

Case Conference:
Post-Operative Radiotherapy for
Non-Small Cell Lung Cancer

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6/1/12

Outline

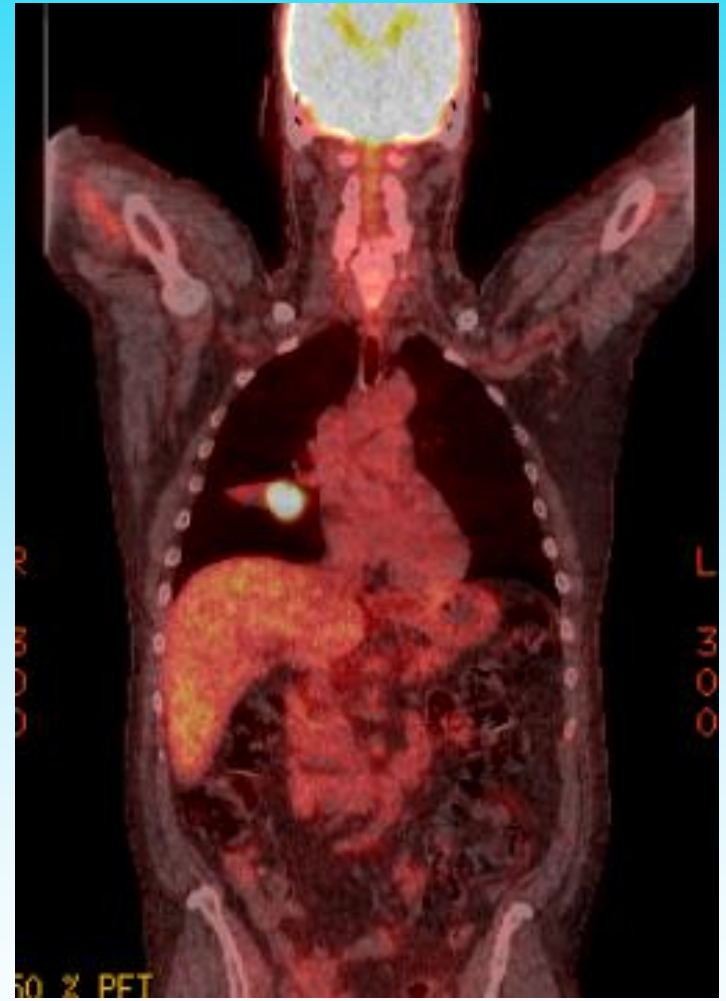
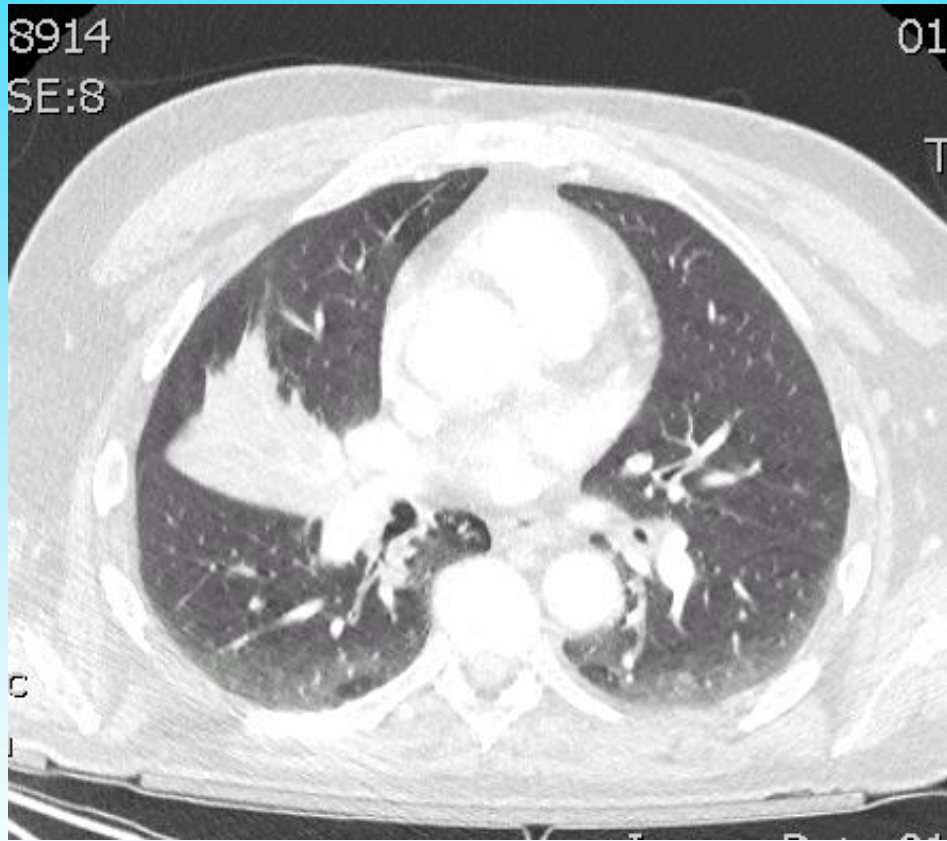
- I. Presentation of Case
- II. Epidemiology
- III. Staging
- IV. Review of Literature
- V. Recommendations
- VI. Additional Discussion

The Case

- **HPI:**
- 54 y/o male presents to UCSD ER with exacerbation of schizophrenia and is found to have a RML mass on CXR, confirmed by CT.
- MRI of brain shows no metastases
- a bronchoscopy shows a RML endobronchial mass. Biopsy shows squamous cell CA.
- a PET scan shows a hypermetabolic RML mass, but no hypermetabolic LNs or distant disease.
- He has a mediastinoscopy by Dr Thistlethwait. Pathology shows 0/15 level 4 and level 7 LNs involved.

