ASTRO ANNUAL refresher COURSE 2021

BEST PRACTICES AND EMERGING TRENDS

March 19-21 *Live* Interactive Virtual Conference

Welcome

Lung Cancer: Learning from the past, focusing on the future, treating in the present

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Disclosure

- My employer is Johns Hopkins Medicine.
- Research grant, Genentech.
- Educational grant, PeerView CME

Learning Objectives

- Develop an understanding of the evolving paradigms in the management of lung cancer
- Teach strategies for rigorous and reproducible decision making in treatment selection and treatment plan review.
- Review new studies in lung cancer, how they can be safely applied in the clinic and what to do when the patient does not easily fit the data.

Health

HEALTH POLICY | GLOBAL HEALTH | THE NEW OLD AGE | SCIENCE | WELL

ANDY WONG/ASSOCIATED PRESS

GLOBAL HEALTH

China Identifies New Virus Causing Pneumonia-Like Illness

The new coronavirus doesn't appear to be readily spread by humans, but researchers caution that more study is needed.

10h ago · By SUI-LEE WEE and DONALD G. MCNEIL JR.

MEL EVANS/ASSOCIATED PRESS

These Patients Are Hard to Treat

A study examined a popular approach that coordinated care for the most expensive patients, and found that the project did not reduce hospital admissions.

15h ago · By REED ABELSON

GLOBAL HEALTH

The Flu Season May Yet Turn Ugly, C.D.C. Warns

Almost as many people are falling ill as did two years ago, in what was a particularly severe flu season. But this season's virus is unusual, and it's too early to tell how dangerous.

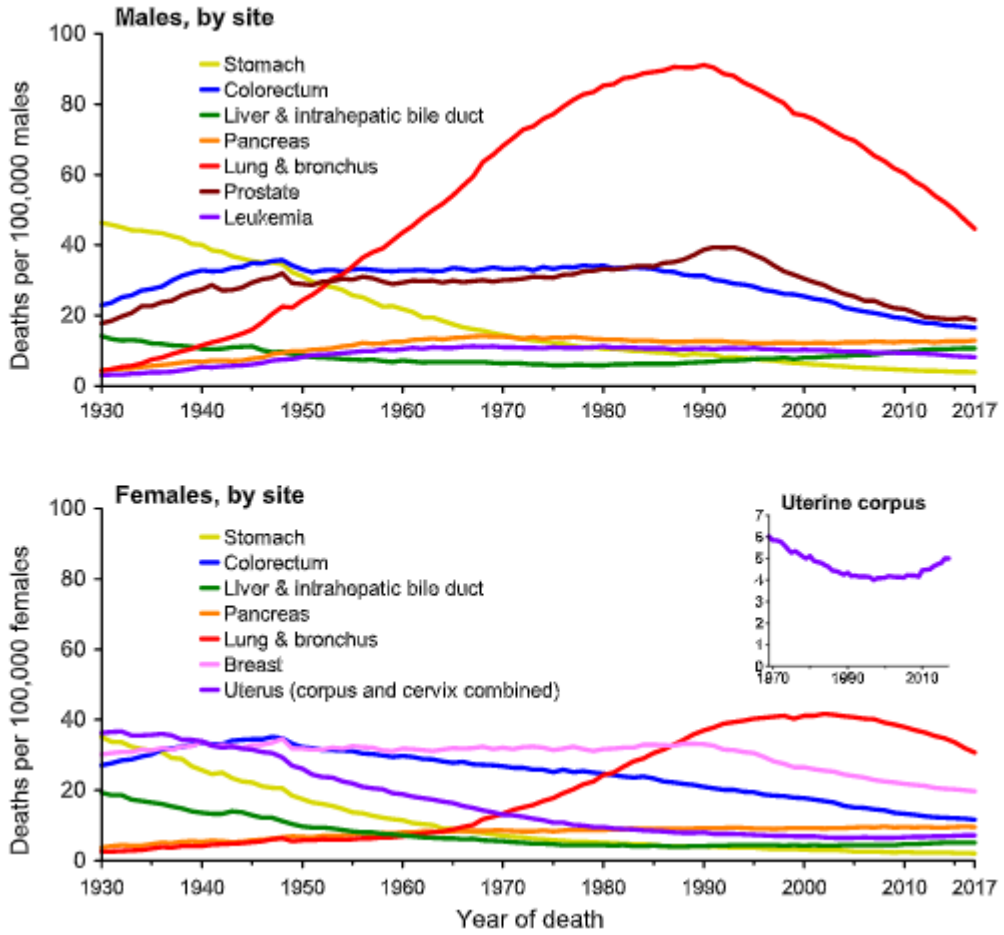
22h ago · By DONALD G. MCNEIL JR.

Cancer Death Rate in U.S. Sees Sharpest One-Year Drop

Breakthrough treatments for lung cancer and melanoma have driven down cancer mortality overall — and from 2016 to 2017 spurred the largest-ever decline.

1d ago · By KNVUL SHEIKH

New York Times, 9 Jan 2020



- Largest single year drop in overall cancer mortality (2016-2017): 2.2%↓
- Decline in death rate from lung cancer:
  - 2008-2013: 3% annual decline
  - 2013-2017: 4.5% annual decline
- Cancer death rates:
  - Slowed in female breast, colorectal cancer
  - Halted in prostate cancer
  - Accelerated reductions in lung cancer

Siegel et al. Ca Cancer J Clin 2020

Patients are living longer

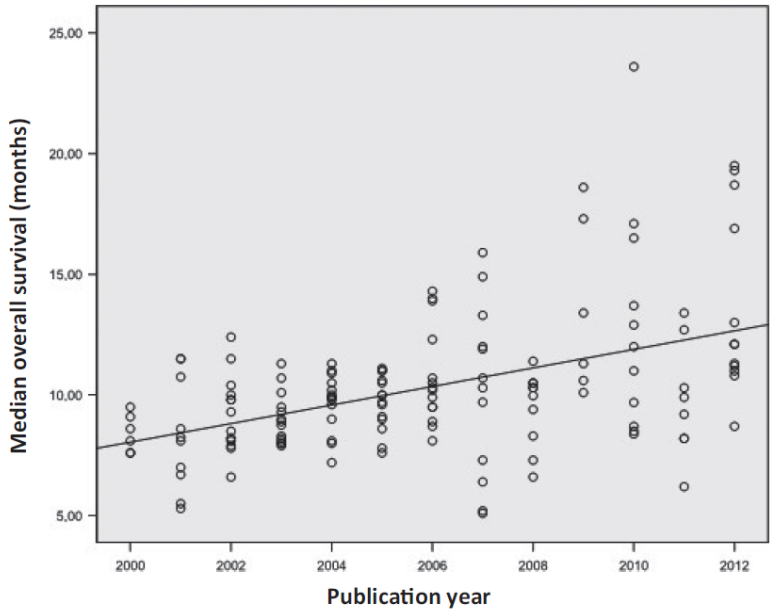


Figure 2. Relationship between year of trial publication and median survival time. Each trial is represented by a circle.

?

2019

Fernandez-Lopez,
Cancer Medicine 2016

Patients are living longer

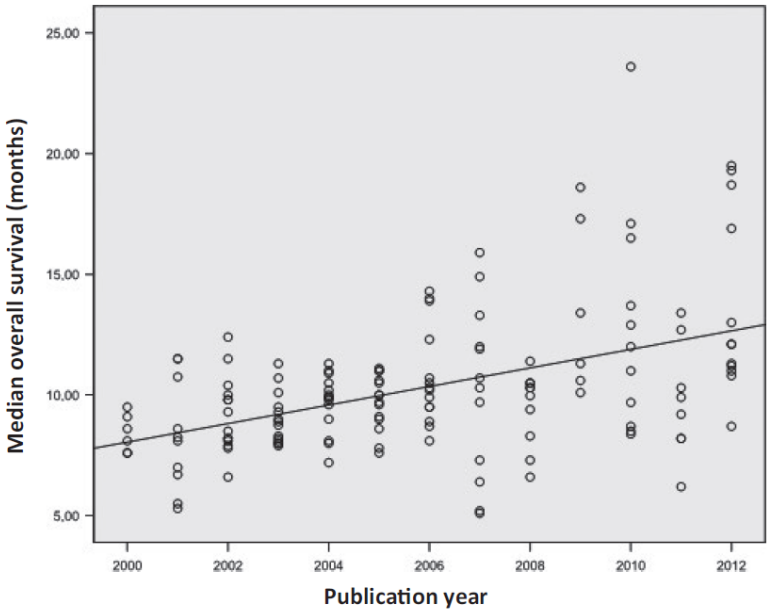
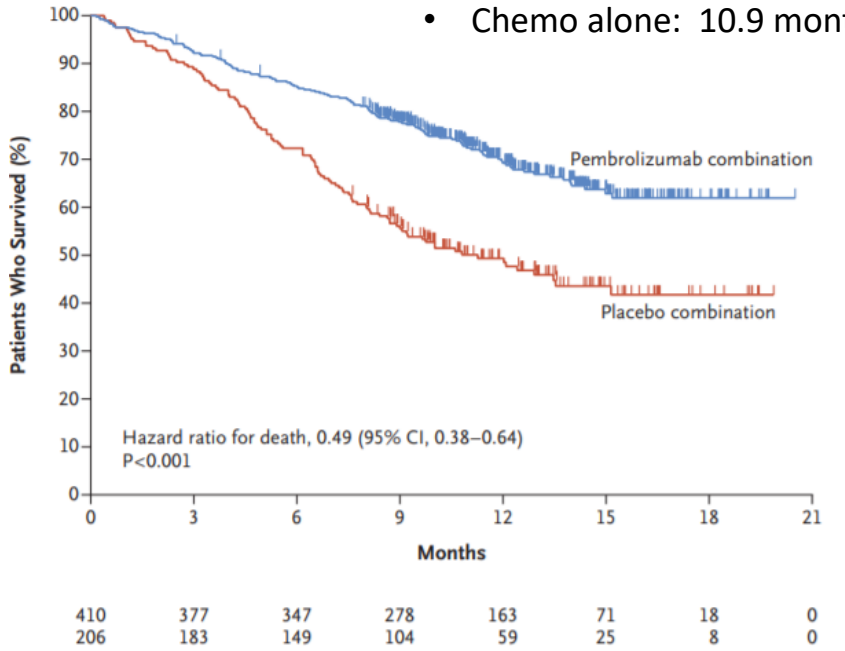


Figure 2. Relationship between year of trial publication and median survival time. Each trial is represented by a circle.

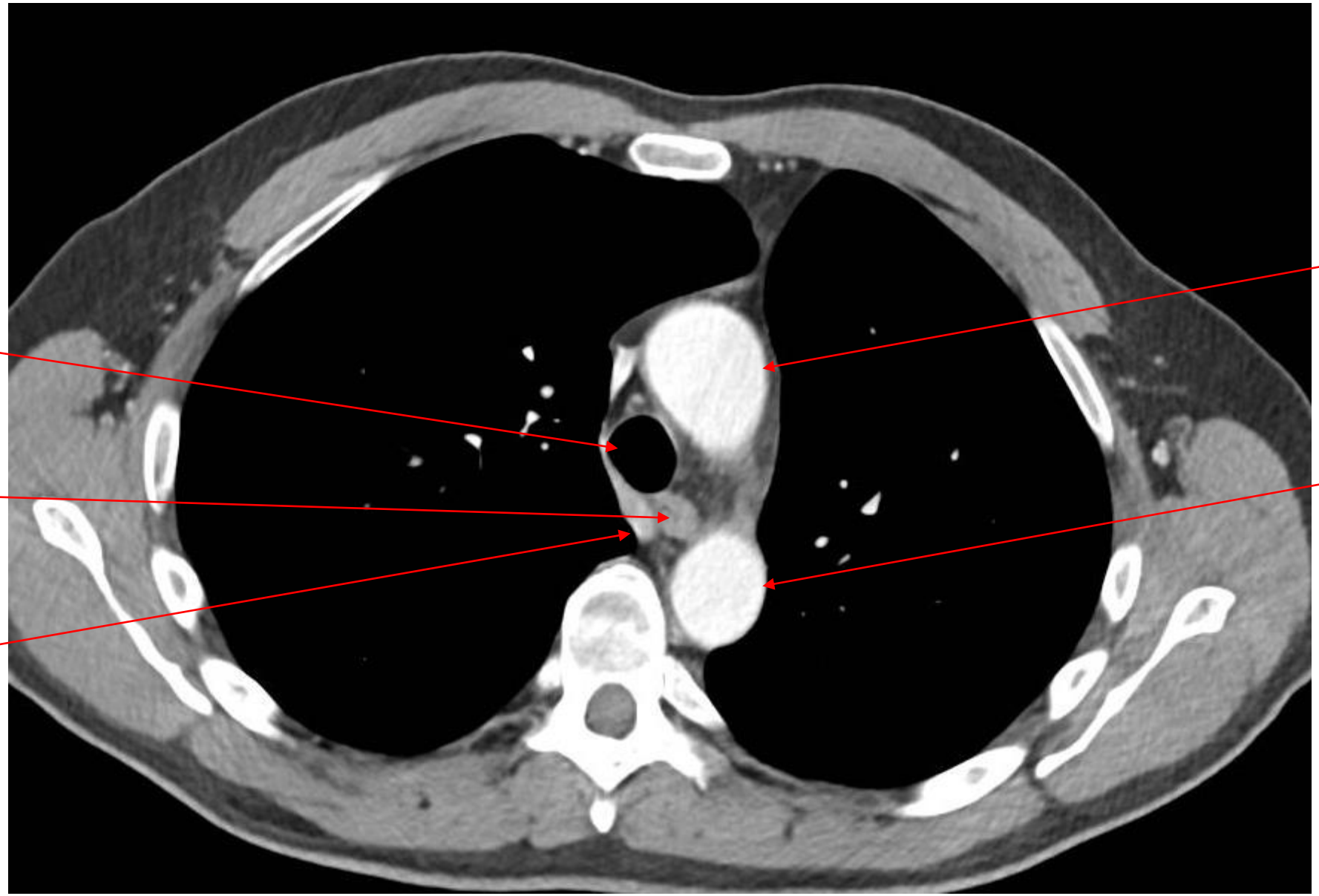
- Median Overall Survival:
  - Pembro + chemo: 22 months
  - Chemo alone: 10.9 months

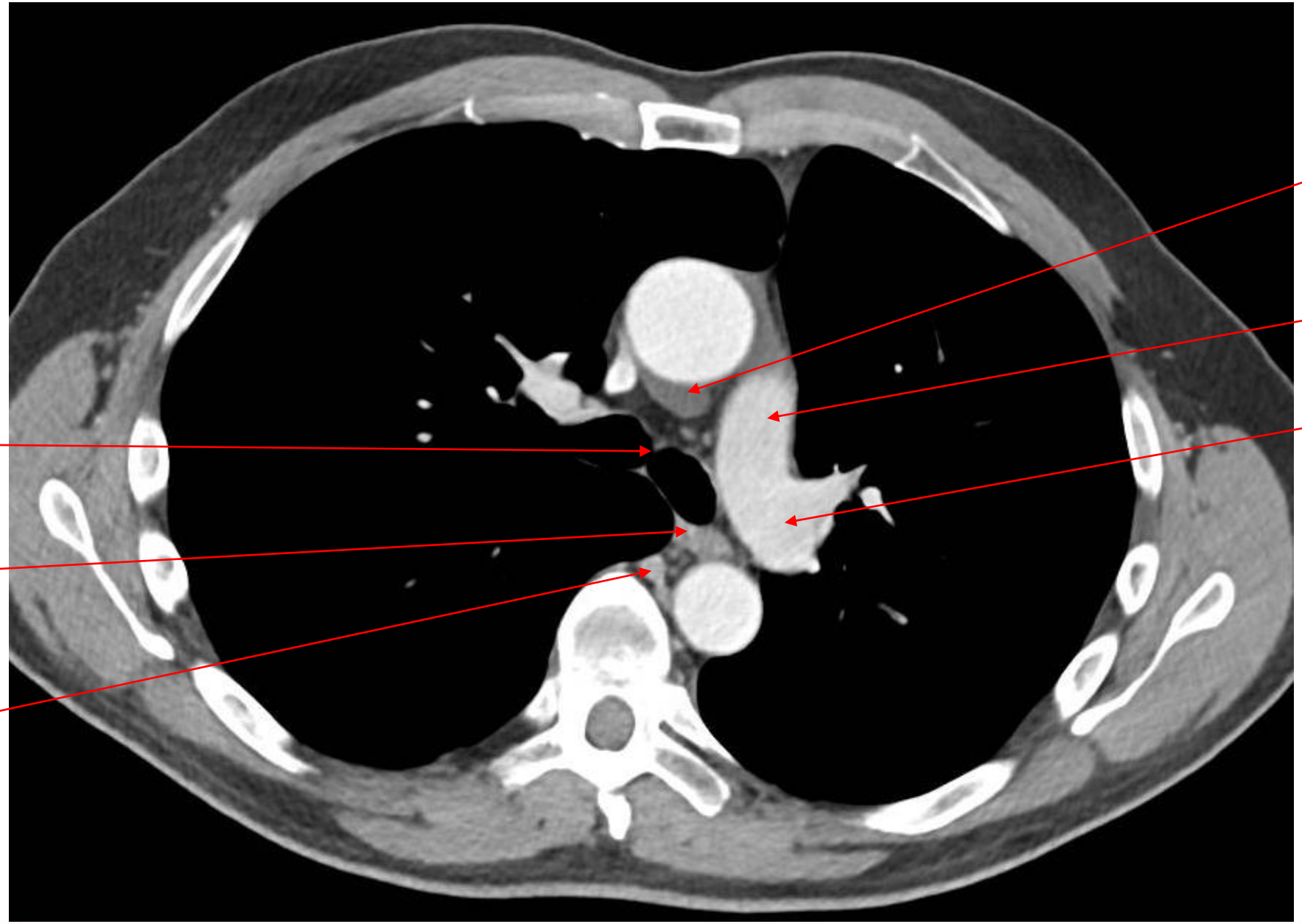


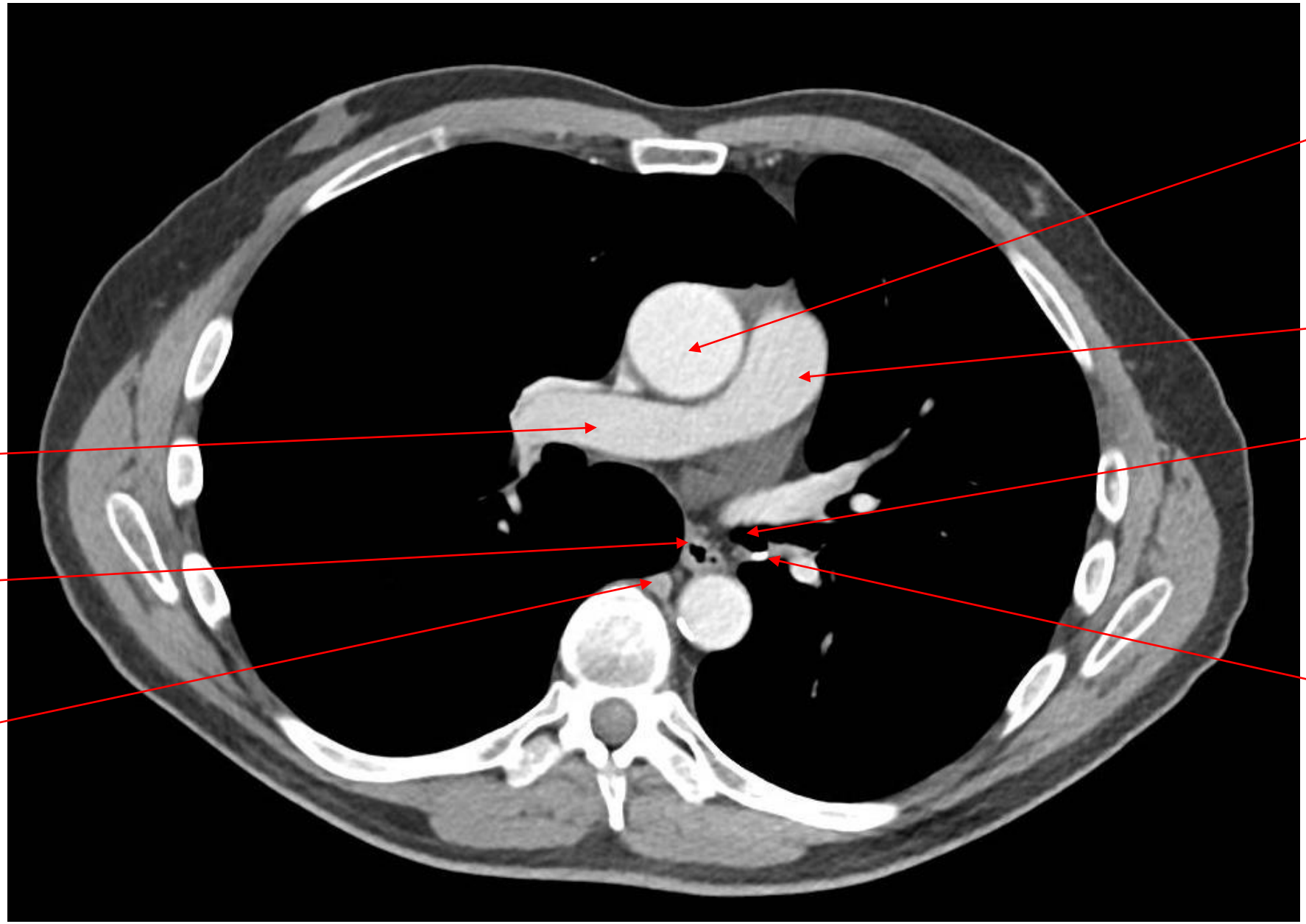
Gandhi, NEJM 2018
Gadgeel, ASCO 2019

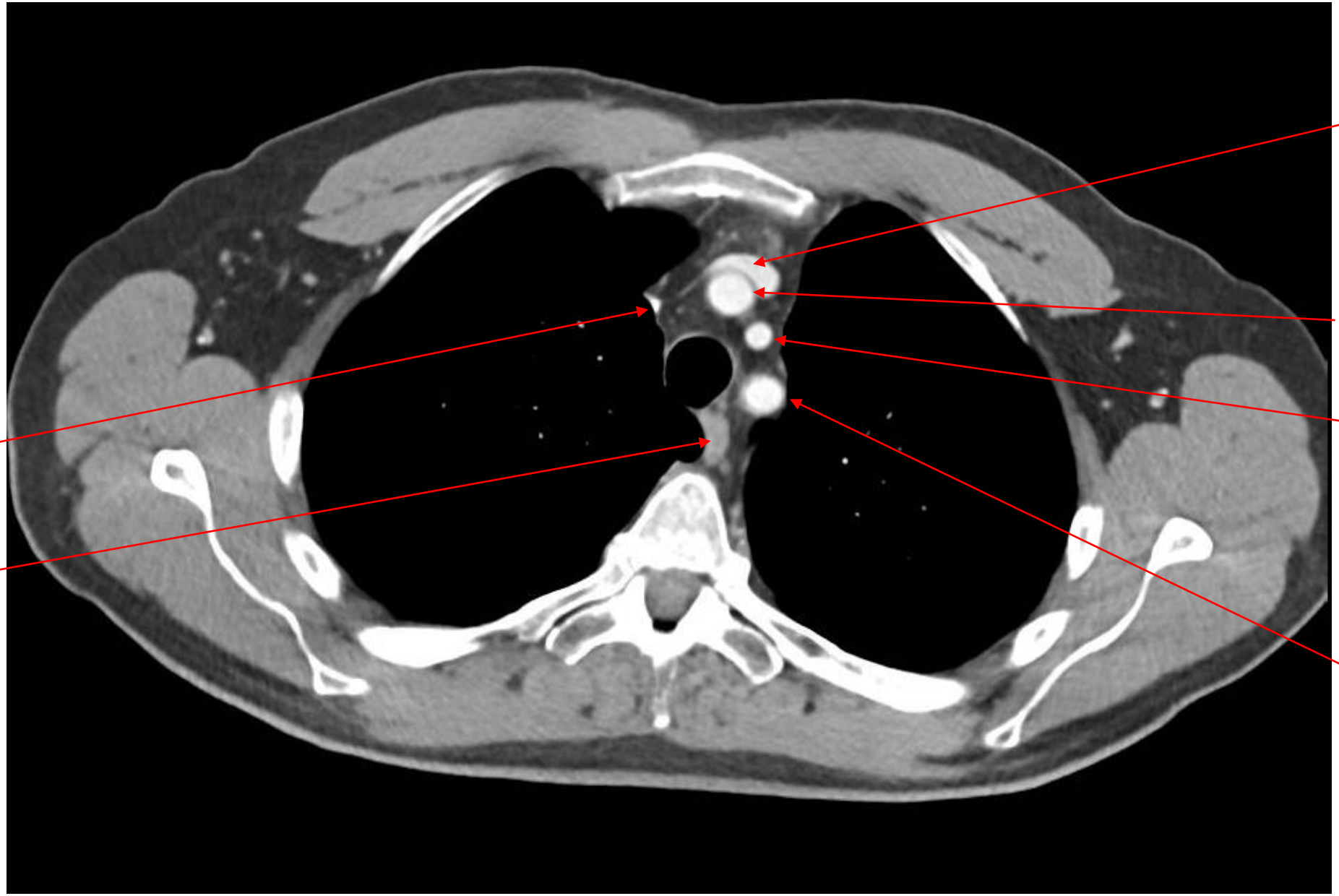
- Review Anatomy/Staging
- Subsections
  - Small cell lung cancer
  - Metastatic NSCLC
  - Locally advanced NSCLC
  - Early stage non-small cell lung cancer (NSCLC)

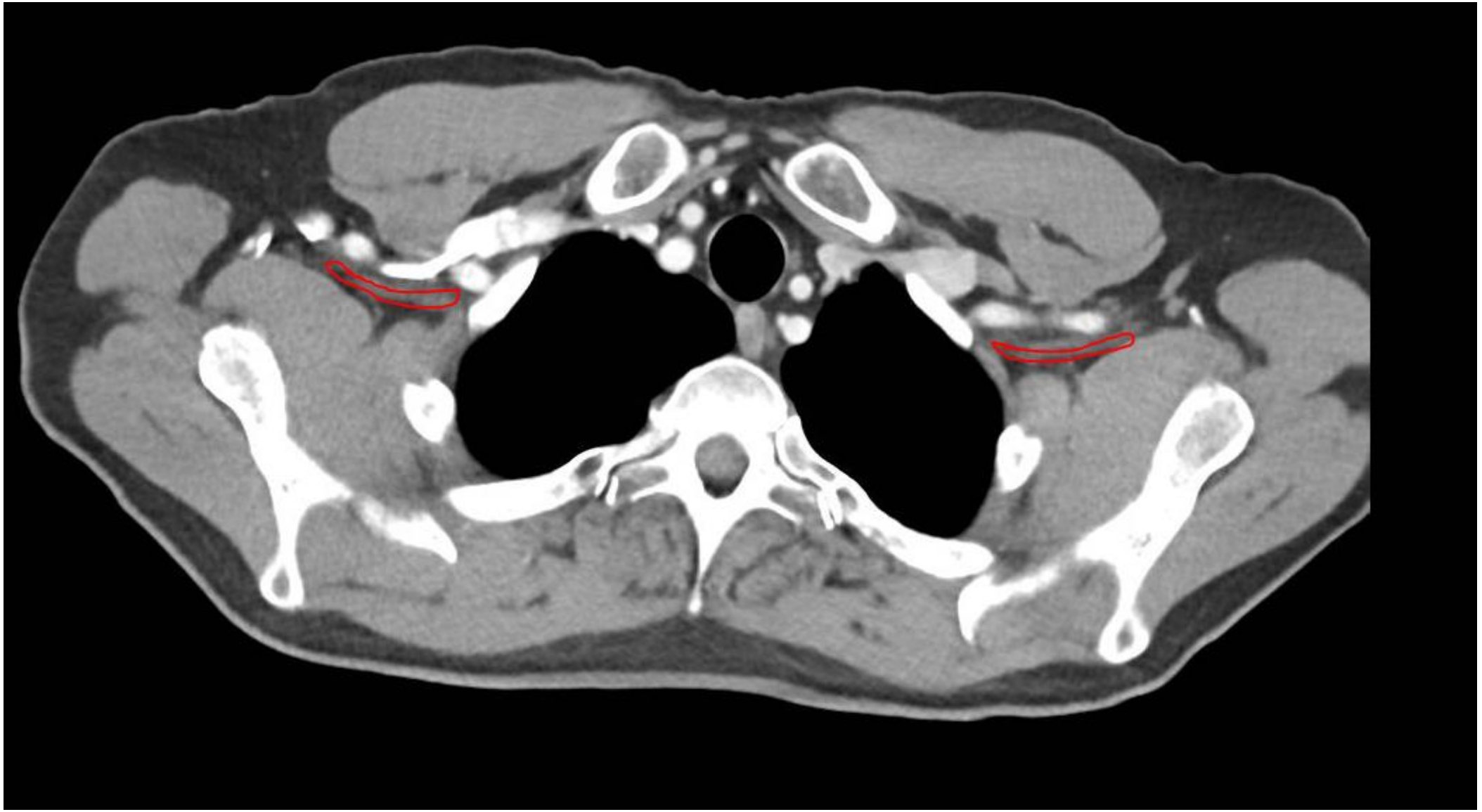
- Case Presentation
- How will I manage this patient?
- Background and key learning points
- Where are we now?
- Where are we going?

