ARRO*Case*
Resectable Locally Advanced (Stage IIIA N2) Non-small Cell Lung Cancer

Craig E. Grossman, MD, PhD, MSCE, PGY-5

Faculty Advisor: Deepinder P. Singh, Assistant Professor

University of Rochester Medical Center

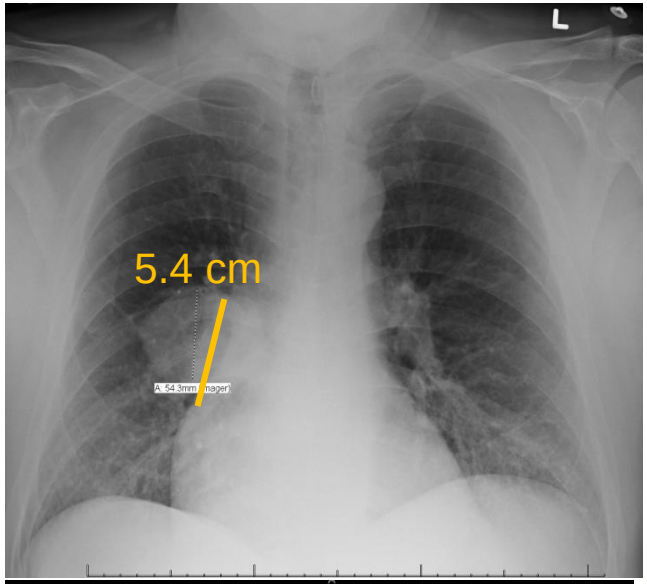
Rochester, New York

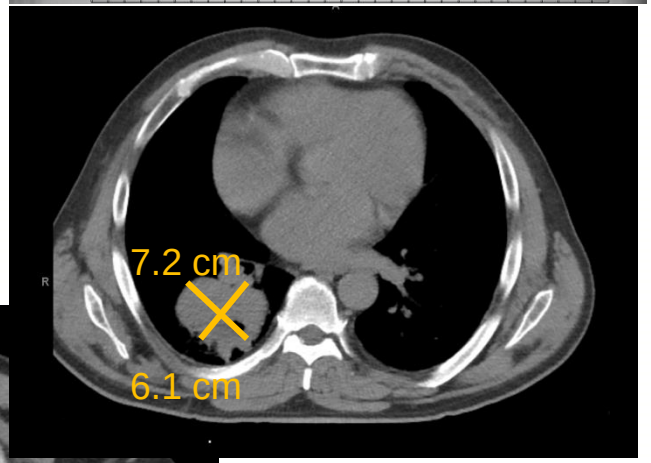
Case Presentation

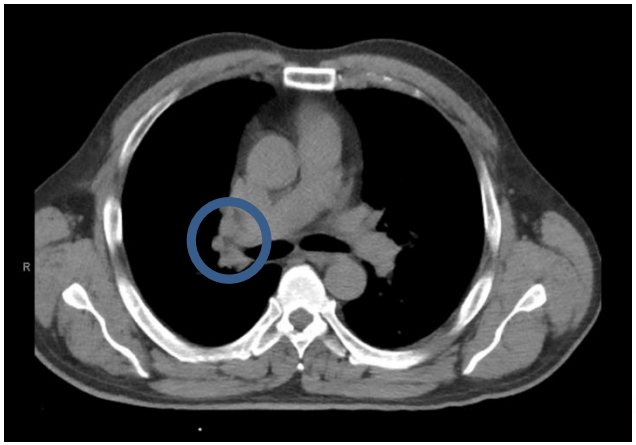
- HPI
  - 61 yo w/ COPD, and history of 40 pack-year smoking and alcohol abuse, presented with abdominal pain in the setting of weight loss. On workup, a right lower lobe lung mass was incidentally detected on CT abdomen/pelvis.
  - Has chronic wheezing and productive cough due to COPD.
  - Denies chest pain, hoarseness, dyspnea, hemoptysis, back/bone pain, H/As, neurocognitive changes, gait disturbance, imbalance.
- PMH: Hypercholesterolemia, COPD, OA
- Social History
  - Works as a seed packer, exposed to dust and the aerosolized treatments for seeds; does not use respiratory protection
  - Smokes 1 pk/d x 40 yrs
  - Drinks 20 cans of beer/wk
- Physical Exam
  - KPS 100 BP 140/83 HR 58 RR 16 T 97.9 Wt 221 lbs
  - Well appearing, thin, but not cachectic
  - No palpable cervical or supraclavicular LAD
  - Lungs: CTAB w/ good breath sounds; no rales, rhonchi, or wheezing
- Diagnostics
  - CBC, Chemistries wnl

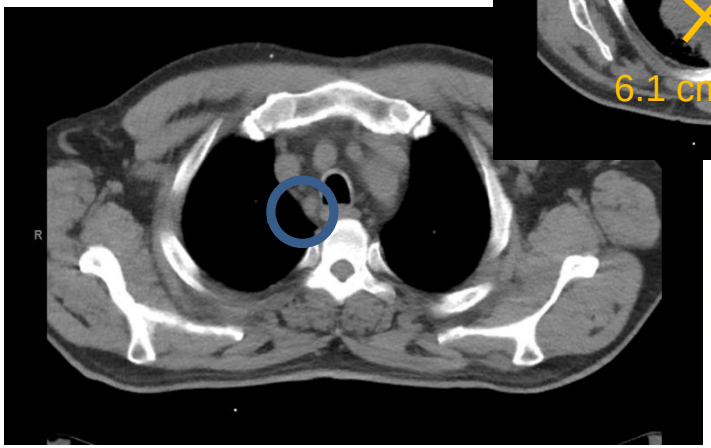
Diagnostic Workup

- CXR
  - 5.4 cm right perihilar mass, likely involving the superior segment of the RLL
- CT chest/upper abdomen
  - Lobulated 7.2 x 6.1 cm mass in superior segment of RLL
  - Right hilar LAD, borderline enlarged 1.3 cm right paratracheal LN



