Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part III

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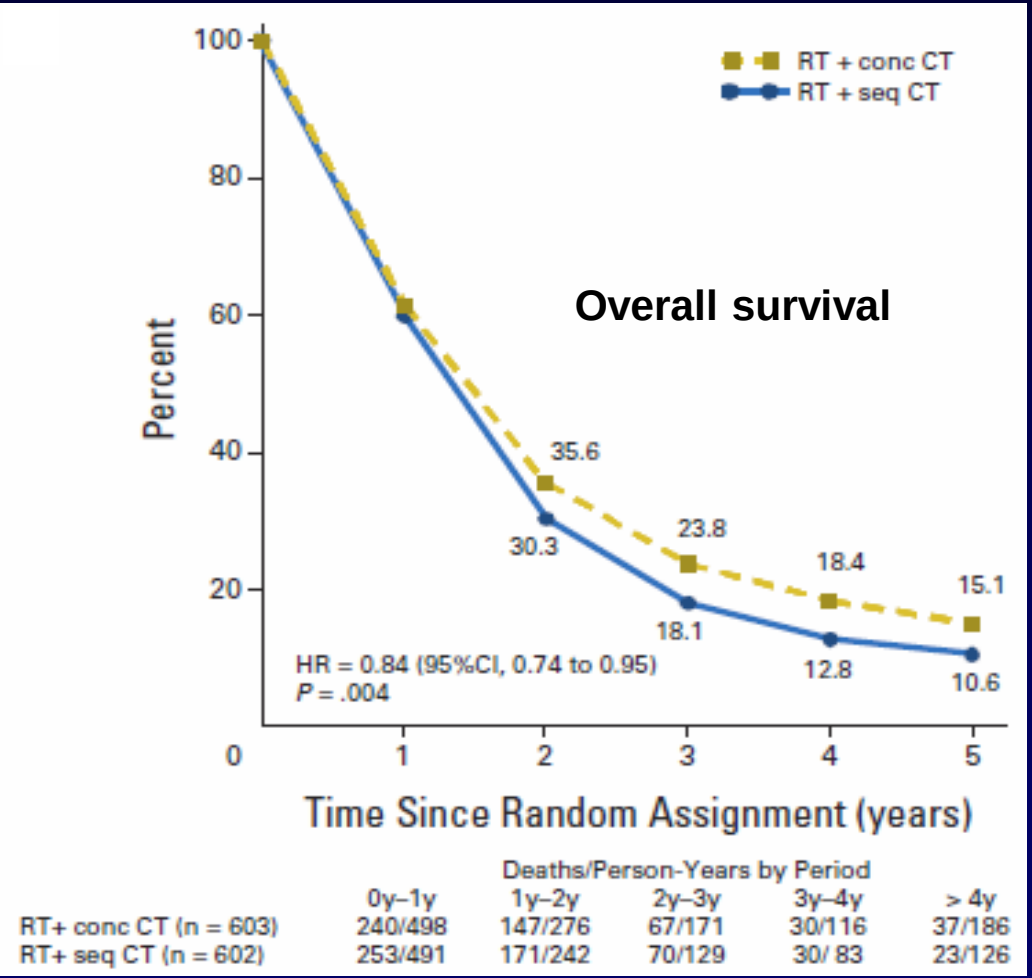
Meta-Analysis of Concurrent vs Sequential Chemo-RT in Stage III NSCLC



Aupérin A, et al. *J Clin Oncol.* 2010;28(13):2181-2190.