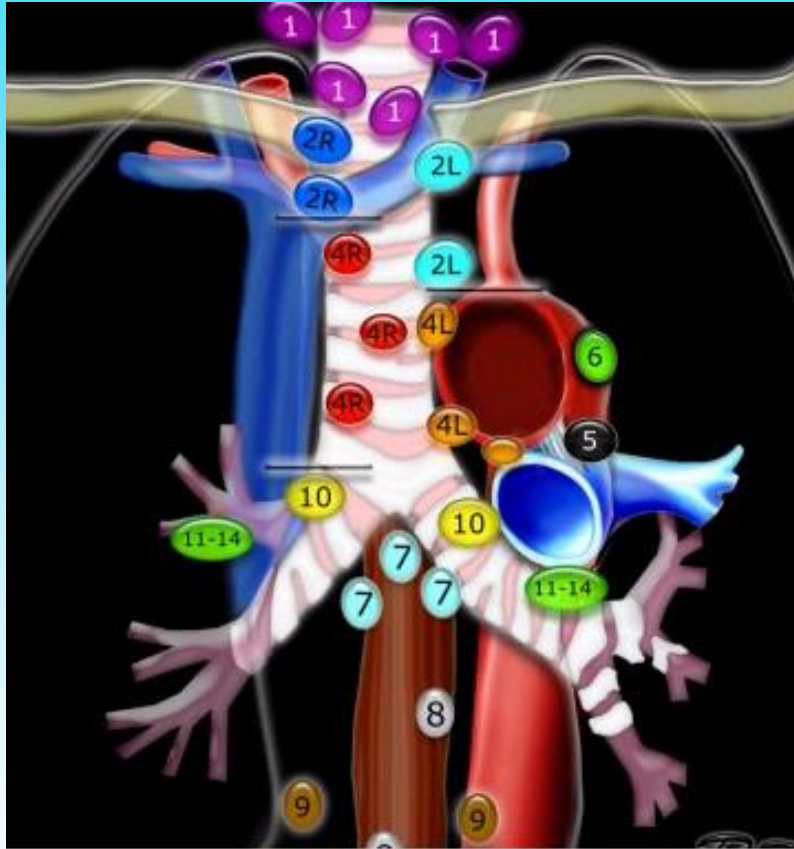
The Case

- **HPI:**
- He undergoes resection of the RML mass and mediastinal LN dissection by Dr Thistlethwait. Pathology shows a 4.0 cm tumor squamous cell CA with 1/16 LNs involved (with positive LN located at the major fissure / pulmonary artery). There is a positive bronchial stump margin.
- Since that time he has recovered very well. He has no respiratory symptoms. He is able to walk several miles. He has no cough, hemoptysis or chest pain. He continues to smoke, although ¼ PPD rather than 2 PPD previously. He denies any bone pain, numbness, weakness or vision changes.



The Case

- **PMH:** NSCLC, COPD, PE, Schizophrenia
- **Meds:** Depakote, Aricept, Zyprexa, Seroquel, Haldol, Trazadone, memantine, risperdal
- **SH:** He has smoked 30 yrs. Curr 1/4 PPD. Prev 2 PPD.
- **FH:** Father colon CA, Mother pancreatic CA
- **PE:**
- Respiratory: Diffuse rhonchi and mild congestion on the right lung fields. Decreased sounds bilaterally.



N2 nodes: (all lie within the mediastinal pleural envelope)

1 - highest mediastinal nodes –

2 - upper paratracheal nodes –

3A and 3P - prevascular (3A) and retrotracheal (3P) nodes

-

4 - lower paratracheal nodes –

5 - subaortic (AP window) -

6 - para-aortic nodes –

7 - Subcarinal

8 - paraesophageal

9 - pulmonary ligament –

N1 nodes: (intrapulmonary and hilar)

10 - hilar nodes

11 - interlobar nodes

12 - lobar

13 - segmental

14 - subsegmental

AJCC 7th edition (2009)

Primary Tumor:

- **T1 - 3 cm or less, surrounded by lung or visceral pleura, not invading into a main bronchus**
 - **T1a - tumor 2 cm or less**
 - **T1b - > 2 cm but ≤ 3 cm**
- **T2 - tumor >3 cm but ≤ 7 cm; or tumor with any of the following: involves main bronchus (2cm or more distal to the carina), invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung**
 - **T2a - >3 cm but ≤ 5 cm (also includes T2 tumors smaller than 3 cm)**
 - **T2b - >5 cm but ≤ 7 cm**
- **T3 - tumor > 7 cm; or tumor that directly invades one of the following: parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumor nodules in the same lobe**
- **T4 - tumor invades: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or separate tumor nodule(s) in a different ipsilateral lobe**

Regional Lymph Nodes:

- **N0 - no nodes**
- **N1 - ipsilateral peribronchial and/or ipsilateral hilar lymph nodes or intrapulmonary nodes**
- **N2 - ipsilateral mediastinal and/or subcarinal nodes**
- **N3 - contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular nodes**

Distant Metastases:

- **M0 - none**
- **M1**
- **M1a - separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion**
- **M1b - distant metastases**

Stage Grouping:

- **IA - T1(a or b) N0**
- **IB - T2a N0**
- **IIA - T1(a or b) N1, T2a N1, T2b N0**
- **IIB - T2b N1, T3 N0**
- **IIIA - T3 N1, T1-3 N2, T4 N0-1**
- **IIIB - N3 any, T4 N2-3**
- **IV - M1a or M1b**

Epidemiology

- Incidence = 164,100 cases/yr.
- Mortality = 156,900 deaths/yr.
- Number 1 cause of cancer death in USA
- >90% a/w smoking or 2nd hand smoke
- Radon exposure and asbestos are also significant risk factors
- Smokers have a 20x higher risk than non-smokers.
- At diagnosis:
 - 15% N0M0
 - 30% N1-3M0
 - 55% M1
- PET has a sensitivity of 79%, specificity of 91%, PPV 90%, NPV 93%
- Brain metastases are found on MRI in 4% of presumed stage I/II pts and 11% of presumed stage III pts

Epidemiology

- Histology:
 - Adenocarcinoma – 40% (is least associated with smoking.)
 - Squamous cell carcinoma - 30%
 - Large cell carcinoma - 15%
 - Small cell carcinoma - 20%
- TTF-1 distinguishes lung adeno from other metastatic adeno primary
- Squamous cell is often more central
- Presenting stage:
 - I = 10%, II = 20%, III = 30%, IV = 40%

Epidemiology

- **Work-up:**

- CBC, BUN, Cr, LFT, Alk Phos, LDH
- CT C/A/P
- WB PET CT
- MRI Brain
- PFT (Need post-op FEV1 of 0.8L and DLCO of 60%)

- **Mediastinoscopy:**

- Cervical approach = Level I – IV
- Chamberlain (Anterior) = Level IV – VII

Pneumonitis Grading

RTOG Grade Definition

- 1 Mild dry cough or DOE not requiring clinical intervention
- 2 Cough requiring narcotic antitussives or dyspnea not at rest
- 3 Severe cough not responsive to narcotics or dyspnea at rest; intermittent oxygen or steroids may be required
- 4 Continuous oxygen or assisted ventilation
- 5 Fatal

NCI CTCAE

- 1 Asymptomatic, radiographic findings only
- 2 Symptomatic, not interfering with ADL
- 3 Symptomatic, interfering with ADL; O₂ indicated
- 4 Life-threatening; ventilatory support indicated
- 5 Death

Recommendations

- Post-op RT is indicated for pN2 disease or + Mgn
 - N2: Chemo -> 50Gy PORT
 - + Mgn: 60Gy PORT -> Chemo
 - Gross Dz: 66Gy PORT -> Chemo

Organ	RT Alone	Chemo/RT
Cord ^a Lung ^b	50 Gy MLD < 20 Gy V20 < 40%	45 Gy MLD < 20 Gy V20 < 35% V10 < 45% V5 < 65%
Heart Esophagus	V40 < 50% D _{max} < 75 Gy V60 < 50%	V40 < 50% D _{max} < 75 Gy V55 < 50%
Kidney ^c	20 Gy (< 50% of combined both kidneys or < 75% of one side of kidney if another kidney is not functional)	Same as RT alone
Liver ^d	30 Gy (< 40%)	Same as RT alone

Trials

LCSG 773

- Lung Cancer Study Group 773 – NEJM 1986
- Prospective RCT of 230 pts with resected NSCLC
- Stage II or III (T3/4 or N1/2)
- Randomized to +/- 50Gy of post-op RT
 - Superior = suprasternal notch -Inferior = 5cm below Carina
 - Ipsilat. = stump/hilum -Contralat. = mediastinal shadow
- Median f/u 3.5 yr

Table 3. Site of First Recurrence (Excluding Second Primary Tumors) in the Study Groups.

SITE	RADIATION (102)		CONTROL (108)		P VALUE*
	NO. (%)	RATE PER PERSON-YEAR	NO. (%)	RATE PER PERSON-YEAR	
Only local (ipsilateral lung or mediastinum)	1 (3)	0.006	21 (41)	0.144	<0.001
Only brain	5 (13)	0.029	6 (12)	0.038	0.850
All other†	32 (84)	0.180	24 (47)	0.152	0.337
	38		51		

*By two-sided log-rank test.

†"All other" includes single sites other than brain or "local" (defined as ipsilateral pulmonary or mediastinal, or a combination thereof) as well as any combination of multiple sites detected on the common date of first recurrence — e.g., liver only, brain plus "local," or liver plus "local."