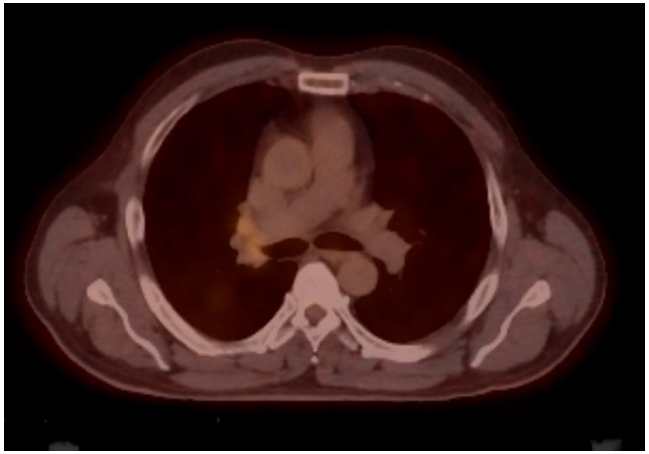


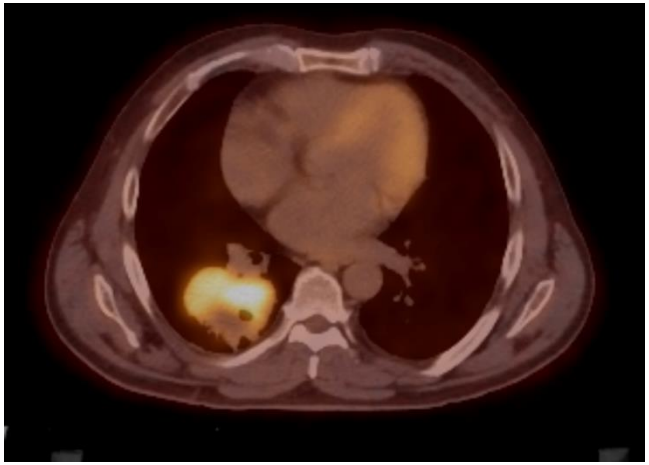


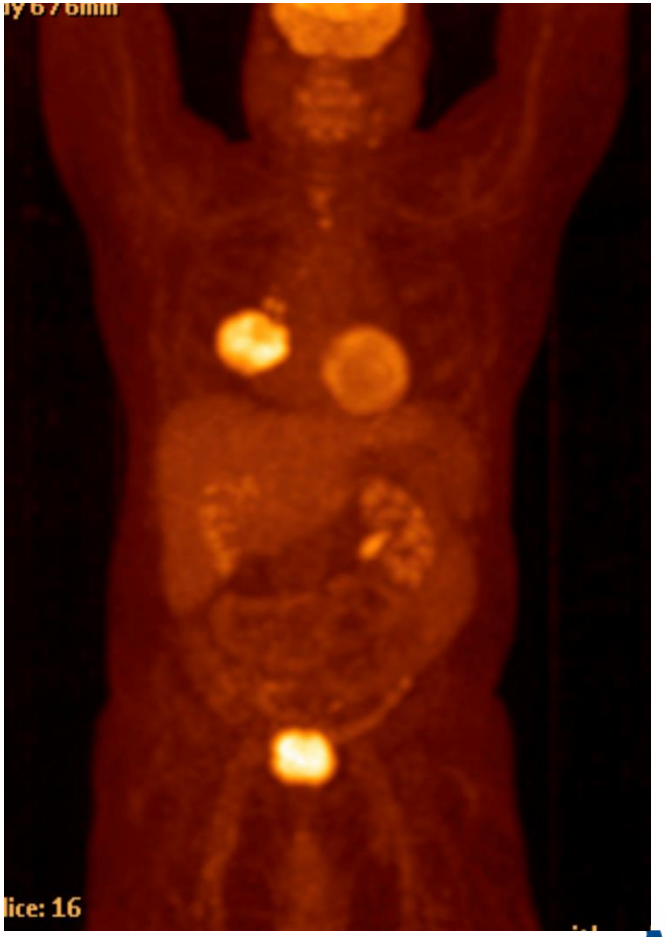


Diagnostic Workup

- PET/CT
  - Hypermetabolic (SUV 17.3) RLL 7.2 x 6.1 cm mass
  - Hypermetabolic (SUV 5.9) hilar LAD; minimally hypermetabolic paratracheal LAD







Diagnostic Workup

- Bronchoscopy & EBUS
  - Extrinsic compression of the RLL superior segment, preventing advancement of the scope; no endobronchial lesions
  - EBUS: SCC
- Mediastinoscopy
  - Level 4R LN: Grade3 SCC
- MRI Brain *(obtain this when patient has stage III-IV disease)*:
  - No intracranial metastases
- PFTs
  - FEV1 3.47 (98%)
  - DLCO 87%

