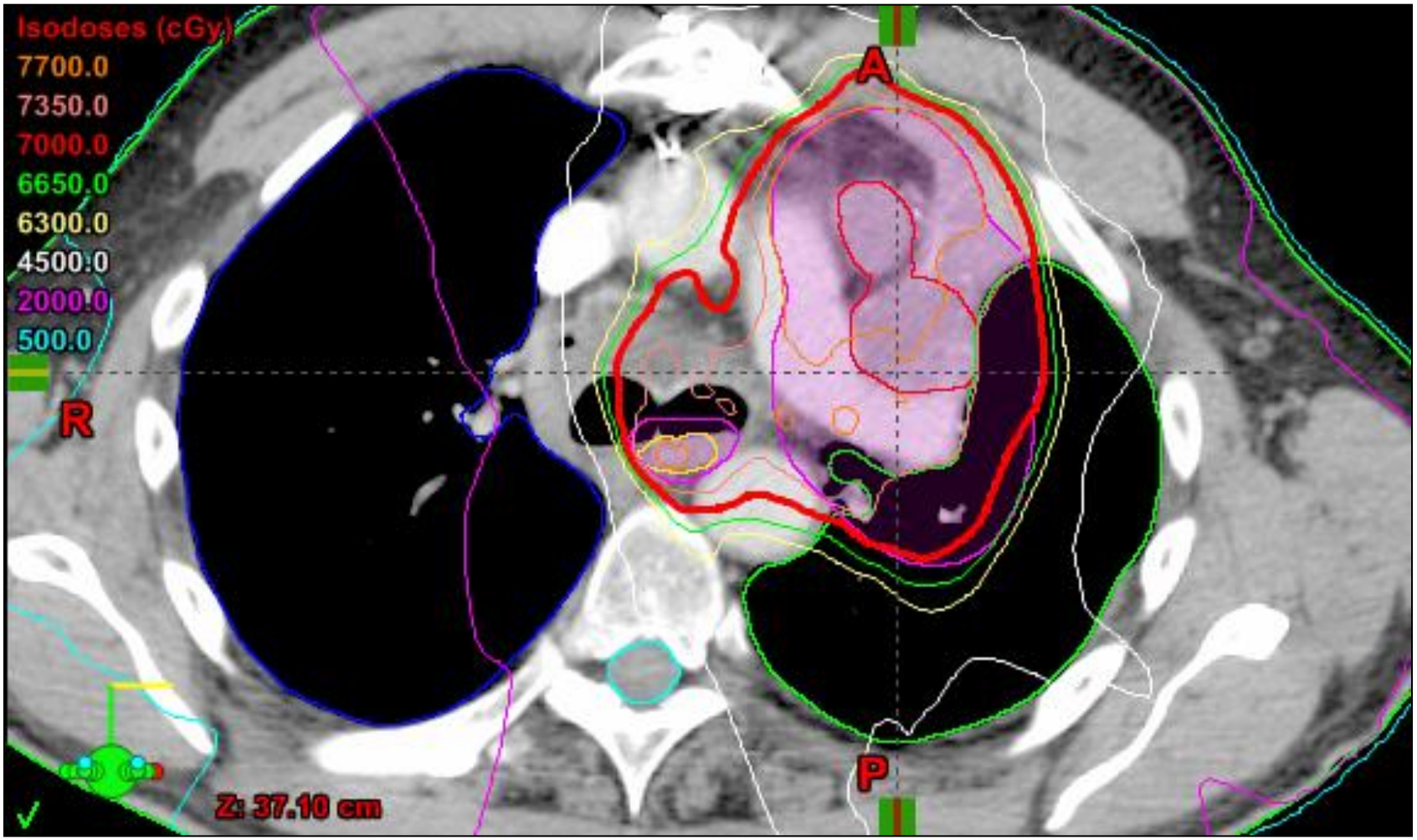
**Note that no beams come from the right side directly through the right lung to reduce the dose to the right lung.



