Stage III Non Small Cell Lung Cancer Concurrent Treatments and Toxicities

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Cancer Education Day

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- No Disclosures

Objectives

- Review the rationale for the treatment of stage III NSCLC (Concurrent Chemo Radiation).
- Review evidence and outcome of the concurrent treatment.
- Review the toxicity of concurrent treatment.
- Review the role of surgery in stage III NSCLC.
- Review the evidence of delivering higher Radiation dose in stage III NSCLC.

Patient description MR. J.H.

65-year-old man

History

Referred for hemoptysis, chronic cough, and progressive dyspnea.

Past medical history: COPD, benign prostatic hypertrophy, depression, Hepatitis C treated and cured.

Past surgical history: Appendectomy and bronchoscopy.

Meds

No drug allergies.
Current medications: Ventolin, Pantolac, Tylenol #3, Flomax, Quetiapine, Ultibro, Cromolyn.

Social

Sister who is supportive. Cocaine abuse by snorting, marijuana use 1-2 joints per week, chronic smoker, few alcoholic drinks per week.

FHx

Nothing notable

PMHx

Physical examination unremarkable

Patient Description Mr. J.H.

- CXR: Opacity in the Left lung, concerning for cancer.
- Ct chest: 6.7 cm speculated mass in the left upper lobe abutting the pleural surface with concern for extension into the mediastinal fat. There were enlarged left hilar, AP window and subaortic lymph nodes.
- CT head: Negative for mets.
- Patient is referred to Lung DAP.

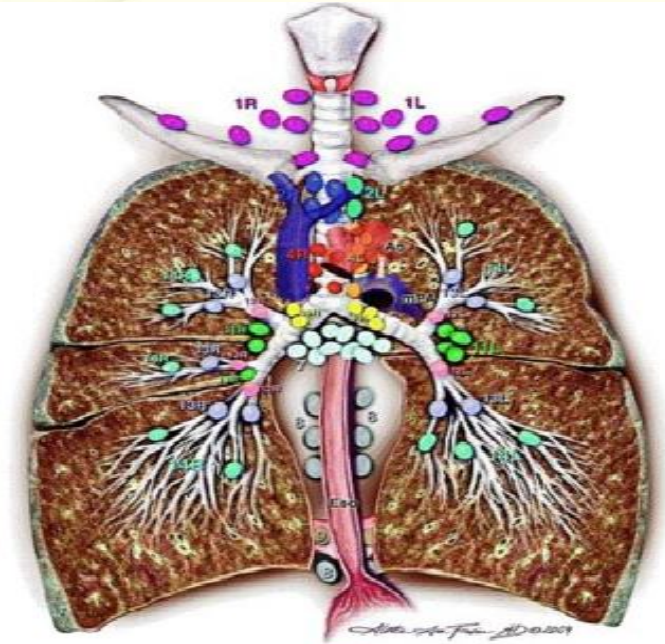
Patient Description Mr. J.H

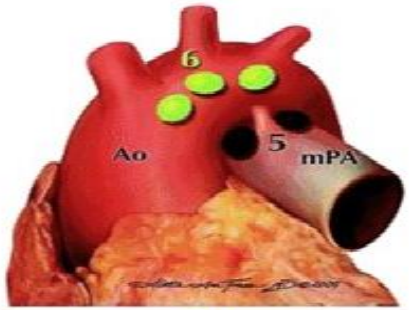
- Bronchoscopy from left upper lobe and 11 L confirmed adenocarcinoma, EGFR negative, ALK negative and PDL1 > 50%.
- Spirometry revealed normal lung function with FEV1 of 85% and diffusion capacity of 90%.
- PET scan: metabolically active left upper lobe mass 6.1 by 5.5 cm, with SUV of 12.5 within malignant range. Hypermetabolic left hilar, stations 5 and 6 mediastinal nodes consistent with malignant involvement. No evidence of distant metastasis.

TNM Staging

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Mediastinal Nodes





Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone

- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Management

- History and Physical (Comorbidities, weight loss, ECOG PS, smoking, etc.)
- CXR, CT chest, PET scan
- Brain imaging (CT or MRI)
- PFT
- Other imaging: bone scan, CT Abd/Pelvis, etc.
- Biopsy: CT guided or bronchoscopy (EBUS).

Radiation Therapy Process

- CT simulation
- 4D CT simulation
- Patient immobilization
- Treatment planning:

  -PET fusion

  -Target volume and organs at risk delineation,

  -Dose calculation, distribution, fields designing
- Treatment delivery
- Treatment verification (IGRT-CBCT)