Tumor Staging, AJCC 7th ed

Primary Tumor	
T1	Tumor ≤3 cm diameter, without invasion more proximal than lobar bronchus
T1a	Tumor ≤2 cm
T1b	Tumor >2 cm, ≤3 cm
T2	Tumor >3 cm, ≤7 cm; or any of the following: • Involves main bronchus, ≥2 cm distal to carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to hilar region but does not involve the entire lung
T2a	Tumor >3 cm, ≤5 cm
T2b	Tumor >5 cm, ≤7 cm
T3	Tumor >7 cm; or any of the following: • Directly invades chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without carina involvement) • Atelectasis or obstructive pneumonitis of the entire lung • Separate tumor nodules in the same lobe
T4	• Tumor invades mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina • Separate tumor nodules in different ipsilateral lodes

N & M Staging

Regional Lymph Nodes	
N0	No regional lymph nodes
N1	Ipsilateral peribronchial and/or hilar LNs and intrapulmonary nodes, including involvement by direct extension
N2	Ipsilateral mediastinal and/or subcarinal LNs
N3	Scalene LNs, supraclavicular LNs, or contralateral mediastinal/hilar LNs

Distant Metastasis	
M0	No DMs
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural/pericardial effusion
M1b	Extrathoracic DMs

AJCC 7th ed Group Staging

Stage Group	5 yr OS	T Stage	N Stage	M Stage
IA	75%	T1a-b	N0	M0
IB	55%	T2a	N0	M0
IIA	50%	T1a-b, T2a	N1	M0
		T2b	N0	M0
IIB	40%	T2b	N1	M0
		T3	N0	M0
IIIA	10-35%	T1-2	N2	M0
		T3	N1-2	M0
		T4	N0-1	M0
IIIB	5-8%	T4	N2	M0
		Any T	N3	M0
IV	<5%	Any T	Any N	M1

Mediastinal LN involvement is at least Stage III

Until 1997, IIIA staging also included T3 N0; now, it is reclassified as Stage II – so trials with Stage III disease that predate 1997 may have patients with better outcomes

Final Diagnosis

- **Right lower lobe SCC, Stage cIIIA (T3 N2 M0)**
  - T3, based on size (>7 cm)
  - N2, based on mediastinal disease, pathologically proven with mediastinoscopy

Stage IIIA NSCLC

- Stratified clinically: bulky or non-bulky mediastinal LN disease
  - Distinction useful in selecting potential patients for upfront surgical resection or for resection after neoadjuvant tx
  - Criteria to define bulkiness[1]
    - Size of a dominant LN >2 cm (short axis diameter on CT)
    - Groupings of multiple smaller LNs
    - ECE
    - >2 LN stations involved
- Stage IIIA comprises about 16% of NSCLC cases
- Stage IIIA is considered resectable; stage IIIB is unresectable

Clinical Case: Stage cIIIA NSCLC

- Because this patient has Stage IIIA NSCLC with FEV1 of 98% and DLCO 87%, he has potentially resectable disease
- Criteria for resectability
  - IIIA or less
  - PFTs (based on American College of Chest Physicians)[2]
    - Predicted postoperative (PPO) FEV1 *and* DLCO >60%: **Low risk** (predicted mortality <1%)
    - PPO FEV1 or DLCO <30%, Cardiopulmonary exercise testing (CPET) should be performed to assess risk:
      - If maximal oxygen consumption (VO2max) is <10 ml/kg/min or <35%: patient is **high risk** (surgical mortality of >10%, and thus should not undergo surgery)
      - If VO2max 10-20 ml/kg/min or 35-75%, patient has a **moderate risk** (risks and benefits of surgery should be discussed with patient)
      - If VO2max >20 ml/kg/min or >75%: patient is **low risk**
    - PPO FEV1 or DLCO <60% and both >30%, patient is low risk if adequate stair climb test; if not, stratify according to CPET test

Treatment of Stage IIIA NSCLC

- A challenging subset of lung cancer patients
  - While there are many potential treatment options, none yields a high probability of cure
- Despite multiple clinical trials, treatment of these patients remains controversial because of limitations in data
  - Heterogeneous patient populations
    - Many trials contained stage I-III disease
    - Often no distinction was made between IIIA and IIIB
    - Staging systems have changed over time
    - Stage III is comprised of a wide range of T and N combinations
  - Improved pretreatment staging over time
    - More accurate assessment with PET, CT, pathologic mediastinal evaluation
  - Improved therapy over time
    - Use of more active systemic therapy (i.e. platinum, targeted therapy), refinements in RT and surgical techniques
  - Patients may have been staged differently
    - Clinical versus pathologic staging
    - Clinical staging may be based on imaging vs. invasive methods
    - Distant metastases often not staged with PET scan
- The role of surgery in N2 disease remains controversial

NCCN Treatment Guidelines Stage IIIA NSCLC[13]

- No strong evidence as to which is best for stage IIIA N2 disease, as outcomes are similar whether definitive local tx is surgery- or RT-based
  - Concurrent CRT is generally the initial treatment for the majority of patients with stage IIIA N2 disease, including unresectable disease
  - For patients with potentially resectable disease, it remains uncertain whether surgery after neoadjuvant tx (CTX or CRT) improves OS over definitive CRT
    - Patients with a single LN <3 cm can be considered for multimodality therapy that includes surgery
    - For pre-op CRT, be prepared upfront to continue to a full (definitive) dose of RT (i.e. ≥60 Gy) without interruption if the patient does not proceed to surgery for some reason
  - For those who are not candidates for combined modality, RT alone is an option
- T3N1 (which have a better prognosis than N2 disease) should be treated with surgery → adjuvant CTX for completely resected disease
  - Exception: Pancoast tumor (T3-4 N1) is generally treated with CRT → surgery
- T4N0-1 Lesions
  - Resectable T4N0-1 lesions are uncommon, and most are treated with definitive CRT
  - Ipsilateral nodules within another lobe and negative mediastinal nodes (T4N0 or T4N1) should be considered candidates for surgery +/- adjuvant CTX
  - Lesions involving the carina, SVC, or vertebral body may benefit from a multimodality approach