Treatment Planning

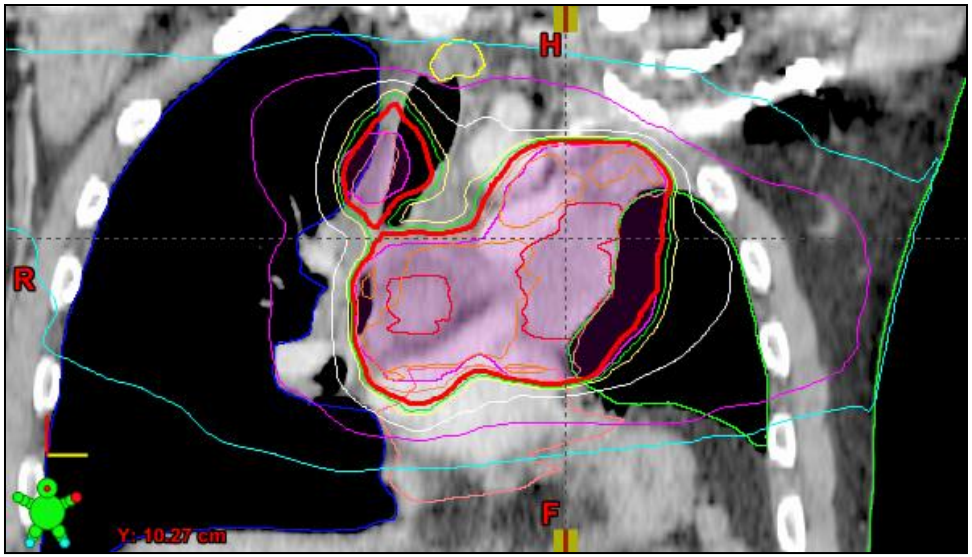
- **<u>What does “Heterogeneity corrections ‘On’” mean?</u>**
  - The lungs attenuate dose less than normal tissue due to the low density of air (~1/4 the density of water)
  - Historically treatments were delivered assuming the entire body, including the lungs, was approximately the density of water
  - Therefore, the dose to the tumor in historical trials was:
    - Cooler on the surface due to a new dose build-up region
    - Hotter centrally due to more radiation penetrating through the low density lung and reaching the tumor
  - Modern treatment planning systems use “heterogeneity corrections” to account for the differences in the tissue density based on the CT scan data
  - With “**Heterogeneity corrections turned ‘On’”** dose at the tumor surface will be hotter and the central dose may be cooler relative to **“Heterogeneity corrections turned ‘Off’”**

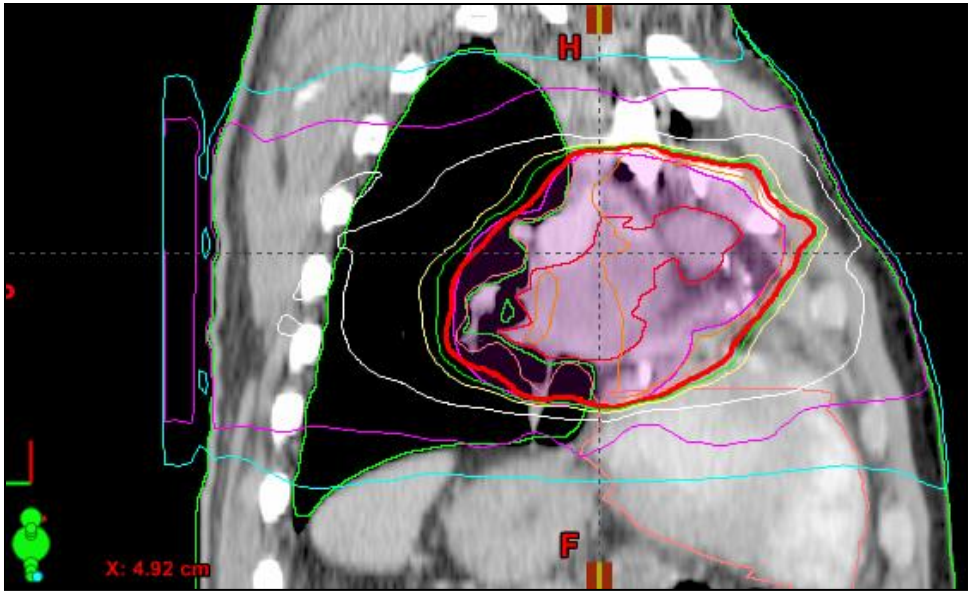
Isodose lines



**Note: The 5 Gy isodose line (cyan) encompasses both lungs at this level. The 20 Gy isodose line (magenta) encompasses the entire left lung. Also, the esophagus is impossible to avoid at this level as it is between the subcarinal disease and primary tumor.