Concurrent Chemo-RT Is Standard of Care in Fit Patients With a Stage III NSCLC [Level 1 Evidence]

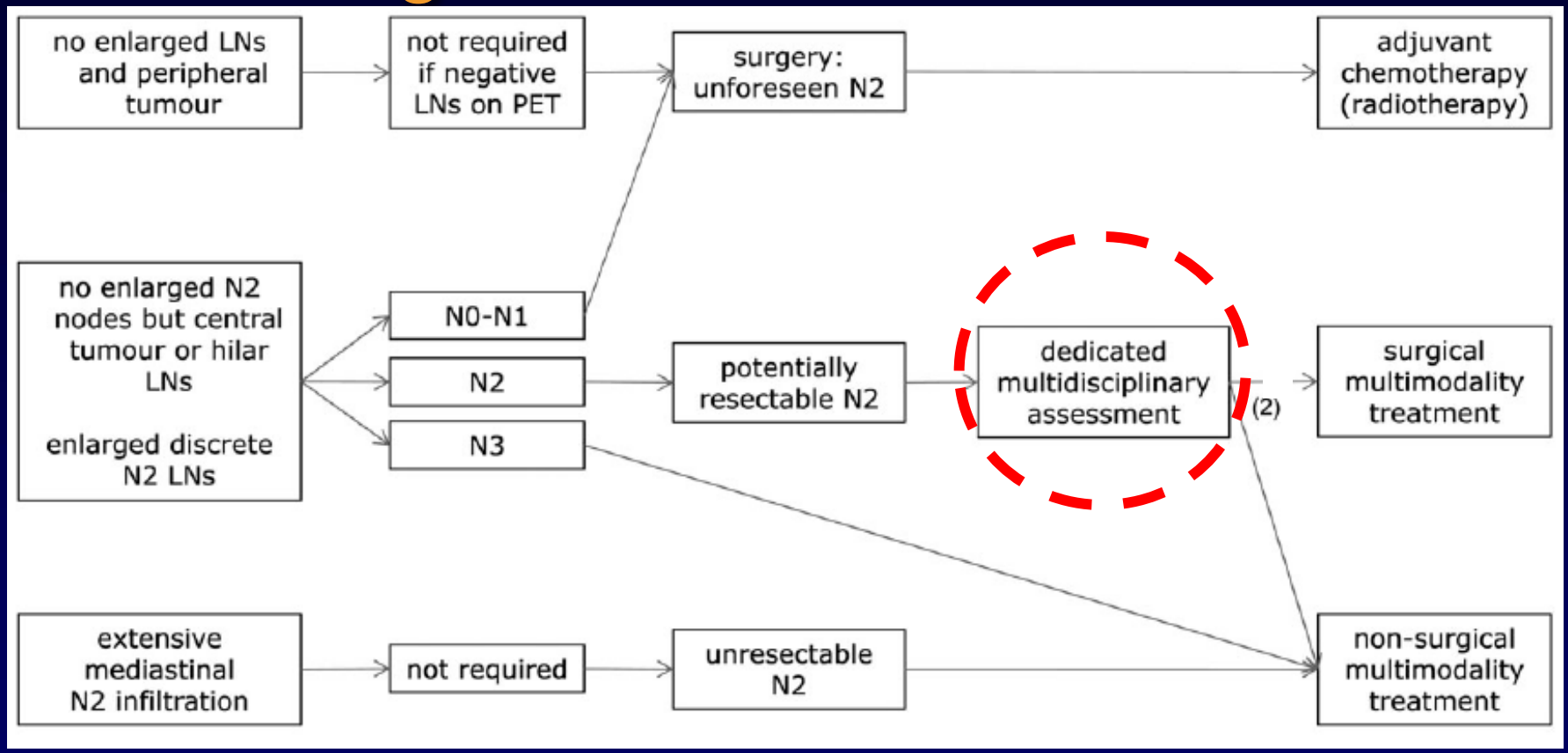
- **INT 0139 (Albain K, 2009)**
  - **Median overall survival: 22.2 months (chemo-RT arm)**

- **RTOG 94-10 (Curran W, 2011)**
  - **Median overall survival 17 months (2-Dimensional radiotherapy)**

- **RTOG 0617 (Bradley J, 2015)**
  - **Median overall survival 28.7 months (standard-dose 60 Gy) and 20.3 months (74 Gy) after high-dose radiotherapy (use of 3-Dimensional radiotherapy mandatory)**

Albain KS, et al. *Lancet*. 2009;374(9687):379-386. Curran WJ Jr, et al. *J Natl Cancer Inst.* 2011;103(19):1452-1460. Bradley JD, et al. *Lancet Oncol.* 2015;16(2):187-199.