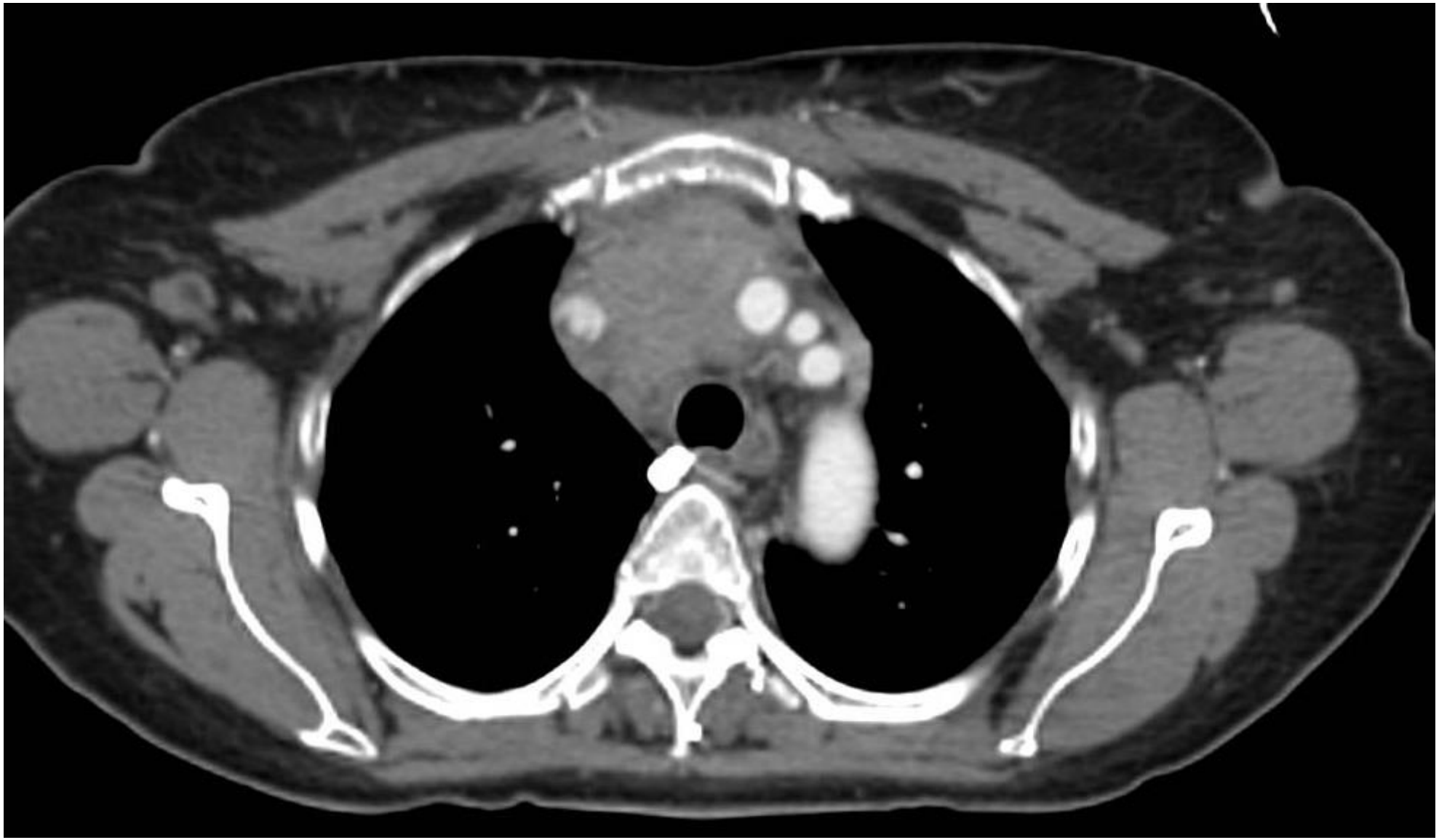

trachea
esophagus
azygous vein
ascending aorta
descending aorta

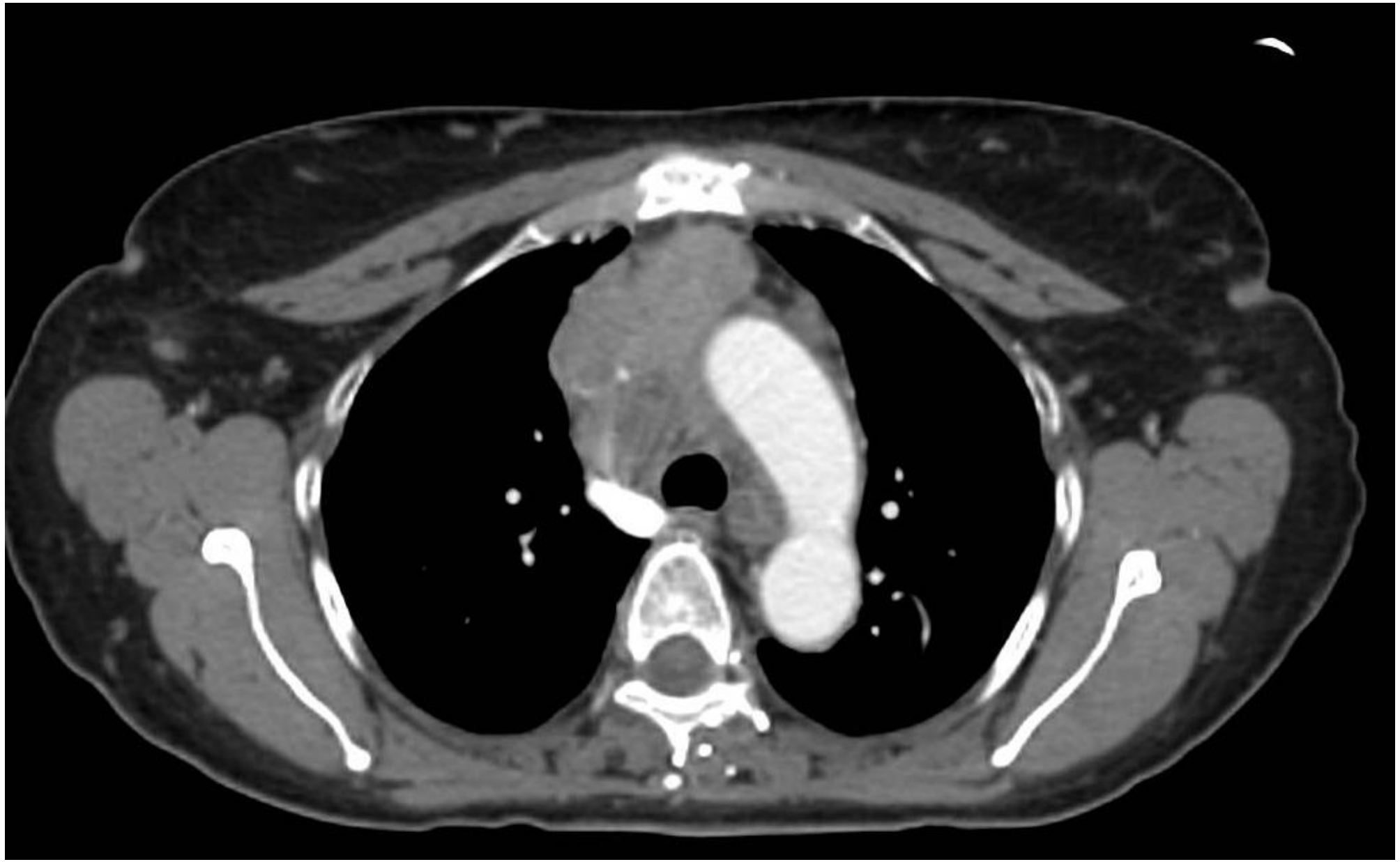

Pericardial recess (not adenopathy!)
Pulmonary trunk
Left main pulmonary artery
carina
esophagus
azygous vein

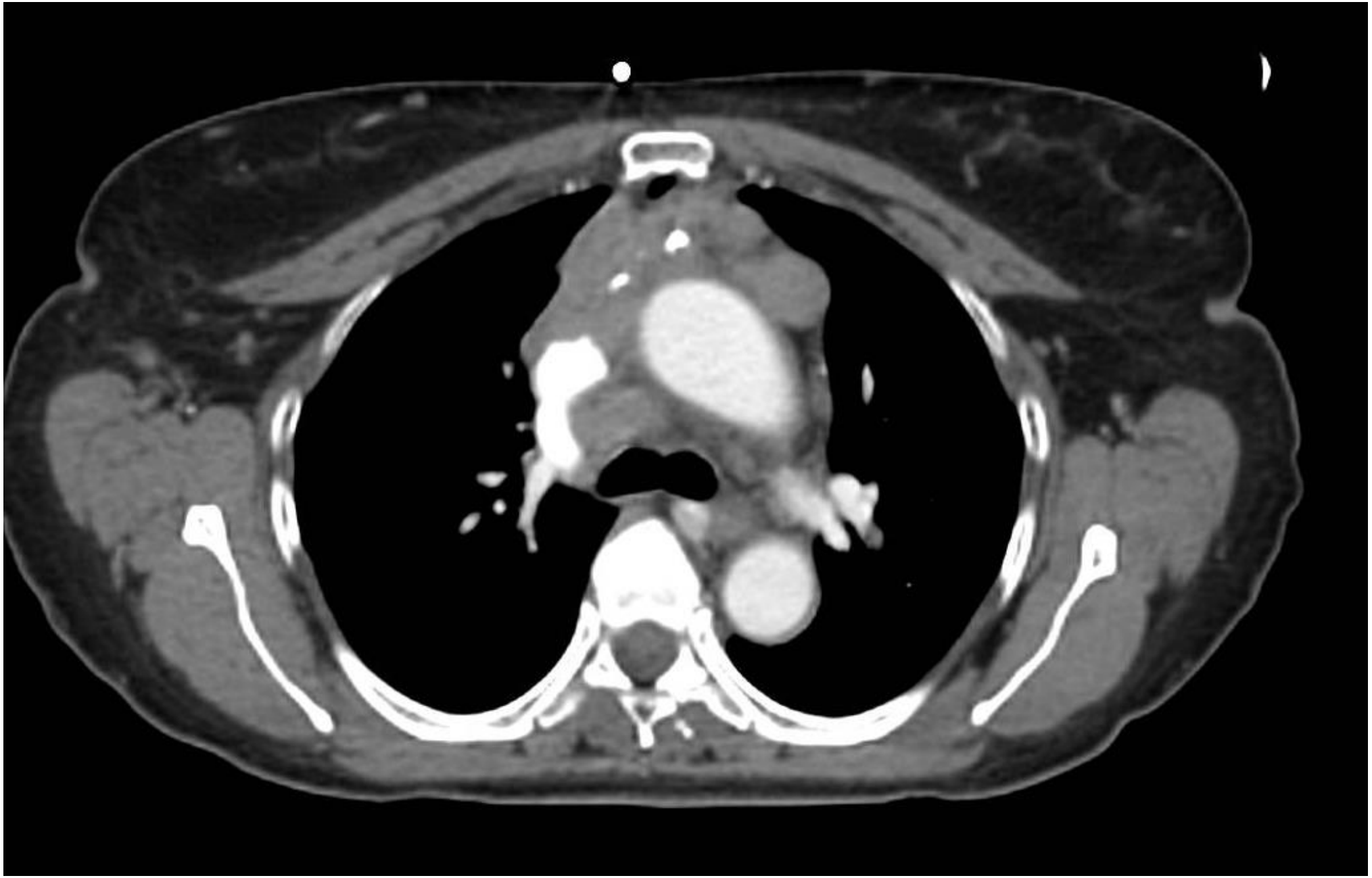

Ascending aorta
Pulmonary trunk
Right pulmonary artery
Left mainstem bronchus
esophagus
azygous vein
LLL bronchial stump


Left brachiocephalic vein
Brachiocephalic artery
Left common carotid artery
Left subclavian artery
Superior vena cava
esophagus



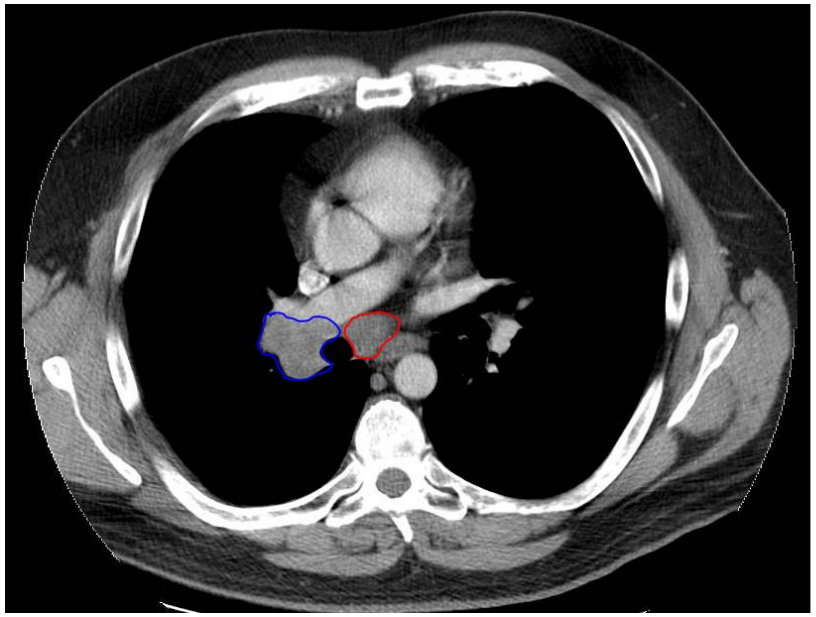






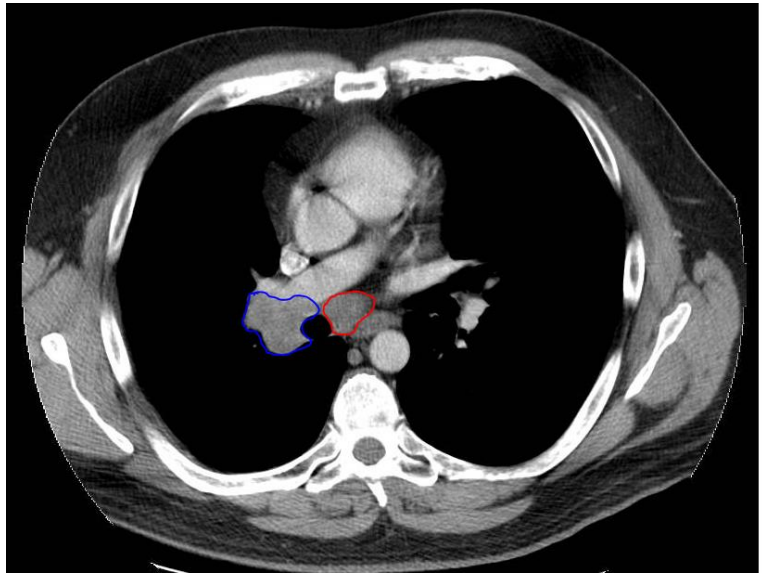
Small Cell: Case Presentation

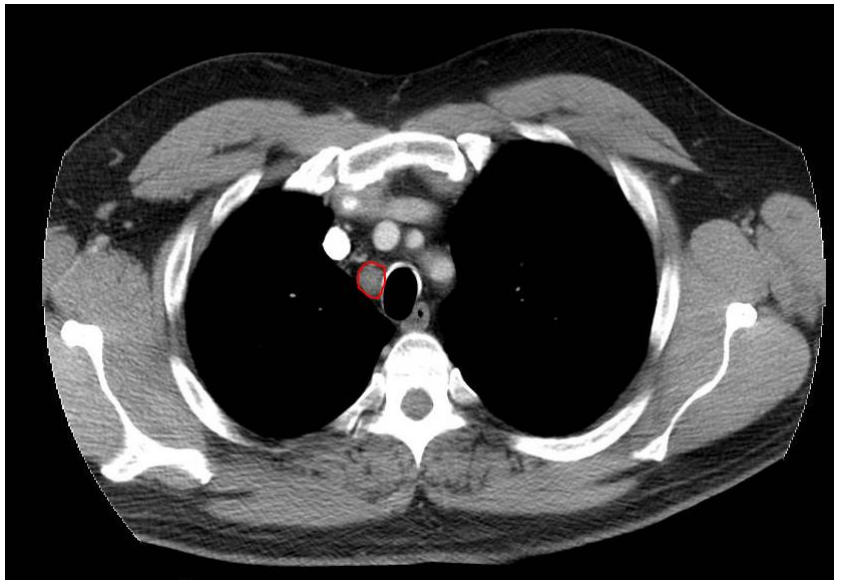
- 48 year old with new cough and intermittent fevers.
  - COVID-19 testing: negative
  - Primary care physician starts an antibiotic and steroids without improvement.
  - Chest CT

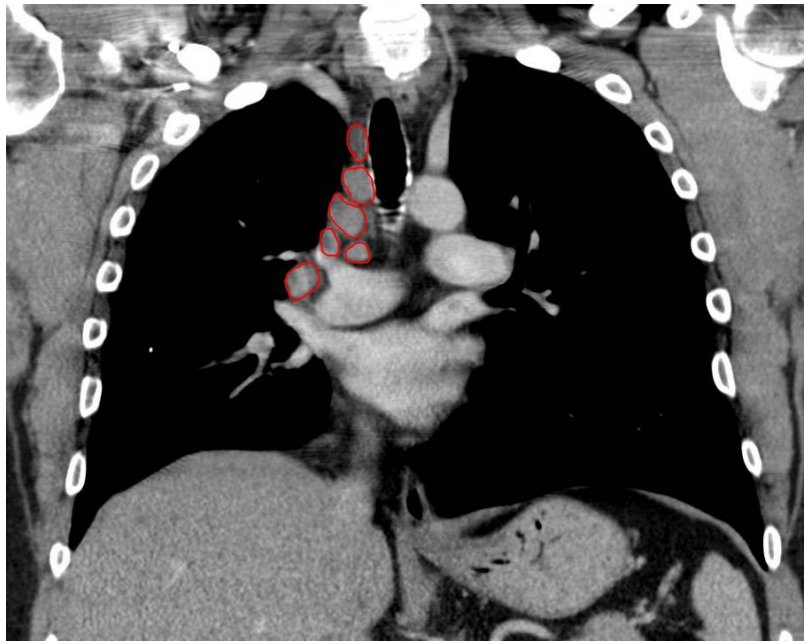


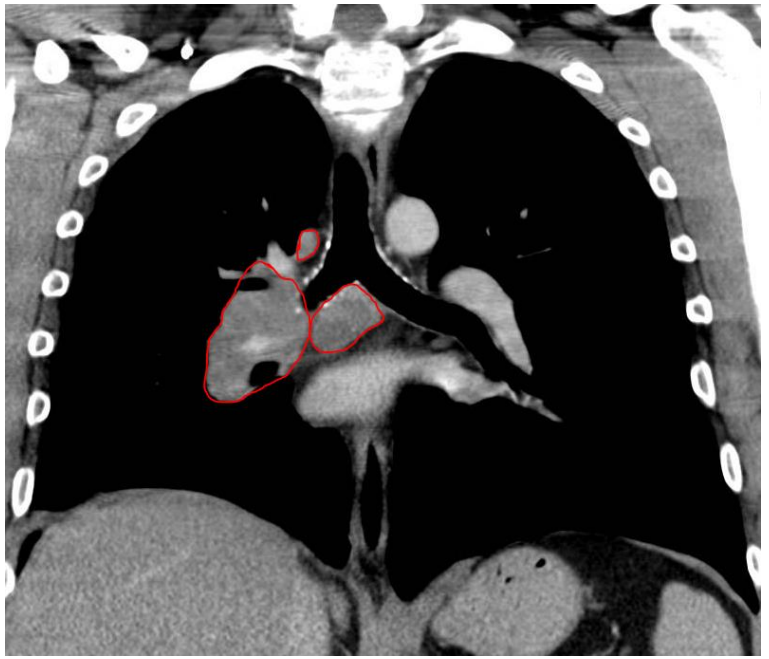
What do you see?

Right hilar (blue) and
subcarinal (red) adenopathy





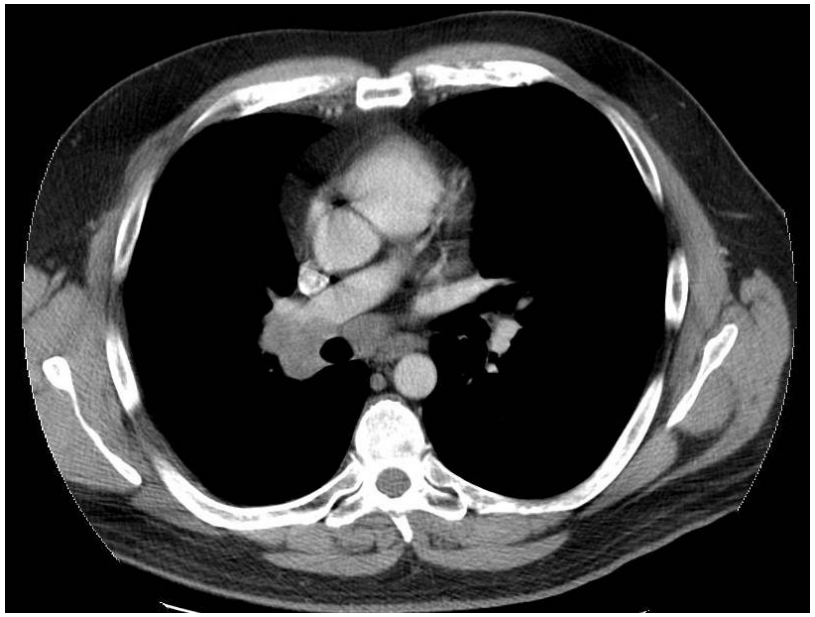




- Right hilar mass: 4.8 cm x 3.2 cm
- Multiple upper and lower right paratracheal lymph nodes
- 2.7cm subcarinal lymph nodes

- What do you do next?
  - After a complete history and physical, all small cell patients need:
    - PET/CT → FDG avid mediastinal and right hilar disease; no distant areas of concern
    - Brain MRI → No CNS metastases
    - Pathologic confirmation → Station 7 LN biopsy: metastatic small cell carcinoma*
    - Mediastinal assessment
      - Mediastinoscopy
      - Bronchoscopy: endobronchial ultrasound (EBUS)

*Positive for TTF-1, synapophysin, chromogranin, CK-7, CAM5.2, CD56
Crush artifact, Ki-67: usually >90%



- Staging:
  - How would you stage this?
  - T4N2M0
    - Why T4?
      - We defined the hilar disease as primary parenchymal disease and it invaded the mediastinum
  - To simplify staging (often the primary tumor is not distinguishable from the adenopathy, we use limited-stage and extensive-stage descriptors.
  - Our patient has limited stage disease
- Recommendations:
  - Smoking Cessation
  - Treatment?

Treatment

- Concurrent platinum/etoposide based chemotherapy x 4 cycles with chest radiotherapy to 45 Gy in 30 fractions (delivered BID)
- Consideration of prophylactic cranial irradiation pending restaging
- Enrollment on the ADRIATIC study:
  - Randomized study of consolidative immunotherapy in LS-SCLC

Treatment: Radiation Considerations

- Concurrent>Sequential
- Shorter time from start of any therapy to end of RT is associated with improved outcome
- Target delineation:
  - Initially involved nodal regions should be targeted
  - Post-chemotherapy volume can be targeted (if not starting concurrent on day one)
  - Elective nodal irradiation (ENI)
    - Evolving
    - Most current studies use involved nodal staging as long as CT and PET are used for target delineation.

LS-SCLC: Treatment techniques

- Does the timing of chemotherapy and completion of chest RT drive outcome?

Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

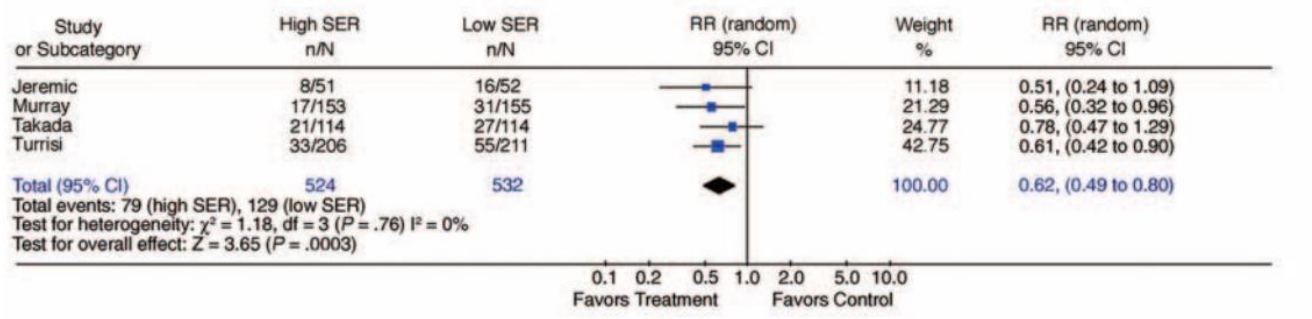
Murray et al[28]

Jeremic et al[31]

Turrisi et al[23]

Takada et al[24]

- Meta-analysis of 4 randomized studies in LS-SCLC
  - Start of any treatment and end of radiotherapy (SER)
- **Results:**
  - Low SER was associated with a higher 5-year overall survival (RR: 0.62, p=0.0003)
  - Each week of extension of the SER beyond that of the study arm with the shortest SER results in an overall absolute decreased in 5 year OS of 1.83%
- **Conclusions:**
  - Although confounded by other drivers of timing, a decrease in SER improves outcome in LS-SCLC



De Ruysscher D J et al. JCO 2006

LS-SCLC: Treatment techniques

- Why involved-nodal versus elective for radiotherapy?

SELECTIVE NODAL IRRADIATION ON BASIS OF ^{18}FDG-PET SCANS IN LIMITED-DISEASE SMALL-CELL LUNG CANCER: A PROSPECTIVE STUDY

- 60 patients with LS-SCLC
- RT to 45 Gy in 30 fractions delivered BID with concurrent platinum/Etoposide
- Target delineation
  - Only the primary tumor and mediastinal lymph nodes involved on pre-treatment PET were included in the target volume
- **Results:**
  - A difference in involved nodal stations between CT alone and PET/CT was found in 30% of patients.
  - Isolated regional failure rate: 3% (2 patients)
  - Grade 3 esophagitis: 12%
- **Conclusions:**
  - If PET/CT is used for target delineation, involved nodal RT planning can be used with low risk of elective nodal failure.

Van Loon J et al. IJROBP 2010

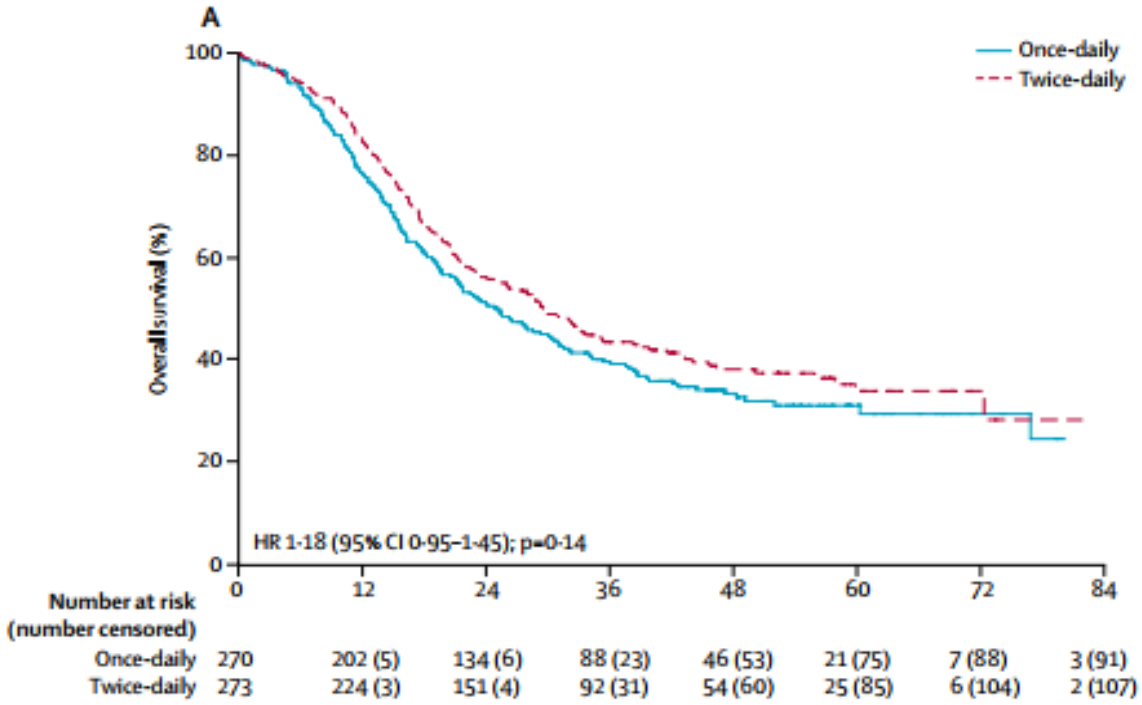
LS-SCLC: Treatment techniques

- Dose:
  - 45 Gy in 1.5 Gy fractions delivered twice daily at an interval of at least 6 hours.
- Target
  - If free breathing (fb), use motion management for parenchymal and nodal disease
  - Contour using mediastinal and lung windows
  - GTV fb, GTV min, GTV max=iGTV or ITV
  - CTV: 5mm expansion (variable)
  - PTV expansion: institutional specific (4mm radial, 7mm superior/inferior)

Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial

- 547 patients with Limited Stage-SCLC randomized to
  - Qday RT 66/33 (n=273) vs
  - BID RT 45/30 (n=274)
- **Results:**
- Median overall survival:
  - BID, 30 mos vs
  - Qday, 25 ms (p=0.14)
- 2-year overall survival: 56% vs 51%
- No difference in grade 3-4 esophagitis between groups (19% BID versus 19% Qday)

"Since the trial was designed to show superiority of once-daily radiotherapy and was not powered to show equivalence, the implication is that twice-daily radiotherapy should continue to be considered the standard of care in this setting"

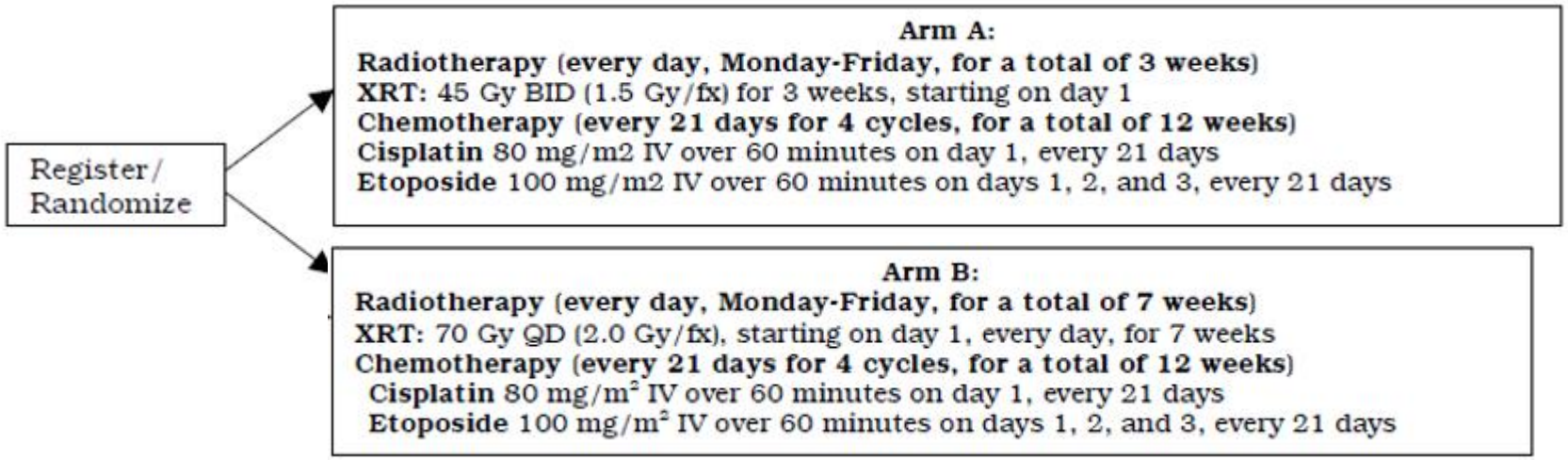


Faivre-Finn C et al. Lancet Onc 2017

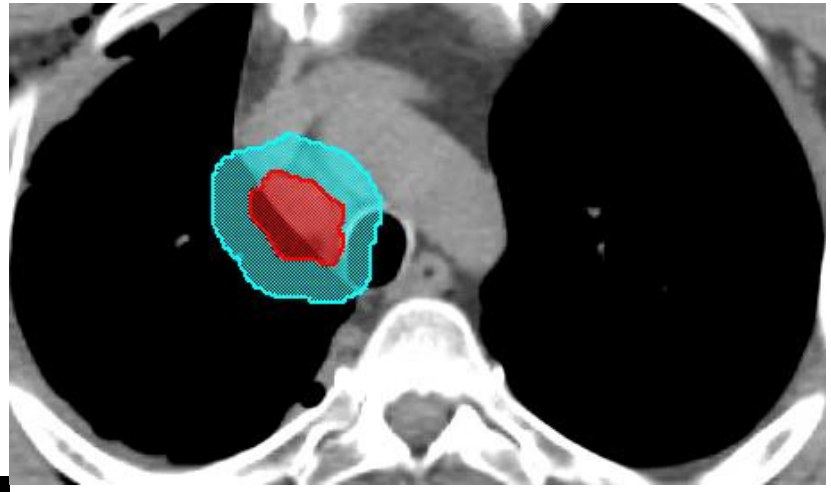
CALGB 30610/RTOG 0538

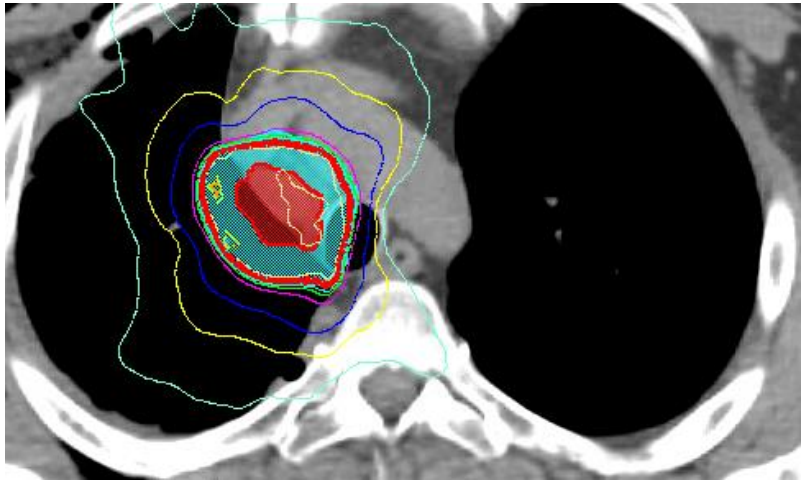
PHASE III COMPARISON OF THORACIC RADIOTHERAPY REGIMENS IN PATIENTS WITH LIMITED SMALL CELL LUNG CANCER ALSO RECEIVING CISPLATIN AND ETOPOSIDE