Table 4. Rates of Recurrence and Death According to Nodal-Disease Status.*

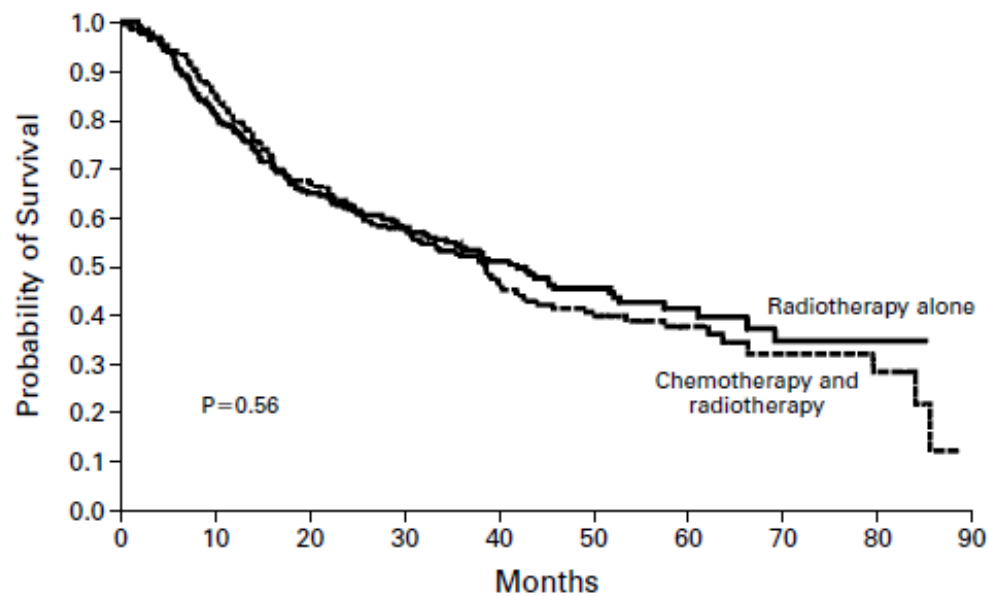
	NO. OF EVENTS	RATE PER PERSON-YEAR	P VALUE†
Recurrence (without 2nd primary)			
N0			
Radiation	1	0.062	0.351
Control	1	0.290	
N1			
Radiation	31	0.264	0.917
Control	37	0.294	
N2			
Radiation	6	0.155	0.031
Control	13	0.453	
Death			
N0			
Radiation	2	0.120	0.306
Control	2	0.426	
N1			
Radiation	31	0.223	0.951
Control	37	0.240	
N2			
Radiation	12	0.285	0.805
Control	12	0.296	

*There were 9 patients with N0 status (7 in the radiation group and 2 in the control group), 157 with N1 status (74 and 83), and 44 with N2 status (21 and 23).

†By two-sided log-rank test.

INT 0115 ECOG 3590 / RTOG 91-05

- Keller et al. – NEJM 2000
- Prospective RCT of 488 pts with resected NSCLC
- Stage II or IIIA (T3/4 or N1/2)
- Received 50.4Gy of post-op RT (+10.8Gy boost for LN ECE)
- Randomized to +/- Cis/Etopo x 4c
 - Cisplatin 60mg/m²
 - Etoposide 120mg/m²
- Median f/u 44 mo.



Median OS 3.2 yrs

	No. OF PATIENTS	No. OF DEATHS	MEDIAN SURVIVAL (mo)
Radiotherapy	242	132	38.8
Chemotherapy and radiotherapy	246	146	37.9

TABLE 4. PATTERNS OF RECURRENCE.*

PATTERN OF RECURRENCE	RADIO THERAPY ALONE (N=234)	CHEMOTHERAPY AND RADIO THERAPY (N=236)	TOTAL (N=470)	P VALUE
	no. of patients (%)			
Intrathoracic	50 (21)	56 (24)	106 (23)	0.11
Distant, excluding central nervous system	54 (23)	45 (19)	99 (21)	0.09
Intrathoracic and distant, excluding central nervous system	16 (7)	12 (5)	28 (6)	0.16
Central nervous system	33 (14)	34 (14)	67 (14)	0.25

TABLE 2. TREATMENT-RELATED ADVERSE EFFECTS.*

ADVERSE EFFECT	RADIOTHERAPY ALONE (N=230)			CHEMOTHERAPY AND RADIOTHERAPY (N=232)		
	GRADE 3	GRADE 4	GRADE 5	GRADE 3	GRADE 4	GRADE 5
	percent					
Leukopenia	<1	—	—	41	38	—
Granulocytopenia	—	1	—	14	60	—
Thrombocytopenia	—	—	—	13	5	—
Anemia	—	<1	—	13	1	—
Sepsis	1	—	—	3	1	<2
Nausea	1	—	—	20	—	—
Vomiting	<1	—	—	10	5	—
Pneumonitis	2	—	1	3	<1	<1
Esophagitis	1	—	<1	14	3	<1

RTOG 97-05

- Bradley et al. – JCO 2005
- Phase II trial of 88pts
- Stage II or IIIA (T3/4 or N1/2)
- Received 50.4Gy of post-op RT (+10.8Gy boost for LN ECE or T3 dz)
- Concurrent Paclitaxel 135mg/m² & Carboplatin 225mg/m²
- Median f/u 56.7 mo.