Potentially Resectable Stage cIII N2 NSCLC

- **After discussion in multidisciplinary tumor board, consensus to treat this patient with neoadjuvant CRT → Surgery**

- Although a high LRF rate with definitive CRT, whether adding surgery improves outcomes remains to be seen
  - Although uncontrolled phase II studies suggest a survival benefit from surgery after neoadj CRT, RCTs have not confirmed a benefit of surgery following either neoadj CRT or sequential CTX-RT
  - Survival benefit with adjuvant surgery may be limited to patients who undergo a lobectomy rather than pneumonectomy (INT 0139)
- Theoretical advantages of induction therapy
  - Decrease in tumor volume prior to surgery
  - Relatively high response rates to CTX
  - Earlier treatment of micrometastatic disease
  - Better tolerance and compliance with induction versus adjuvant CTX

Evidence for Neoadjuvant Treatment of Resectable Stage cIIIA N2 NSCLC

- Induction Chemotherapy improves OS compared to surgery alone based on classic Roth (MDACC)[3] and Rosell (Spain)[4] studies
  - Note, staging system has changed since these studies
  - >50% of patients received PORT in each arm in Roth study; all patients received PORT in Rosell study
  - 5 yr OS improved with NeoAdj CTX → Surgery vs. Surgery alone (53% vs. 24%, Roth; 17% vs. 0%, Rosell)
- No clear benefit of Induction CTX → RT (→ Surgery) vs. Induction CTX (→ Surgery) based on SAKK 16/00 Phase III RCT for Stage cIIIA N2 NSCLC[5]
  - Arms
    - 117 pts: CDDP/Docetaxel x3 → 44/2 Gy TRT → Surgery
    - 115 pts: CDDP/Docetaxel x3 → Surgery
  - Outcomes: Median EFS and OS similar between arms

	Median EFS p=NS	Median OS	cCR/pCR	Nodal downstaging to N1 or N0
Indxn CTX → RT → S	12.8 mo	37.1 mo	3%/16%	64%
Indxn CTX → S	11.6 mo	26.2 mo	2%/12%	53%

Trimodality tx for Stage cIIIA N2 NSCLC

- INT 0139/RTOG 93-09 (n=396)[6]: Surgery after induction CRT for Stage cIIIA N2
  - Stage IIIA (T1-3 pN2): CDDP/VP-16 x3 + 45 Gy → Randomization (ITT):
    - If no progression in the surgery arm, resection performed (n=202) → CTX x2 or
    - Complete RT to 61 Gy (n=194) → CTX x2
  - Surgical arm: 88% were eligible for thoracotomy
    - 71% had complete resection; pCR: 18% of thoracotomies
  - No difference in OS between surgery and definitive CRT, while improved PFS and fewer local-only relapses w/ surgery

	5 yr OS (p=0.10)	**5 yr PFS** (p=SS)
CRT → Surgery	27%	22%
CRT	20%	11%

  - Although LRR was significantly lower w/ surgery (10%) vs. definitive CRT (22%, p=0.002), the difference in DM failure was not significant (37% vs. 42%, p=0.35)

Albain. Lancet. 2009.

INT 0139: Surgery After Induction CRT for Resectable Stage cIII N2 Disease

- Possibly no benefit in OS w/ surgery because of high mortality rate (8%) during the perioperative period for surgery arm (vs. 2% w/ CRT)
  - Lobectomy (1%), pneumonectomy (26%) – greatest risk with right-sided pneumonectomies (40%, 11/29 right pneumonectomies died)
- Matched analysis of subset of pts (based on KPS, age, sex, T stage) in the CRT group with lobectomy or pneumonectomy group
  - 5 yr OS improved w/ lobectomy (36%) vs. definitive CRT matched cohort (18%, p=0.002)
  - 5 yr OS was nonsignificantly worse w/ pneumonectomy (22%) vs. definitive CRT matched cohort (24%)
- Conclusion: Tri-modality therapy is not better than CRT for N2, and possibly unsafe for right-sided pneumonectomies!

Trimodality tx for Stage cIIIA N2 NSCLC

- National Cancer Database retrospective study of 11,242 pts with stage cIIIA N2 disease suggested an advantage of neoadjuvant vs. adjuvant tx[7]
  - Induction CRT followed by lobectomy/pneumonectomy in appropriately selected patients had improved outcomes

	5 yr OS
NeoCRT → Lobectomy	34%
NeoCRT → Pneumonectomy	21%
Lobectomy → Adj Tx	20%
Pneumonectomy → Adj Tx	13%
CRT	11%

What RT dose should be used for Indxn CRT?