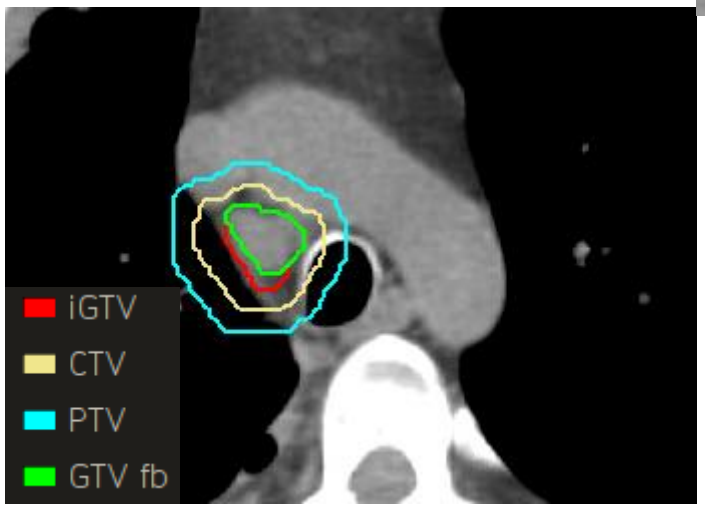
Schema (1 cycle = 21 days)
Patients will receive 4 cycles of chemotherapy on all arms

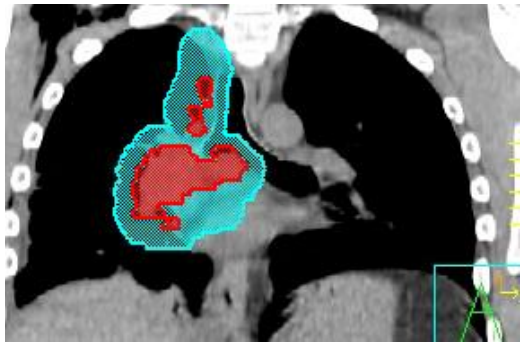


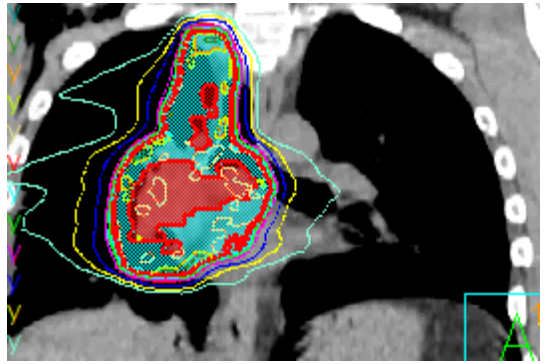
VMAT: 2 arcs
150 cGy x 30 fractions to 95% isodose line

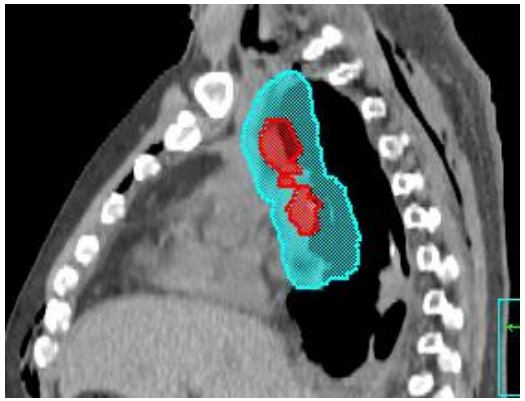


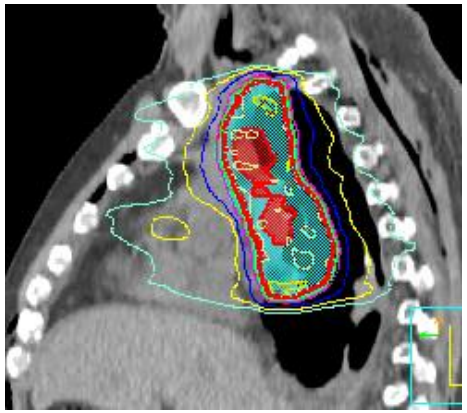






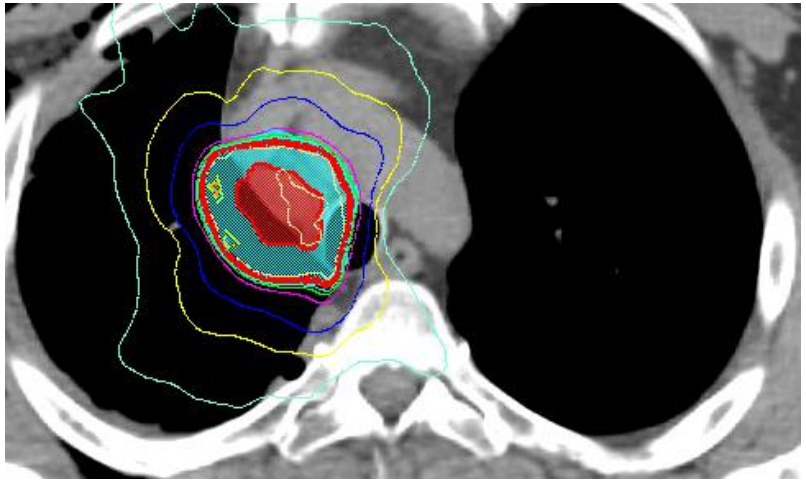


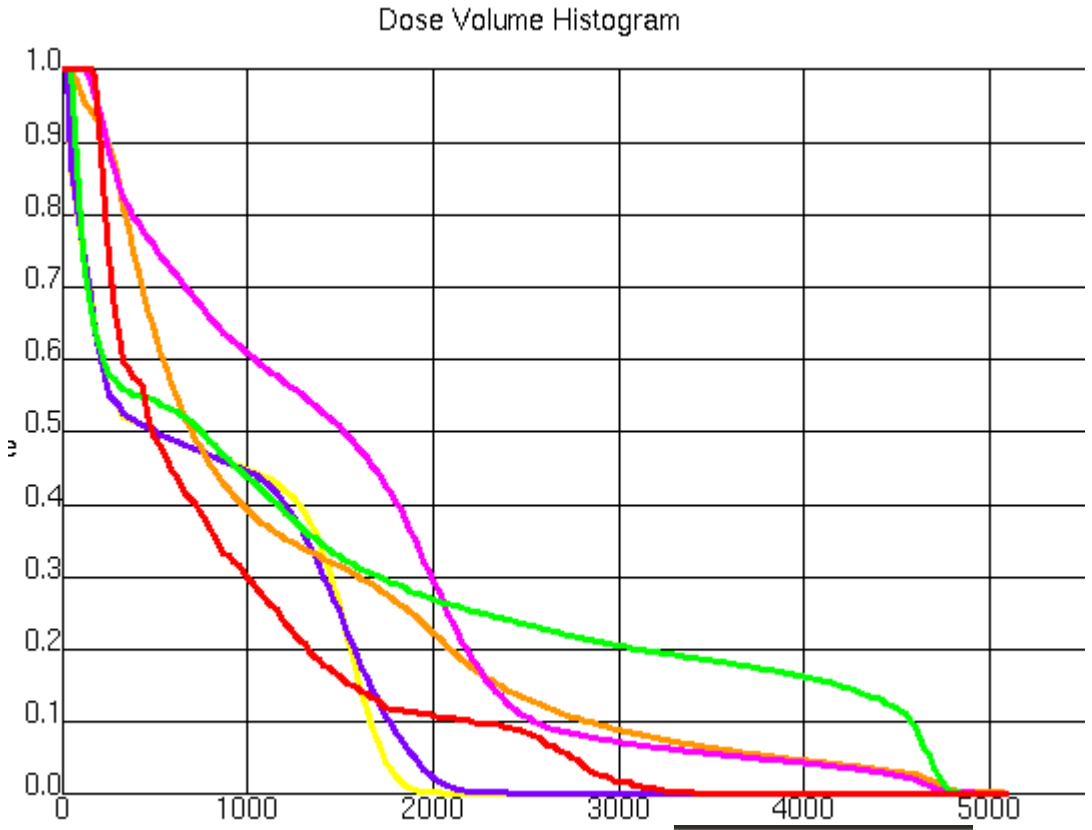




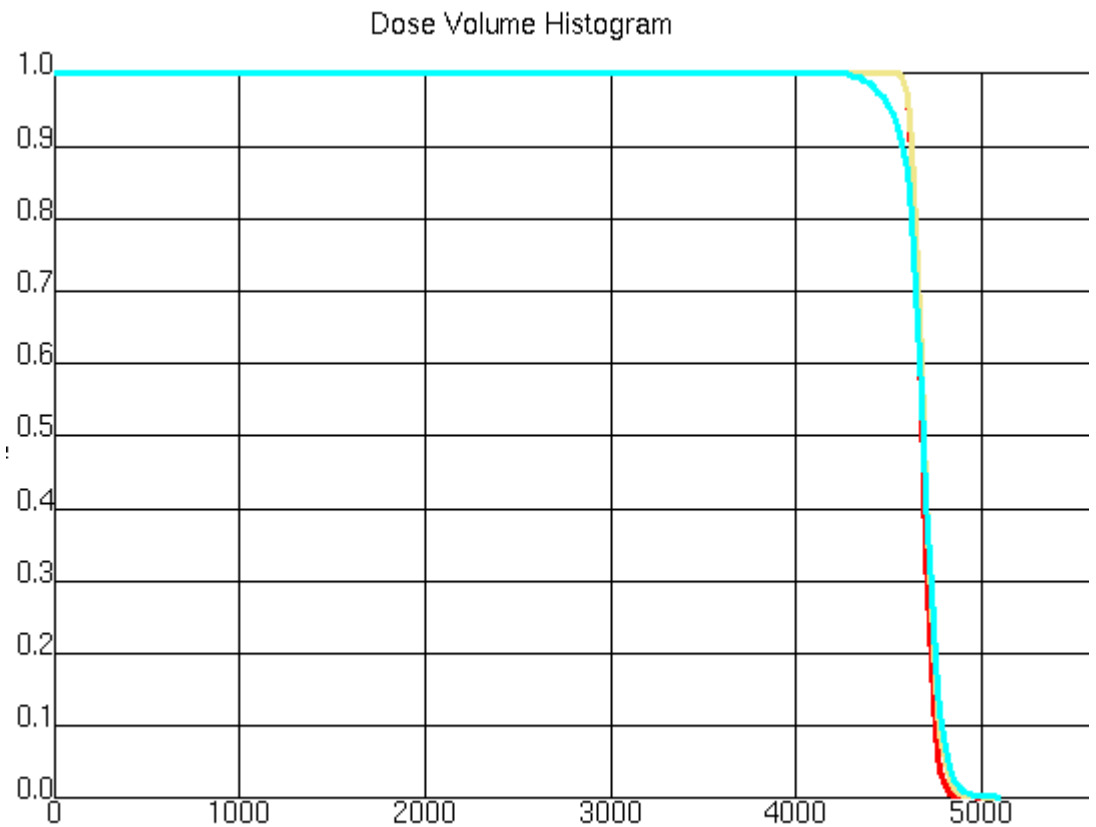
Plan Evaluation

- Lay of the land—get a general sense of the areas you are treating to focus your attention on the DVH
- Safety
- Coverage
- Isodose lines—hot spots/cold spots
- Recheck prescription





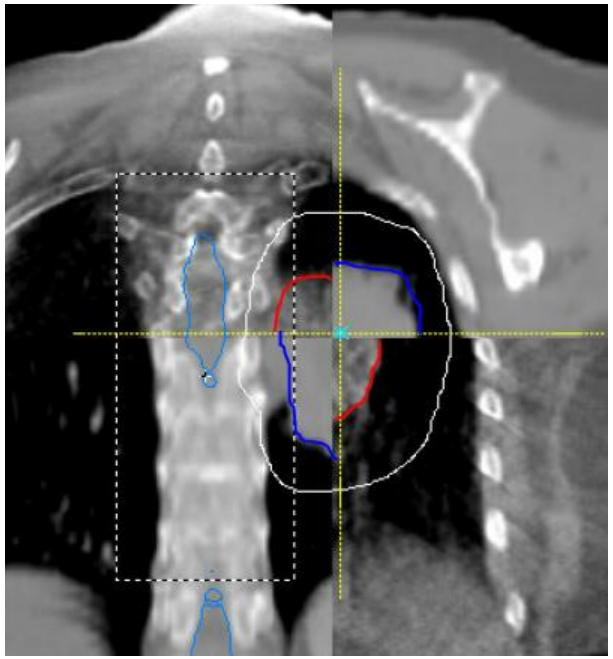
	Max.	Mean
spinal canal	2053.0	613.5
SpinalCanal_PRV04	2403.5	621.9
Lungs-ITV	5087.2	1207.0
Pericardium	4929.8	1474.5
Esophagus	4849.5	1418.8
R_brachialplexus	3412.1	806.5



	Min.	Max.	Mean
iGTV	4536.1	4961.4	4683.6
CTV	4482.9	4996.3	4695.9
PTV	4032.0	5087.2	4680.2

SCLC: Limited Stage, Key Points

- If the patient started chemo >one week before RT, carefully evaluate your daily image guidance.
    - Adaptive replanning may be necessary.
- Treatment toxicity
    - Watch patient during blood count nadir
    - Beware of esophagitis the last few days of radiation and the week thereafter.

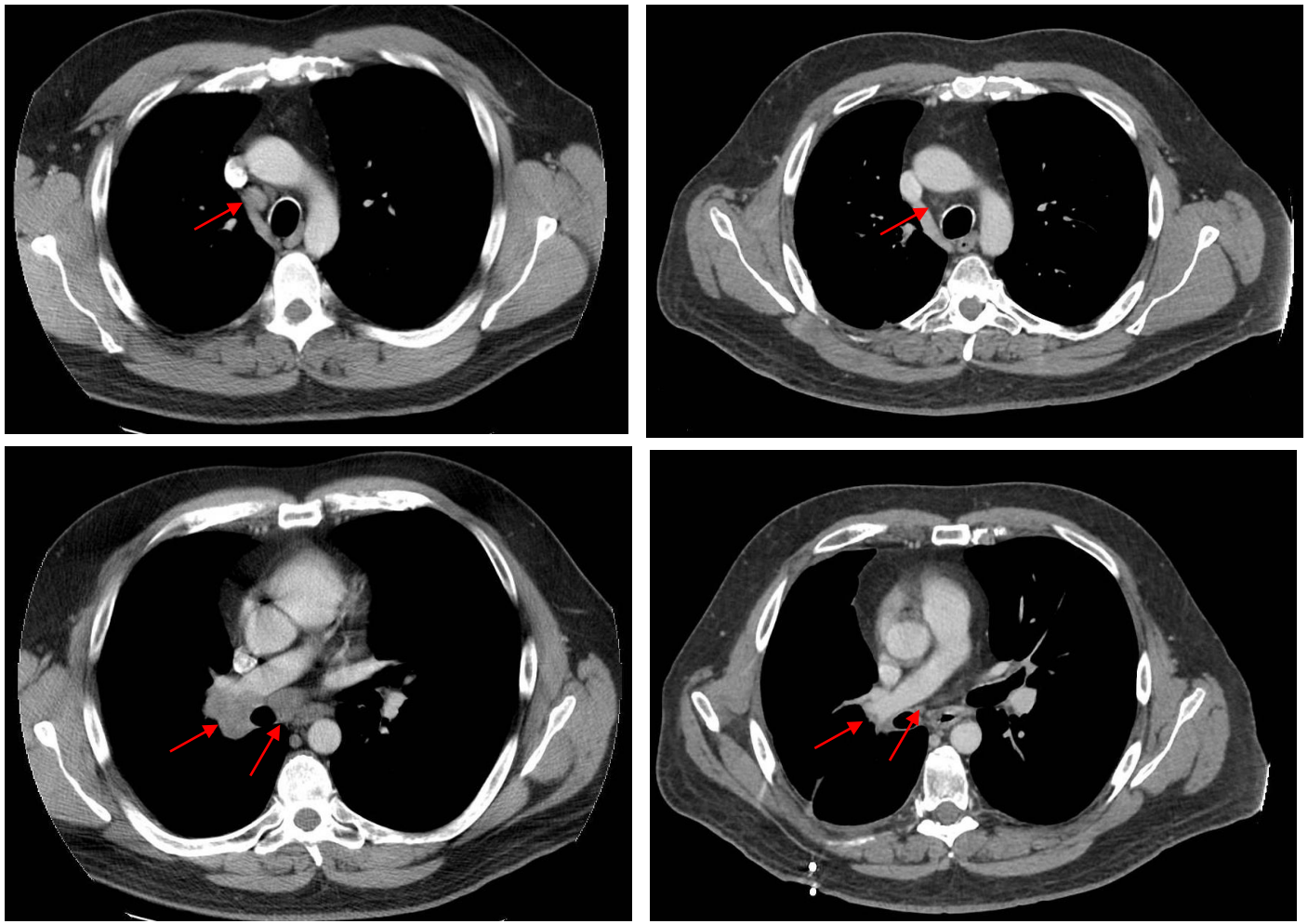


Response assessment

- Studies ?
  - CT chest/abdomen/pelvis
  - Brain MRI
- Next Steps ?
  - Prophylactic cranial irradiation

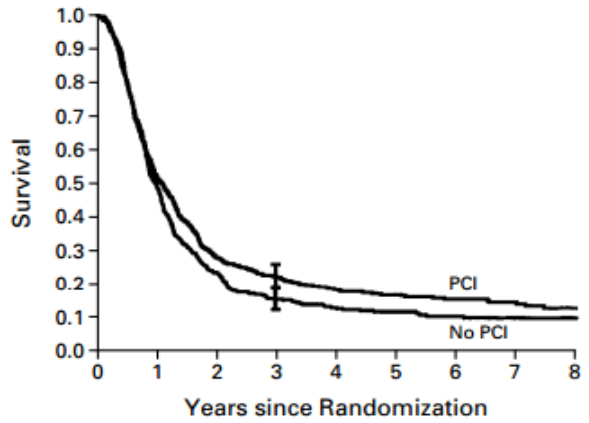
Pre-treatment

Post-treatment



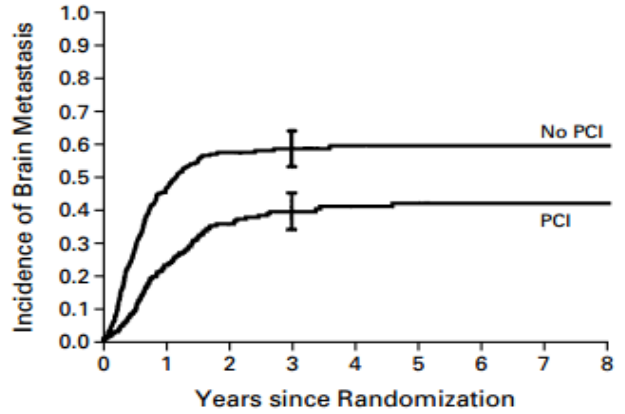
PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

- Meta-analysis of seven trials of PCI vs no PCI that included 987 patients
- **Results:**
  - 3 year overall survival:
    - 5.4% absolute improvement with PCI: 20.7% vs 15.3% (p=0.01)
  - Cumulative incidence of brain mets decreased, 59% vs 33% (p<0.001)
- **Caveats:**
  - We have no single randomized study with OS benefit to PCI in LS-SCLC
  - This study included patients with complete remission of tumor as defined by chest x-ray



No. at Risk

No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17



No. at Risk

No PCI	457	171	88	57	41	32	21	18	14
PCI	524	248	133	96	66	52	40	29	17

Auperin A et al. NEJM 1999

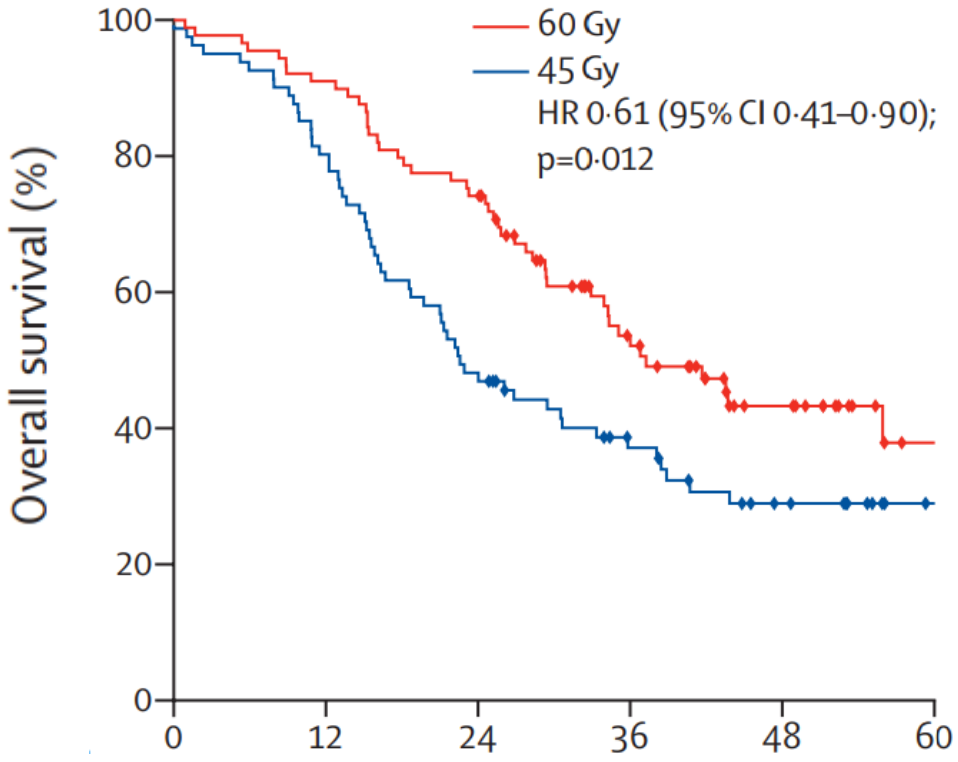
Where are we going in LS-SCLC

- Dose escalation
- Consolidative immunotherapy
- Hippocampal avoidance PCI

Where are we going in LS-SCLC? Dose escalation

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

- 176 patients with Limited Stage-SCLC randomized to
  - BID RT 60/40 (n=89) vs
  - BID RT 45/30 (n=81)
- **Results:**
  - Median follow up: 49 months
  - 2-year survival:
    - 60 Gy: 74.2%
    - 45 Gy: 48.1% (p=0.0005)
  - Progression free survival (HR: 0.75 (p=0.13)
  - Toxicity
    - Serious adverse events were balanced between the arms
      - 60 Gy: 55 events in 38 patients
      - 45 Gy: 56 events in 44 patients
    - Treatment-related deaths
      - N=3 in both groups
  - Prophylactic cranial irradiation
    - In both groups, 85% of patients received PCI

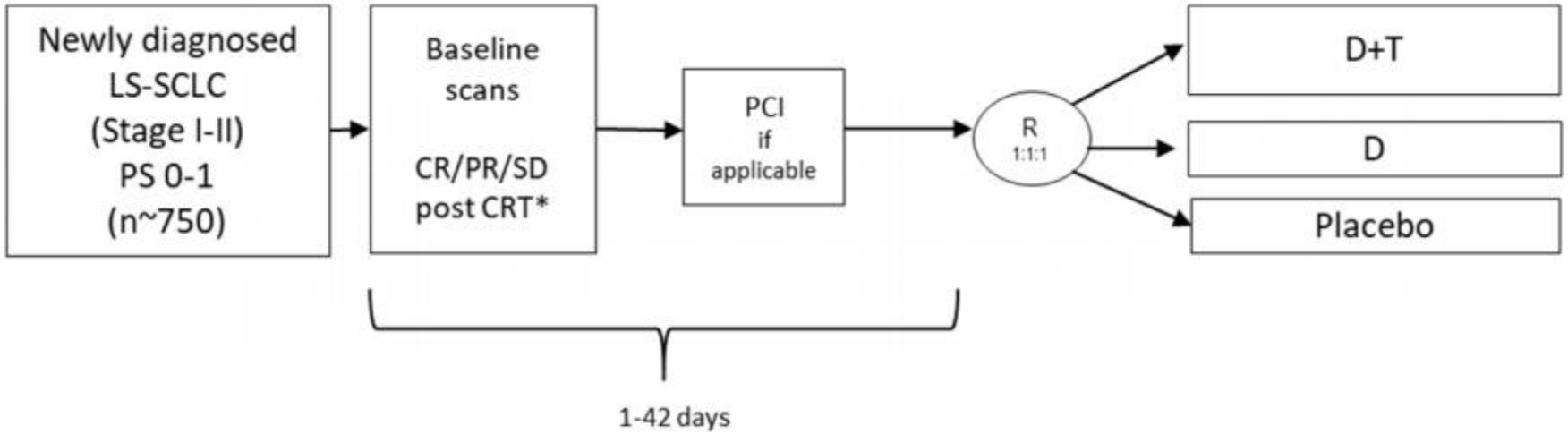


Henning B et al. Lancet Onc 2021

Where are we going in LS-SCLC?

Consolidative immunotherapy

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)



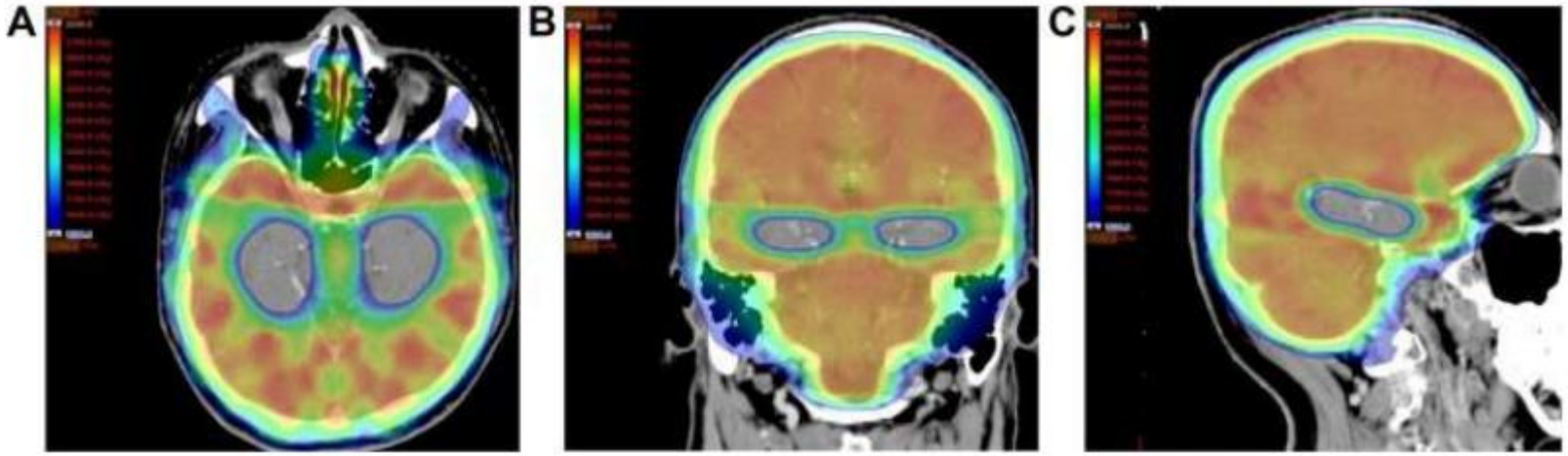
*CRT
Chemo: 4 EP Cycles (3 permitted)
RT: either 60-66Gy/Gy/QD/6wks or 45Gy/BD/3wks

Baseline scans include RECIST1.1 tumour assessment scan and brain MRI or CT scan

Stratification:
Stage I/II vs III
PCI: Yes vs No

Currently enrolling patients

PCI in SCLC:Hippo-Avoidance



- NRG CC001
  - 518 patients randomized to HA-WBRT vs. WBRT for patients with brain mets
  - Results: Lower rates of neuro-cognitive failure
  - No difference in OS, relapse (CNS) or toxicity

Gondi ASCO 2019
Yeo, S Onco Targets Ther 2017

HA-PCI

- Three studies:
  - NKI/Dutch Cancer Agency (n=168) closed, published JTO 2021
  - Spain/PREMER (n=150) closed, presented ASTRO 2019
  - RTOG CC003 (n=304) currently enrolling
- Outcomes:

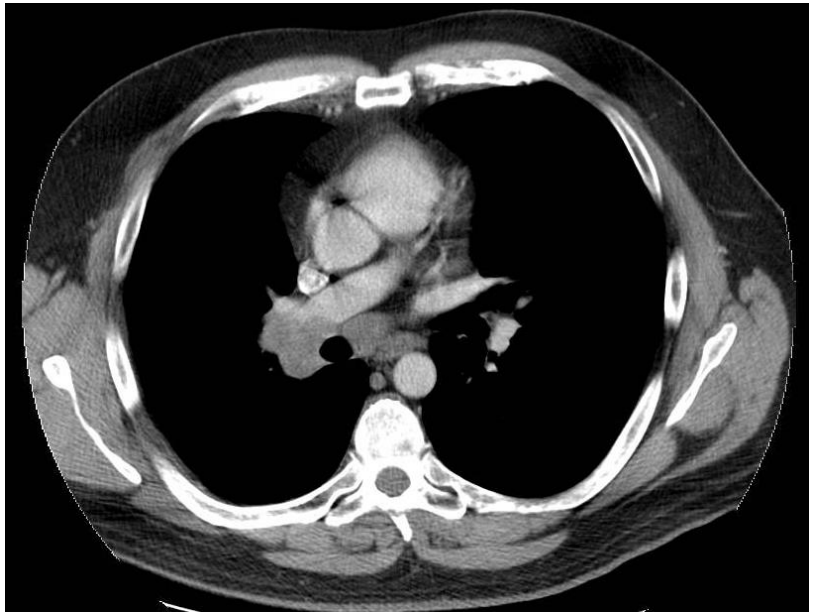
Agency	Primary endpoint(s)	Neurocognition Tools	Sample
RTOG CC003 (NCT02635009)	Neurocognitive decline Intracranial relapse rate	HVLT-R delayed recall deterioration status, defined using the Reliable Change Index (RCI) (Phase III), @ 6mo	304
NKI/Dutch Cancer Agency (NCT01780675)	Neurocognitive decline	HTLV-R @ 4months vs. baseline <5pt difference = success	168
Spain/PREMER (NCT02397733)	Neurocognitive decline	Free and Cued Selective Reminding Test (base vs. 3 mo)	150

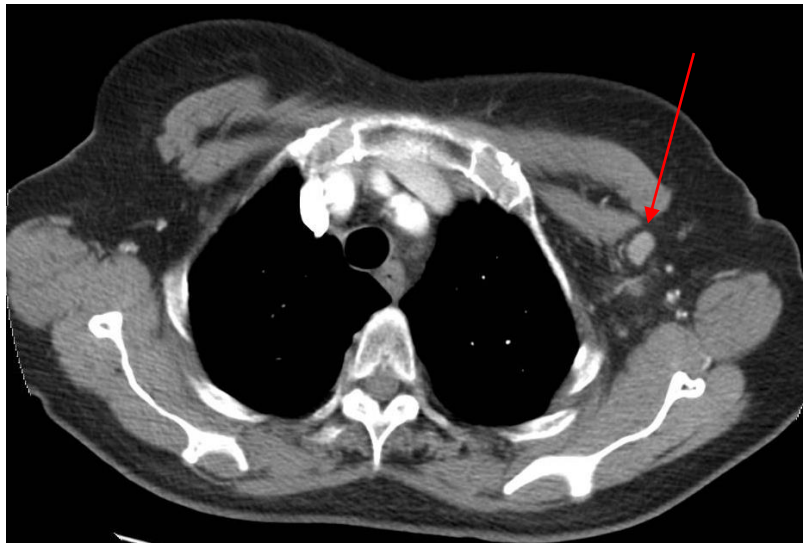
Take home points: HA-PCI

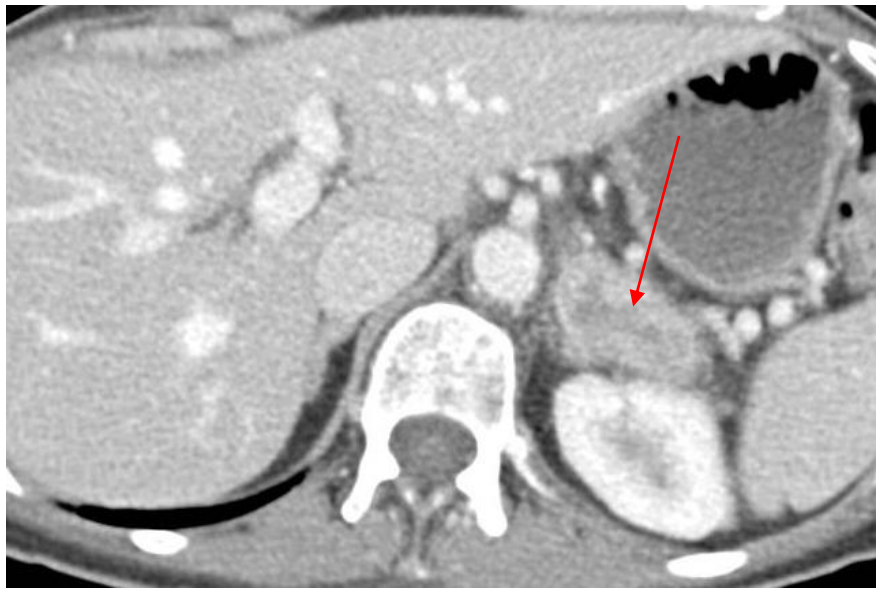
- Results:
  - NKI: HVLT negative
  - Spain: FCSRT positive, but limited replication data available for this endpoint
  - Risk of brain metastases and/or hippocampal recurrence is low with HA-PCI
- HA-PCI is an excellent option for carefully selected patients enrolled on a clinical trial. Please consider enrolling on CC-003!