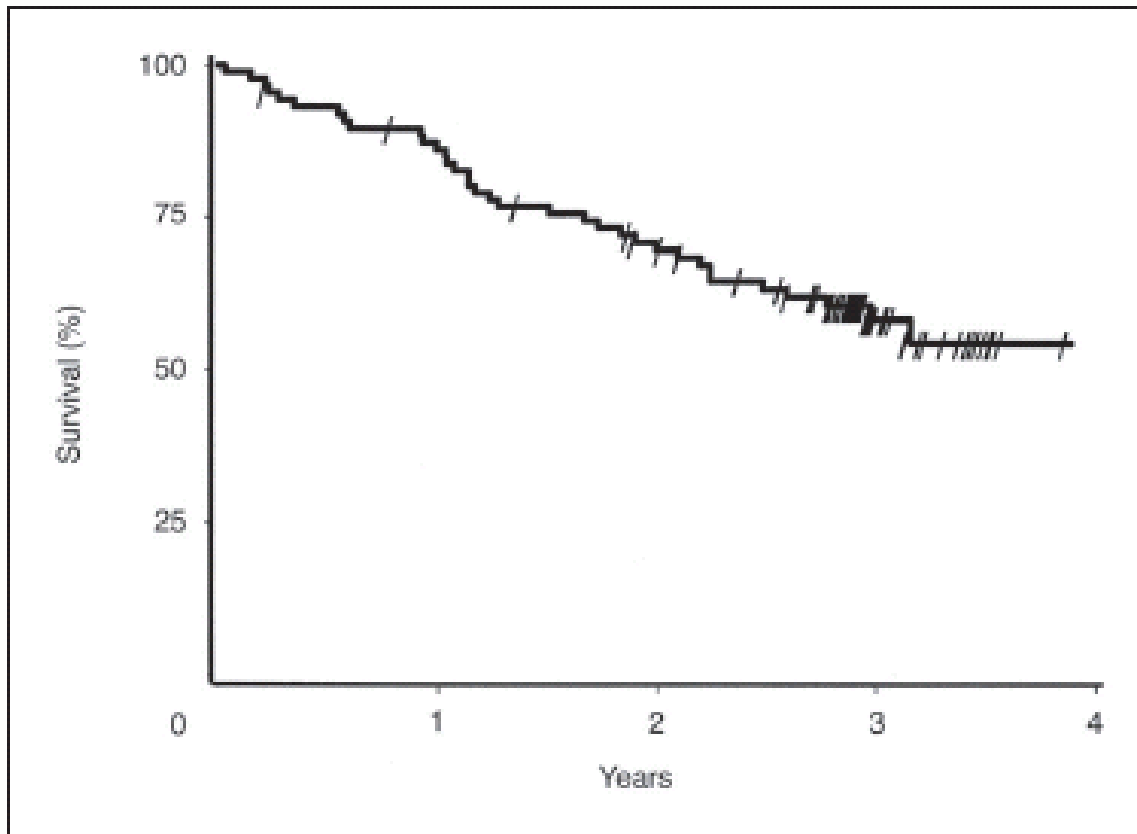


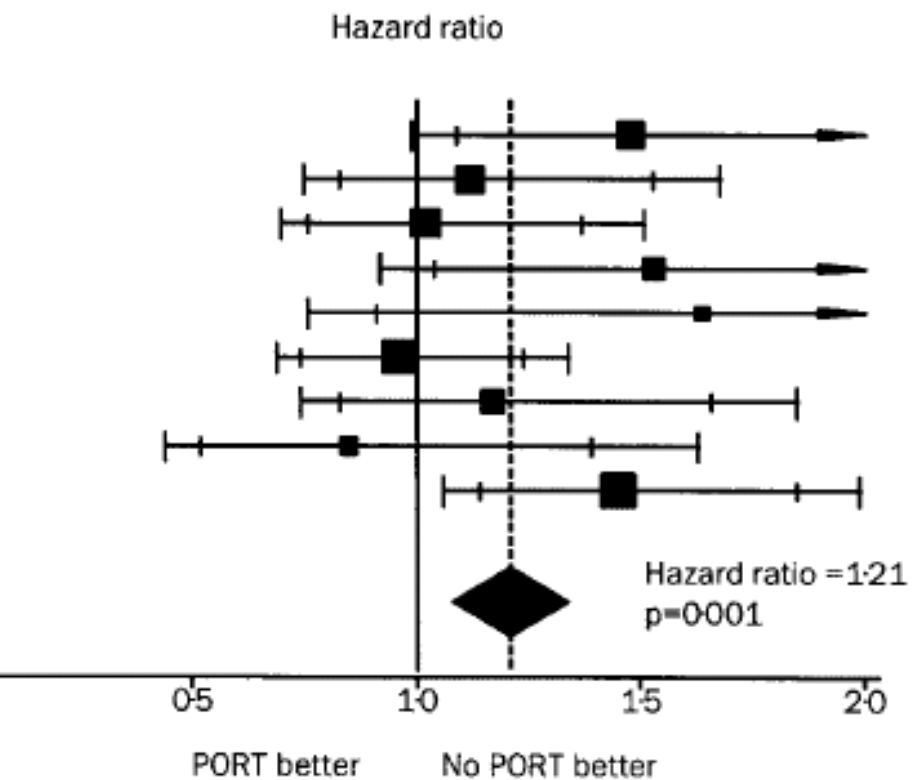
Fig 1. Overall survival.

-Median OS =
4.7 yrs

-Compares
favorably w/
RTOG 9105

PORT Meta-Analysis

- Lancet 1998
- 2128 pts, 9 randomized trials, stage I-III
- Analyzed by intention to treat
- Median f/u 3.9 yrs.
- Problems:
 - 25% patients had T1N0 disease
 - Poor staging
 - 4 of the trials used Co-60 (5-year OS: Co-60 = 8% vs. MV = 30%)
 - Poor technique (incl lateral fields)
 - Tx to 60Gy in up to 3Gy fractions