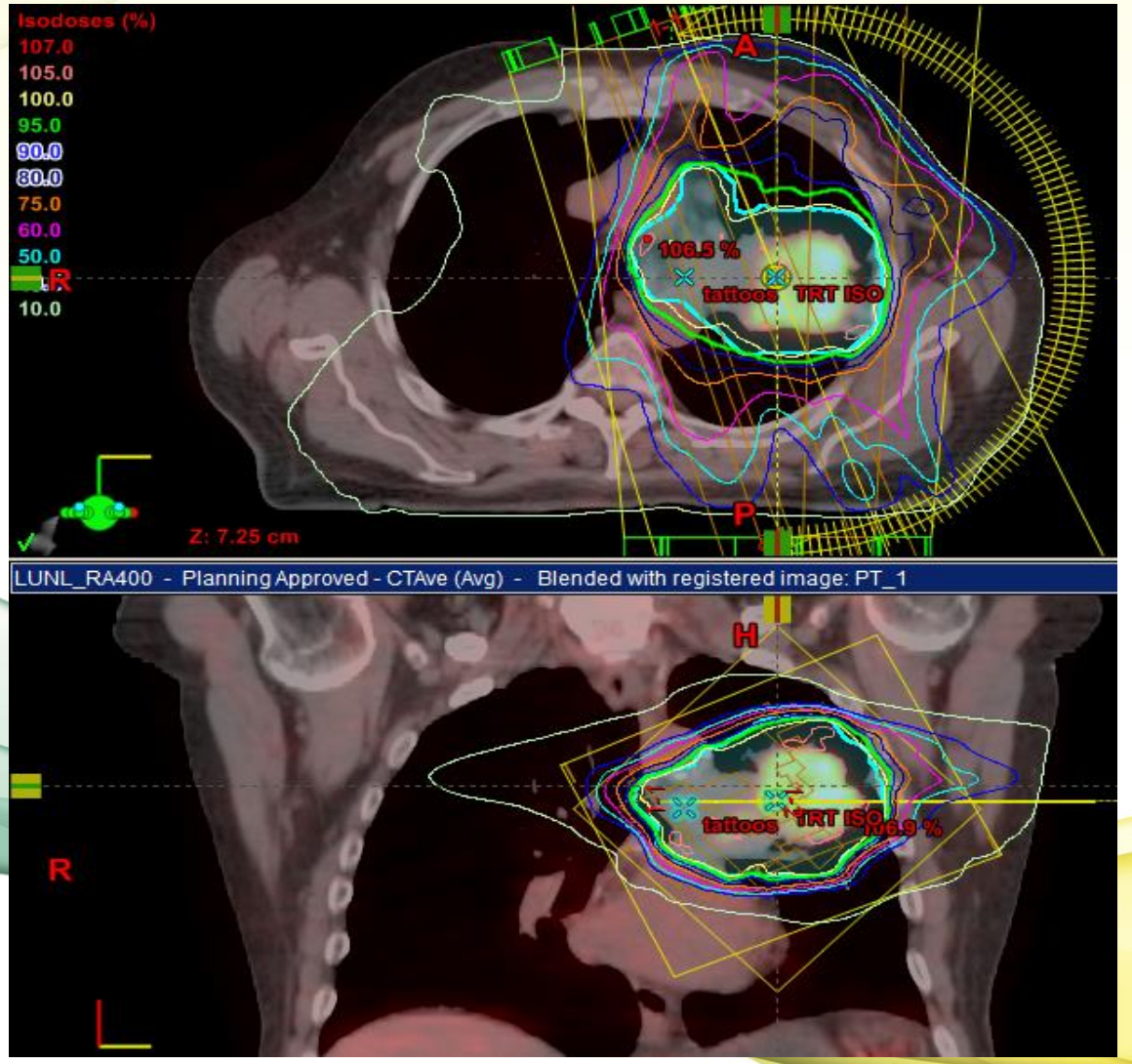
Concurrent Chemo Radiation

- Radiation 60Gy/30 fractions/6 weeks
- Cisplatin+ etoposide week 1 and 5 of Radiation

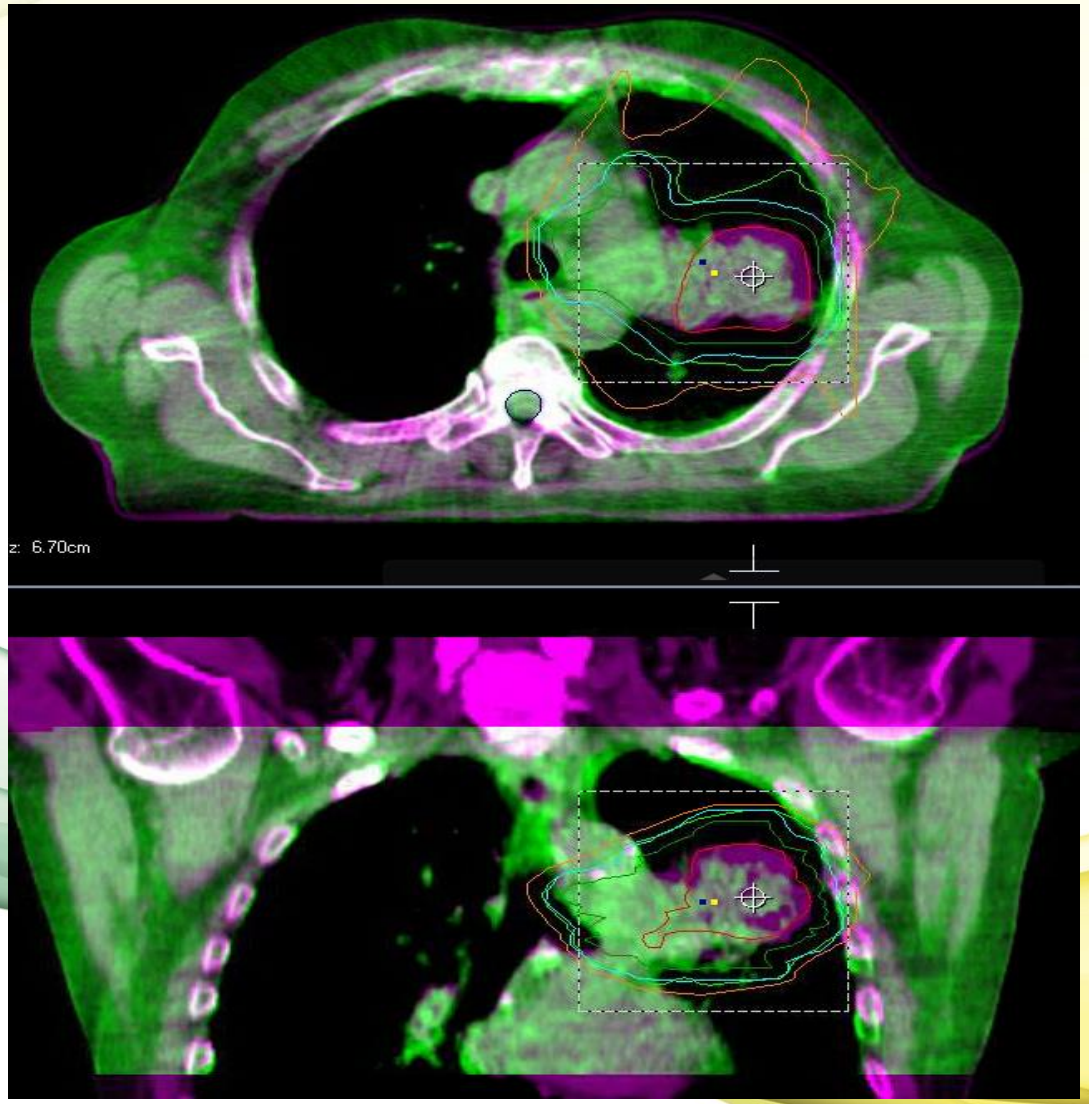
-Management of side effects during treatment