Case Presentation: SCLC

- Same patient as before.
- Now with additional findings:
  - Left axillary and left adrenal metastases







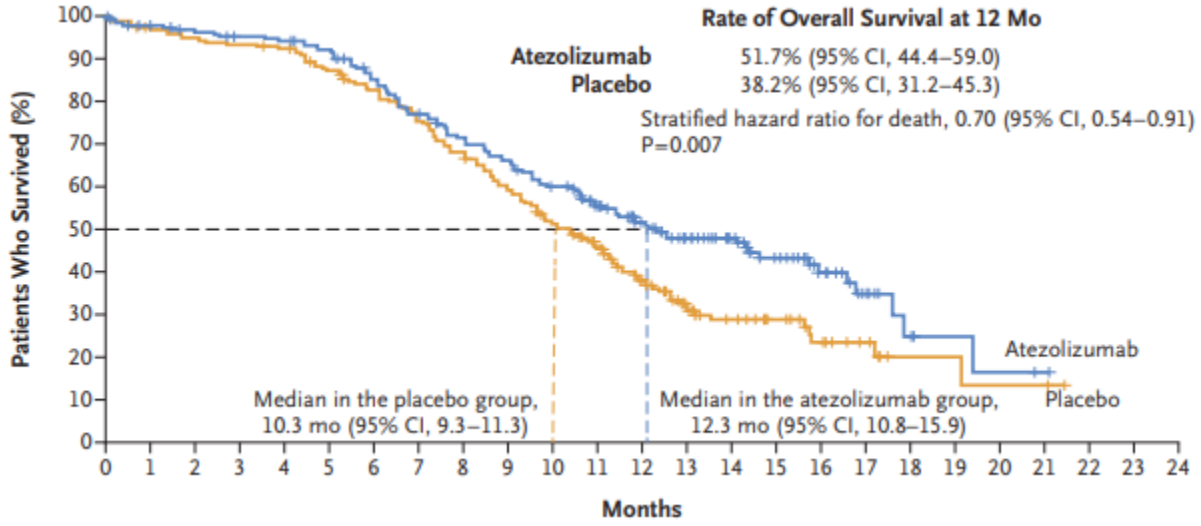
- Staging ?
  - T4N2M1
  - Our patient has extensive stage disease
- Recommendations:
  - Smoking Cessation
  - Treatment?

Treatment

- Concurrent platinum/etoposide and immunotherapy x 4 cycles.
- After assessment of tumor response, consideration of:
  - Chest RT
  - PCI
  - Maintenance immunotherapy

Immunotherapy in ES-SCLC

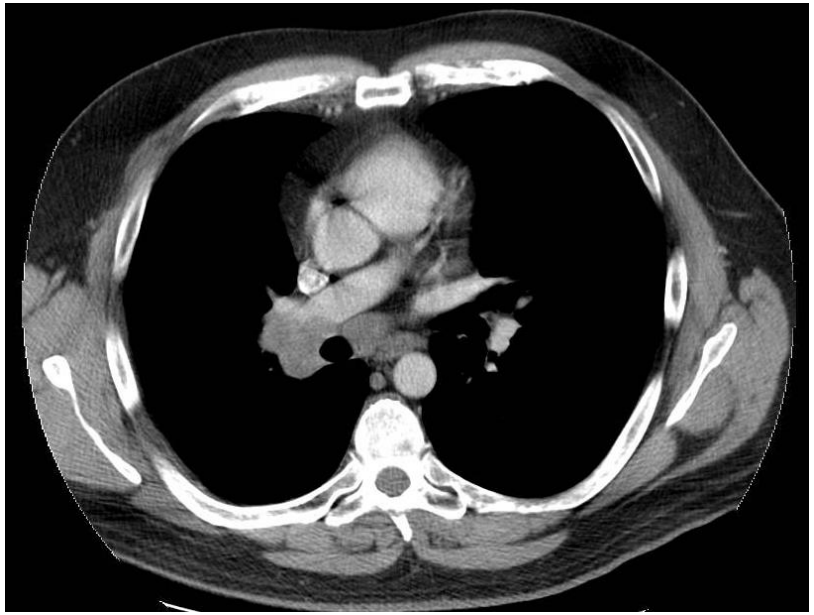
- IMpower 133, randomized phase III
  - N=201: atezolizumab+platinum-etoposide→ maintenance atezolizumab
  - N=202: platinum-etoposide
- Outcome:
  - Median overall survival:
    - 12.3 mos vs. 10.3 months favors atezo (p=0.007)

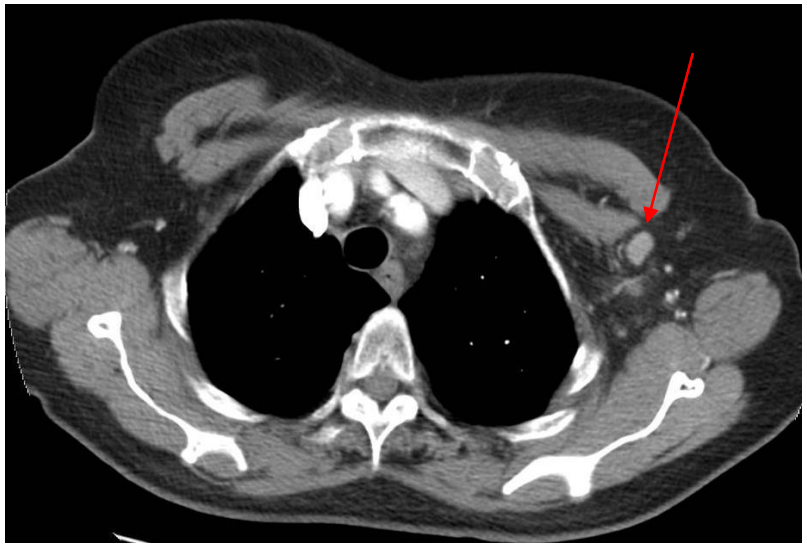


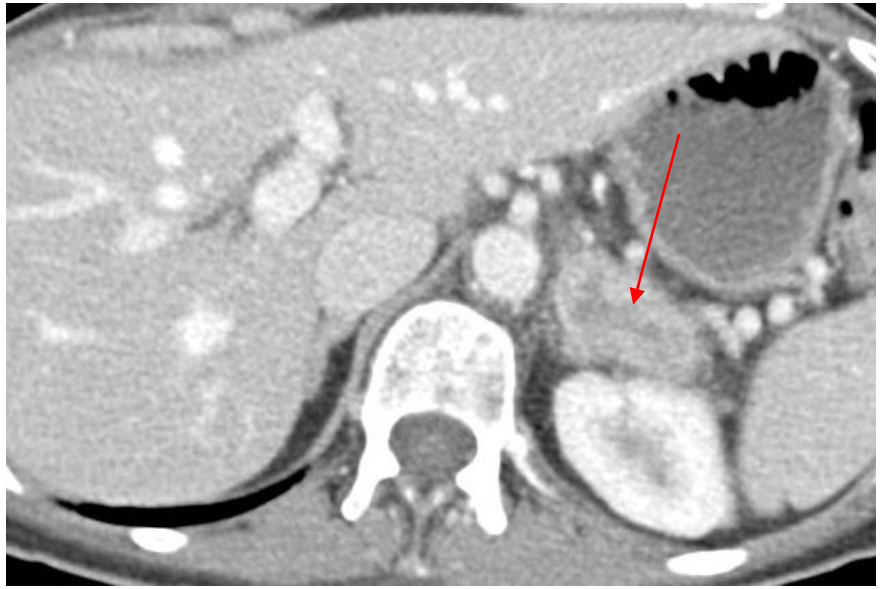
Horn et al., NEJM 2018

Case Presentation: SCLC

- After 4 cycles of chemo-immunotherapy, restaging shows a partial response to therapy with no new disease







Treatment

- Concurrent platinum/etoposide and immunotherapy x 4 cycles
- Disease response:
  - CT c/a/p → Partial response to therapy with no new areas of disease
  - Brain MRI → No CNS metastases
- **Treatment options?**
  - Chest RT
  - PCI
  - Maintenance immunotherapy

Chest RT in extensive stage small cell

- Jeremic
- Gore (RTOG 0937)
- CREST

Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

- 210 patients with extensive stage-SCLC who received three cycles of platinum/etoposide chemo.
- For those with complete response in distant sites and at least partial response in the chest (n=109), randomization to
  - 3 additional cycles of chemo alone RT 60/40 (n=89) vs
  - As above with chest RT, 54 Gy in 36 fractions (BID)
- **Results*:**
  - Median overall survival:
    - chemoRT: 17 months
    - chemo: 11 months
  - 3-year survival:
    - chemoRT: 22%
    - chemo: 9%
  - 5-year survival
    - chemoRT: 9.1%
    - chemo: 3.7%

*All results reported at statistically significant but only one P value reported (P=0.41)

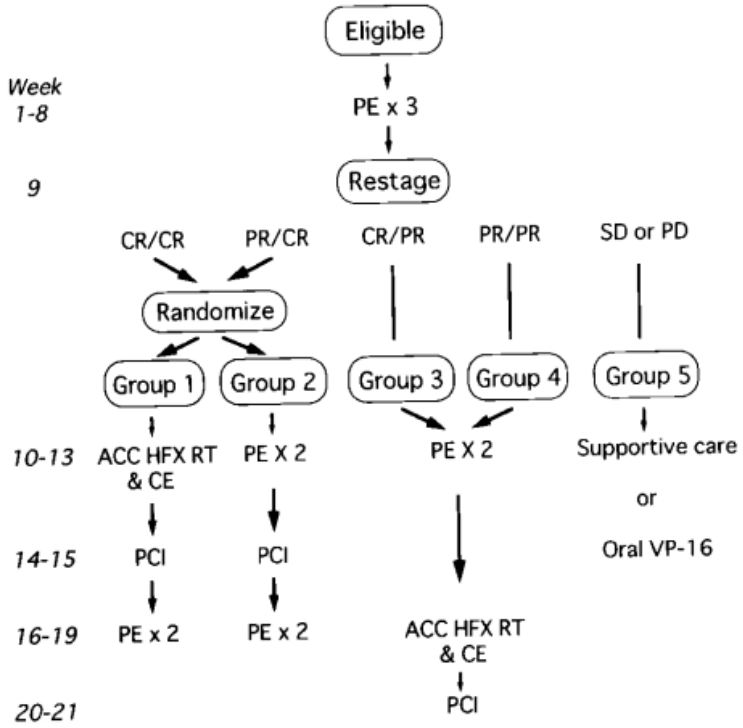


Fig 1. Treatment schema. VP-16, etoposide.

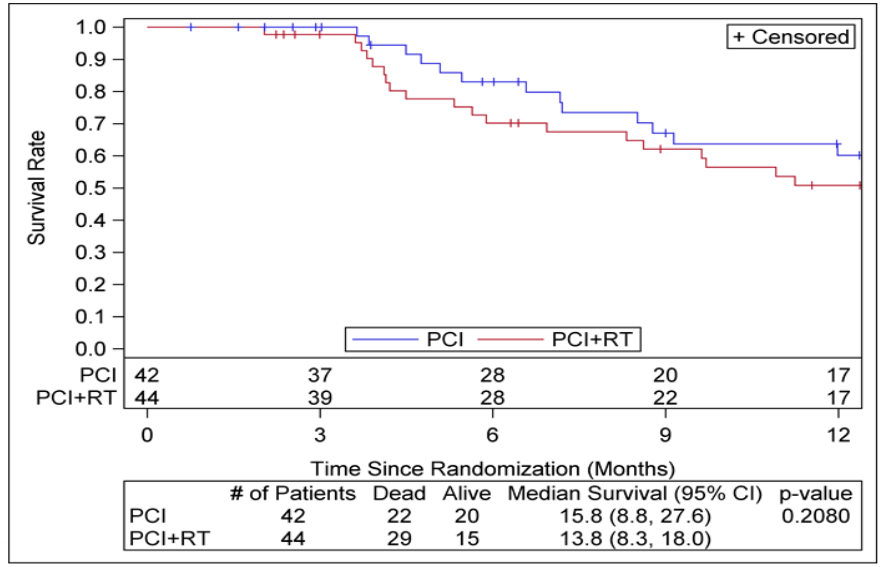
Jeremic B et al. JCO 1999

Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937

- 97 patients with extensive stage-SCLC who 4-6 cycles of chemotherapy with at least PR and no new areas of disease
- Max of 4 metastatic sites
  - Randomized to
    - PCI vs
    - PCI + consolidative RT to chest and residual metastatic sites
- **Results:**
  - Closed for futility at interim analysis
  - 1-year survival:
    - PCI alone: 60.1%
    - PCI+chestRT: 50.8%

S	**Response to Treatment**	**R**	**Arm 1: Prophylactic Cranial Irradiation**
T	1. Complete Response (CR)	**A**	2.5 Gy per fraction for a total of 25 Gy
R	2. Partial Response (PR)	**N**	
A		**D**	**Arm 2: Prophylactic Cranial Irradiation**
T		**O**	2.5 Gy per fraction for a total of 25 Gy
I	**Number of Metastatic Lesions**	**M**	and
F	1. 1	**I**	**Consolidative Radiation to**
Y	2. 2-4	**Z**	**Locoregional and Residual Metastatic Disease**
	Age	**E**	45 Gy at 3 Gy per fraction*
	1. <65		
	2. ≥65		*Acceptable alternative regimens: 30-40 Gy in 10 fractions

Overall Survival



Gore E et al. JTO 2017

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

- 498 patient with extensive stage-SCLC who 4-6 cycles of chemotherapy with at least PR and no new areas of disease
- Randomized to
    - PCI alone vs
    - PCI + thoracic radiotherapy (TRT), 30 Gy in 10 fractions
- **Results:**
    - 1-year survival:
        - PCI+TRT: 33%
        - PCI alone: 28% (p=0.066)
    - 2-year survival:
        - PCI+TRT alone: 13%
        - PCI alone: 3% (p=0.004)
    - 6-month progression free survival
        - PCI+TRT: 24%
        - PCI alone: 7% (p=0.01)

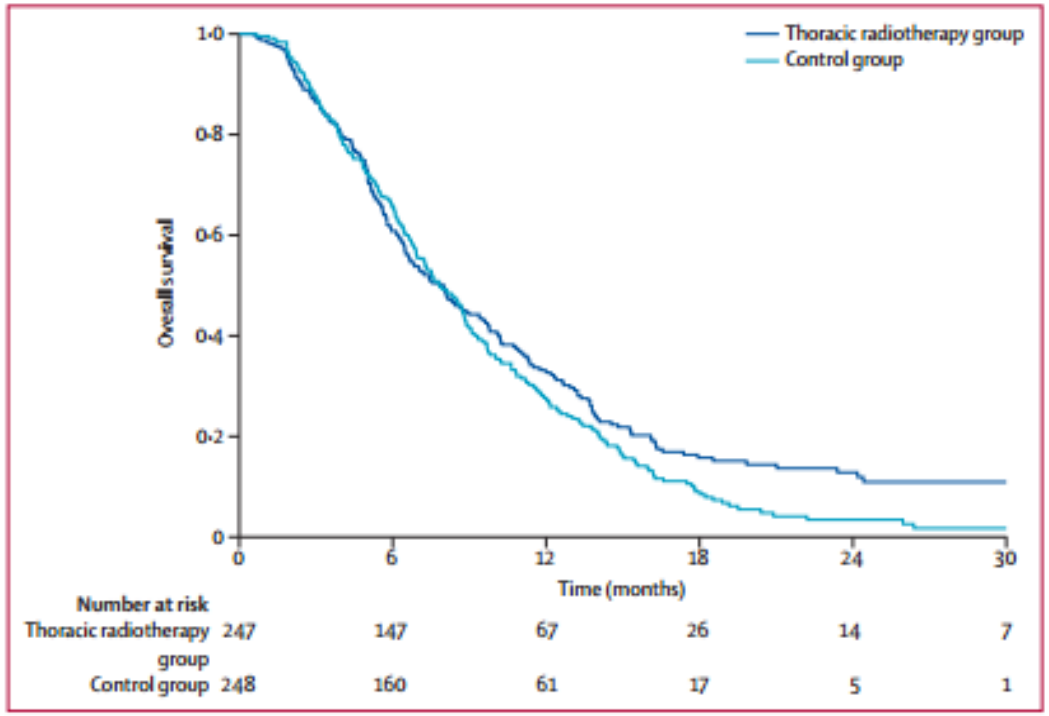


Figure 2: **Kaplan-Meier curves for overall survival**

Caveats:

-Patients with brain metastases and malignant effusions were not included.

- The 2 year OS and 6-month PFS outcomes were unplanned secondary analysis

Slotman B et al. Lancet 2015

Chest RT in extensive stage small cell

- Jeremic---positive study for chest RT, definitive doses
- Gore (RTOG 0937)—negative study for chest RT, definitive doses
- CREST—positive study for chest RT, palliative doses
- Conclusions:
  - In general, the use of consolidative chest RT with definitive doses should be used with caution
  - However, in patients with good performance status with an excellent response to chemotherapy, a higher dose of thoracic RT (i.e. 45 Gy in 15 fractions) may be appropriate *(from ASTRO clinical practice guidelines for SCLC)*

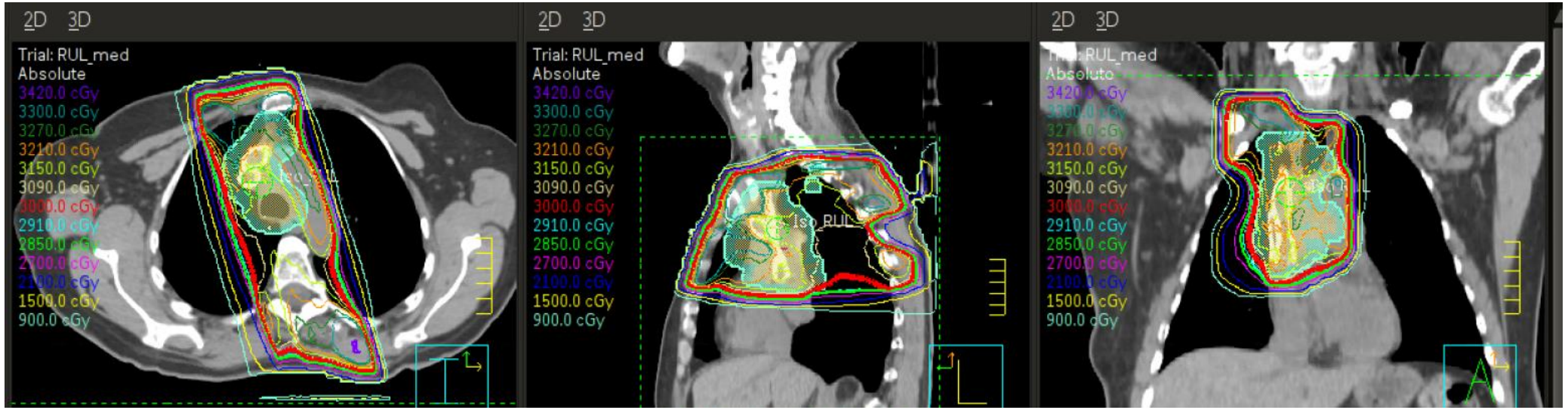
Simone C et al. PRO 2020

Treatment

- **Treatment options?**
  - Chest RT → 30 Gy in 10 fractions using 3D conformal technique (CREST)
  - PCI → ?
  - Maintenance immunotherapy → ?

ES-SCLC: Radiation Considerations

- The CREST trial gave 30 Gy in 10 fractions using conformal techniques
  - Target volumes included
    - residual gross primary disease (post chemo)
    - Initially involved sites of disease
  - 15mm margin to account for microscopic disease and setup errors



Treatment

- **Treatment options?**
  - Chest RT → 30 Gy in 10 fractions using 3D conformal technique (CREST)
  - PCI → ?
  - Maintenance immunotherapy → ?

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

- 286 patients with extensive stage-SCLC with response to chemotherapy randomized to
  - PCI vs
  - No PCI
- **Results:**
  - Symptomatic brain mets:
    - Favors PCI (HR: 0.27, P<0.001)
  - Cumulative risk of brain mets at 1 year:
    - PCI: 14.6%
    - No PCI: 40.4% (P<0.001)
  - 1 year overall survival
    - PCI: 27.1%
    - No PCI: 13.3% (p=0.003)

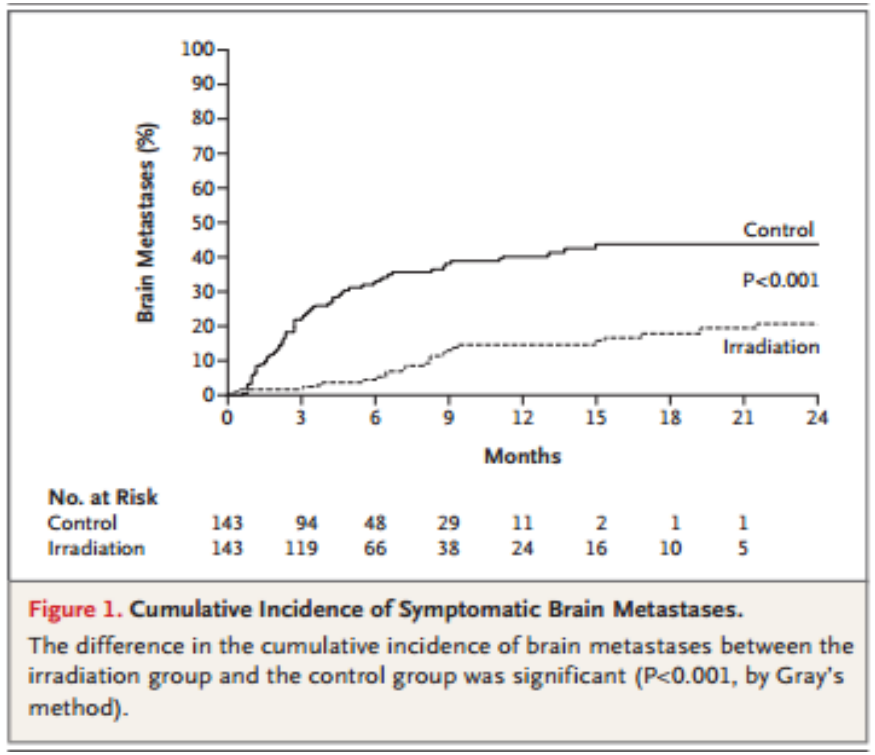


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

Caveats:

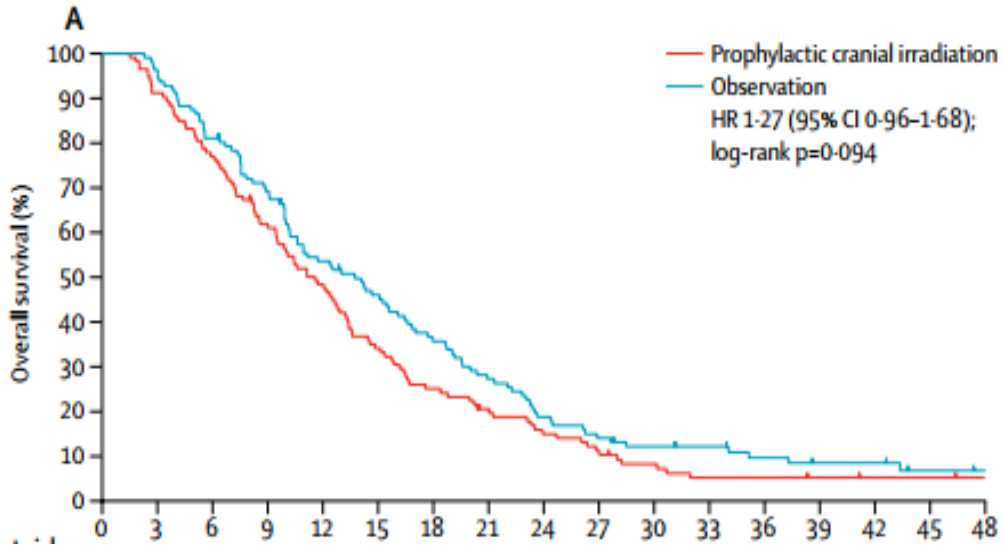
-CNS staging not required prior to study entry

-CNS imaging done only for symptomatic disease, not for routine surveillance.

Slotman B et al. NEJM 2007

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

- 224 patients with extensive stage-SCLC with response to chemotherapy and no brain mets randomized to
  - PCI vs
  - Observation (surveillance brain MRI q3mos)
- **Results*:**
  - Median OS:
    - PCI: 11.6 mo
    - Observe: 13.7 mo, p=.094
  - Cumulative incidence of brain mets:
    - 6 months (15% versus 46%) (favors PCI)
    - 12 months (33% versus 59%) (favors PCI)
    - 18 month (40% versus 64%) (favors PCI)



Caveats:

- study was terminated early because of futility on interim analysis
- Brain RT given to 83% of patients who developed brain mets in the observation group.

If PCI is deferred in ES-SCLC, brain MRI every 3 months is critical!

Takahasi T et al. Lancet Oncol 2017

Treatment

- **Treatment options?**
  - Chest RT → 30 Gy in 10 fractions using 3D conformal technique (CREST)
  - PCI → Deferred opting instead for serial brain MRIs
  - Maintenance immunotherapy → Currently receiving maintenance atezo

Treatment

- **Treatment options?**
  - Chest RT → 30 Gy in 10 fractions using 3D conformal technique (CREST)
  - PCI → Deferred opting instead for serial brain MRIs
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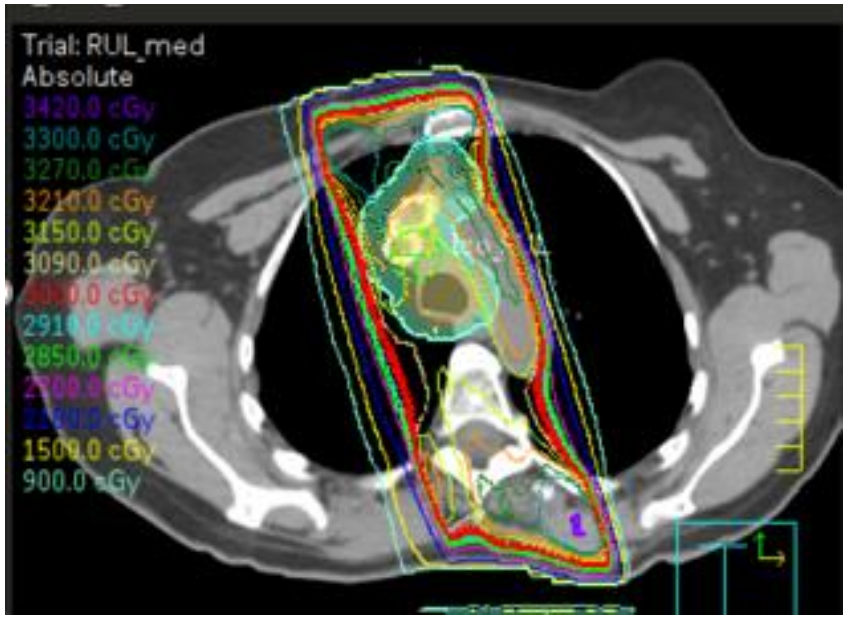
Small Cell lung Cancer: Final thoughts

- Outcomes that were stagnant for years are now improving
- The data defines a clear pathway for treatment
- There will still be need to customize treatment options for patients.



71 year old with SVC compression and malignant effusion

- Treated with chemo urgently; atezo added for c2-4
- Comes for consolidative treatment options
  - Although the CREST data did not include patients with a malignant effusion, she was treated with chest RT (30 Gy in 10 fractions) because her effusion resolved and all of her initial tumor was bulky mediastinal disease.

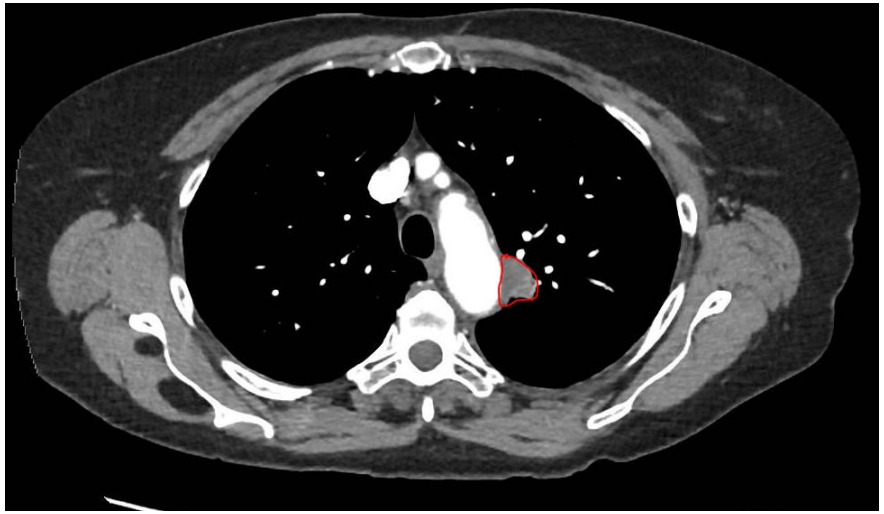
- Review Anatomy/Staging
- Subsections
  - Small cell lung cancer
  - Metastatic NSCLC
  - Locally advanced NSCLC
  - Early stage non-small cell lung cancer (NSCLC)

- Case Presentation
- How will I manage this patient?
- Background and key learning points
- Where are we now?
- Where are we going?

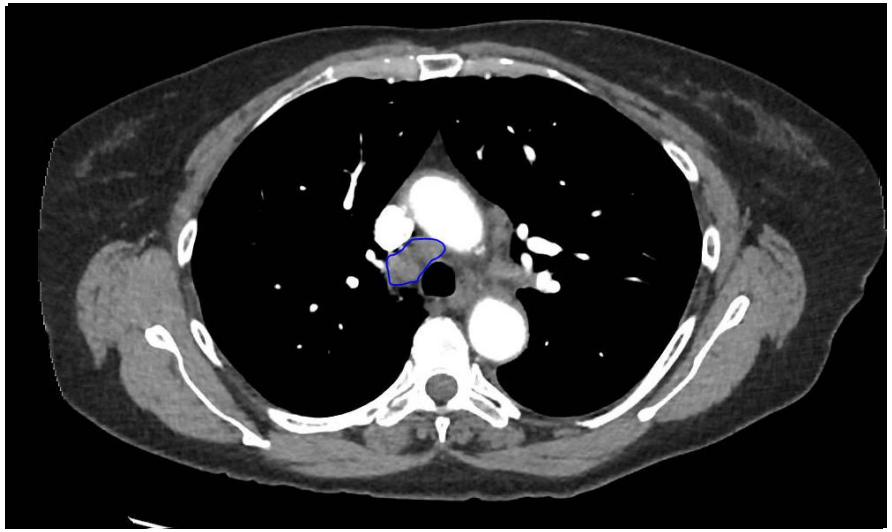
Advanced Stage NSCLC: Case Presentation

- 69 year old former smoker active rheumatoid arthritis on immunosuppression has chest pain and undergoes chest RT in the ED.

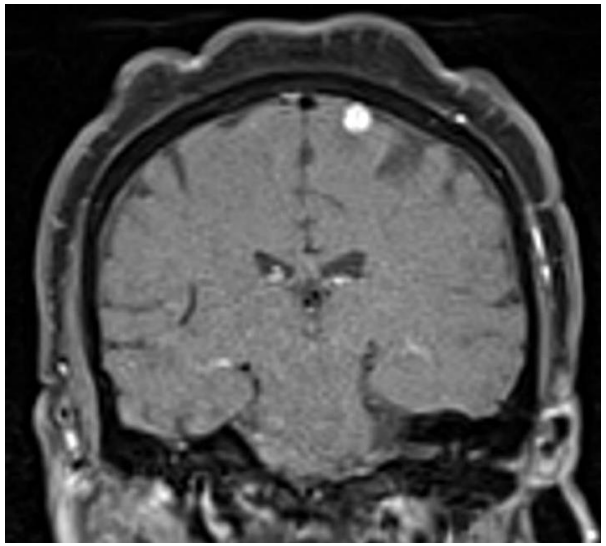
What do you see?