Stage III NSCLC: Guidelines



- **For resectable LA-NSCLC, especially single nodal stage N2 disease, both definitive chemoradiotherapy and induction therapy followed by surgery are options [level II, A]**
- **Surgery is preferably considered in patients in whom a complete resection by lobectomy is expected. [level II, B] More complex surgical resections after induction treatment should be carried out in experienced centers [level III, B]**

Vansteenkiste J, et al. ESMO Clinical Practice Guidelines, *Ann Oncol.* 2013;24 Suppl 6:vi89-vi98.

Combined-Modality Trials With Surgery

Trial	Inclusion	Study Question	N	Answer	Post-Therapy 30-Day Mortality	5-Year Survival*
EORTC 08941[1]	Unresectable IIIA/N2	CT-S vs CT-RT	579	NO difference	4% NR	16% 14%
INT 0139[2]	Potentially resectable IIIA/N2	CRT-S vs CRT	429	NO difference	8% 2%	27% 20%
ESPATUE[3]	IIIA/N2 and IIIB	CT-CRT-S vs CT-CRT-CRTb	246	NO difference	6% 3%	44% 41%
SAKK 16/00[4]	Potentially resectable IIIA/N2	CT-RT-S vs CT-S	232	NO difference	0% 3%	40% 34%

CT, induction chemotherapy; RT, radiotherapy; S, surgery; CRT, concurrent chemoradiotherapy; CRTb, concurrent chemoradiotherapy boost

1. Van Meerbeeck J, et al. *J Natl Cancer Inst.* 2007;99(6):442-450; 2. Albain KS, et al. *Lancet.* 2009;374(9687):370-386. 3. Eberhardt W, et al. *J Clin Oncol.* 2014;32(5s): Abstract 7510. 4. Pless M, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1195O.