-CBC monitoring during treatment.

Radiation Treatment Delivery



Cone Beam CT During Treatment



Radiation Toxicity

- Fatigue
- Radiation dermatitis
- Cough
- Esophagitis
- Radiation pneumonitis
- Heart injury
- Brachial plexopathy (apical tumors)
- Spinal cord injury

Chemotherapy Toxicity

- Hair loss
- Mouth sores
- Nausea and vomiting
- Anemia
- Neutropenia
- Thrombocytopenia
- Fatigue
- Renal toxicity
- Ototoxicity

Treatment Challenges in Stage III NSCLC

- Tumor heterogeneity within NSCLC.
- Requirement to simultaneously control the disease locoregionally and systemically.
- Treatment related toxicity.
- Patient related factors (weight loss, PS, age, comorbidities).

Rationale for Concurrent ChemoRadiation

- Tumor response enhancement:

  -Chemo can modify/add DNA damage caused by Radiation and enhance the effect.

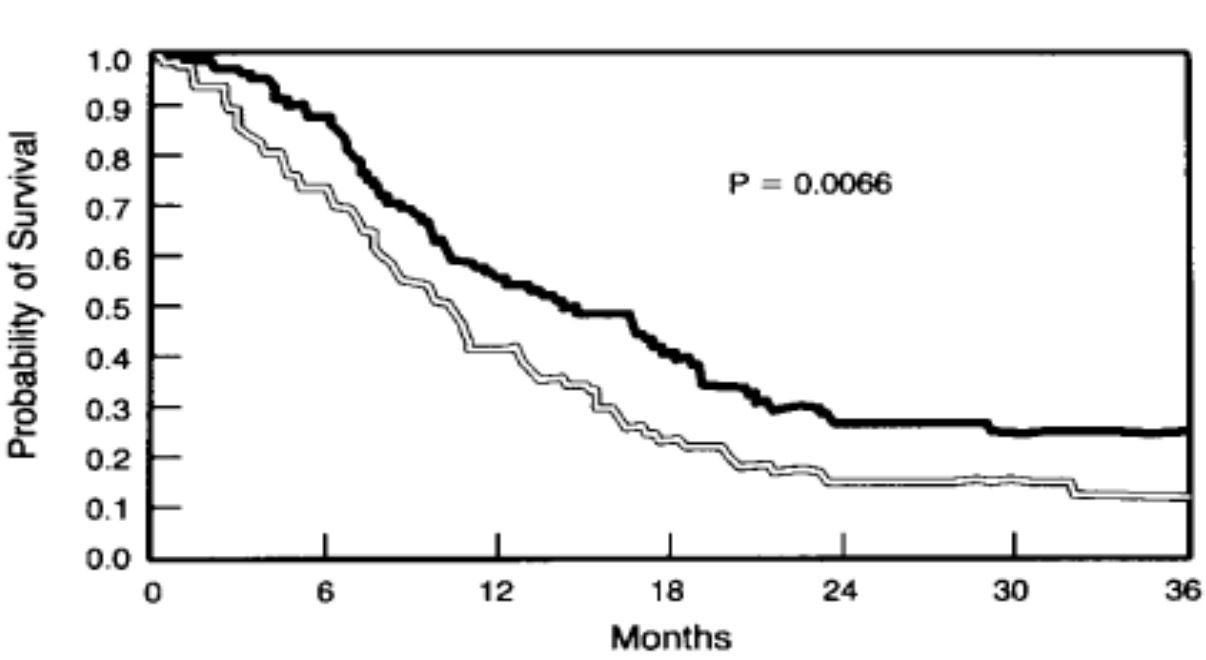
- Spatial cooperation:

  -Radiation effect predominantly at primary and regional sites.

  -Chemo effect on distant sites (micromets)

Induction (Sequential) Chemo Followed by Radiation vs. Radiation

Dillman et al NEJM Oct 1990



Group	Alive	Died	Total	Median Survival (mo)
1	20	58	78	13.8
2	9	68	77	9.7

Concurrent Chemo Radiation is Superior to Sequential Chemo>Radiation

Table 1 Phase III Trials Assessing Chemotherapy and Radiation Therapy in the Treatment of LA-NSCLC