- Previously, 45-50 Gy (INT 0139 used 45/1.8 Gy)
- ***NCCN 2016 guidelines revised the recommendation to 45-54 Gy***
  - National Cancer Database study compared RT doses of 1041 cIIIA pts treated (1998-2005) with induction CRT[8]
    - 45-54 Gy associated with improved OS, shorter hospitalizations, less likelihood of prolonged hospitalization
    - Residual nodal disease seen less often after 54-74 Gy
    - No difference in margin status or adverse surgical outcomes

	36-45 Gy	45-54 Gy	54-74 Gy
Median OS (p=0.01)	31.8 mo	**38.3 mo**	29.0 mo
Residual nodal disease (p=0.004)	31.8%	37.5%	**25.5%**
Negative margins (p=0.5)	9.9%	7.5%	8.5%
Median hospital length stay (p=0.052)	7 days	**6 days**	6 days
Prolonged (>6 days) hospitalization (p=0.01)	55.4%	**38.9%**	44.6%

- RTOG 02-29 (Phase II, cIIIA-B, CRT→Surgery)[9]: 50.4 Gy to N2+ nodes, 61.2 Gy to gross tumor
  - Low incidence of postop mortality (3%) – suggesting doses could be further increased above 54 Gy

Since ~15-30% of locally advanced NSCLC patients develop brain metastases, why not prophylax the brain?

No survival benefit has been demonstrated in the face of neurocognitive toxicity, and thus it is not standard of care

PCI is not recommended for Stage cIII NSCLC

- Currently not considered standard of care due to neurotoxicity of WBRT, and no OS benefit
- RTOG 0214[10, 11]
  - cIIIA-B NSCLC treated w/ RT or surgery +/- CTX who did not have disease disease progression were randomized to observation vs. PCI (30/2 Gy)
  - Closed early due to slow accrual (only 356 of targeted 1058 enrolled)
  - Outcomes

	1 yr OS (p=NS)	**1 yr DFS** (p=NS)	**1 yr Brain mets** (p=0.004)
PCI	76%	56%	8%
Observation	77%	51%	18%

    - No difference at 1 yr in global cognitive function (MMSE), QOL, or ADLs; but trend for greater decline in patient-reported cognitive function and immediate and delayed recall w/ PCI
  - Conclusion: PCI decreased rate of brain metastases, but not OS or DFS

PCI is not recommended after Trimodality for Stage cIII NSCLC

- German multicenter study (Pottgen, JCO, 2007)
  - RCT of 112 pts w/ operable cIIIA based on mediastinoscopy staging
    - Surgery → 50-60 Gy
    - CDDP/VP-16 x3 → CRT(CDDP/VP-16, 45/1.5 Gy BID) → Surgery → PCI (30/2 Gy)
  - Terminated early due to slow accrual after benefit of adjuvant CTX shown
  - Outcomes
    - Decreased 5 yr brain first failure w/ PCI (8% vs. 35% no PCI, p=0.02)
    - Decreased 5 yr any brain failure w/ PCI (9% vs. 27% no PCI, p=0.04)
    - No difference in toxicity

Clinical Case

Clinical Case: Treatment Regimen

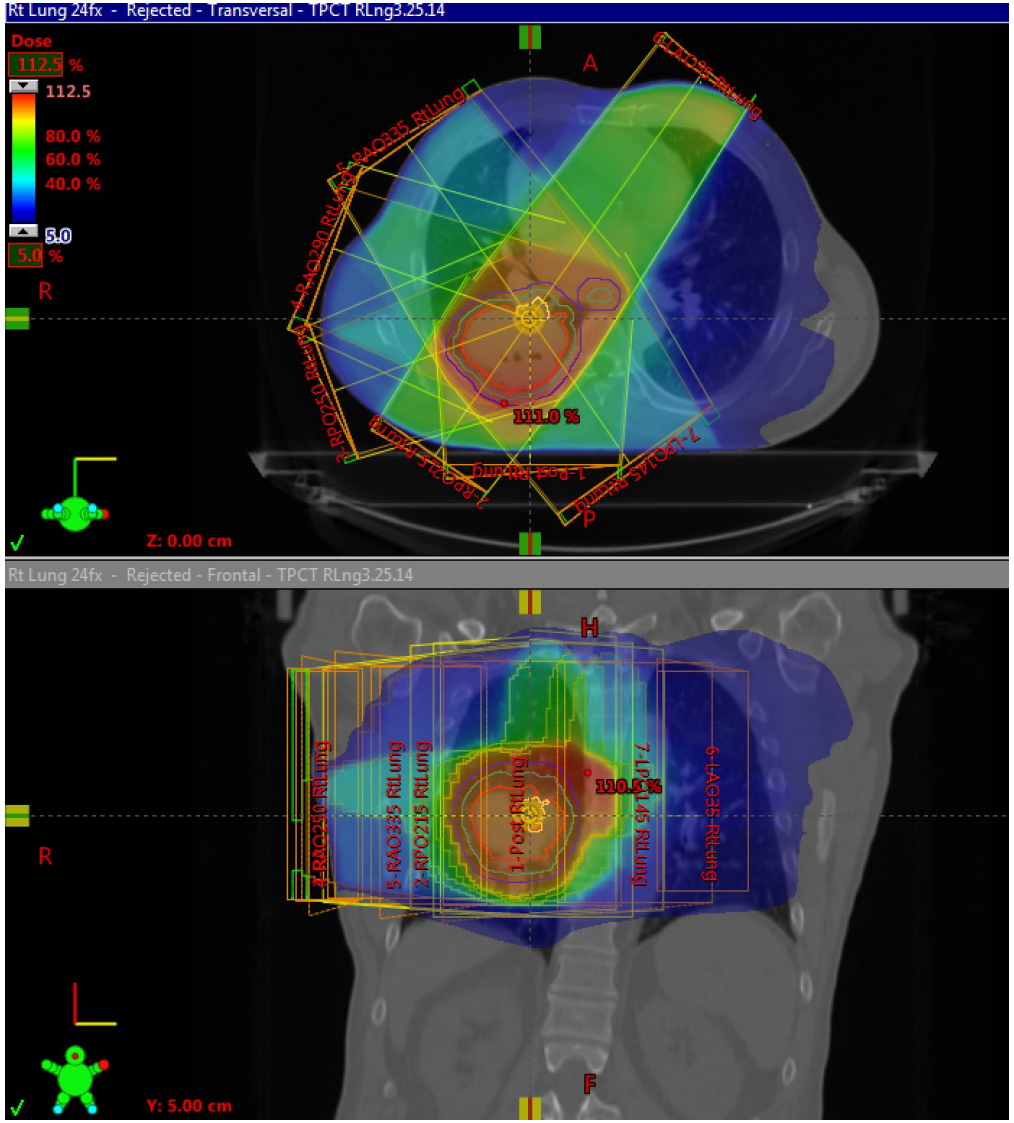
- Because the patient had potentially resectable disease, he underwent Indxn CRT
  - Chemotherapy (weekly) x6
    - Carboplatin 300 mg
    - Taxol 50 mg/m^2
  - RT: 50/2 Gy to PTV, beginning on day 1 of chemotherapy
    - Although we used 3DCRT, protocol allowed for IMRT
- Simulation
  - Patient position: supine, arms above head
  - Immobilization: vacuum bag
  - CT scan (2.5 mm slices): without and with contrast to help delineate nodal volumes and mediastinal vasculature