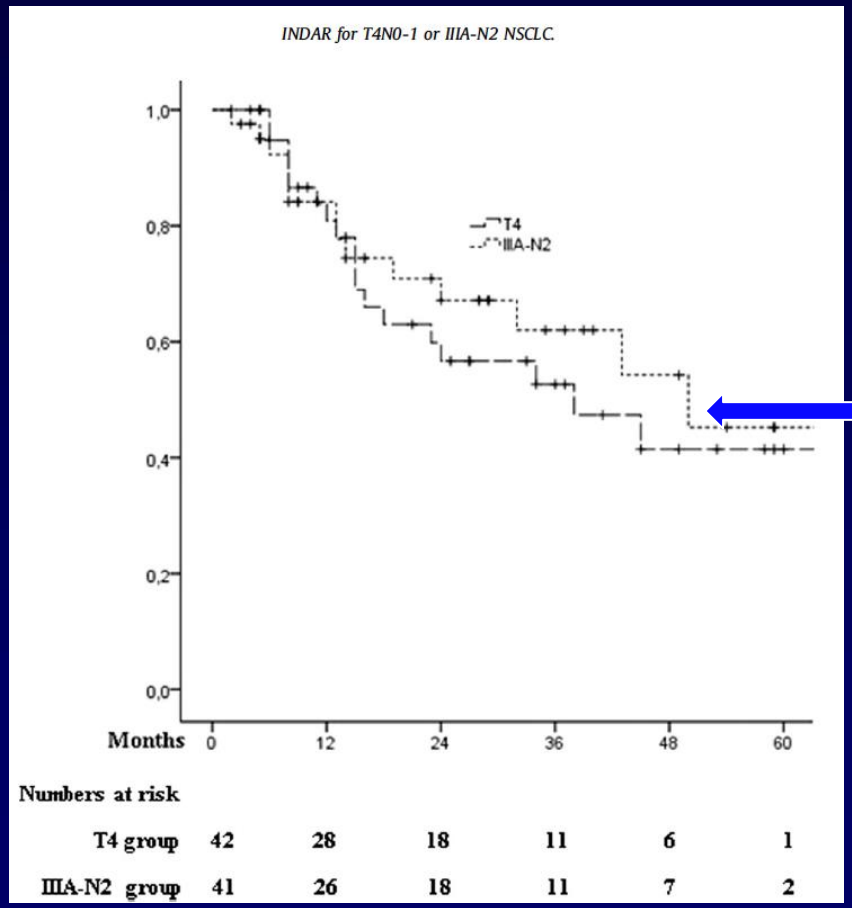
Combined-Modality With Surgery

- Concurrent chemo-RT increases likelihood of downstaging nodal disease[1]
- Most patients who are candidates for trimodality (chemo-RT-surgery) finally do not undergo surgery[1]
- Introducing a gap during preoperative concurrent chemo-RT for preoperative restaging decreases the effectiveness of a standard treatment (concurrent chemo-RT)

1. Cerfolio RJ, et al. *Ann Thorac Surg.* 2008;86(3):912-920.

CT-RT Results in Single Station IIIA-N2

- 83 patients included in 2 prospective trials
- Stage T4N0-1 or IIIA-N2 with 1 pathologic nodal station, treated with CT-RT with concurrent or sequential platinum-based chemotherapy



Median OS = 24 months
5 year OS = 24%

Reymen B, et al. *Radiother Oncol.* 2014;110(3):482-487.

Which treatment strategy would you recommend if the same patient were to have multiple sites N2 disease (size of the lymph nodes 1.5-3.5 cm)?

1. Neoadjuvant chemo → surgery
   (if PET/CT restaging = N0-1) +/- radiotherapy (RT)
2. Induction concurrent CRT (45-50 Gy) → surgery
3. Definitive concurrent CRT (60-74 Gy)
4. Definitive concurrent CRT → consolidation chemotherapy
5. Induction chemotherapy → concurrent CRT

Which Dose of Radiotherapy?

- **RTOG 0617: Dose of 74 Gy (37 fractions) was inferior compared to 60 Gy (in 30 fractions)**

- **Use of 60 Gy versus ‘intermediate high doses’ of 60-74 Gy: Analysis in 1274 patients found similar OS between 2 propensity score balanced groups**

Bradley JD, et al. *Lancet Oncol.* 2015;16(2):187-199. Rodrigues G, et al. *Int J Radiat Oncol Bios Phys.* 2015; 91(1):133-139

Which Chemotherapy in Chemo-RT?

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2015
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5, 29–33; concurrent thoracic RT[a] (preferred)*
- Cisplatin 100 mg/m^2 days 1 and 29; vinblastine 5 mg/m^2/weekly x 5; concurrent thoracic RT[b] (preferred)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)
- Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d] (nonsquamous)

- **NCCN guidelines (v 4.2015): "This regimen can be used as neoadjuvant chemotherapy**
- **Cisplatin-etoposide is the preferred regimen. If weekly carboplatin and pacitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin-radiotherapy, the treating physician should consider 2 cycles of full-dose platinum therapy after local treatment is completed"**

National Comprehensive Cancer Network. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 12 March 2015.

Cisplatin or Carboplatin-Based Chemo-RT

- SEER-Medicare registry, 1878 patients >65 years of age with unresected stage III NSCLC that received concurrent CRT (2002-2009)
- Carboplatin-based CRT was associated with similar long-term survival but lower rates of toxicity
- Adjusted rates of neutropenia, anemia, and thrombocytopenia lower among carboplatin-treated patients

Ezer N, et al. *Radiother Oncol.* 2014;112(2):272-278.

Cisplatin or Carboplatin-Based Chemo-RT

- Veterans Health Administration 1842 patients treated with concurrent radiotherapy with EP or CP from 2001-2010
- EP used in 27% (n=499) and not associated with a survival advantage
- Treatment with EP associated with more hospitalizations, infections, acute kidney disease/dehydration

EP, etoposide + cisplatin; CP, carboplatin + paclitaxel

Santana-Davilia R, et al. *J Clin Oncol.* 2015;33(6):567-574.