Trials	Accrual Period	*n*	Arms	RT Dose (Gy/F)	Response	MST (mo)	Long-Term Survival	Toxicities Pneumonitis (G3+)	Esophagitis (G3+) (%)
WJLCG	1992-1994	314	MVP-RT	56/28	CR 2.6% and PR 81.4%	16.5*	15.8% (5 y)	2%	4
Furuse et al[8]			MVP × 2 → RT		CR 1.3% and PR 65.1%	13.3	8.9% (5 y)	2%	3
RTOG 9410	1994-1998	407	PVbl-RT	63/34	CR 42% and PR 28%	17.0*	16% (5 y)	4%	23
Curran et al[9]			PVbl × 2 → RT		CR 30% and PR 32%	14.6	10% (5 y)	9%	4
GLOT-GFPC NPC 95-10	1996-2000	205	EP-RT → PVr × 3	66/33	CR 9% and PR 40%	16.3	20.7% (4 y)	5%	32
Fournel et al[10]			PVr × 3 → RT		CR 4% and PR 50%	14.5	18.6% (4 y)	11%	3
FNCLCC and IFCT	1996-2003	427	PVr × 2 → Cb-RT	66/33	NR	14	NR	NR	3.4
Gervais et al[11]			PVr × 2 → Cb-RT			11			4.1
Czech Republic study		102	PVr × 1 → PVr-RT	60/30	CR 21% and PR 59%	16.6*	18.6% (3 y)	4%	18
Zatloukal et al[12]			PVr × 4 → RT		CR 17% and PR 30%	12.9	9.5% (3 y)	2%	4
CTRT99/97	1997-2003	214†	TCb × 2 → TCb-RT	60	CR 12.1% and PR 34.3%	18.7	NR	0	12.8
Huber et al[13]			TCb × 2 → RT		CR 5.3% and PR 33.6%	14.1		0	6.5
CALGB/ECOG	NR	283	PVbl × 2 → Cb-RT	60/30	CR 18% and PR 40%	13.4	13% (4 y)	1%	12
Clamon et al[14]			PVbl × 2 → RT		CR 10% and PR 48%	13.5	10% (4 y)	5%	4
EORTC 08972	1997-2003	158	GP × 2 → P-RT‡	66/24	CR 12.1% and PR 34.3%	16.5	34% (3 y)	18%	14
Belderbos et al[15]			GP × 2 → RT		CR 5.3% and PR 33.6%	16.2	22% (3 y)	14%	5

Abbreviations: Cb, carboplatin; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EP, cisplatin-etoposide; FNCLCC, French National Federation of Cancer Centers; GLOT-GFPC NPC 95-10, Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-The French Pneumology Group NPC 95-10; GP, gemcitabine-cisplatin; IFCT, French intergroup for thoracic oncology; NR, not reported; P, cisplatin; PR, partial response; PVbl, cisplatin-vinblastine; PVr, cisplatin-vinorelbine; TCb, paclitaxel-carboplatin; WJLCG, West Japan Lung Cancer Group.

*Significantly different ($P < 0.05$).

†Patients were randomly assigned.

‡Low-dose cisplatin (6 mg/m^2).

Meta-Analysis of Concomitant Versus Sequential ChemoRadiation

Auperin et al JCO May 2010

- 1205 pts, 6 trials.
- Median FU 6 years.
- The primary outcome was overall survival.
- Secondary outcomes were progression-free survival, cumulative incidences of locoregional and distant progression, and acute toxicity.

Meta-Analysis of Concomitant Versus Sequential ChemoRadiation

Auperin et al JCO May 2010

- Significant improvement in overall survival with concurrent ChemoRadiation compared to sequential treatment,5.7% (18.1% to23.8%) at 3 years, and 4.5% (10.6% to15.1%) at 5 years. HR=0.84,95%CI=0.740.95,*P*=0.004.
- For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; *P*=0.07), in favor of concurrent treatment.
- Concurrent treatment decreased locoregional progression by 6% (34.1% to28.1%) at 3 years and by 6.1% (35%to28.9%) at 5 years (HR, 0.77; 95% CI, 0.62 to 0.95; *P*=0.01).

Meta-Analysis of Concomitant Versus Sequential ChemoRadiation

Auperin et al JCO May 2010

- No significant effect on development of distant mets (HR, 1.04; 95% CI, 0.86 to 1.25; *P*=0.69).
- Concurrent treatment increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; *P*=0.001).
- There was no significant difference in acute pulmonary toxicity.
- Concurrent radiochemotherapy, as compared with sequential radiochemotherapy, improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control, but at the cost of manageable increased acute esophageal toxicity.

Meta Analysis Concurrent vs Sequential ChemoRadiation

O'Rourke et al-Cochrane database sys review 2010

- 6 Trials, 1024 patients analyzed.
- Significant 10% Absolute OS benefit in favor of concurrent treatment at 2 years, HR=0.74,95%CI:0.62-0.89
- Relative risk of death 4% vs 2%,not significant (RR 2.02,95%CI:0.90-4.52)
- Higher esophageal toxicity in concurrent treatment RR=4.96,95%CI=2.17-11.37.

Intergroup 0139 Study

Albain et al Lancet Aug 2009

- ?Role of surgery after chemoradiation
- Patients with stage T1-3pN2M0 NSCLC were randomized before induction chemoRT
- 396 patients

Intergroup 0139 Study

Albain et al Lancet Aug 2009

396 patients

- Arm 1: 2 cycles of cisplatin-etoposide and Radiation 45Gy/25 fractions, if no progression, followed by Thoracotomy, then 2 additional chemo cycles.