Among all pts there was a detriment to PORT

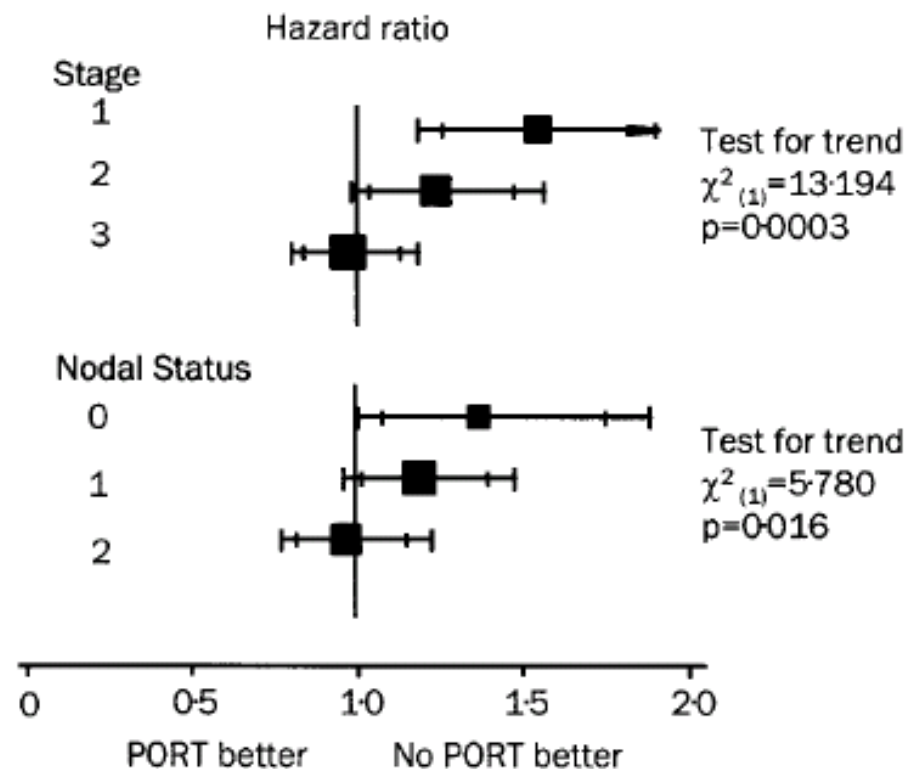


Figure 6: **Stage and nodal status subgroup analysis for survival**
Format as for figure 1.

This detriment was limited to
Stg I/II & N0/1 pts

SEER

- SEER – JCO 2006
- Review of 7456 pts with Stg II or III (N0-N2) NSCLC
- Excluded pts who died within 4mo of diagnosis
- Analyzed outcome by N status
- Median f/u 3.5 yrs.

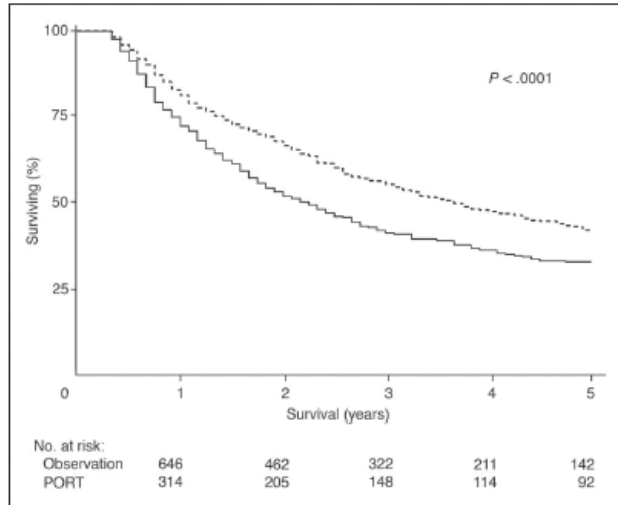


Fig 3. Plot of overall survival for N0 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.

N0

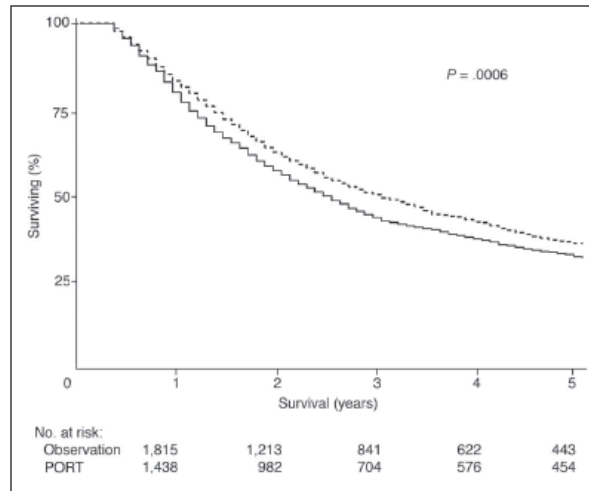


Fig 4. Plot of overall survival for N1 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.

N1

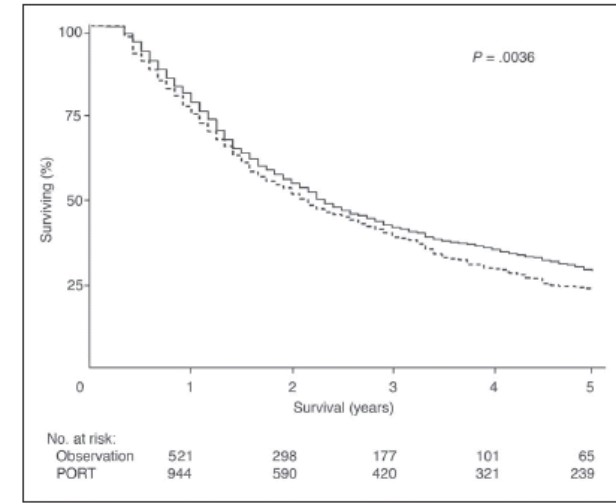


Fig 5. Plot of overall survival for N2 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.

N2

ANITA

- Douillard et al. – IJROBP 2008
- Review of pts who received PORT on this chemo trial
- 232/840 (28%) received RT (8% of N0 pts, 35% of N1, 52% of N2).
- RT was 45-60 Gy sequentially 2 wks after chemo
- Pts randomized to +/- adj Navelbine/Cisplatin

Table 3. ANITA trial results: Percentage of patients with 5-year survival, according to treatment received by nodal status

Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association.; PORT = postoperative radiation therapy.