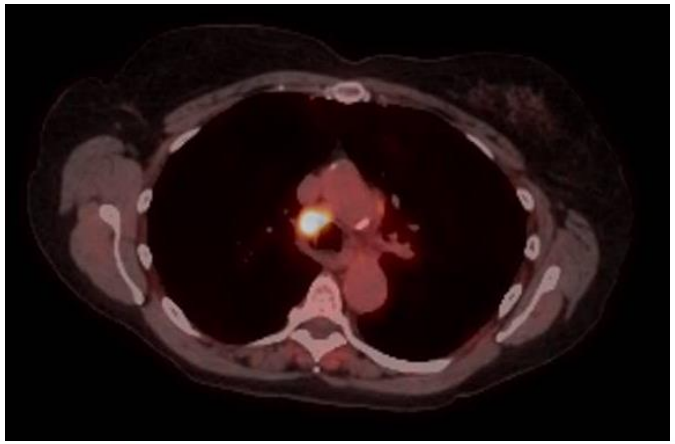


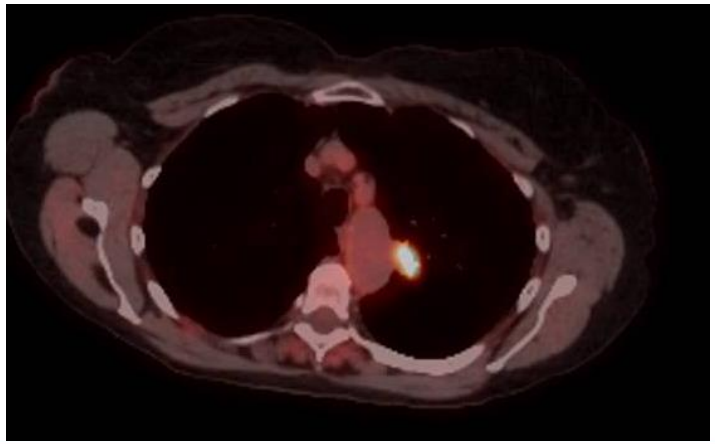
LUL lesion (red) and adenopathy (blue)



- Next steps?
  - After complete history and physical
    - EBUS 4R lymph node → Adenocarcinoma
    - PET/CT → LUL primary, 3cm, right paratrachaeal, no other sites
    - Brain MRI → 7mm focus left central gyrus
    - Next Gen Sequencing → KRAS, no actionable mutations

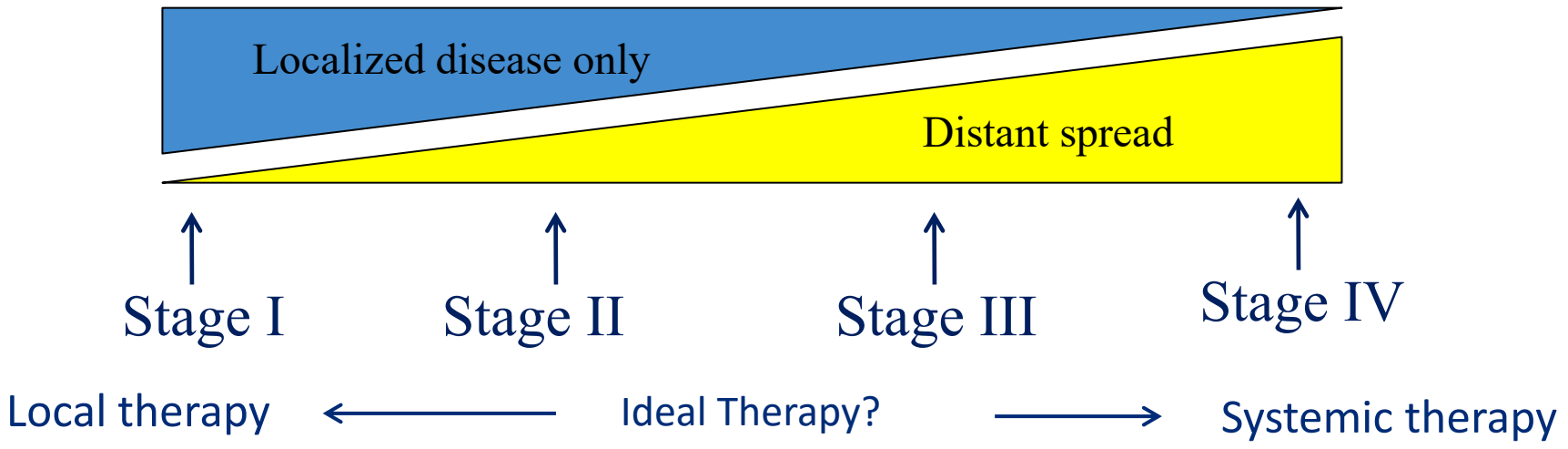




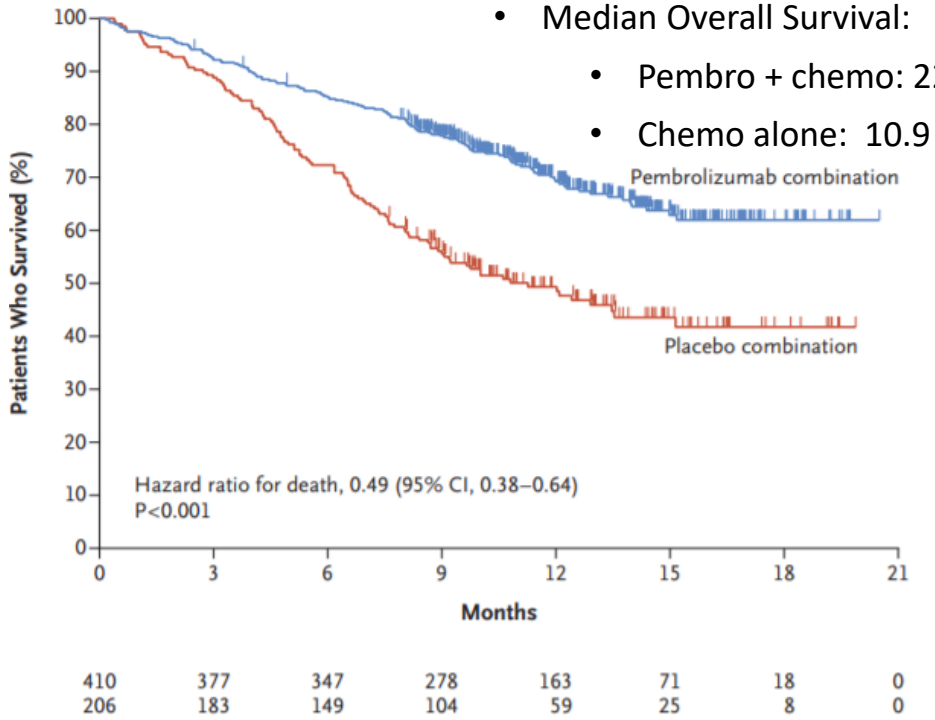


Principles to guide local therapy in metastatic disease (specific to NSCLC)

- Palliation of symptoms
- CNS disease (regardless of symptoms
- Oligo-metastatic disease
- Isolated-progressive disease



- Stage?
  - T4N3M1a
- Treatment?
  - Platinum doublet*
  - Re-evaluation for consolidative chest RT
  - Brain SRS



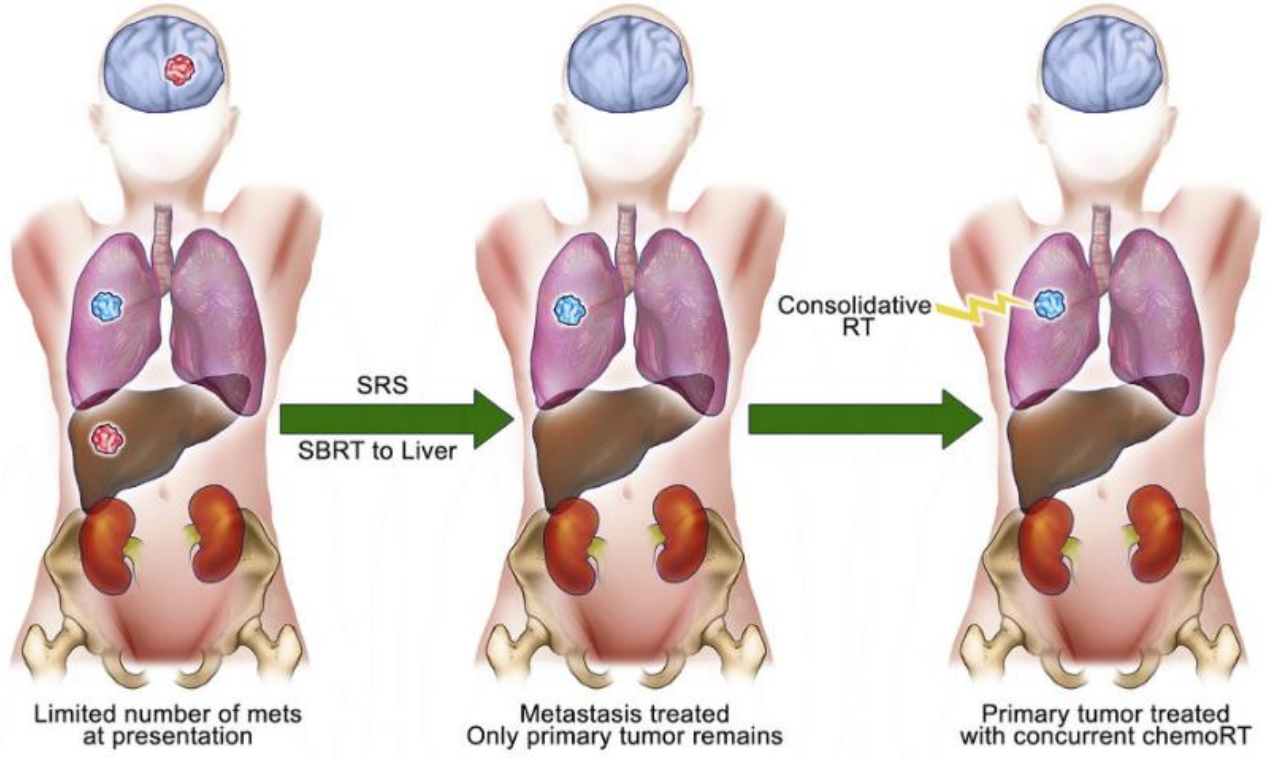
- Median Overall Survival:
  - Pembro + chemo: 22 months
  - Chemo alone: 10.9 months

*use of immunotherapy (IO) has been shown to improve outcomes in metastatic NSCLC. However, the patient's active auto-immune disease resulted in treatment with chemotherapy alone.

Gandhi et al., NEJM 2019

Oligo-metastatic versus isolated progression

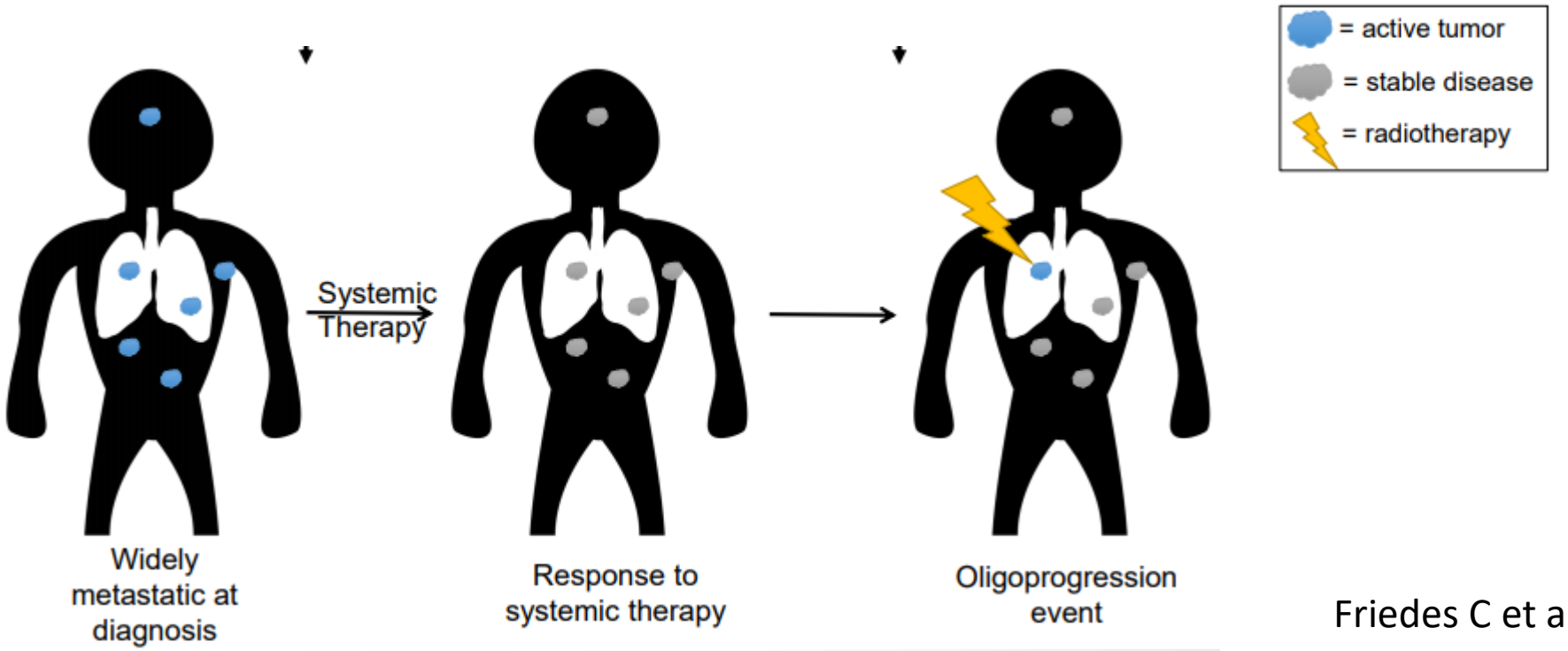
- Oligo-metastatic disease



Friedes C et al. Clin Lung Ca 2020

Oligo-metastatic versus isolated progression

- Isolated progression of metastatic disease

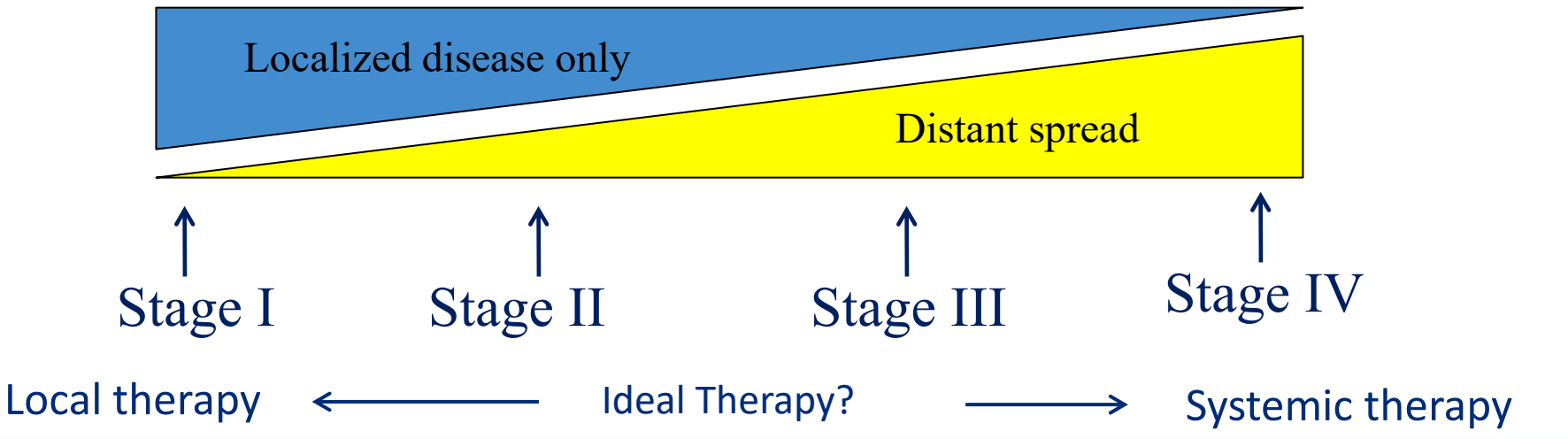


Friedes C et al. Cancer 2020

Principles to guide local therapy in metastatic disease (specific to NSCLC)

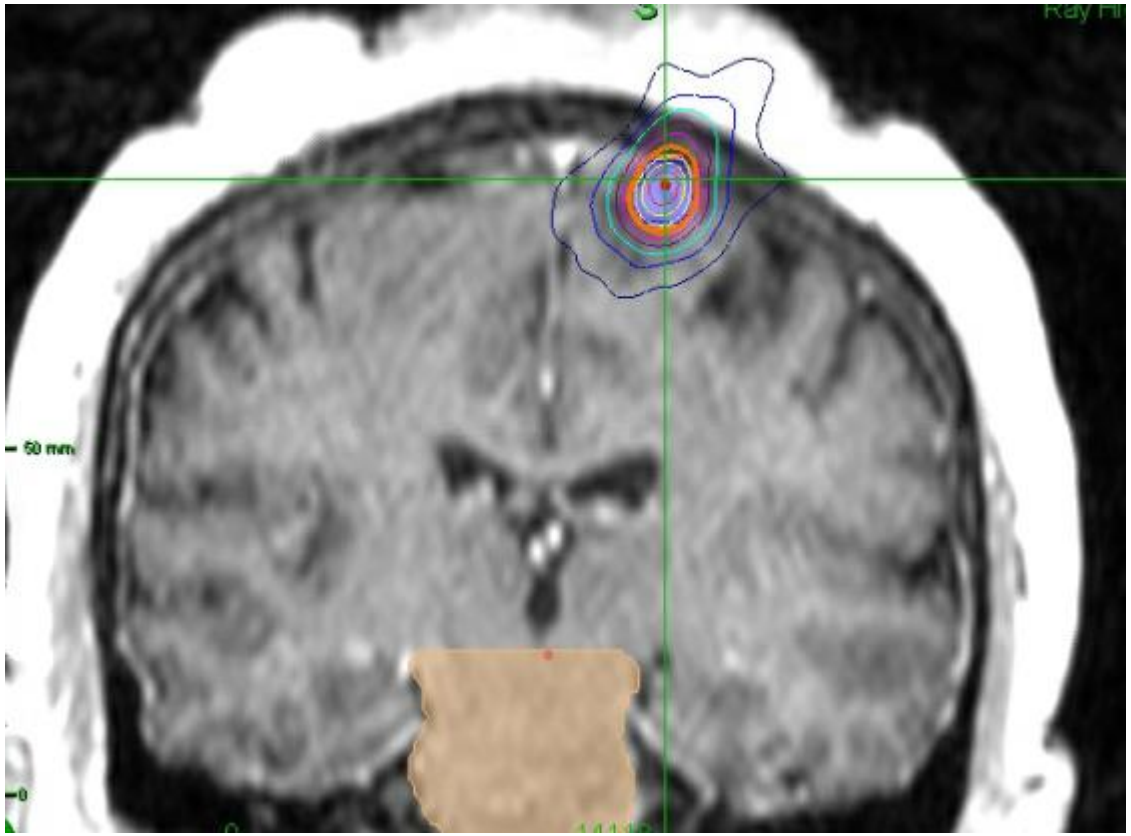
- Palliation of symptoms
- CNS disease (regardless of symptoms)
- Oligo-metastatic disease
- Isolated-progressive disease

You may be overusing local therapy in metastatic disease if the indication cannot fit into one of these categories!



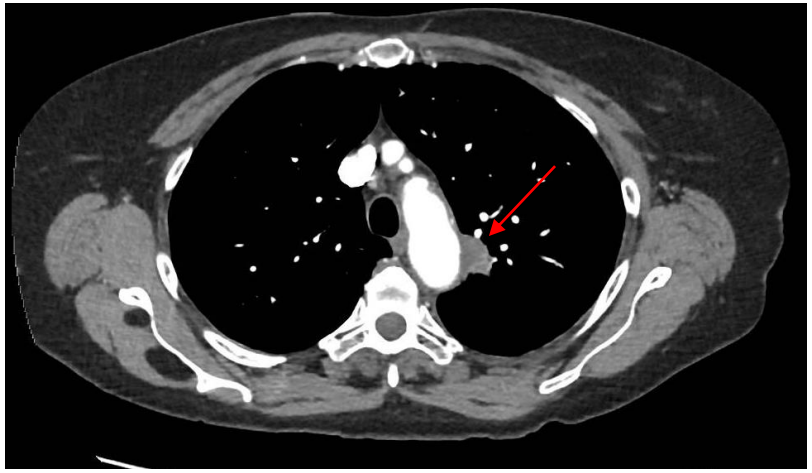
Case Presentation: Advanced Stage NSCLC

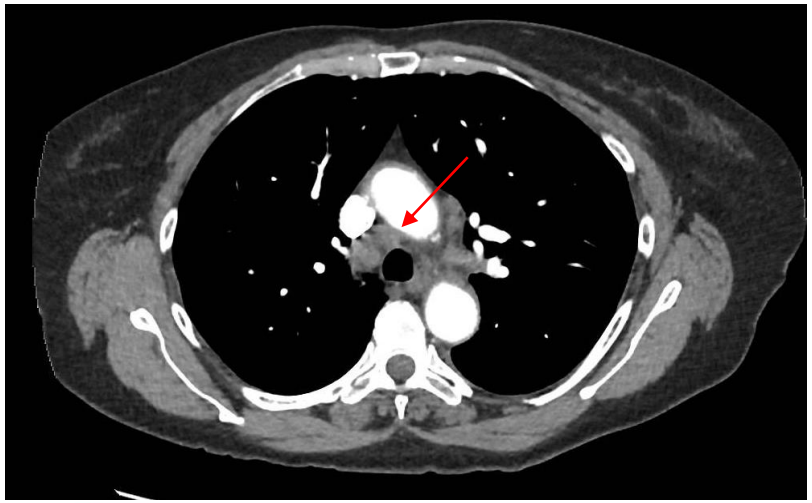
- Pemetrexed + platinum x 12 weeks
- Brain SRS (18 Gy x 1)



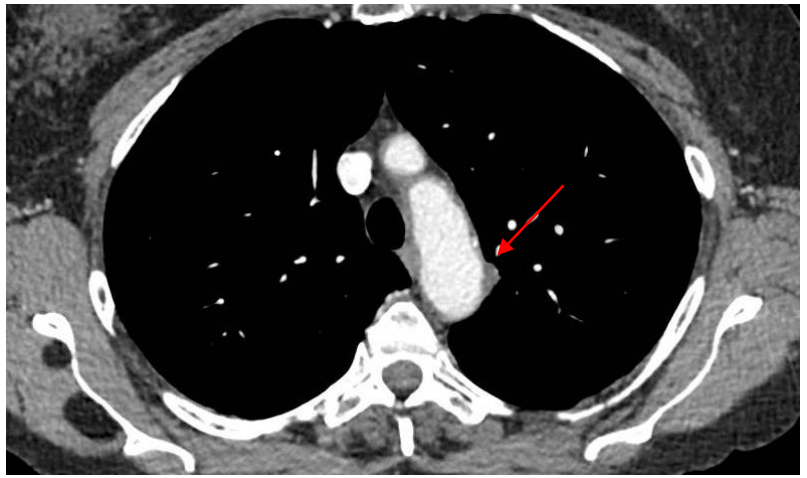
- Re-evaluate:
  - Tolerating therapy well
    - CT body
    - Brain MRI

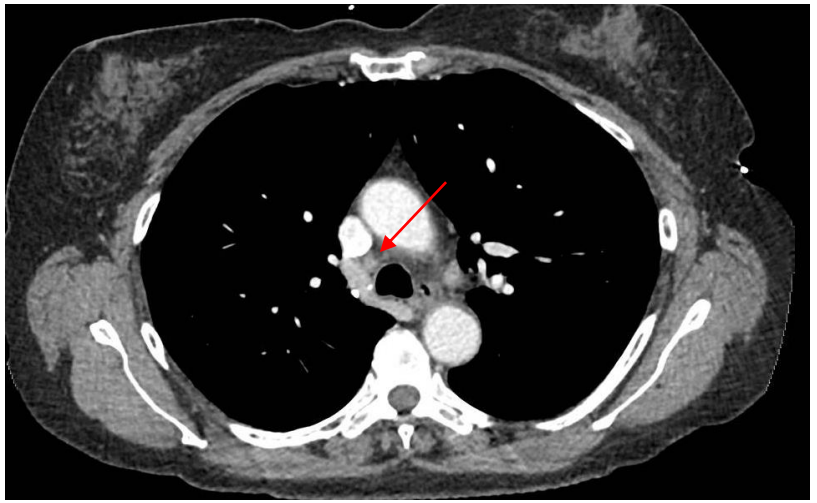
Pre chemo



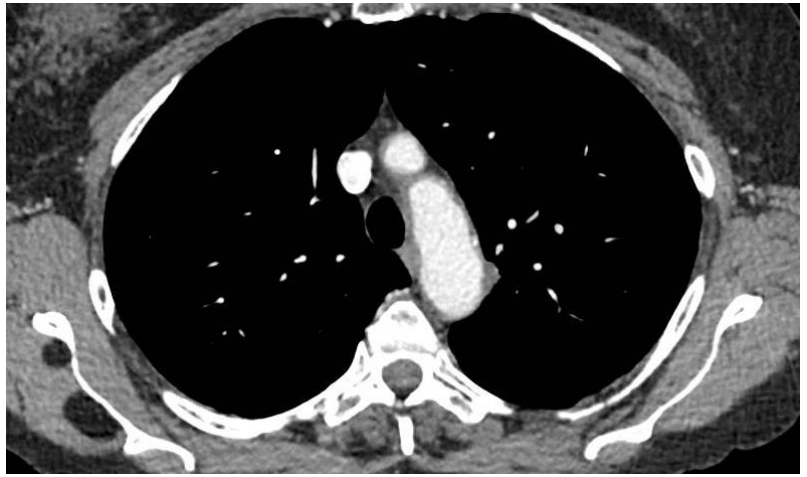


Post chemo





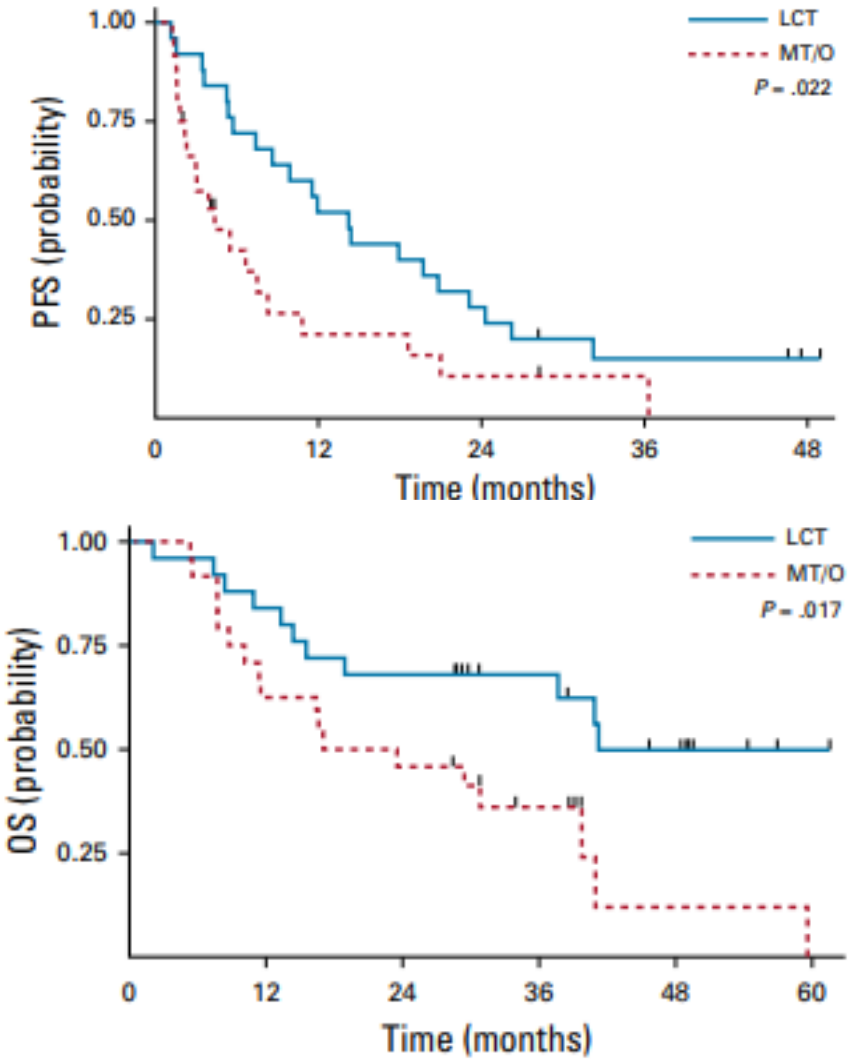
- Re-evaluate:
  - Tolerating therapy well
    - CT body → Interval reduction in primary tumor + adenopathy with no new sites of concern
    - Brain MRI → No enhancing lesions to suggest metastatic disease



- What is next?
  - Maintenance chemotherapy vs
  - Local consolidative therapy

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

- Multi-center phase III randomized study of patients with </=3 metastases and no progression after 3 months of upfront systemic therapy.
- Randomized to:
  - Maintenance therapy/observation(MT/O) vs
  - Local consolidative therapy (LCT)
- Outcome:
  - Median follow up: 38.8 months
  - PFS:
    - MT/O: 4.4 months
    - LCT: 14.2 months (p=0.022)
  - Overall survival
    - MT/O: 41.2 months
    - LCT: 17.0 months (p=0.034)

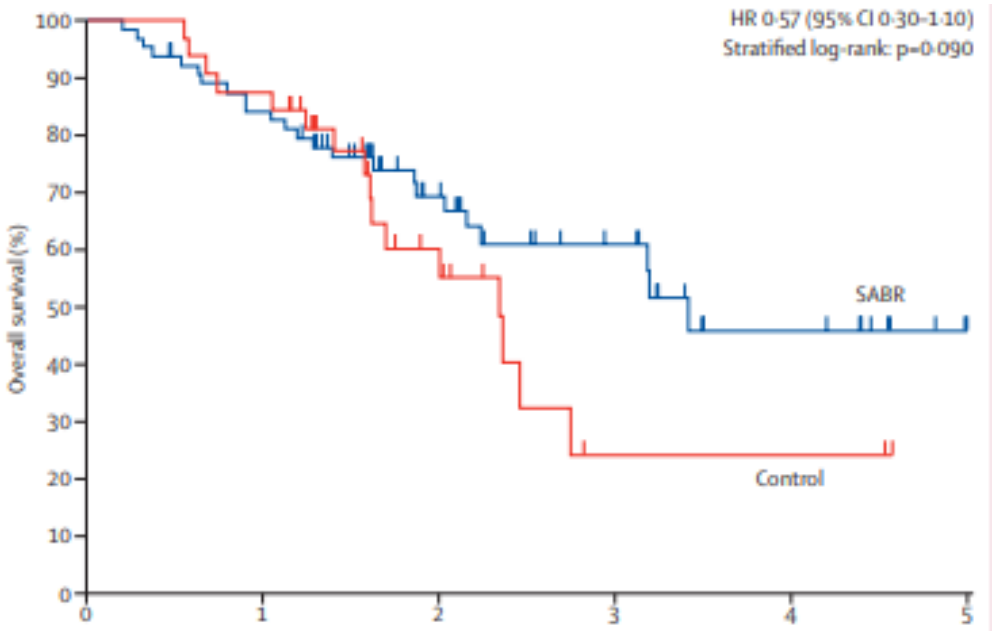


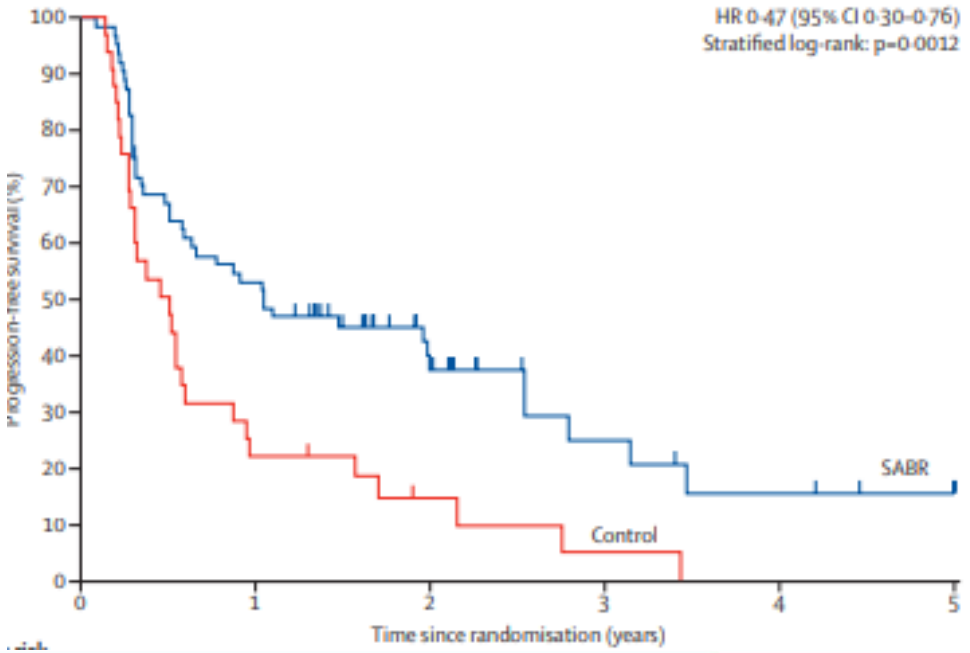
Gomez al., JCO 2019

- Caveats to Gomez et al. data:
  - Closed at interim analysis of PFS benefit in LCT arms
  - LCT given to all active disease sites
  - The role of LCT in the era of immunotherapy is being defined
  - LCT was non-uniform and optimal dose, fractionation and technique needs to be defined.