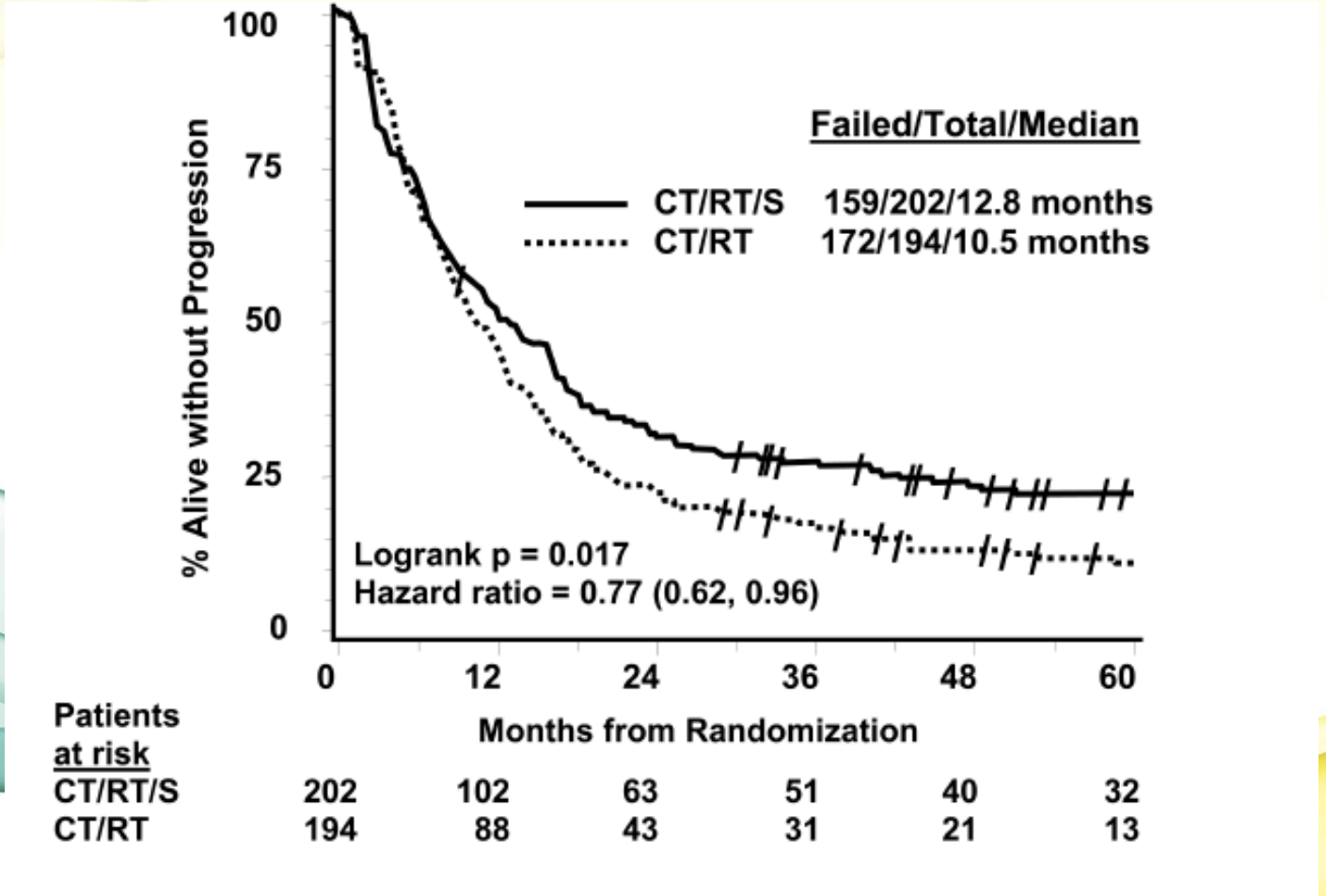
VS

- Arm 2: 2cycles of cisplatin-etoposide and Radiation 45Gy/25 fractions, if no progression, continue to 61Gy with additional chemo

- The primary endpoint was overall survival (OS)