* Chemotherapy consisted of vinorelbine + cisplatin.

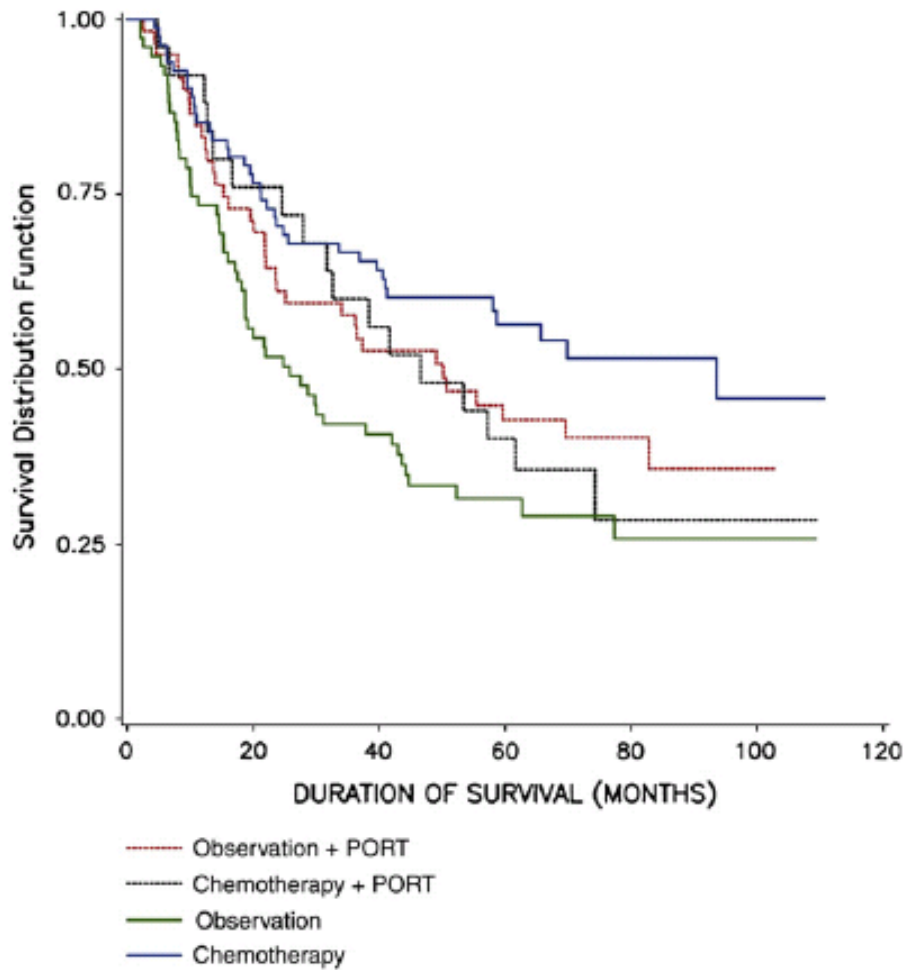


Fig. 2. Overall survival according to treatment received in the pN1 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

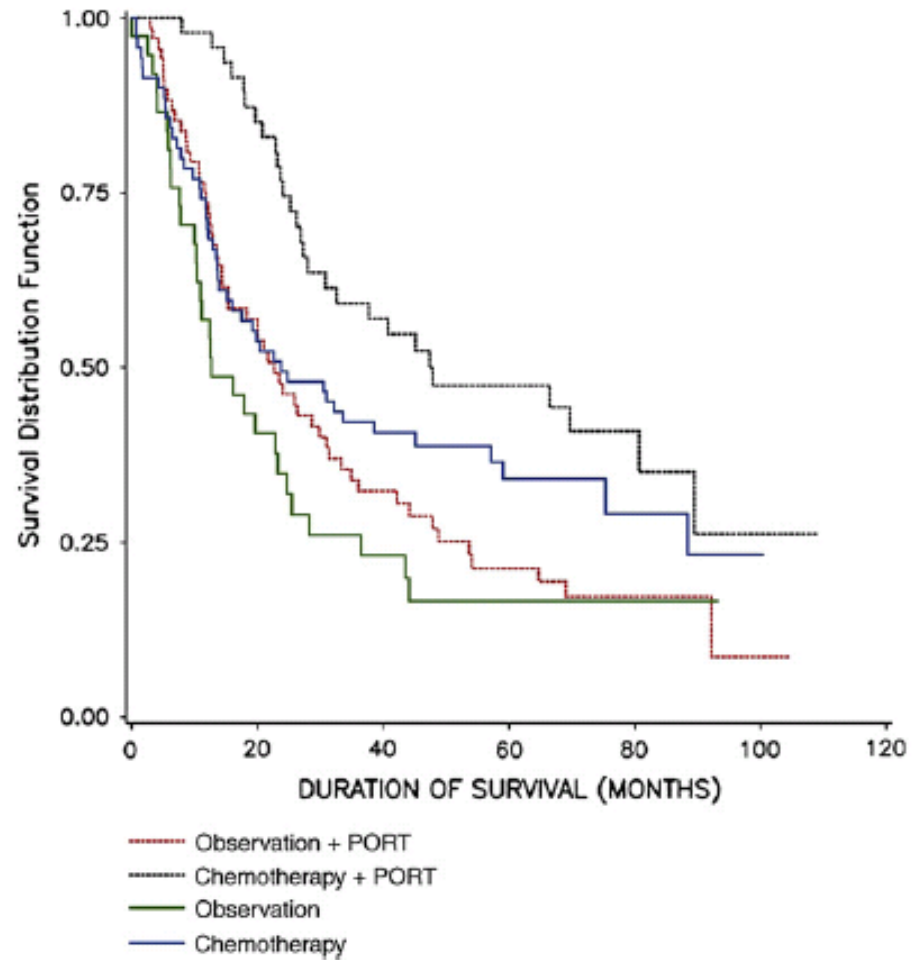


Fig. 3. Overall survival according to treatment received in the pN2 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