Symptomatic Radiation Pneumonitis (RP): A Meta-Analysis

- Individual patient meta-analysis in 836 patients treated with concurrent chemo-RT; median dose 60 Gy; median follow-up 2.3 years
- Cisplatin/etoposide (38%), carboplatin/paclitaxel (26%)
- Overall rate of RP 30% (n = 249), fatal RP in 1.9% (n = 16)

Multivariable analysis of factors predictive of symptomatic radiation pneumonitis in the validation dataset (n = 279)

	Multivariable Analysis		
Factor	OR	95% CI	*P* Value
Age (per 10-year increase)	1.38	0.95-2.01	.089
Chemotherapy regimen			<.001
Cisplatin-etoposide	1	Reference	
Carboplatin-paclitaxel	5.52	2.25-13.55	
Other	3.39	1.50-7.68	
Volume of lung receiving ≥20 Gy (V_{20})	1.07	1.03-1.11	<.001

Palma DA, et al. *Int J Radiat Oncol Biol Phys.* 2012;85(2):444-450.

Consolidation Chemotherapy is Unproven in LA-NSCLC

- Pooled analysis of 41 studies, including 7 phase III studies and 34 phase II studies with 45 arms (consolidation chemotherapy, CCT+: 25; CCT−: 20)
- Comparable for clinical stage, PS, histology, sex, and median age between the two groups
- No statistical difference in pooled mOS between **CCT+** (19.0 month; 95% CI, 17.3-21.0) and **CCT−** (17.9 month; 95% CI, 16.1-19.9). No differences in grade 3-5 toxicities in pneumonitis, esophagitis, and neutropenia
- **Addition of CCT did not lead to significant survival prolongation or risk reduction in death**

Tsujino K, et al. *J Thorac Oncol*. 2013;8(9):1181-1189.

PROCLAIM Trial: Stage III NSCLC (Closed)

RANDOMIZE

CONCURRENT

Arm A

Pemetrexed: (500 mg/m^2), IV on D1, 22 and 43
Cisplatin: (75 mg/m^2) iv after Pem on D1, 22 and 43
TRT: 66 Gy in 33 fx (daily 2 Gy fx; Mon-Fri) 3 cycles, vitamins, dexamethasone

Arm B

Etoposide: (50 mg/m^2) IV on D1-D5, D29-D33
Cisplatin: (50 mg/m^2) IV after etoposide on D1, 8, 29, 36
TRT: 66 Gy in 33 fx (daily 2 Gy fx; Mon-Fri) 2 cycles

3-5 weeks

CONSOLIDATION

Pemetrexed: 500 mg/m^2, IV on D1 every 21 days x 4 cycles, vitamins, dexamethasone

<u>Dealer's choice</u>: 2 cycles of

1. Etoposide 50 mg/m^2 days 1-5 and 29-33 and cisplatin 50 mg/m^2 days 1, 8, 29, and 36
2. Paclitaxel 200 mg/m^2 and carboplatin AUC = 6 both on days 1 and 22
3. Vinorelbine 30 mg/m^2 days 1, 8, 22 and 29 and cisplatin 75 mg/m^2 days 1 and 22

Chemo to commence with the first day of RT

ClinicalTrials.gov: Identifier: NCT00686959

Targeted Therapy and Radiotherapy in Stage III NSCLC

Phase III Trials Evaluating *EGFR* Inhibitors

- **SWOG 0023[1]: Following concurrent chemo-RT, gefitinib led to decreased survival as a result of tumor progression, and not gefitinib toxicity; unselected population**
- **RTOG 0617 trial[2]: Standard-dose vs high-dose chemo-RT paclitaxel-carboplatin ± cetuximab; use of cetuximab was associated with a higher rate of grade 3 or worse toxic effects (205 [86%] of 237 vs 160 [70%] of 228 patients; *P*<.0001).**

1. Kelly K, et al. *J Clin Oncol.* 2008;26(15):2450-2456. 2. Bradley JD, et al. *Lancet Oncol.* 2015;16(2):187-199.

How Would I Treat This Patient?

- Definitive concurrent CRT (66 Gy)
- Cisplatin/etoposide regimen
  - "EP 50/50" regimen
  - 3 weekly cisplatin 75 mg/m^2 with etoposide 120 mg/m^2 days 1-3