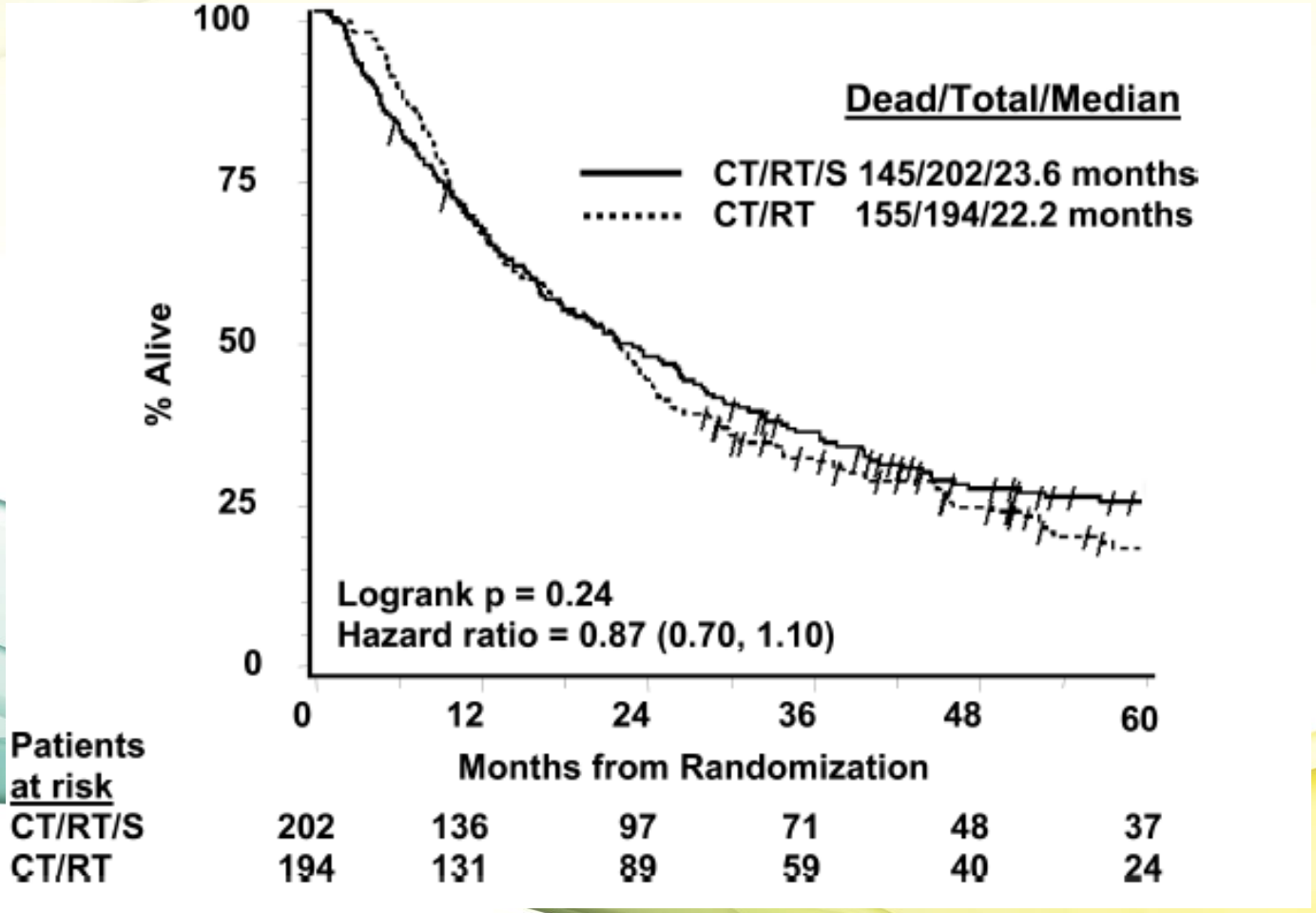
5year DFS

Albain et al Lancet Aug 2009



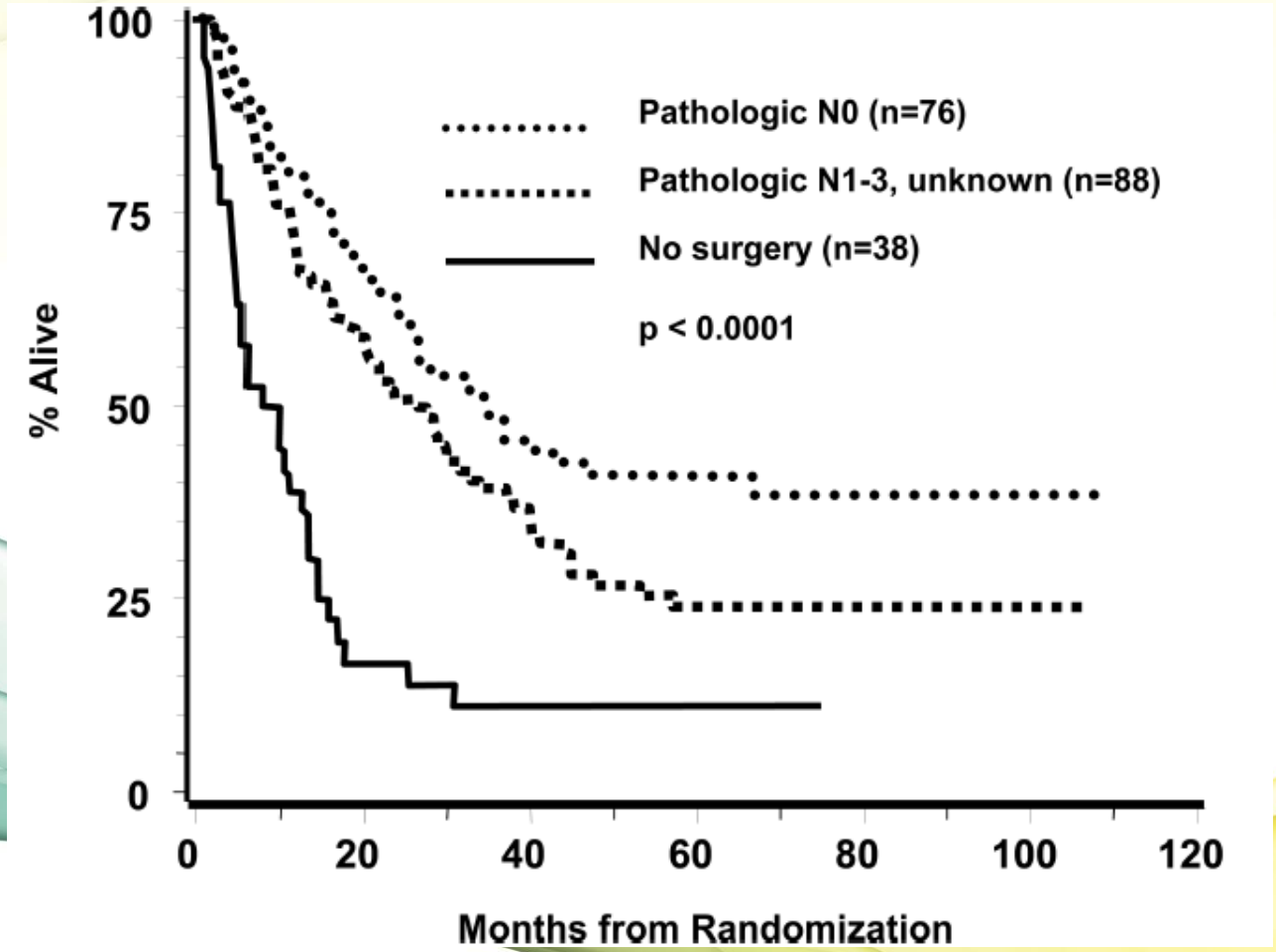
Overall Survival

Albain et al Lancet Aug 2009



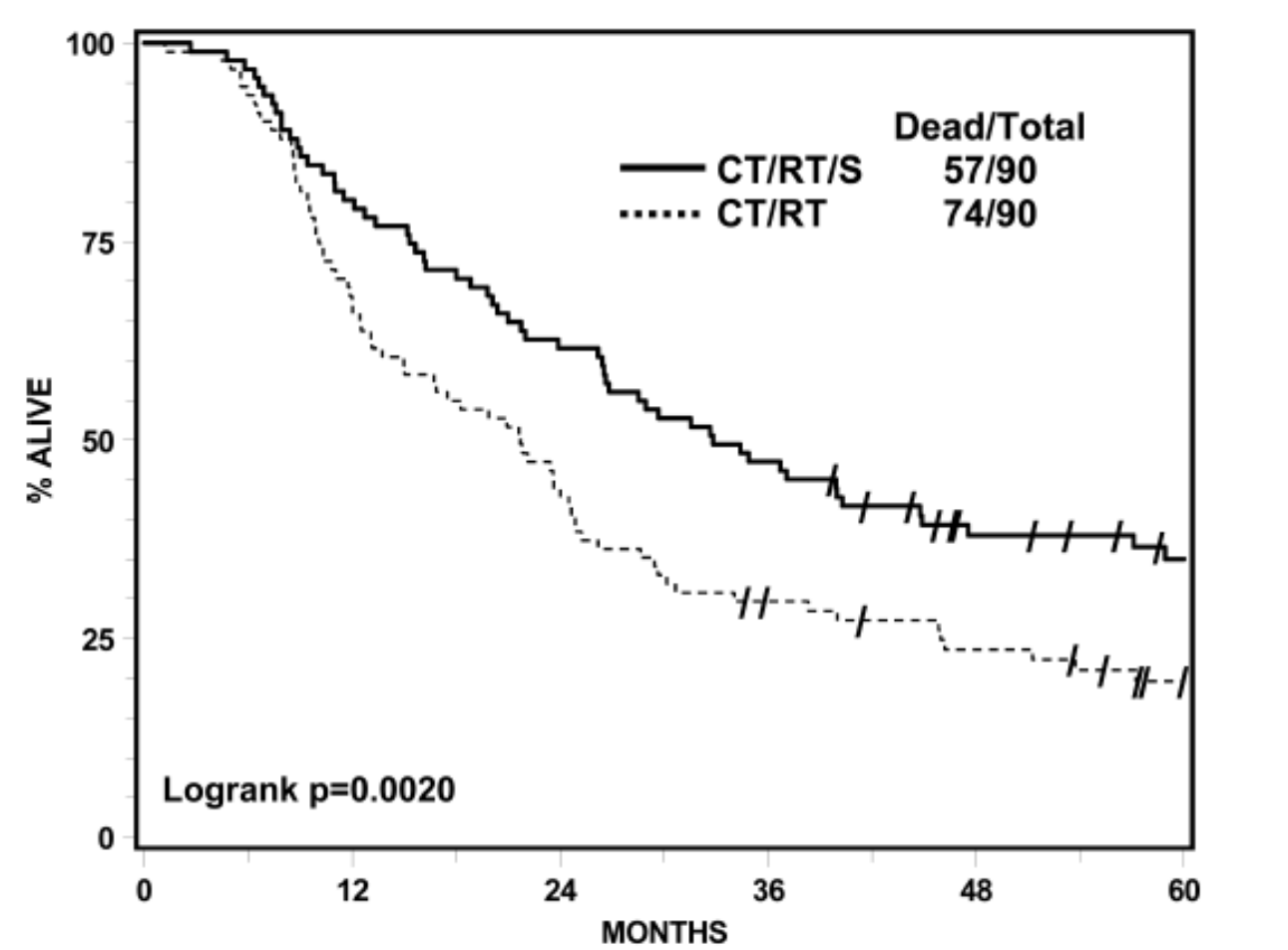