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

- Multi-center phase II randomized study of 99 patients with metastatic carcinoma
  - Inclusion:
    - Life expectancy: at least 6 months
    - ECOG PS 0-1
    - 1-5 metastatic lesions
- Randomization:
    - Standard of Care (SOC)
    - Standard of Care+SABR to all metastatic lesions
- Outcome:
  - Overall Survival
    - SOC: 28 months
    - SOC+SABR: 41 months (p=0.09)
  - Progression-free survival
    - SOC: 6 months
    - SOC+SABR: 12 months (p=0.0012)





Palma al., Lancet 2019

- Caveats to SABR COMET data:
  - 18% of patients had primary lung cancer
  - ~50% of all metastases from any histology were to the lung
  - 3 treatment related deaths

	All patients (n=99)	Control group (n=33)	Stereotactic ablative radiotherapy group (n=66)	p value
Adverse event grade ≥2	55 (56%)	15 (46%)	40 (61%)	0·15
Related adverse event grade ≥2	22 (22%)	3 (9%)	19 (29%)	0·026
Adverse event associated with death (grade 5)	3 (3%)	0	3 (5%)	0·55
Fatigue*	..	..	..	0·45
Grade 2	6 (6%)	2 (6%)	4 (6%)	..
Grade 3	1 (1%)	1 (3%)	0	..
Dyspnoea*	..	..	..	1·00
Grade 2	1 (1%)	0	1 (2%)	..
Grade 3	1 (1%)	0	1 (2%)	..
Pain (any type)*	..	..	..	0·14
Grade 2	5 (5%)	0	5 (8%)	..
Grade 3	3 (3%)	0	3 (5%)	..

Data are n (%). *Treatment related.

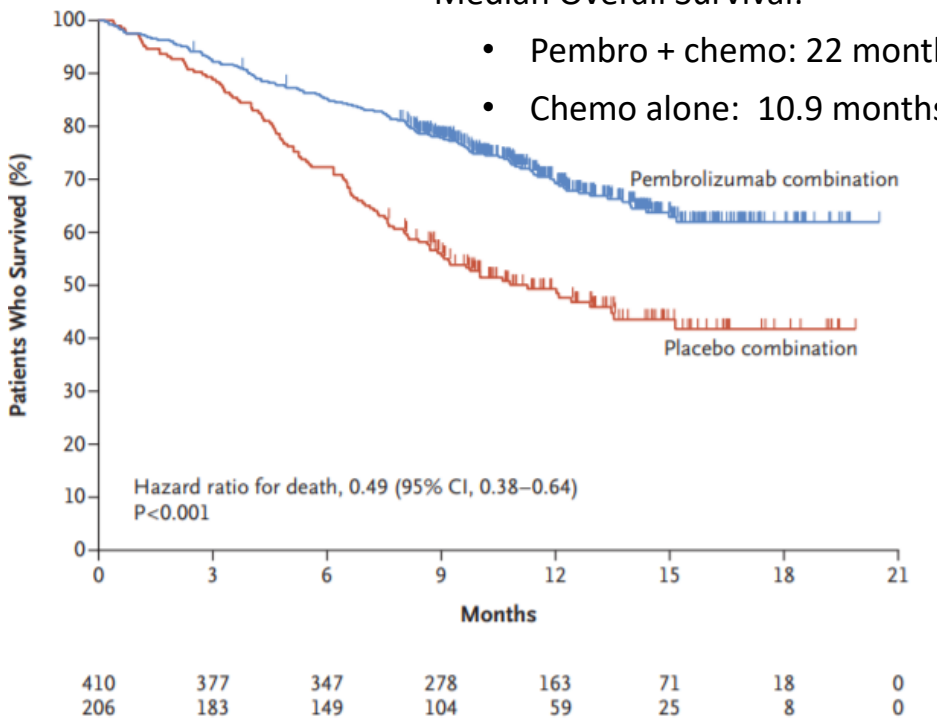
Table 2: **Summary of adverse events**

Palma al., Lancet 2019

Oligo-metastatic Lung Cancer

- We should be cautious about applying the consolidative local therapy data
- The studies that showed benefit:
  - Had limited numbers
  - Had significant toxicity
  - Were largely not done in the immunotherapy era.
- Who should get consolidative RT?
  - Good performance status
  - Shared decision making
  - Enroll on NRG-LU002

- Median Overall Survival:
  - Pembro + chemo: 22 months
  - Chemo alone: 10.9 months



Gandhi et al., NEJM 2019

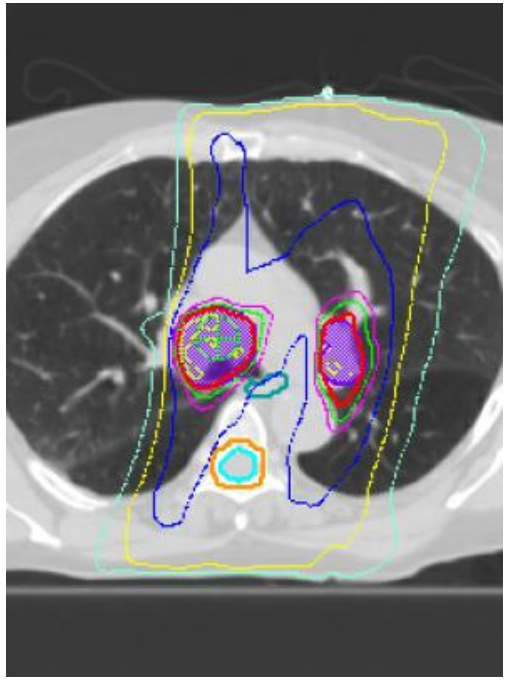
The future

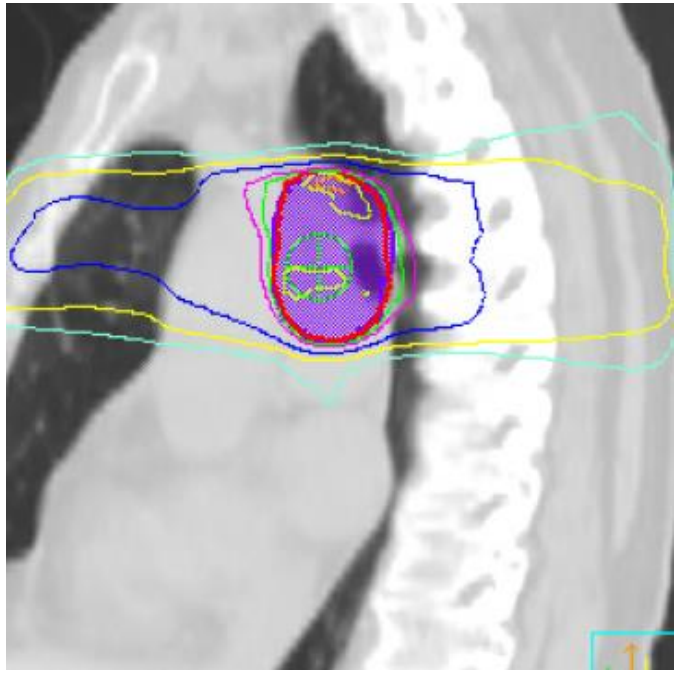
- NRG LU002
  - Planned accrual 400 patients, 2:1 randomization

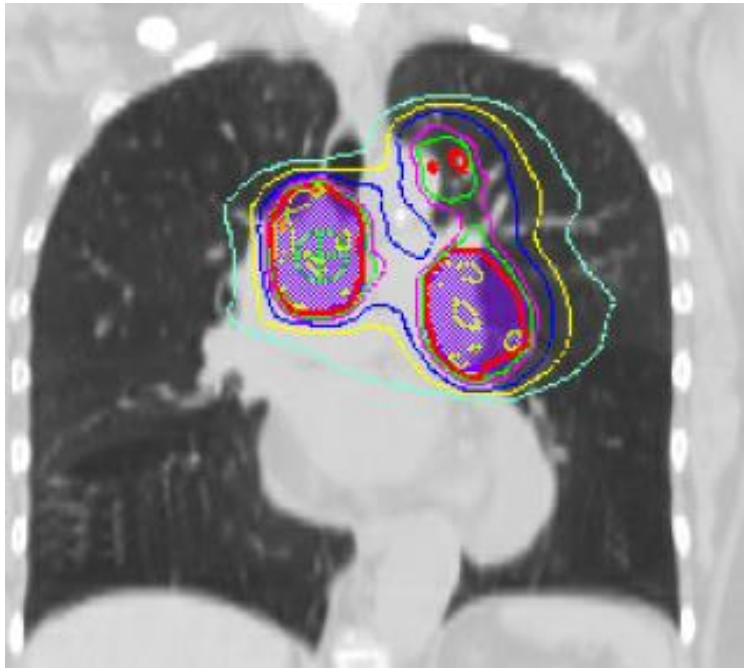
Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery	STRATIFY	Histology: Squamous vs. Non-squamous Systemic Therapy: Immunotherapy vs Cytotoxic Chemotherapy	RANDOMIZE	**Arm 1:** Maintenance systemic therapy alone **Arm 2:** SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.

Case Presentation

- In shared decision making with the patient, we opted for consolidative chest RT
  - 66 Gy in 33 fractions using VMAT (2 arcs)







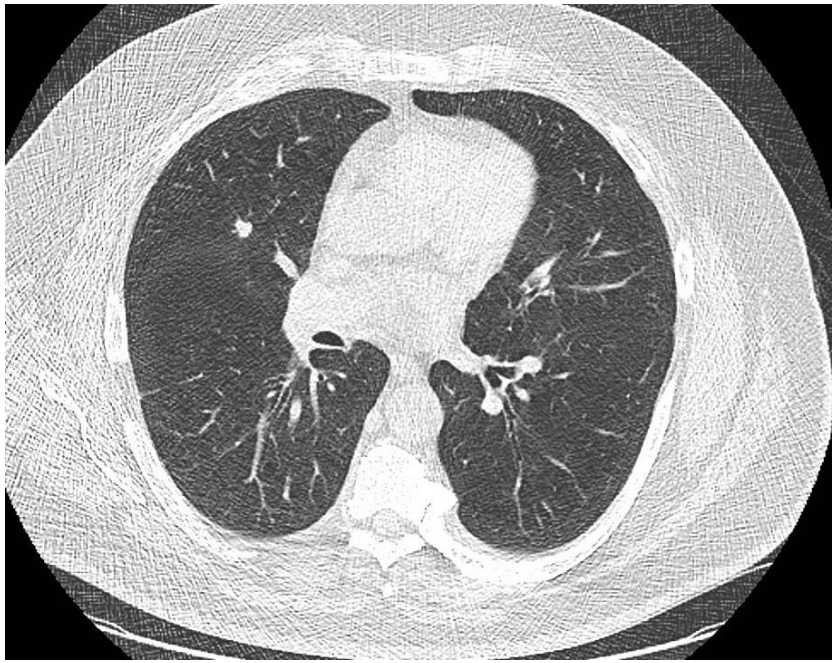
- Review Anatomy/Staging
- Subsections
  - Small cell lung cancer
  - Metastatic NSCLC
  - Locally advanced NSCLC
  - Early stage non-small cell lung cancer (NSCLC)

- Case Presentation
- How will I manage this patient?
- Background and key learning points
- Where are we now?
- Where are we going?

Locally Advanced Stage NSCLC: Case Presentation

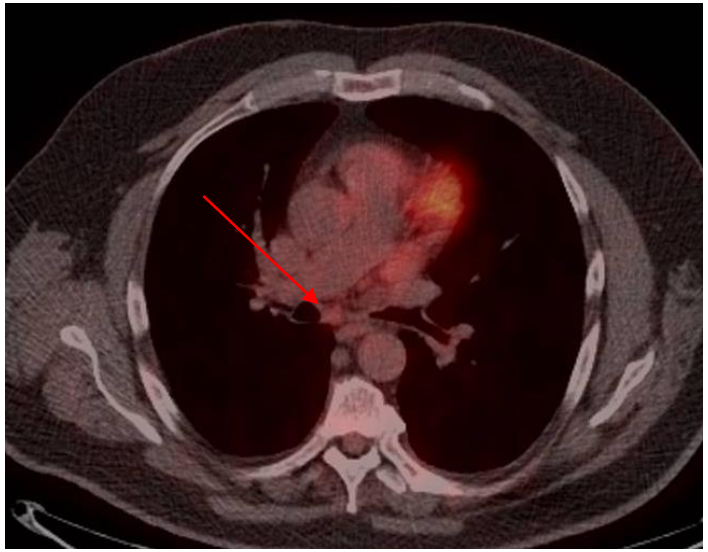
- 64 year old retired firefighter who undergoes lung cancer screening; former smoker, quit 2 years ago.

What do you see?



Work Up

- Next steps?
  - After complete history and physical
    - Prior imaging
    - Pulmonary Function Tests
    - PET/CT



1. 1 cm spiculated non-FDG avid nodule in the anterior segment of the right upper lobe.
2. Prominent subcentimeter non-FDG avid right paratracheal and subcarinal lymph nodes. No FDG avid lymphadenopathy or metastases.

SPIROMETRY

		Ref	Pre Meas	Pre % Ref
FVC	Liters	4.17	2.39	57
FEV1	Liters	3.12	1.64	52
FEV1/FVC	%	75	68	91
FEV6	Liters	3.95	2.32	59
FEF25-75%	L/sec	2.54	0.85	34
FIVC	Liters		2.54	
PEF	L/sec	8.31	6.06	73
Vol Extrap	Liters		0.03	
MVV	L/min	126		
f	BPM			

DIFFUSION CAPACITY Hb: 14.3 gm/dL

		Ref	Pre Meas	Pre % Ref
DLCO	mL/min/mmHg	30.6	20.5	67
DL Adj	mL/min/mmHg	30.6	20.6	67
DLCO/VA	mL/min/mHg/L	4.94	4.23	86
DL/VA Adj	mL/min/mHg/L	4.94	4.26	86
VA	Liters	6.13	4.84	79
IVC	Liters		2.60	
BHT	Sec		9.34	

Work Up

- Now what?
  - Straight to resection
  - Empiric SBRT
  - Needle biopsy of lung lesion
  - Surveillance x 3 months
  - EBUS
- Although small, given its central location, the patient underwent EBUS
  - Station 7: adenocarcinoma, TTF-1 positive

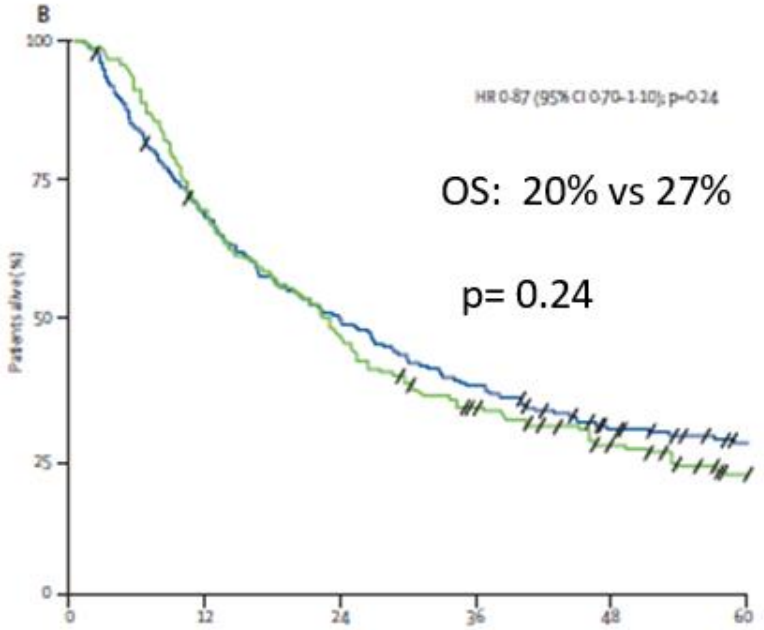
Staging

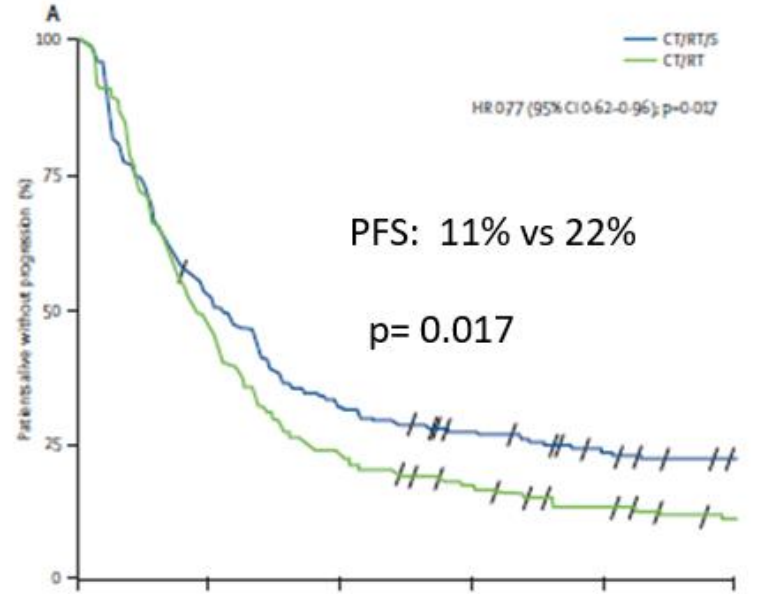
- Any additional studies?
  - Brain MRI
- Stage?
  - T1aN2M0 NSCLC
- Treatment options?
  - Induction chemotherapy followed by resection (? PORT)
  - Induction chemoRT followed by resection
  - Definitive chemoRT followed by consolidative immunotherapy
  - (watch for induction chemoIO followed by resection)

- Treatment options:
  - Induction chemoRT followed by resection (Albain)
  - Definitive chemoRT followed by consolidative immunotherapy (PACIFIC)
  - Induction chemotherapy followed by resection (Pless)
  - (watch for induction chemoIO followed by resection)

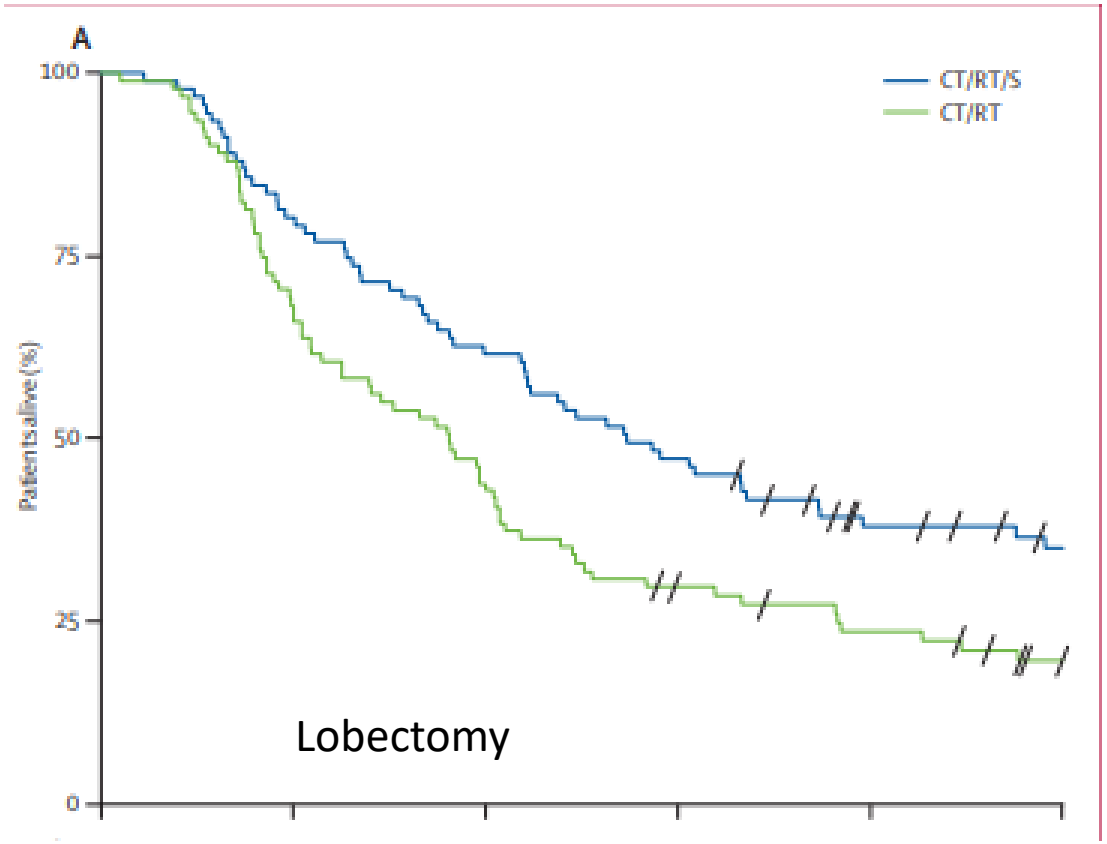
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

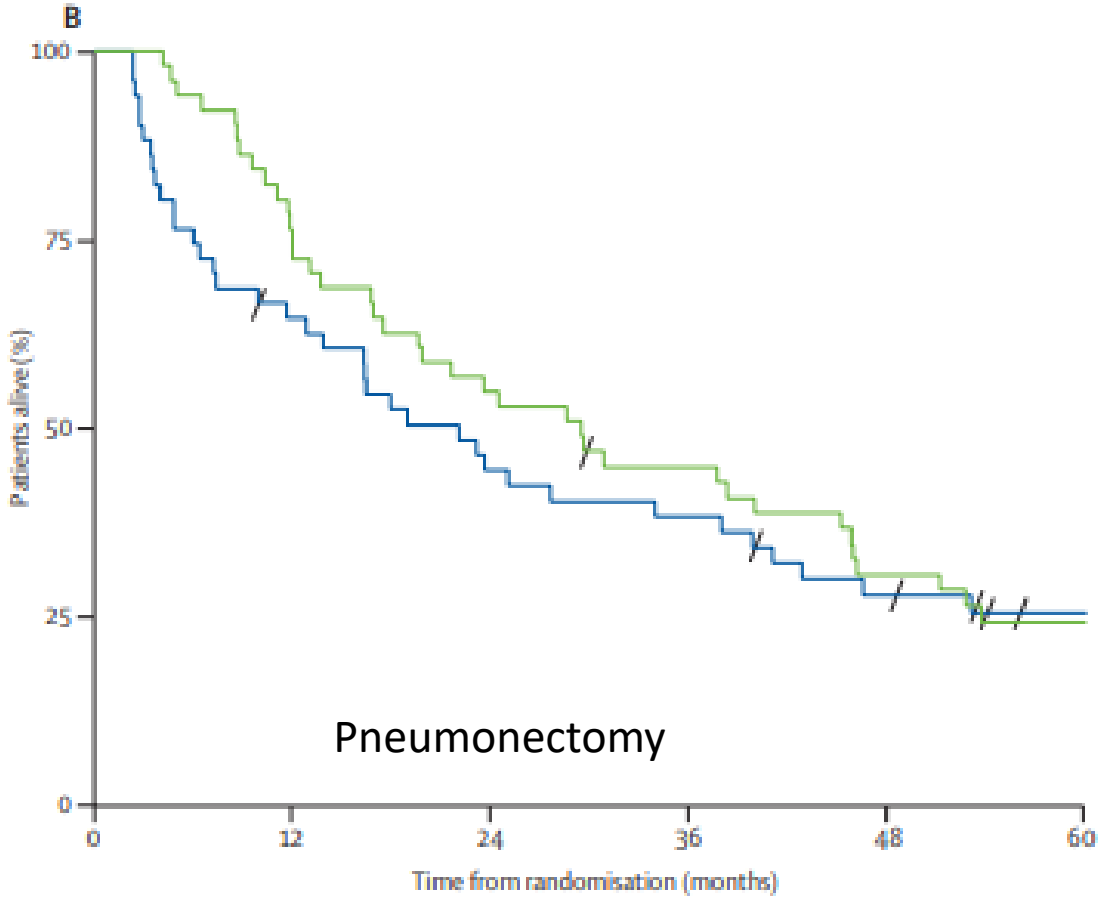
- Randomized study of 202 patients with T1-3pN2 NSCLC
- Randomization:
  - Arm 1: Cis/Etop (2 cycles)/RT (45 Gy) → rescan (no progression) → resection → 2 cycles chemo
  - Arm 2: Cis/Etop/RT (61 Gy) → 2 cycles chemo
- Outcome:
  - Median overall survival:
    - chemoRT → resection: 23.6 months
    - chemoRT: 22.2 months (p=0.24)
  - Progression free survival:
    - chemoRT → resection: 12.8 months
    - chemoRT: 10.5 months (p=0.017)





Albain al., Lancet 2009





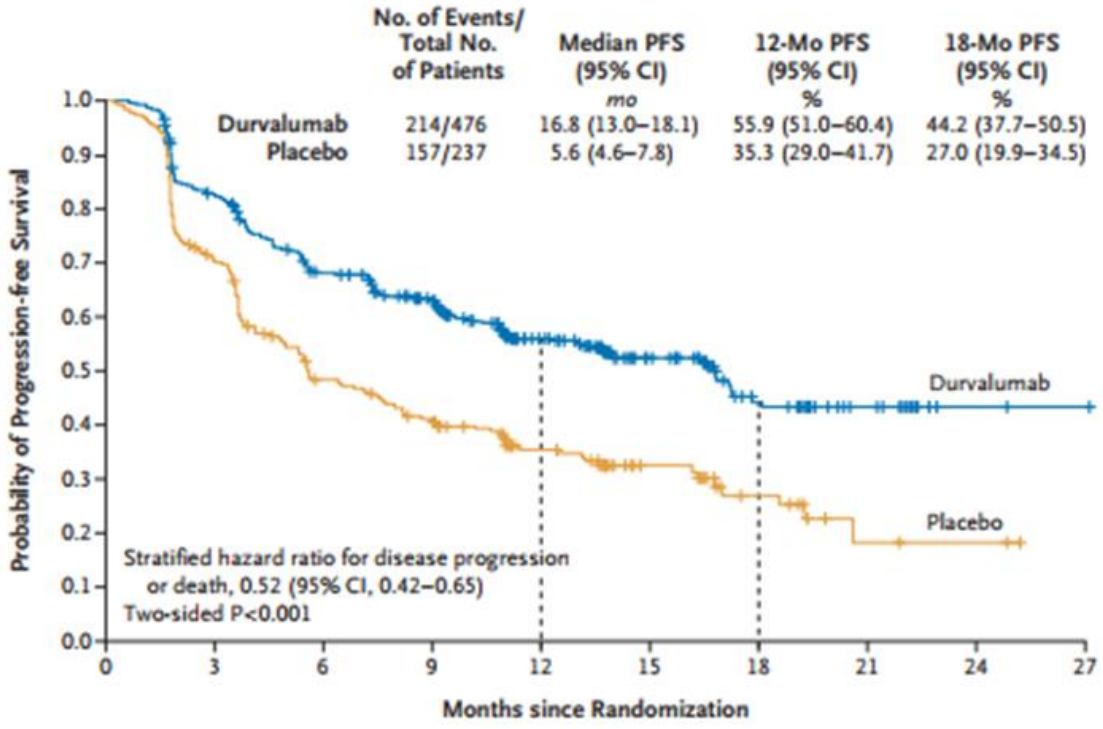
Exploratory Analysis

Improved OS for patients who underwent a lobectomy (vs. chemoRT alone) but not for patients who underwent a pneumonctomy (vs chemoRT)

Albain al., Lancet 2009

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

- 713 patients with LA-NSCLC, unresectable stage 3 NSCLC treated with chemoRT randomized 12 months of:
  - Durvalumab
  - Placebo
- Outcome:
  - Median progression free survival
    - Durva: 16.8 months
    - Placebo: 5.6 months

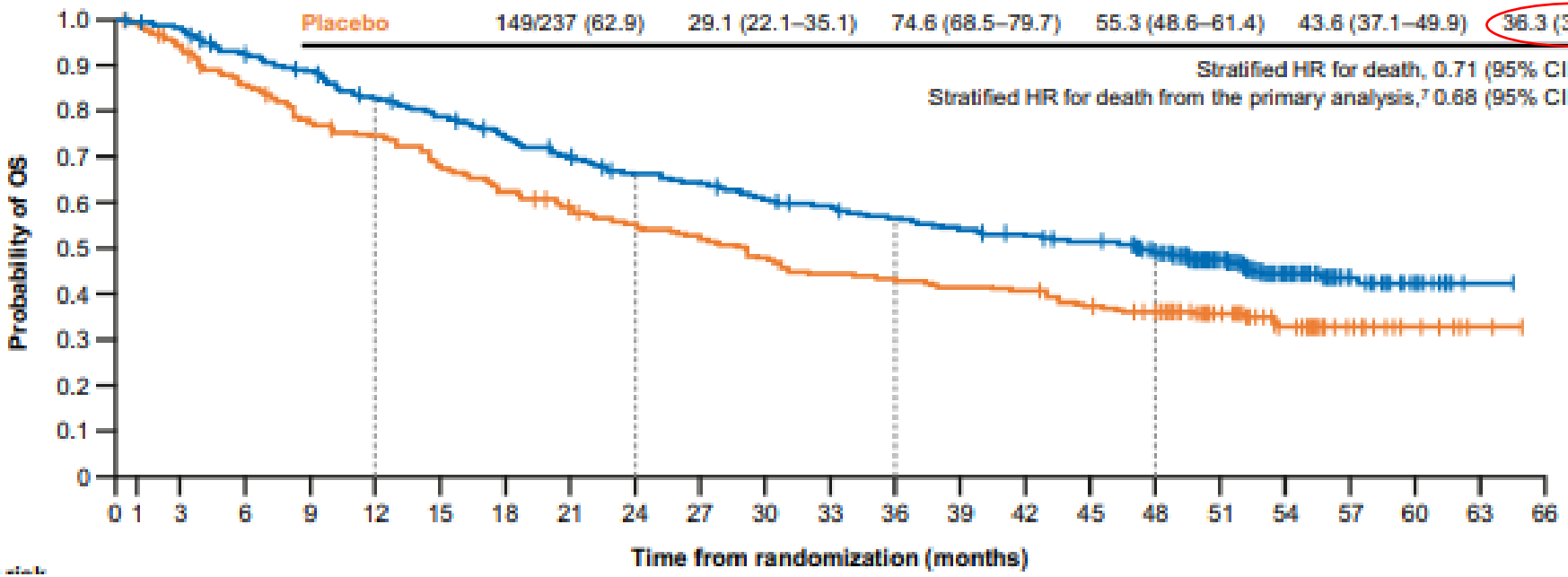


Antonia S, NEJM 2017

Updated PACIFIC outcomes at 4 years:

	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

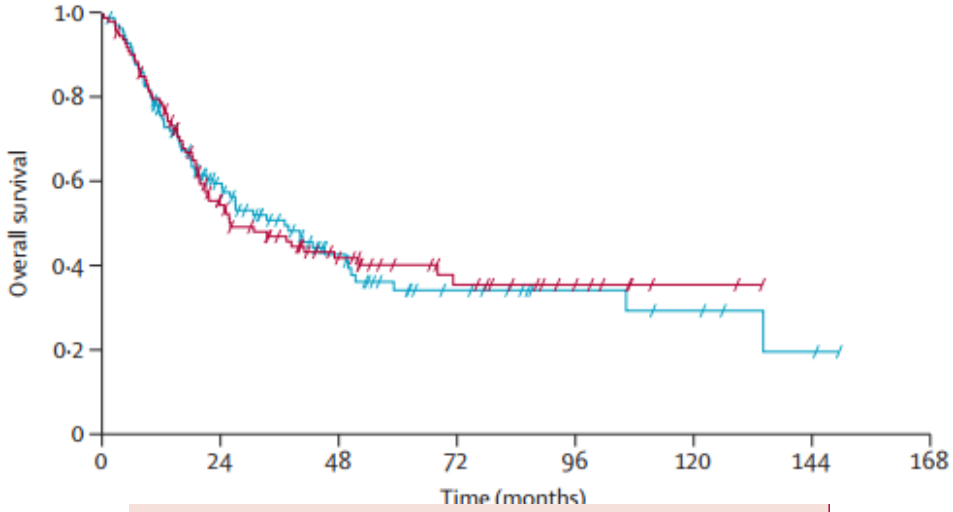
Stratified HR for death, 0.71 (95% CI: 0.57–0.88)
Stratified HR for death from the primary analysis,[7] 0.68 (95% CI: 0.53–0.87)



Faivre-Finn et al, JTO 2021

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

- 232 patients with stage IIIa/N2 NSCLC randomized to:
  - chemo x 3 cycles →RT alone (44 Gy/22 fr →resection
  - chemo x 3 cycles → resection
- Outcomes:
  - No difference in event-free or overall survival
  - Disappointing rates of nodal downstaging with chemoRT



	Chemoradiotherapy group (n=99)	Chemotherapy group (n=94)
Types of surgery		
Lobectomy	58 (59%)	59 (63%)
Bilobectomy	13 (13%)	9 (10%)
Pneumonectomy	25 (25%)	19 (20%)
Resection score		
R0	90 (91%)	76 (81%)
R1	6 (6%)	11 (12%)
R2	3 (3%)	7 (8%)
Nodal downstaging (to N1 or N0)	63 (64%)	50 (53%)
Pathological complete remission	16 (16%)	11 (12%)

Table 5: Types of surgery and outcomes

Pless M et al. Lancet 2015

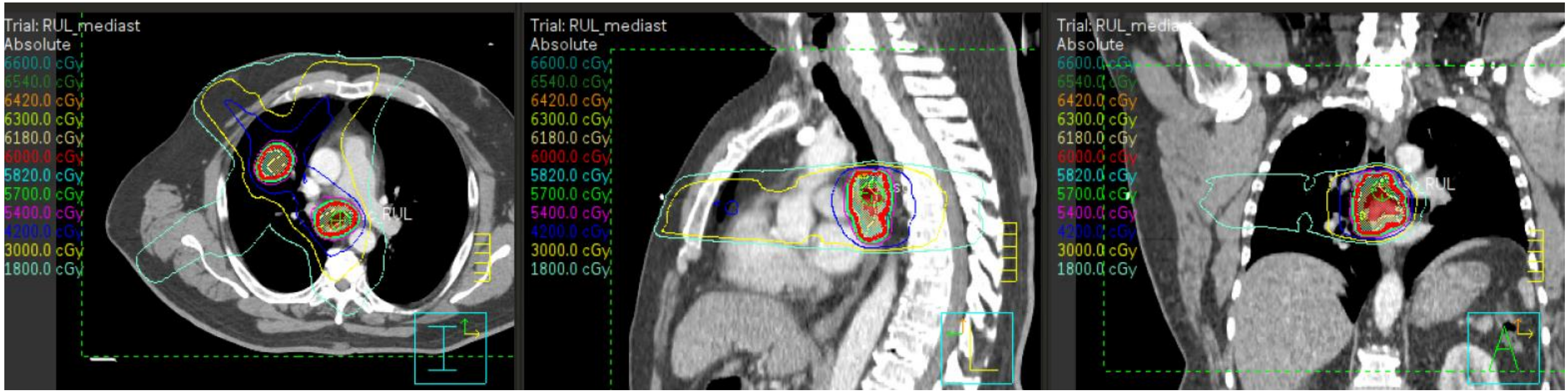
Key points in evaluating locally advanced NSCLC

For our patient:

- Medical operability
  - Is the patient able to tolerate resection? → Obesity but no other medical problems
- Technical operability
  - Nature of the N2 disease
    - Single- vs multi- station → Single station
    - Bulky vs non-bulky → Non-bulky
  - Primary can be removed with R0 resection
  - Extent of resection
    - Lobectomy vs Pneumonectomy → Lobectomy
  - Pulmonary reserve
    - Resection>pulmonary reserve? → PFTs aren't perfect but quant V/Q scan suggests sufficient pulmonary reserve
- Patient preference

For our patient

- Concurrent chemoradiation to 60 Gy in 30 fractions followed by assessment for resection



A few words on dose in stage III NSCLC

- For definitive chemoRT:
  - Studies have failed to show a benefit to dose escalation in unresectable NSCLC >60 Gy
    - R0617*: 60 Gy vs 74 Gy
      - Outcome: median OS: 28.7 mos vs 20.3 mo (favors standard dose over high dose) (p=0.004)
- For neoadjuvant chemoRT:
  - Although the historic induction dose for NSCLC was set by the Albain data at 45 Gy, other studies have shown 60 Gy prior to resection is safe in high volume centers.
    - ROG 0229^: 61.2 Gy pre-operative to resection:
      - 14% grade 3 pulmonary complications
      - 3% grade 5 toxicity
      - 2 year overall survival: 54%

*Bradley J et al., Lancet Oncology 2015
^Suntharalingam M et al., IJROBP 2012

Technique

- IMRT vs 3D
  - RTOG 0617
    - 482 patients, 53% treated with 3D and 48% treated with IMRT
      - IMRT group had larger PTVs than 3D group (427mL versus 486 mL, p=.005)
      - IMRT group had more stage IIIb disease (30.3% versus 38.6% (p=0.056)
      - No difference in OS, PFS,LC or distant mets between the groups (3D versus IMRT)
      - IMRT associated with less grade ≥3 pneumonitis (7.9% versus 3.5%, p=0.039)
      - IMRT had lower heart doses, lower V40 which was significantly associated with OS on adjusted analysis

Table 5. Multivariable Logistic Regression Analysis of CTCAE ≥ Grade 3 Pneumonitis

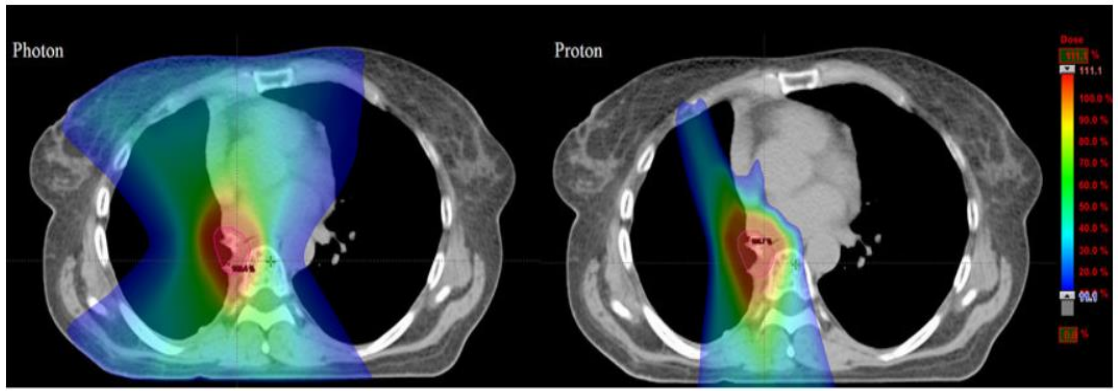
Covariate	Comparison	OR (95% CI)	*P*
RT technique	3D-CRT (RL) *v* IMRT	0.410 (0.171 to 0.986)	.046
AJCC stage group	IIIA (RL) *v* IIIB	2.276 (1.009 to 5.137)	.048
Lung V20, %	Continuous	1.071 (1.008 to 1.137)	.026
PTV, mL	Continuous (log-transformed)	1.701 (0.708 to 4.085)	.235

NOTE. Results from multivariable logistic regression analysis stratified by radiation therapy (RT) dose levels.

Abbreviations: 3D-CRT, three-dimensional conformal external beam radiation therapy; AJCC, American Joint Commission on Cancer; CTCAE, Common Terminology Criteria for Adverse Events (version 3); IMRT, intensity-modulated radiation therapy; lung V20, percentage of lung that receives ≥ 20 Gy; OR, odds ratio; PTV, planning treatment volume; RL, reference level.

Chun S et al. JCO 2017

Technique



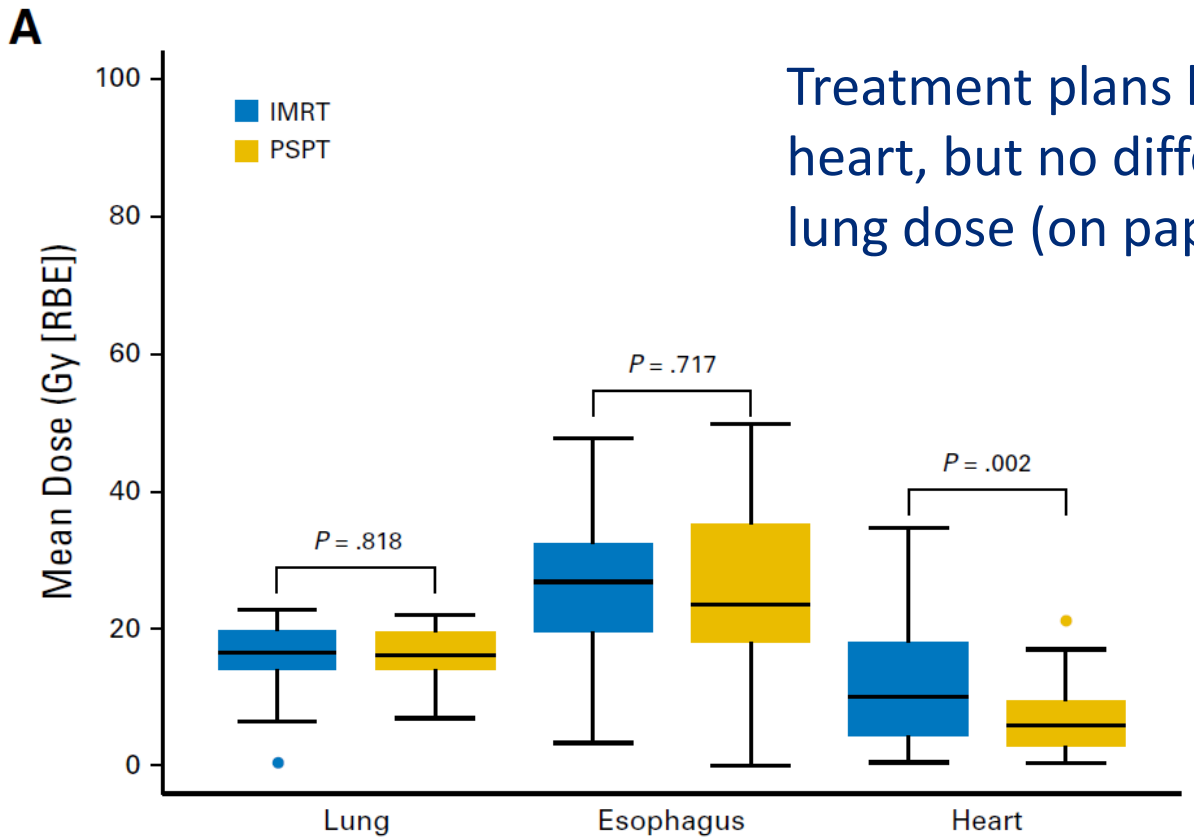
Diwanji., Transl Lung Cancer Res 2017

- Protons vs photons
  - 149 patients with non-surgical locally advanced NSCLC
  - n=92 IMRT—photons
  - n=57 PSPT—protons
  - Randomization was permitted only if IMRT and PSPT both met pre-specified plan objectives.
  - Primary Outcome: cumulative rate of ≥ grade 3 radiation pneumonitis (RP) or local failure (LF)

IMRT = intensity-modulated radiation therapy; PSPT = passively scattered proton therapy

Liao et al., JCO 2018

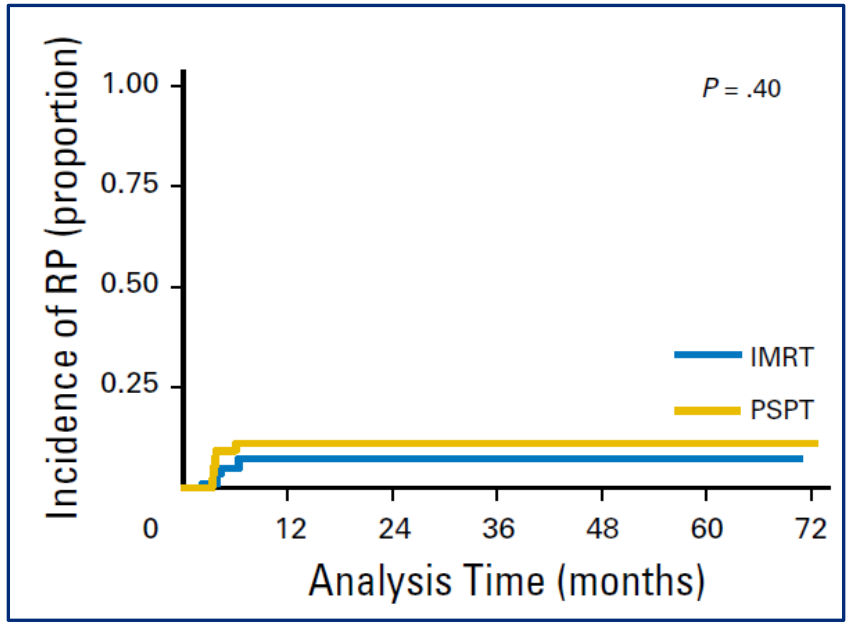
Randomized Evidence: Protons versus Photons



Treatment plans had better sparing of the heart, but no difference in esophageal or lung dose (on paper)

Liao et al., JCO 2018

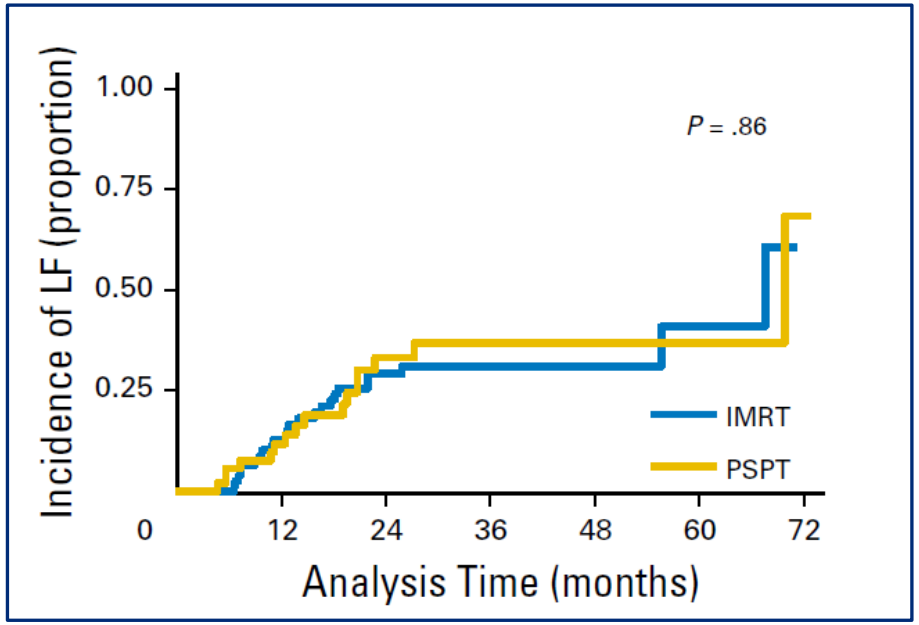
Randomized Evidence: Protons versus Photons



Radiation Pneumonitis (RP) at 12 months:

IMRT— 6.5%

PSPT—10.5%



Local Failure (LF) at 12 months:

IMRT—10.9%

PSPT—10.5%

Liao et al., JCO 2018

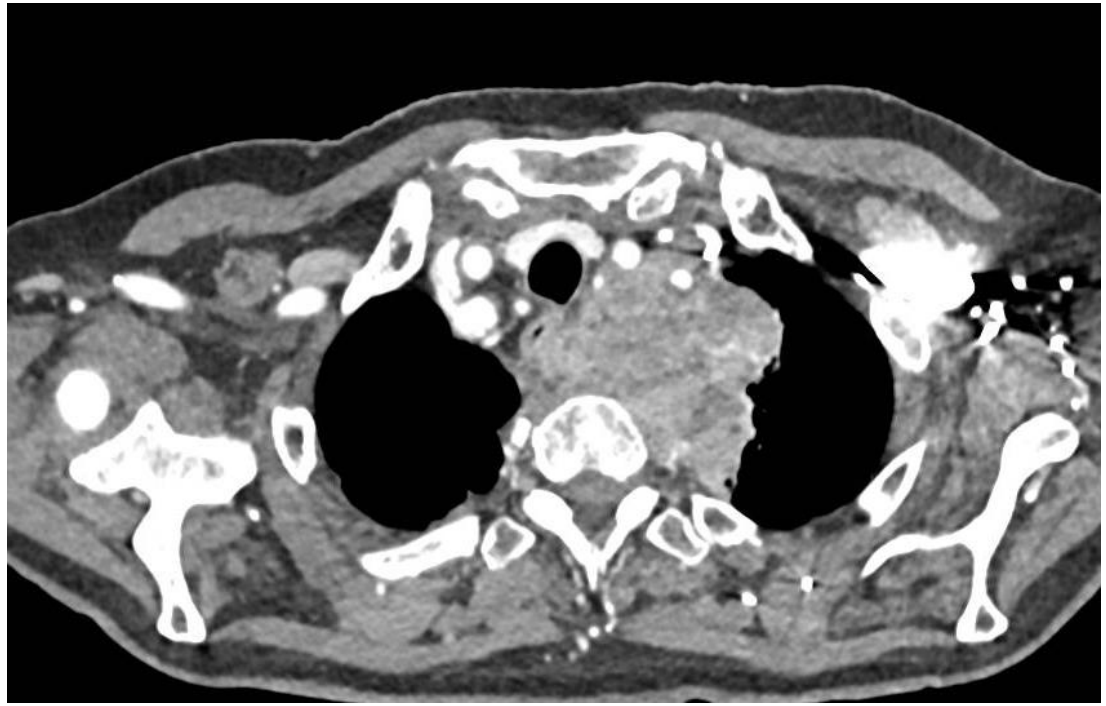
- Caveats:

1. enrollment of patients with acceptable plans, both IMRT and PSPT
2. proton technique—PSPT
3. exploratory analysis of time enrolled (is this a learning curve?)
   - Cumulative rate of RP and LR:
     - IMRT—21.1% (early) versus 18.2% (late)
     - PSPT--31.0% (early) versus 13.1% (late)

- The Future:
  - Phase II study of IMRT versus next generation proton IMPT (NCT01629498)

Practice with a locally advanced checklist

- Medical operability
  - Is the patient able to tolerate resection?
- Technical operability
  - Nature of the N2 disease
    - Single- vs multi- station
    - Bulky vs non-bulky
  - Primary can be removed with R0 resection
  - Extent of resection
    - Lobectomy vs Pneumonectomy
  - Pulmonary reserve
    - Resection>pulmonary reserve?
- Patient preference



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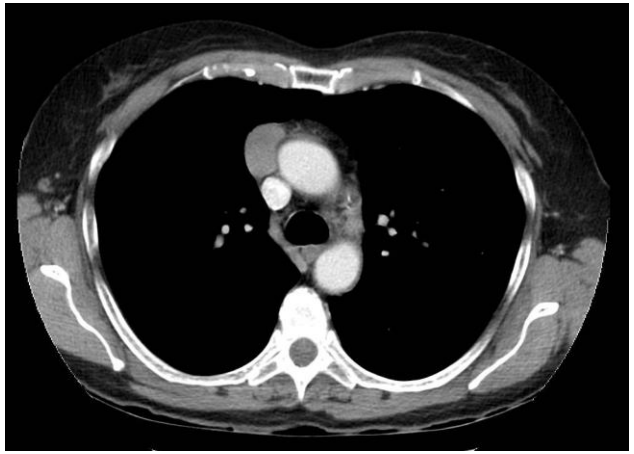

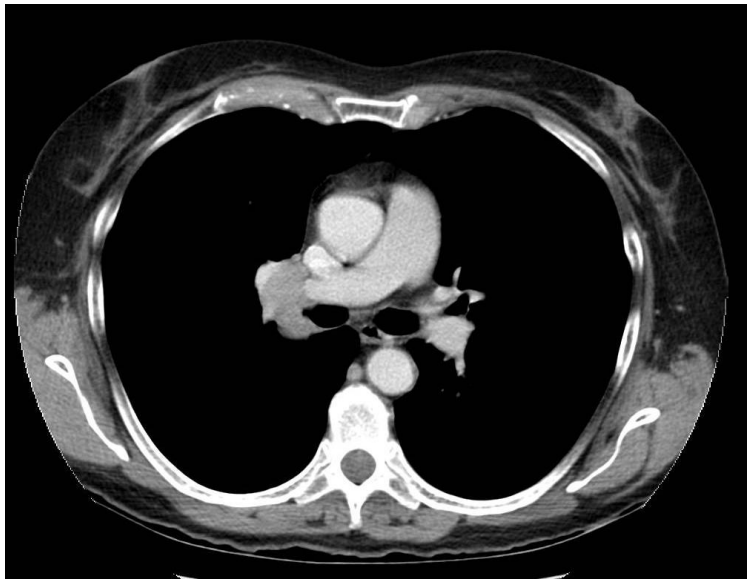

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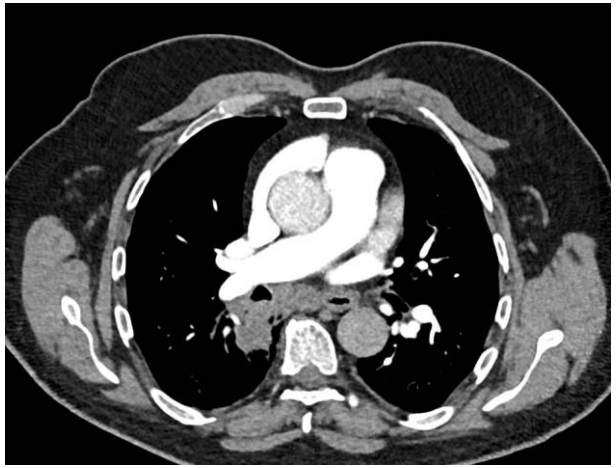
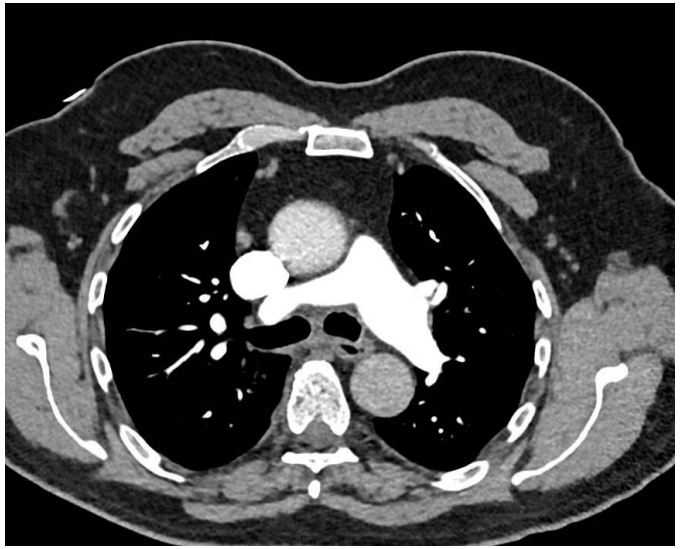
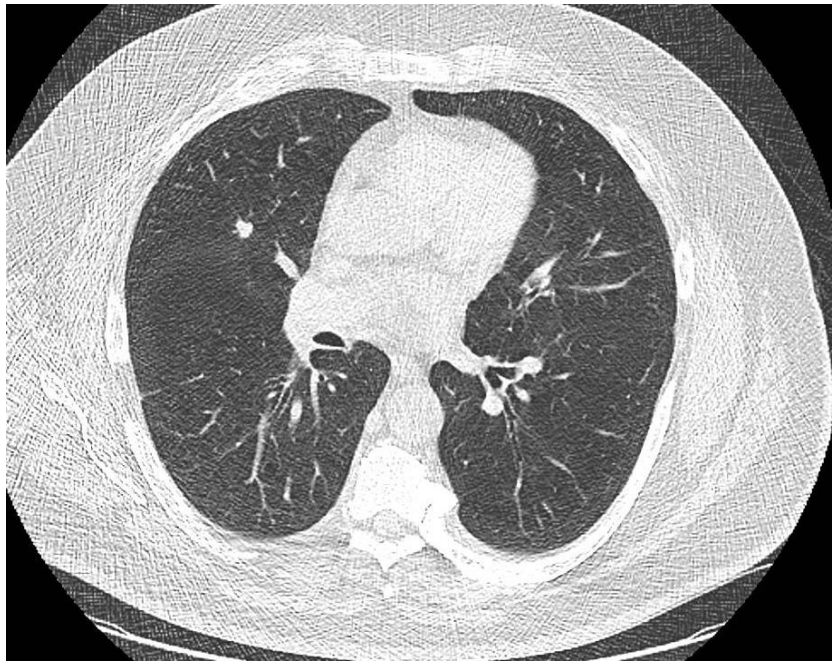




Back to our patient…

- 64 year old retired firefighter who undergoes lung cancer screening; former smoker, quit 2 years ago.



Instead of getting an EBUS, he goes directly to surgery and has resected a pT1bN2 NSCLC with negative margins. The involved LN is station 7 with a 3mm focus

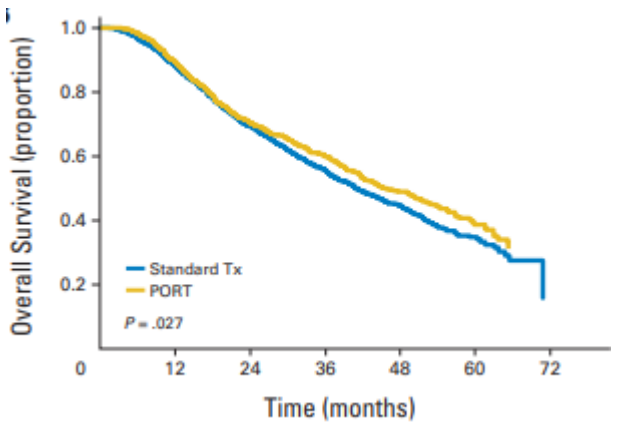
Next steps?

adjuvant chemotherapy ?

adjuvant radiation?

Management of pN2 disease after resection

- In patients who have resected N2 disease without induction radiation, the role of post operative RT (PORT) has been controversial
  - The PORT meta-analysis was methodically flawed, but suggested a harm in PORT.
  - Subgroup and retrospective data have suggested an improvement in patients with N2 disease who have PORT
    - ANITA* subgroup
    - NCDM^, JCO 2015

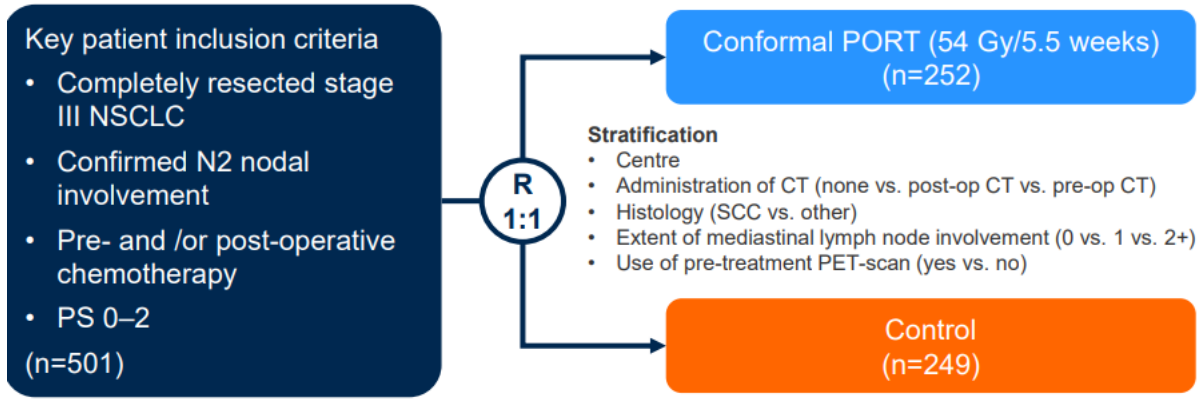


*Douillard J. et al, IJROBP 2008
^Robinson C. et al., JCO 2015

Lung-ART

LBA3: An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK) NCT00410683 – Le Pechoux C, et al

- **Study objective**
  - To assess the efficacy and safety of post-operative conformal radiotherapy (PORT) in patients with completely resected pN2 NSCLC



Primary endpoint

- DFS

Secondary endpoints

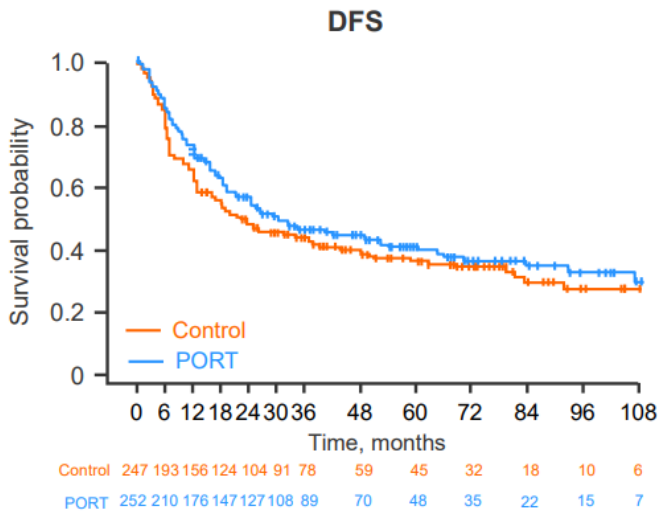
- OS, patterns of relapse, local failure, second cancers, safety

Le Pechoux C, et al. Ann Oncol 2020;31(suppl):Abstr LBA3

*Le Pechoux C. et al, ESMO 2020

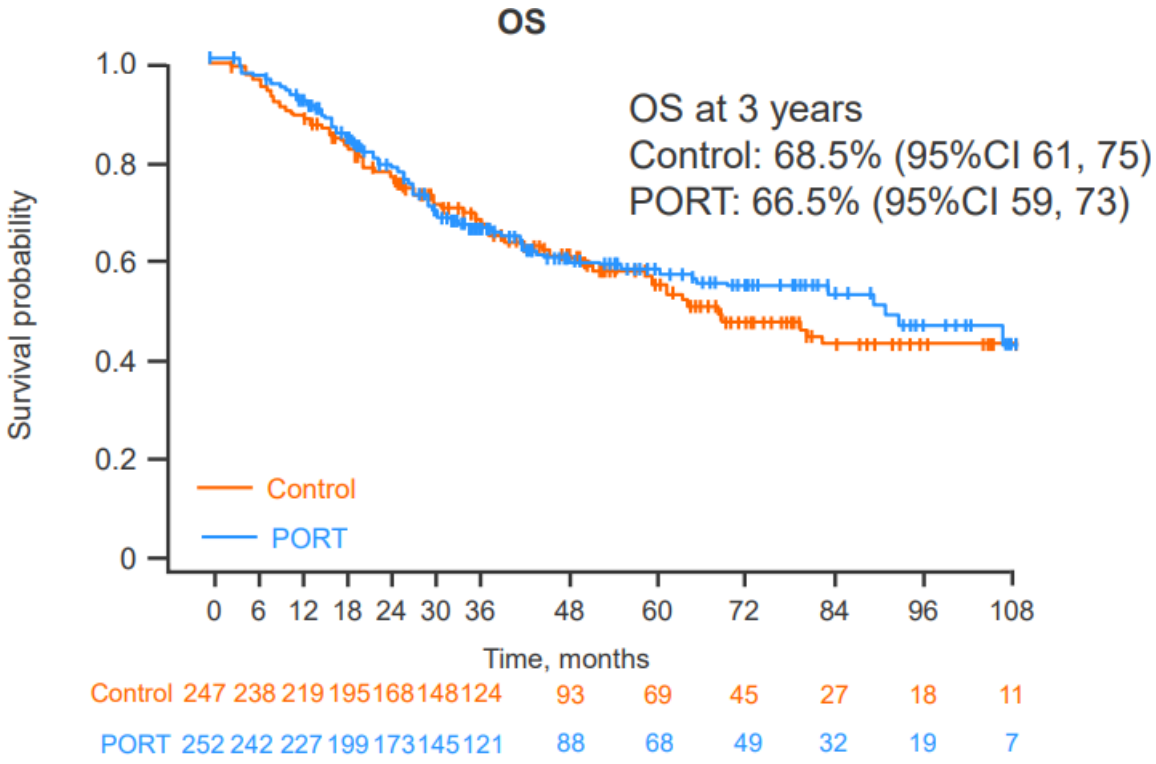
Lung-ART

- **Key results**



	Control	PORT
Median DFS, months (95%CI)	22.8 (17, 37)	30.5 (24, 49)
HR (95%CI)	0.58 (0.67, 1.07); p=0.16	
3-year DFS, % (95%CI)	43.8 (37, 51)	47.1 (40, 54)