Open RTOG Trials

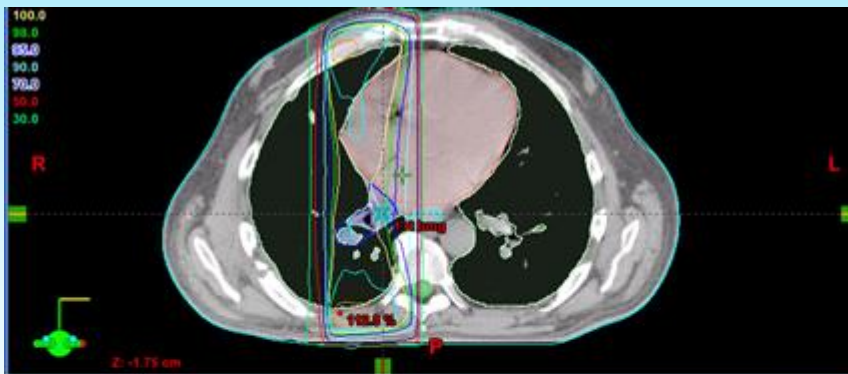
-Currently there are no RTOG trials open for post-operative patients with NSCLC.

The case

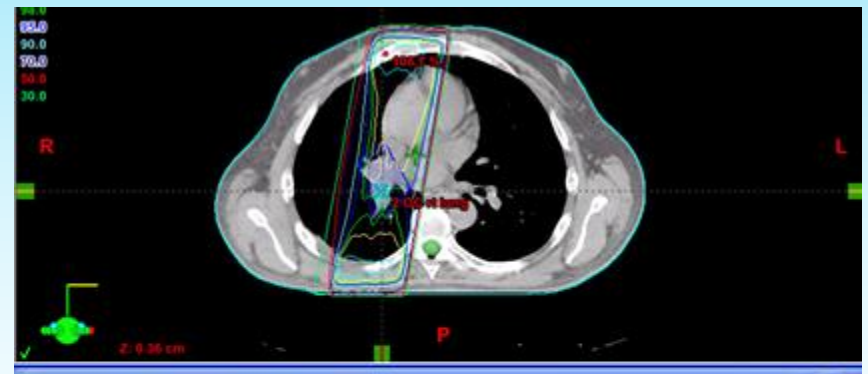
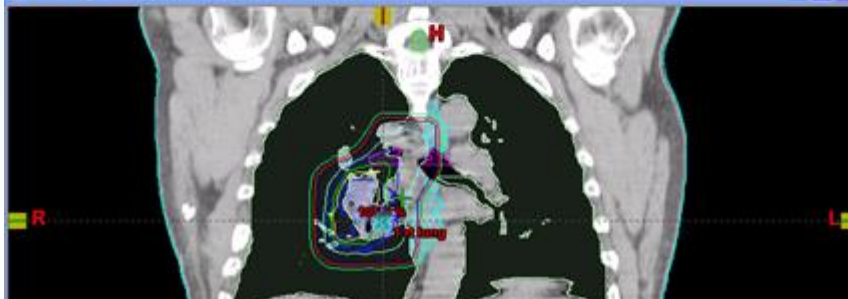
-54 y/o man with T2a N1 M0, Stage IIA NSCLC, s/p RML lobectomy
Med. LND with positive stump margin.

-He was treated with 3D CRT – 40Gy AP/PA, 10Gy OC, 10Gy Bst to
+mgn

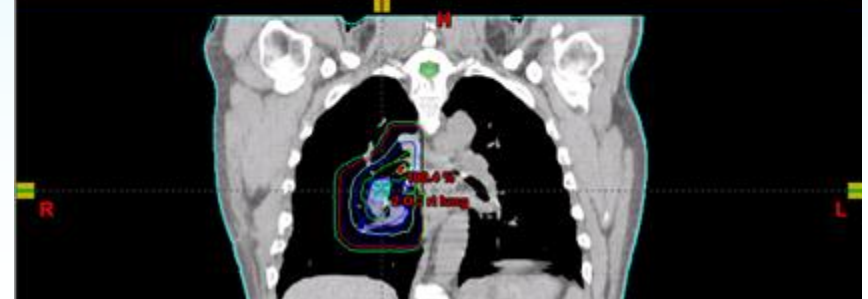
-At last f/u 3/2012 he is clinically NED without any toxicity



1 Rt Lung - Unapproved - Frontal - CT Chest 090111



2 OC Rt Lung - Unapproved - Frontal - CT Chest 090111



Questions?

- Thank you!

- Additional References:

- Halperin, Perez & Brady “Principles and practice of Radiation Oncology” 5th ed.
- AJCC cancer staging handbook 7th ed.
- Hansen and Roach III “Handbook of evidence-based Radiation Oncology” 2nd ed.
- http://en.wikibooks.org/wiki/Radiation_Oncology
- Hall and Giaccia “Radiobiology for the radiologist” 6th ed.