OS in arm1 by Pathologic Subtype Following Thoracotomy

Albain et al Lancet Aug 2009



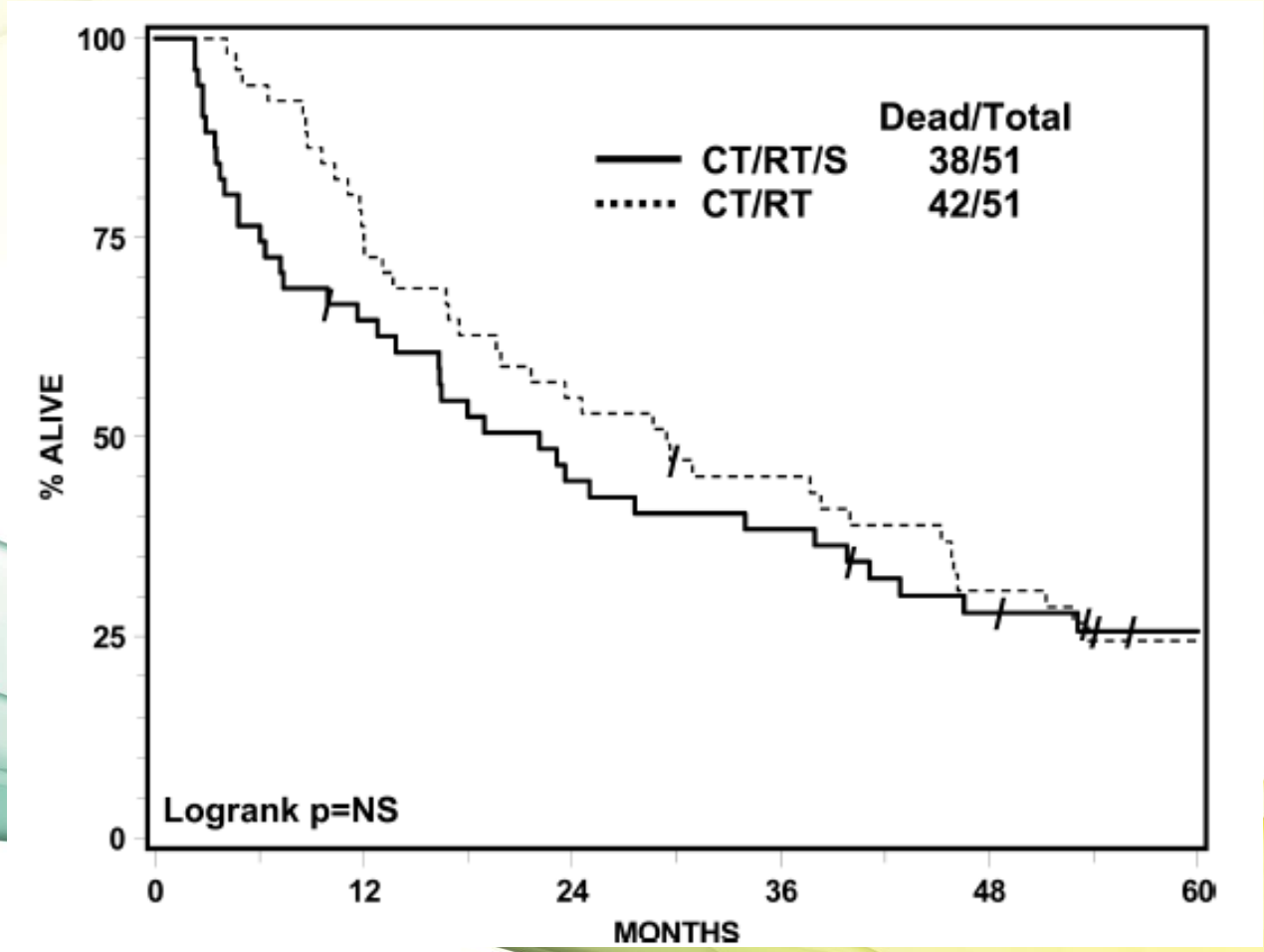
OS Lobectomy Subset in Arm 1 vs Matched Cohort in Arm 2