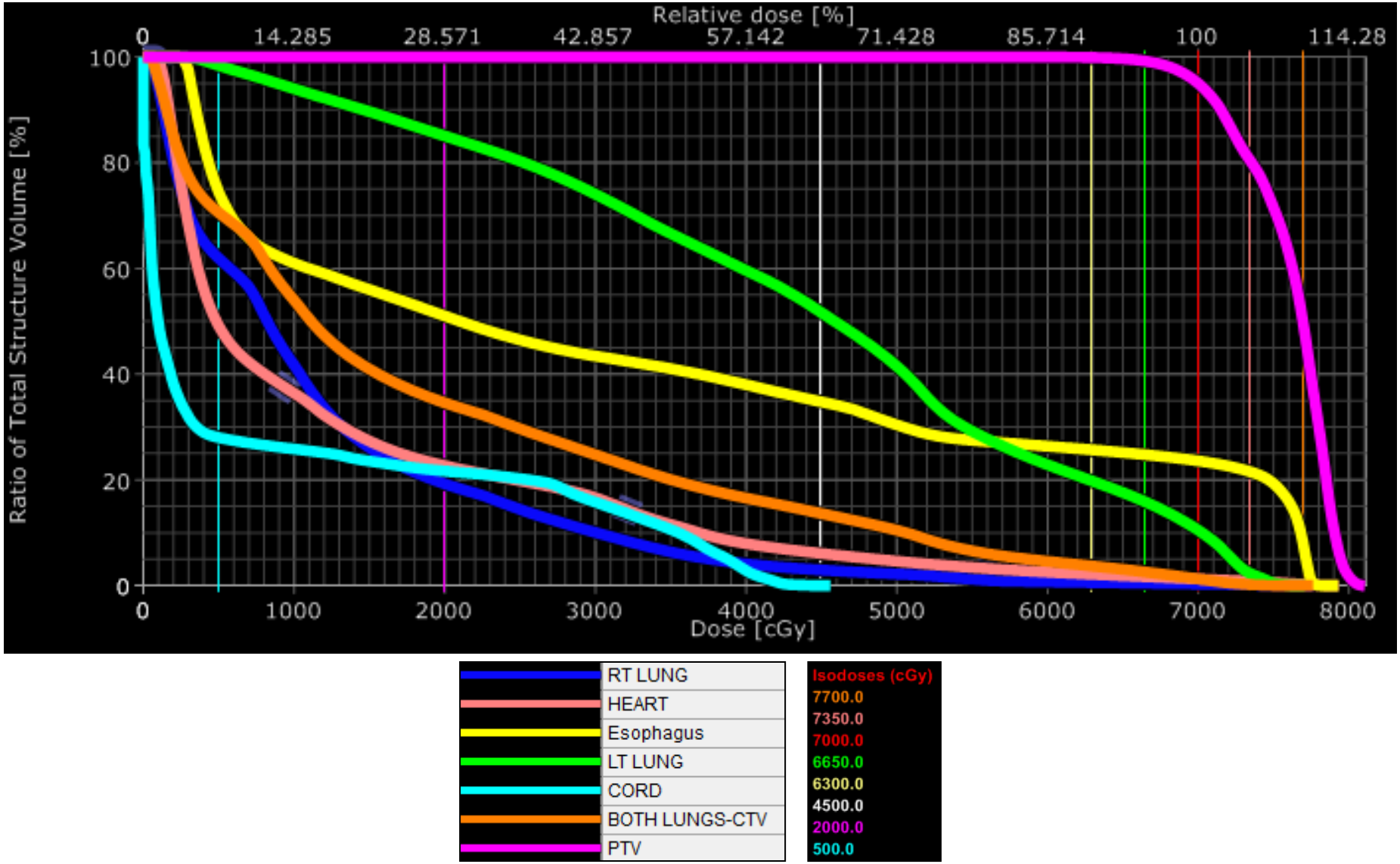
Isodose lines





**Note that the 5 Gy isodose line includes the entire left lung and majority of the right lung. Also, notice that the 20 Gy isodose line encompasses the entire left lung.