Clinical Case: Treatment Planning

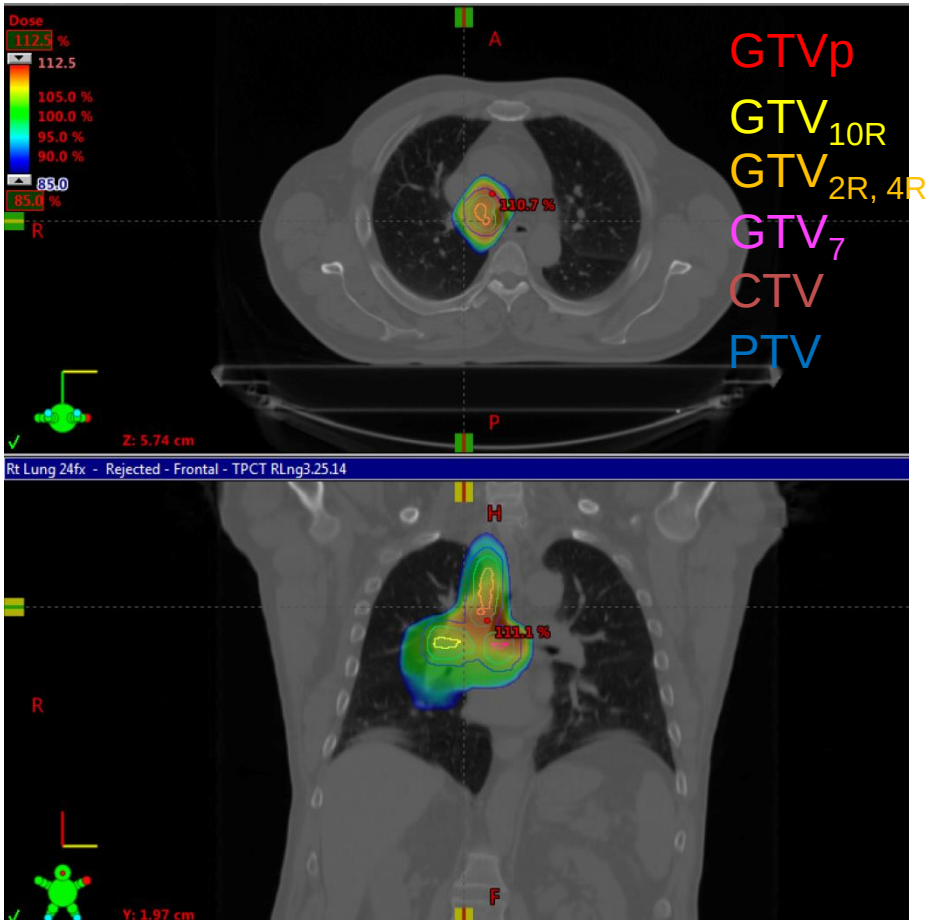
- Follow guidelines outlined in RTOG 0839: Phase II study of Preop CRT +/- Panitumumab in Stage IIIA N2 NSCLC[12]
- Volumes
  - GTV
    - Fuse PET to planning CT to assist with delineation of primary tumor and nodal volumes
    - Contour tumor and only clinically involved nodes from this patient's workup (2R, 4R, 10R, 7)
      - Positive lymph nodes, defined as clinically positive nodes seen either on the planning CT (> 1 cm short axis diameter) or on pre-treatment PET/CT scan (SUV > 3), and any known involved nodal level found on mediastinoscopy or biopsy, regardless of CT or PET/CT findings.
    - Do not treat elective nodal volumes; no evidence for benefit
  - CTV: 0.7 cm expansion (protocol stipulates 0.5-1.0 cm)
  - PTV: 1 cm longitudinal, 0.5 cm radial expansion
- *We could have used a breath-hold or free-breathing ITV (4DCT) planning and treatment technique*