DFS components (first event), n (%)	Control	PORT
All DFS events	152	144
Mediastinal relapse	70 (46.1)	36 (25.0)
Brain metastases	27 (17.8)	34 (23.6)
Other metastases	71 (46.7)	71 (49.3)
Death	8 (5.3)	21 (14.6)



- **Conclusions**
  - In patients with stage IIIA, N2 NSCLC, the use of PORT after complete resection did not significantly increase DFS and resulted in a higher incidence of toxicities

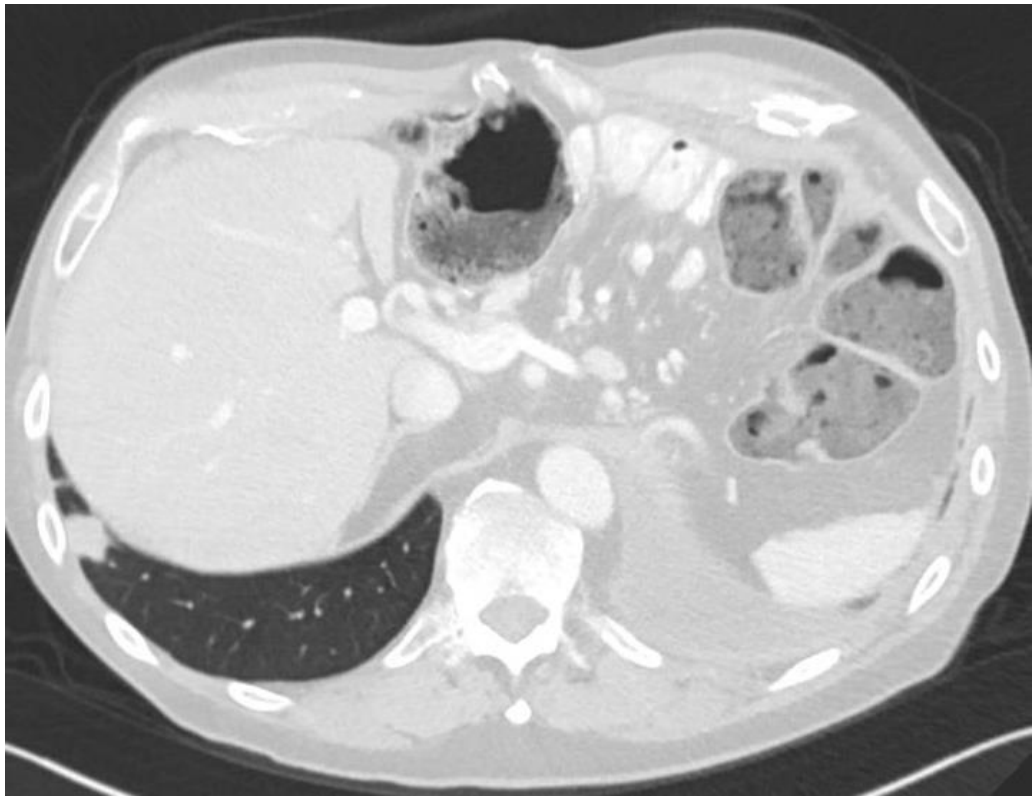
*Le Pechoux C. et al, ESMO 2020

Locally Advanced NSCLC

- Take Home Points
  - Ask the fundamental questions:
    - Medical operability
    - Technical operability
  - Outcomes in stage III disease are improving
  - If inoperable, chemoRT followed by durva is standard of care
  - If operable, induction therapy followed by resection is standard
    - If induction is given with chemoRT, higher mediastinal clearance, but no data it improves outcomes over chemo alone
    - If induction is given with chemo, the role of PORT is likely to decrease with the forthcoming publication of the Lung-ART data
  - Most stage III patients are not operable for either medical or technical reasons

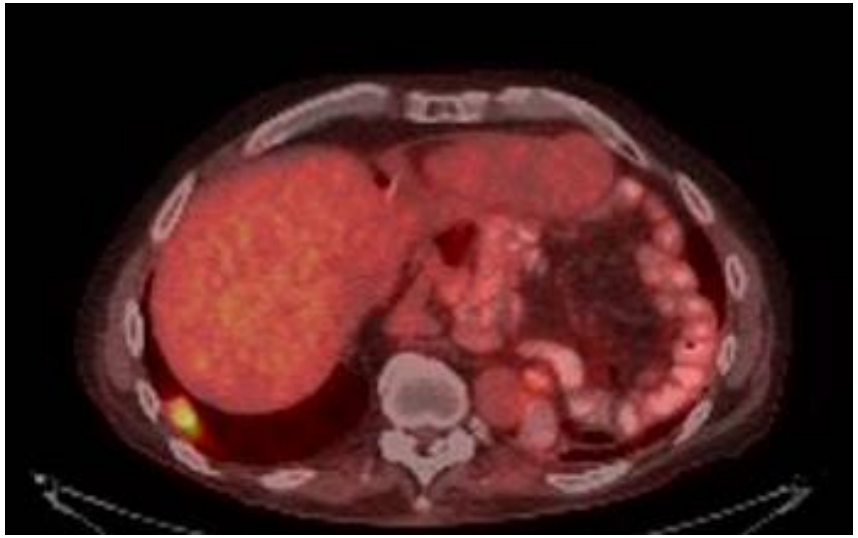
Early stage disease: Case Presentation

- 75 year old with a growing pulmonary nodule
  - Currently 14mm in size
  - Scan from 6 months prior showed a 7mm nodules
  - Current smoker



Early stage disease: Case Presentation

- Next Steps?
  - Pulmonary function tests
    - FEV1: 1.70L
    - FVC: 2.5 L
    - DLCO: 55% predicted
  - PET/CT
  - EBUS:
    - Not critical if PET is negative but would be reasonable
    - Any central lesion or peripheral >2cm

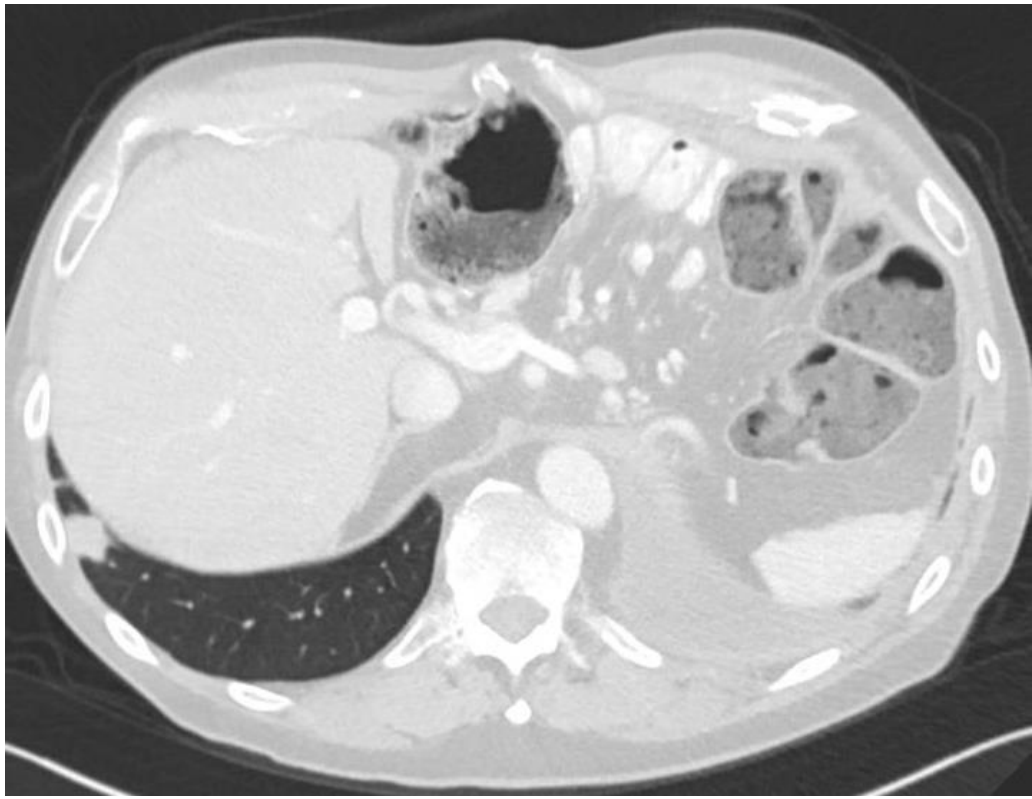


Early stage disease: Case Presentation

- Stage?
  - T1bN0M0
- Management?
  - Meets with a surgeon
    - Not a candidate for a RLL lobectomy but sublobar resection is feasible
  - Role of SABR?
    - Resection is both therapeutic and diagnostic.
    - Standard of care is resection if lobectomy is undertaken, but for sublobar resection, SABR can be considered as well
      - ASTRO management guidelines recommend biopsy for all pulmonary nodules prior to resection.
      - If patients decline biopsy, empiric SABR in appropriate clinical contexts may be reasonable.

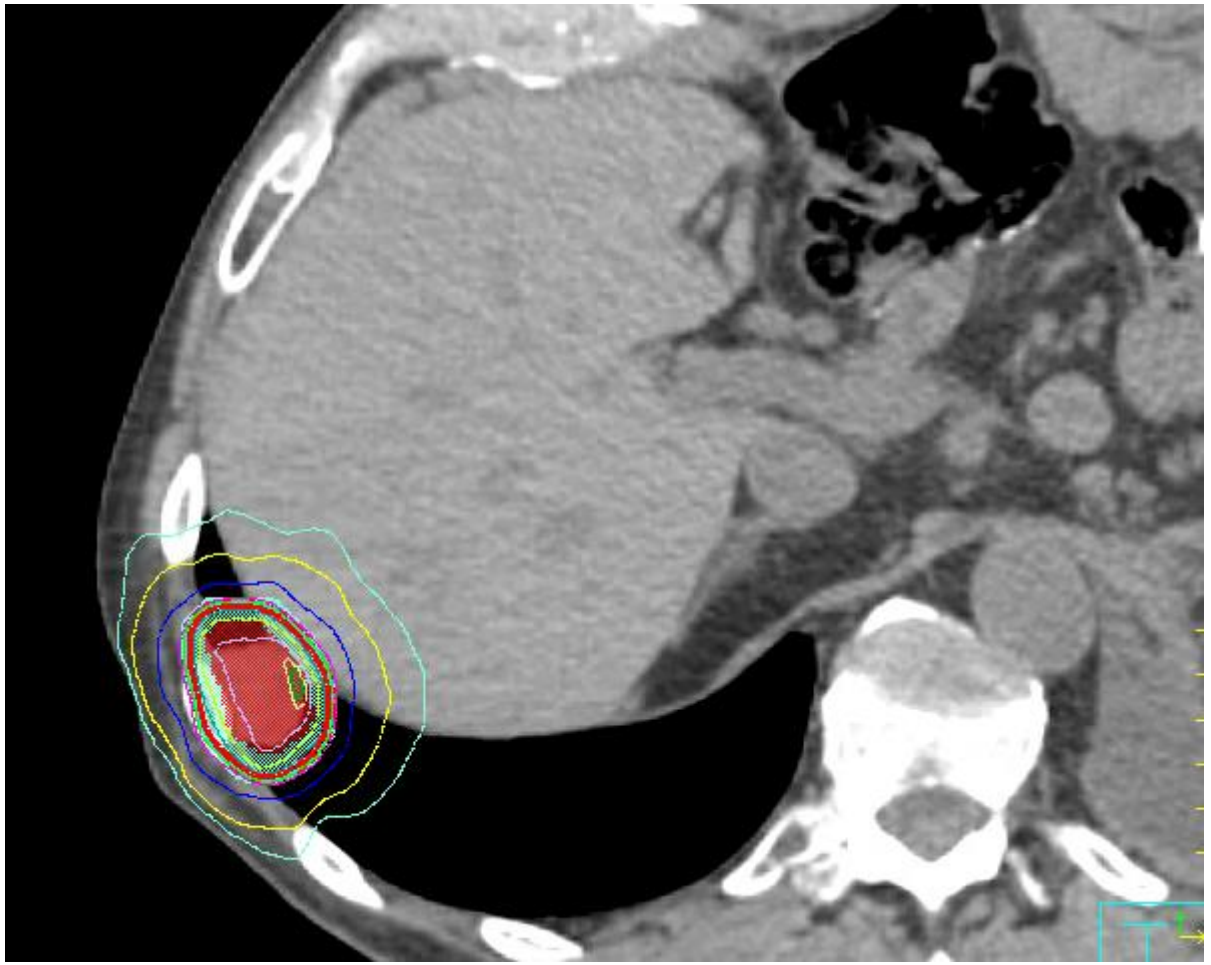
The patient opts for SABR

- SABR, 50 Gy in 5 fractions
  - Breath hold to limit motion
- A few thoughts:
  - No CTV expansion
    - Direct from GTV to PTV
  - Do not limit PTV coverage to meet a chest wall constraint
  - But advise patient of risk of chest wall pain from SABR
  - Remember—skin!!!

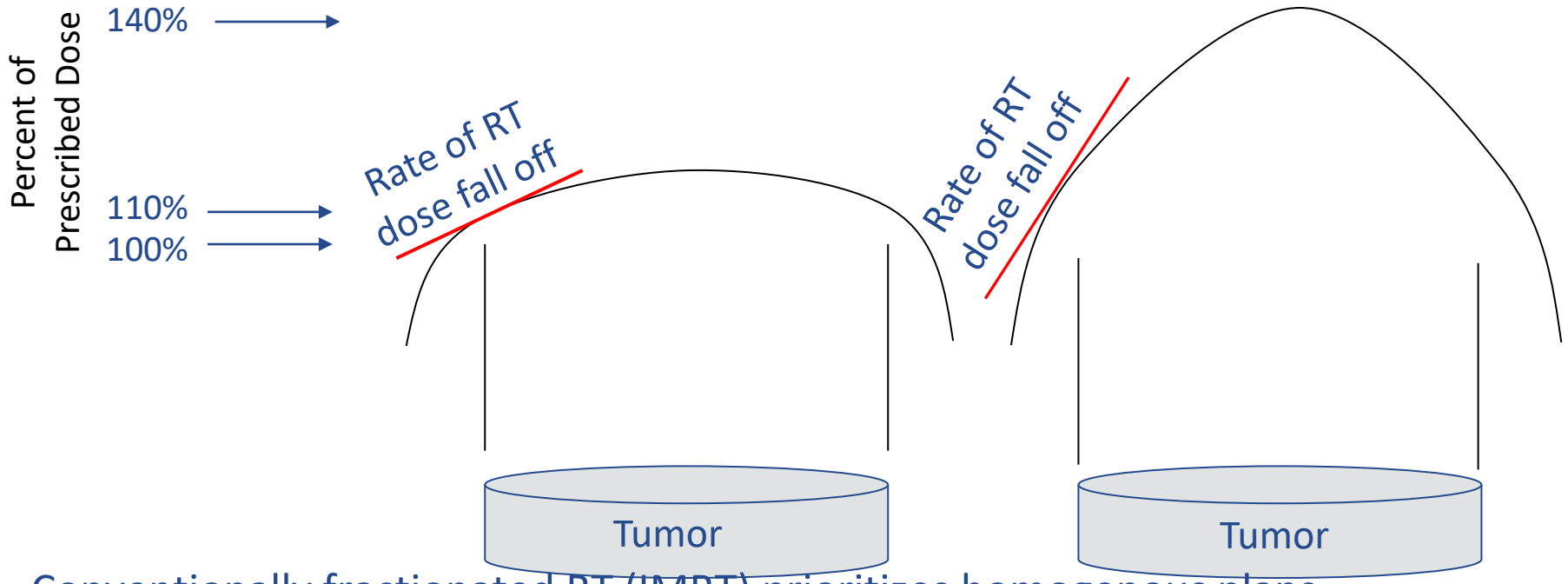


Peripheral SABR

- Remember to prescribe non-homogenous dose optimization
- i.e. should be prescribe between 60% and 90% isodose line.
- Why?



Dose fall off is inversely correlated with homogeneity



- Conventionally fractionated RT (IMRT) prioritizes homogenous plans but dose falls off more slowly
- SBRT results in very hot plans that quickly fall off and minimize dose to normal tissues. They also have higher mean doses to target.

SABR: Dose

- To maximize outcome, SABR dose is optimized with BED of 100 Gy or more
  - 257 patients with stage I NSCLC treated with SABR
  - Local progression was correlated with RT dose

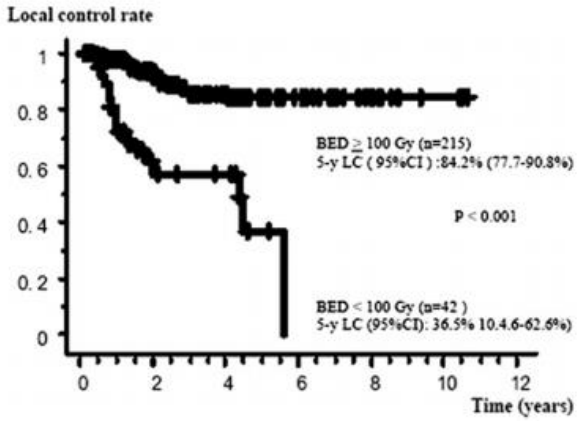


FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

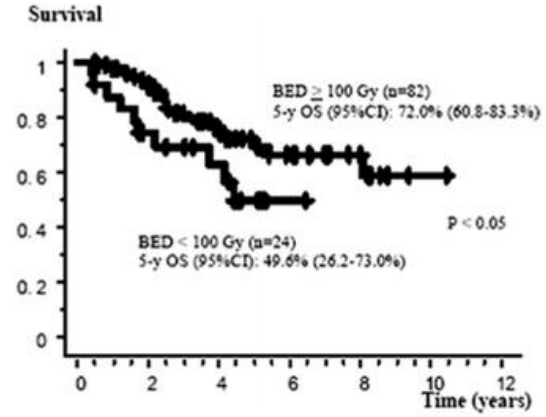


FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

Onishi H et al., JTO 2007

Technique

- Phase 2 study of stage I peripheral NSCLC patients randomized to:
  - 34 Gy x 1
  - 48 Gy x 4
- Outcomes:
  - 2 year overall survival
    - 34/1: 61.3%
    - 48/4: 77.7%
  - 2 year disease free survival
    - 34/1: 56.4%
    - 48/4: 61.1%
  - 1 year primary tumor control
    - 34/1: 97.0%
    - 48/4: 92.7%

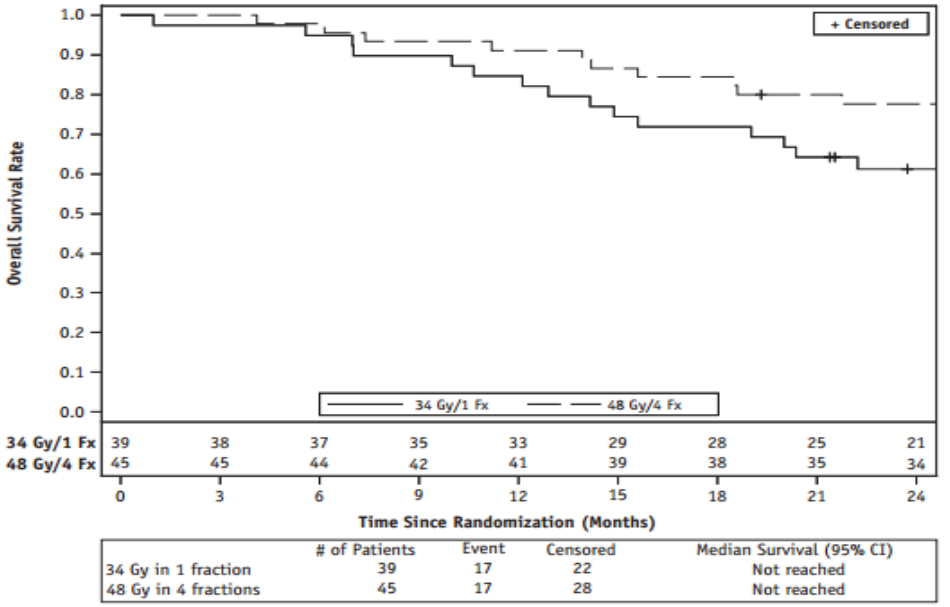


Fig. 1. Overall survival for patients treated with 34 Gy and 48 Gy. *Abbreviation:* Fx = fraction.

Videtic G et al., IJROBP 2015

Technique

Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non–Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial

- Center Tumors
  - 120 patients with medically inoperable, biopsy proven, T1-2 (<5cm) centrally located^ NSCLC treated with dose-escalating 5 fraction SBRT (started 10 Gy x 5 and escalated at 0.5 Gy per fraction until 12 Gy x 5 cohort was filled);
  - Central definition^: within or touching the zone 2cm around the proximal bronchial tree or immediately adjacent to the mediastinal or pericardial pleura
  - Outcomes:
    - During therapy, no dose limiting toxicities occurred that prevented continued dose escalation.

Bezjak A et al., JCO 2019

Technique

Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non–Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial

TABLE 2. DLTs by Dose Level (as Determined by Independent Review)

Treatment Arm	Evaluable Sample Size	No. of DLTs	Probability (95% CI)	DLTs	Grade	Days Since End of SBRT
Level 5: 10 Gy/fx	8	0	2.0 (0.6 to 5.1)			
Level 6: 10.5 Gy/fx	6	1	2.7 (0.8 to 6.5)	Death NOS	5	147
Level 7: 11 Gy/fx	13	1	4.3 (1.5 to 9.6)	Sinus bradycardia	5	130
Level 8: 11.5 Gy/fx	32	2	5.7 (2.1 to 12.0)	Hypoxia	3	88
				Hypoxia	3	166
Level 9: 12 Gy/fx	30	1	7.2 (2.8 to 14.5)	Pneumonitis	3	174
				Pleural effusion	3	264

Abbreviations: DLT, dose-limiting toxicity; fx, fraction; NOS, not otherwise specified; SBRT, stereotactic body radiotherapy.

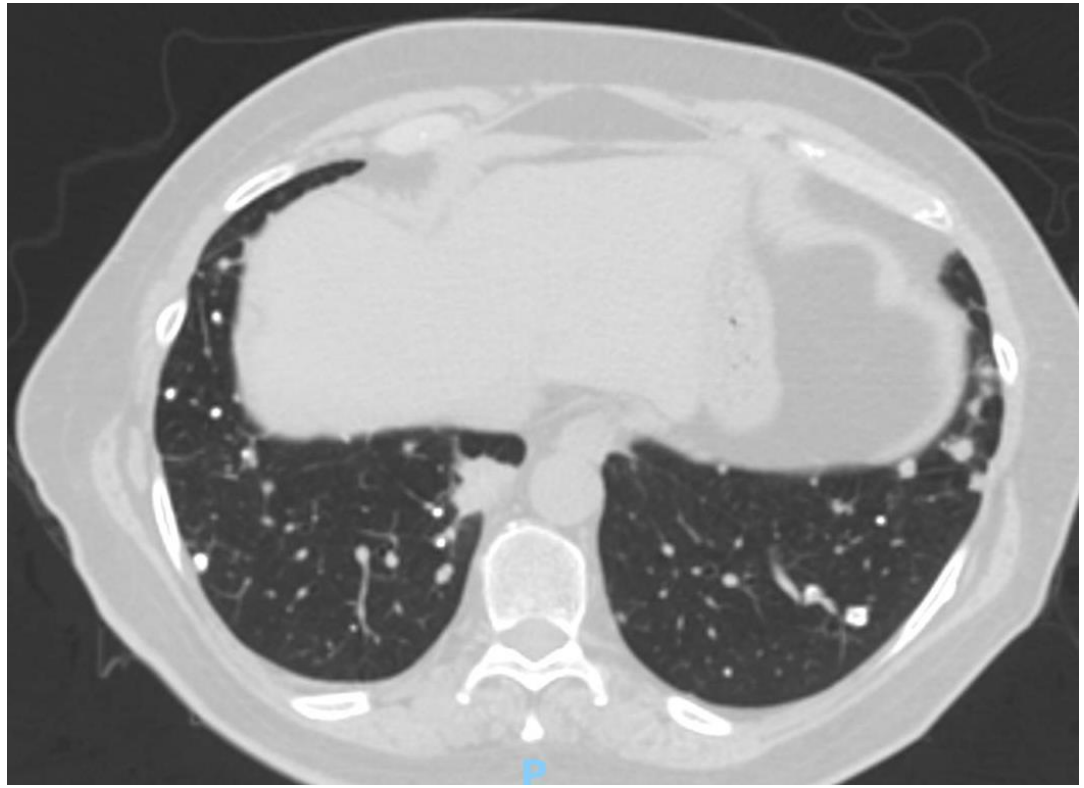
TABLE 4. Relapse Pattern and Outcomes

	Outcomes, No. (%)				
Relapse Pattern	Level 5: 10.0 Gy/fx (n = 8)	Level 6: 10.5 Gy/fx (n = 7)	Level 7: 11.0 Gy/fx (n = 14)	Level 8: 11.5 Gy/fx (n = 38)	Level 9: 12.0 Gy/fx (n = 33)
Local control rate, % (90% CI)					
1 year	100 (NA)	100 (NA)	100 (NA)	92.1 (86.8 to 100)	97.0 (90.9 to 100)
2 year	87.5 (62.5 to 100)	100 (NA)	85.7 (64.3 to 100)	89.4 (81.6 to 97.4)	87.9 (78.8 to 97.0)

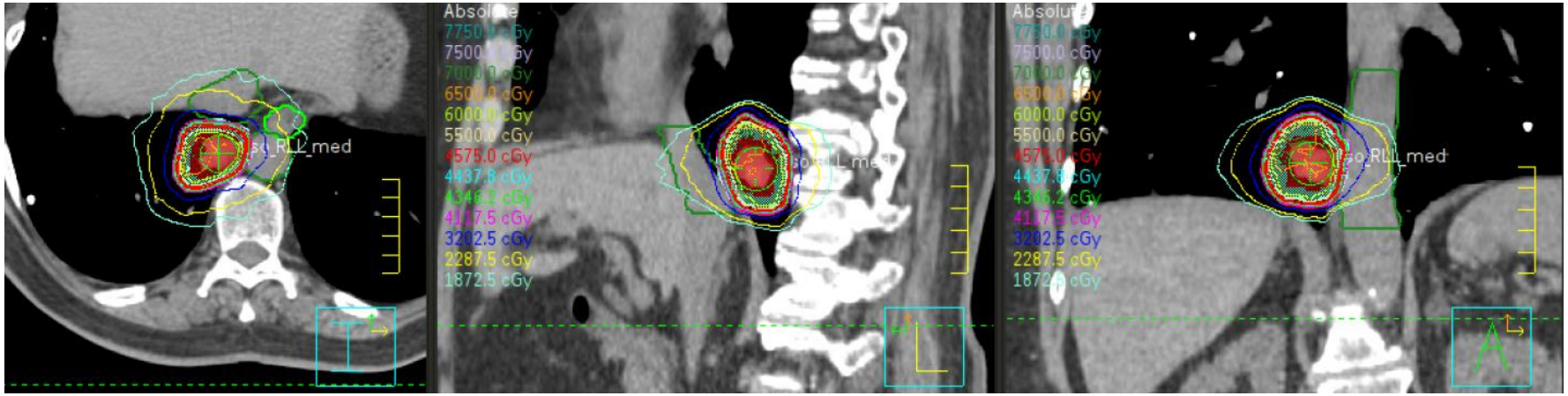
Bezjak A et al., JCO 2019

Caveats: SABR for central tumors

- Excellent local control (~90%)
- 2 year overall survival (~70%) comparable to reports of SABR for patients with peripheral tumors
- Highest dose level (12 Gy/fx) had a DLT of 7.2%.
- 2 grade 5 events (1.7%)
- Toxicity can come late
- Not many ultra-central tumors include—difficult to know how to apply to these patients.
- If using SABR for central tumors, involve the patient in the decision making and inform of possible grade 5 risks.



SpinalCanal_at_risk	13.75	2080 cGy	<	0.35 cc	0.35 cc	0.00 cc
SpinalCanal_at_risk	13.75	1450 cGy	<	1.2 cc	1.2 cc	0.01 cc
SpinalCanal_at_risk	13.75	Max	<	2600 cGy	2600 cGy	1452.04 cGy
SpinalCanal_PRV04	37.81	2080 cGy	<	0.35 cc	0.35 cc	0.00 cc
SpinalCanal_PRV04	37.81	1450 cGy	<	1.2 cc	1.2 cc	0.39 cc
SpinalCanal_PRV04	37.81	Max	<	2600 cGy	2600 cGy	1575.52 cGy
Lungs	5577.53	Mean	<	400 cGy	400 cGy	222.78 cGy
Lungs	5577.53	2000 cGy	<	4.5 %	4.5 %	1.42 %
Lungs	5577.53	1000 cGy	<	12 %	12 %	4.95 %
d2cm_id_spillage	41951.60	Max	<	2554 cGy	2987 cGy	2149.20 cGy
4575 (RLL_med_nodule) / PTV ABC (5mm exp)	28.26/27.46	ratio Ratio	<	1.2	1.5	1.03
2287.5 (RLL_med_nodule) / PTV ABC (5mm exp)	118.72/27.46	ratio Ratio	<	4.4	5.4	4.32
dmax_hd_spillage	42209.80	4804 cGy	<	4.1 cc	4.1 cc	1.44 cc
iBloodVessel_at_risk	61.47	5300 cGy	<	10 cc	10 cc	0.00 cc
iBloodVessel_at_risk	61.47	Max	<	5300 cGy	5300 cGy	5285.91 cGy
iEsophagus_at_risk	18.82	1880 cGy	<	5 cc	5.9 cc	5.88 cc
iEsophagus_at_risk	18.82	Max	<	3500 cGy	3500 cGy	3085.77 cGy
iPericardium_at_risk	196.91	2800 cGy	<	15 cc	15 cc	0.00 cc
iPericardium_at_risk	196.91	Max	<	3400 cGy	3400 cGy	1969.82 cGy
Trachea_at_risk	33.84	1560 cGy	<	4 cc	4 cc	0.00 cc
Trachea_at_risk	33.84	Max	<	3480 cGy	3480 cGy	6.97 cGy
Lungs	5577.53	1160 cGy	<	1500 cc	1500 cc	202.75 cc
Lungs	5577.53	1240 cGy	<	1000 cc	1000 cc	177.40 cc
Skin_at_risk	4011.94	3320 cGy	<	10 cc	10 cc	0.00 cc
Skin_at_risk	4011.94	Max	<	3600 cGy	3600 cGy	1218.31 cGy



Suggestions for treating central tumors

- Any of the following fractionation patterns is reasonable:
  - 50 Gy in 5 fractions
  - 60 Gy in 15 fractions
  - 66 Gy in 33 fractions
- Meet published normal tissue constraints:
  - NCCN
  - TG101
  - R0813
- Do what you are comfortable with doing. If treating a central lesion, make sure your technology is contributing to patient safety and success.
  - Motion management
  - Breath hold
  - 3d and 4D cone beams

Final Conclusions

- The field of lung cancer is quickly evolving and changes will be disruptive.
  - Outcomes in lung cancer have never been better.
- Standards of care are shifting which means that shared decision making between patients and physicians is critical.
  - More systemic (immunotherapy) in earlier stage disease.
  - More local therapy in advanced stage disease
- A rationale approach to a lung cancer patient often starts with careful consideration of medical fitness and technical operability.
- Use a list (i.e. stage III disease, plan evaluation, local therapy in metastatic disease)
- Practice within your comfort zone—published normal tissue constraints can act as a vanguard to keep treatment safe for our patients.