Dose Volume Histogram



Critical Structures/Dose Constraints

	NCCN Guidelines
– Lungs	V20 ≤ 30-35%, V5 ≤ 70%*, Mean lung dose ≤ 20 Gy
– Spinal cord	Max ≤ 50 Gy
– Esophagus	Mean ≤ 34 Gy, Max ≤ 105%**
– Heart	V40 ≤ 80%, V45 ≤ 60%, V60 ≤ 30%, Mean ≤ 35 Gy
– Brachial Plexus	Max ≤ 66 Gy

*Note: 2013 NCCN guidelines recommend V5 ≤ 65%.

**Note: esophagus dose is a “soft” constraint due to frequent proximity to primary tumor and involved nodes making it nearly impossible to achieve the above dose constraints.

Follow-up

- **NCCN guidelines for follow-up (if no clinical/radiographic evidence of progression):**
  - H&P and chest CT +/- contrast every 6-12 months for 2 years, then annually
  - Smoking cessation advice, counseling, pharmacotherapy
  - PET or brain MRI not indicated

- At follow-up visits monitor for resolution of acute toxicity (esophagitis, fatigue) and for radiation pneumonitis

Radiation Pneumonitis

- Presents 6 week to 3 months after completion of radiation
- Type 1 pneumocytes die, type 2 proliferate leading to subacute inflammatory reaction
  - Lower lobe of lung may be more susceptible of radiation pneumonitis
- Patients present with cough, shortness of breath/dyspnea on exertion, possibly fevers or O_2 dependence
- Imaging will show changes within radiation field
- Treat with prednisone 60 mg qday for 2 weeks, then gradually taper over 3-12 weeks
  - If symptoms flare, increase prednisone, then re-taper
- Improves for up to 18 months, unlikely to improve after 18 months

References

1. Bradley JD, Moughan J, Graham MV, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys. Jun 1 2010;77(2):367-372.

2. Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/− cetuximab for stage IIIa/IIIb non-small cell lung cancer: Preliminary findings on radiation dose in RTOG 0617 (late-breaking abstract 2). Presented at the 53rd Annual Meeting of the American Society of Radiation Oncology, October 2–6, 2011, Miami, FL.

3. Chapet O, Kong FM, Quint LE, et al. CT-based definition of thoracic lymph node stations: an atlas from the University of Michigan. Int J Radiat Oncol Biol Phys. Sep 1 2005;63(1):170-178.

4. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. Oct 5 2011;103(19):1452-1460.

5. Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst. Sep 4 1996;88(17):1210-1215.

6. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer. J Natl Compr Canc Netw. Oct 1 2012;10(10):1236-1271.

7. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. J Clin Oncol. Sep 1 2005;23(25):5910-5917.

8. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. Sep 1999;17(9):2692-2699.

9. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). Clin Lung Cancer. Sep 2006;8(2):116-121.

10. Giraud P, Antoine M, Larrouy A, et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys. Nov 1 2000;48(4):1015-1024.

11. Jalal SI, Riggs HD, Melnyk A, et al. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. Ann Oncol. Jul 2012;23(7):1730-1738.

12. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst. Mar 20 1991;83(6):417-423.

13. Lynch R, Pitson G, Ball D, Claude L, Sarrut D. Computed tomographic atlas for the new international lymph node map for lung cancer: A radiation oncologist perspective. Practical Radiation Oncology. 2013;3(1):54-66.

14. Perez CA, Stanley K, Grundy G, et al. Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. Cancer. Sep 15 1982;50(6):1091-1099.

15. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst. Feb 1 1995;87(3):198-205.

16. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol. May 20 2008;26(15):2457-2463.

17. Vokes EE, Herndon JE, 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol. May 1 2007;25(13):1698-1704.