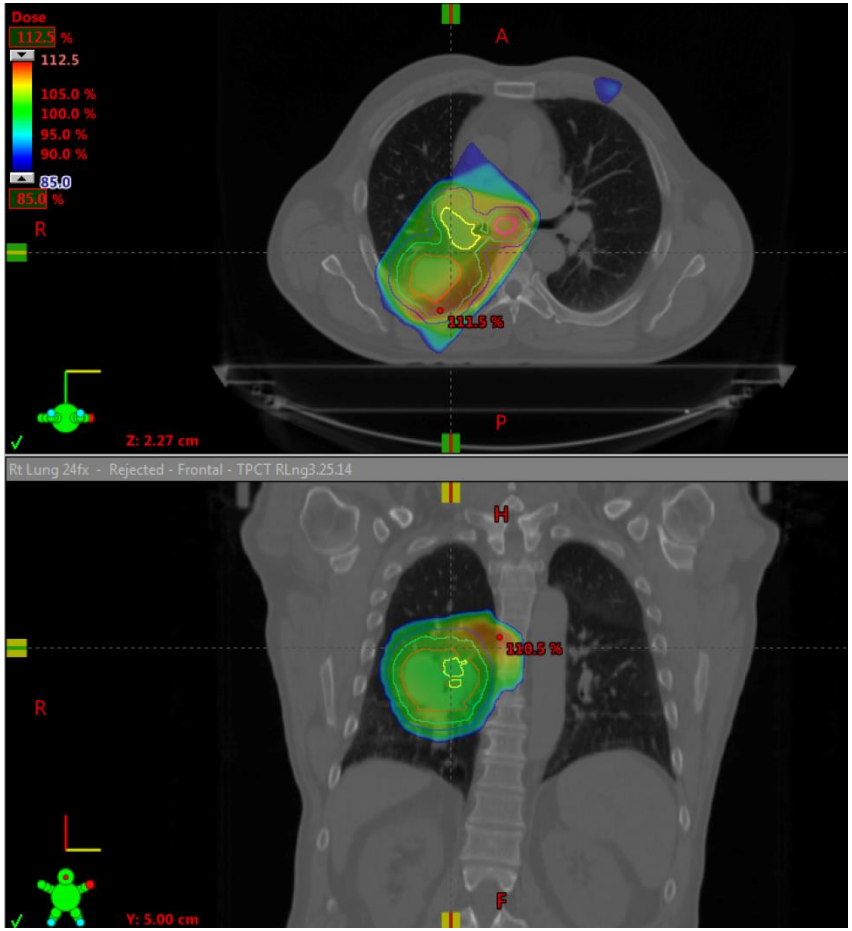
Clinical Case: RT Treatment

- 3DCRT
  - 7 fields, 6 MV photons
  - Daily kV setup; twice a week CBCTs
- Dose Constraints (per RTOG 0839[12])
  - 95% of PTV should be covered by 100% isodose line
  - Maximum dose of the PTV should be <120% of prescribed dose

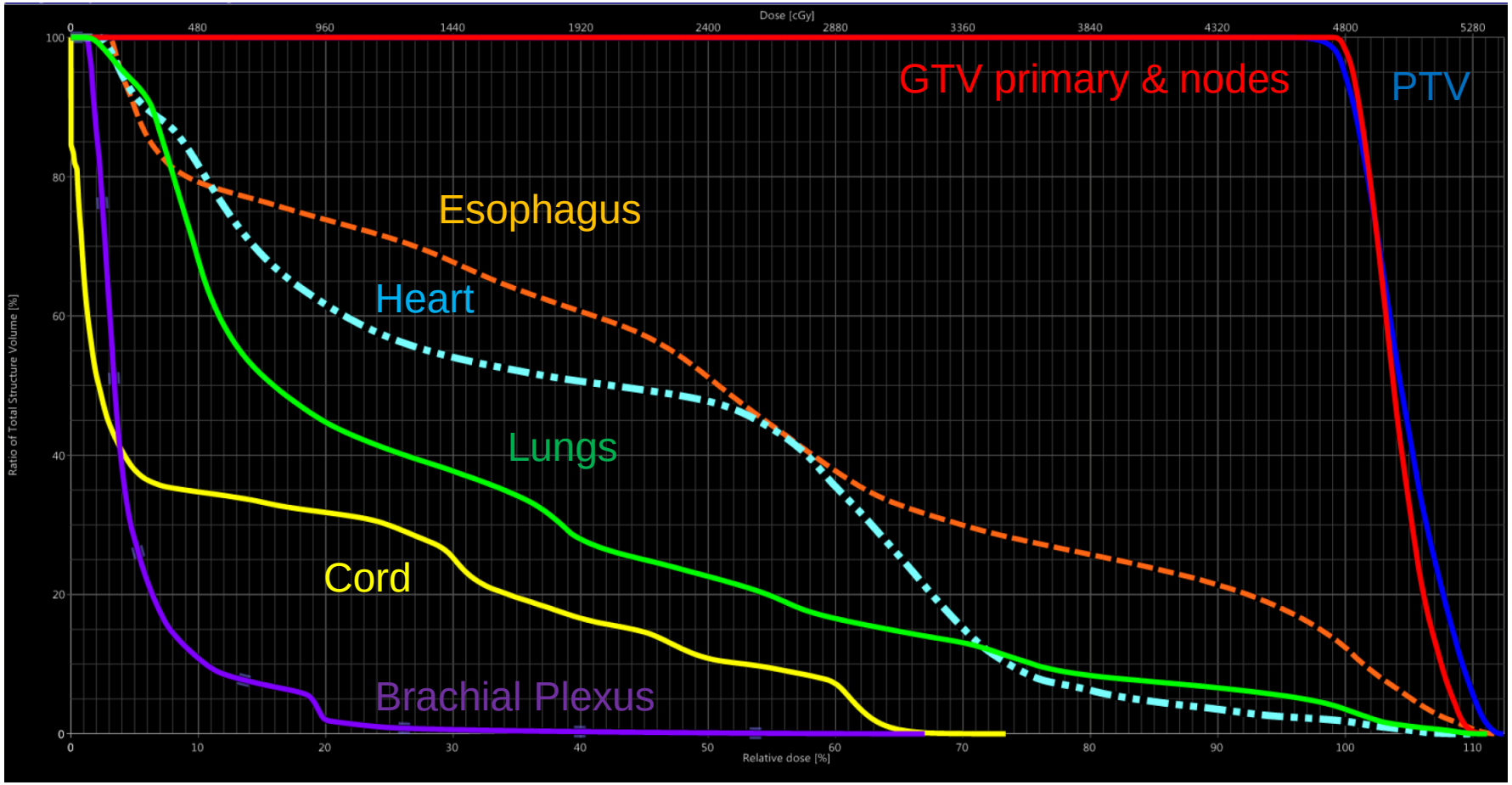


Clinical Case: RT Treatment





Clinical Case: DVH

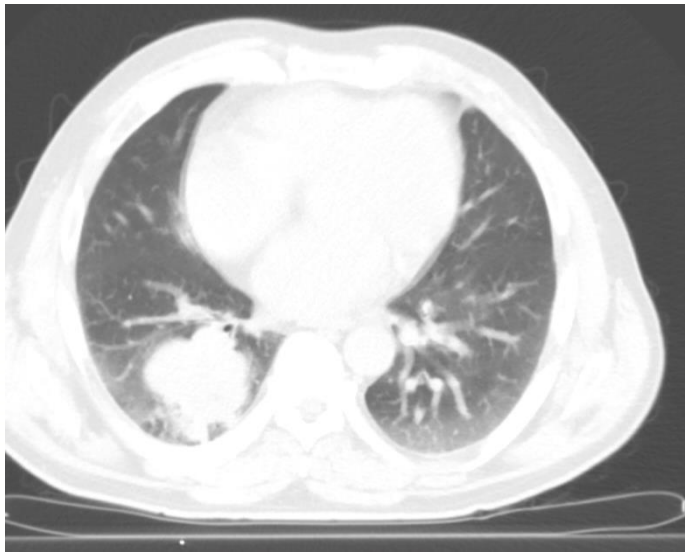


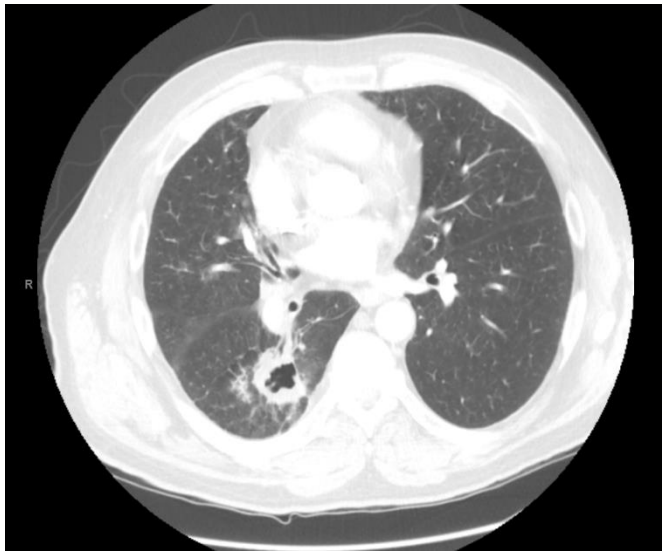
Dose Constraints (based on RTOG 0839[12])

- Lungs: V20 <37%
- Spinal Cord: max <50.5 Gy
- Esophagus: mean dose <40 Gy
- Heart
  - V60 → <1/3
  - V45 → <2/3
  - V40 → 100% of the heart
- Brachial Plexus: max <66 Gy

Clinical Case: Post-Induction Diagnostics

- CT Chest
  - Interval decrease in size of RLL lung mass (from7.2 x 6.1 cm to 5.1 x 5 cm), compatible with treatment response
  - Increased necrosis within the mass
  - Adjacent to the mass, there is a groundglass opacity, related to radiation changes





- MRI Brain: no intracranial metastases

Clinical Case: RLL Lobectomy (1 mo post CRT)

- LNs
  - 0/4 Right level II & IV (upper and lower paratracheal)
  - 0/11 Right level VII (subcarinal)
  - 0/1 Right level IX (N2, pulmonary ligament)
  - 0/7 Right level X (N1, hilar)
  - 0/1 Right level XI (N1, interlobar)
- Right Lower lobectomy
  - 3 cm, G3 SCC; <10% residual viable tumor
  - Negative margins
  - ypT1b ypN0

Survivorship Care – NCCN 2016[13]

- Follow-up
  - H&P and chest CT q 6-12 mo x 2 yrs, then annually
  - Smoking cessation advice, counseling, pharmacotherapy
  - PET or brain not indicated
  - Immunizations
    - Annual influenza vaccine
    - Herpes zoster vaccine
    - Pneumococcal vaccination with revaccination as appropriate
- Health Promotion/Wellness
  - Maintain healthy weight, consume healthy diet
  - Physically active lifestyle
  - Limit EtOH consumption
- Cancer screening, age appropriate – colorectal, prostate, breast

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