Albain et al Lancet Aug 2009



OS Pneumonectomy Subset in Arm 1 vs Matched Cohort in Arm 2

Albain et al Lancet Aug 2009



Worst Toxicity Anytime

Albain et al Lancet Aug 2009

Toxicity	Arm 1 (n = 202)			Arm 2 (n = 194)		
	Grade			Grade		
	3	4	5*	3	4	5*
Leukopenia	82	15	0	76	31	0
Neutropenia	54	23	0	47	33	0
Anemia	25	1	0	42	5	0
Thrombocytopenia	10	4	0	12	11	0
Worst hematologic toxicity per patient	89	28	0	75	50	0
Nausea and/or emesis	17	3	0	37	7	0
Neuropathy	10	0	0	4	3	0
Esophagitis	17	3	0	37	7	0
Stomatitis and/or mucositis	6	0	0	4	1	0
Pulmonary*	17	1	13	24	4	3
Other gastrointestinal or renal	6	4	0	5	2	0
Cardiac	4	3	3**	7	2	0
Miscellaneous infection	5	1	0	8	0	0
Hemorrhage	0	0	1	0	1	0
Fatigue	11	0	0	9	0	0
Anorexia	3	0	0	4	3	0
Allergy	1	0	0	3	0	0

Interpretation

Albain et al Lancet Aug 2009

- There was no significant survival advantage to surgery after chemoRT, despite improved PFS.
- Both chemoRT with definitive RT and chemoRT followed by resection (preferably lobectomy) are options for patients with stage IIIA(N2) NSCLC.
- In general surgery following chemoRT for stage III NSCLC is not universally acceptable, should be discussed in multidisciplinary approach and offered on case by case basis.

Radiation Dose Escalation
RTOG 0617
Bradley et al Lancet Oncology 2015

- Phase III multi-centre, 434 patients, Nov. 2007-Nov. 2011.
- 2 cycles Carbo/paclitaxel concurrently with RT 60Gy, then 2 add cycles of chemo,+/- maintenance cetuximab.

VS

- 2 cycles Carbo/paclitaxel concurrently with RT 74Gy, then 2 add cycles of chemo,+/- maintenance cetuximab.

Radiation Dose Escalation
RTOG 0617
Bradley et al Lancet Oncology 2015

- Median overall survival was 28.7 months (95% CI 24.1–36.9) for patients who received standard-dose
- Radiotherapy and 20.3 months (17.7–25.0) for those who received high-dose radiotherapy (hazard ratio [HR] 1.38, 95% CI=1.09–1.76; p=0.004).
- Median follow-up for the cetuximab comparison was 21.3 months (IQR 23.5–29.8).
- Median overall survival in patients who received cetuximab was 25.0 months (95% CI 20.2–30.5) compared with 24.0 months (19.8–28.6). In those who did not (HR 1.07, 95% CI 0.84–1.35; p=0.29).

Radiation Dose Escalation
RTOG 0617

Bradley et al Lancet Oncology 2015

- No statistical differences in grade 3 or worse toxic effects between radiotherapy groups.
- Cetuximab was associated with a higher rate of grade 3 or worse toxic effects (205 [86%] of 237 *vs* 160 [70%] of 228 patients; $p<0.0001$).
- There were more treatment-related deaths in the high-dose chemoradiotherapy and cetuximab groups (radiotherapy comparison: 8 *vs* 3 patients; cetuximab comparison: 10 *vs* 5 patients.
- There were no differences in severe pulmonary events between treatment groups.
- Severe esophagitis was more common in patients who received high-dose chemoradiotherapy than in those who received standard-dose treatment (43 [21%] of 207 patients *vs* 16 [7%] of 217 patients; $p<0.0001$).

Radiation Dose Escalation
RTOG 0617

Bradley et al Lancet Oncology 2015

- Interpretation:

-74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than 60 Gy plus concurrent chemotherapy for patients with stage III non-small-cell lung cancer, and might be potentially harmful.

-Addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in overall survival for these patients.

Conclusions

- Concurrent chemoradiation is the standard of care for medically fit stage III NSCLC.
- Platin based chemo combination plus 60Gy is most commonly used.
- Toxicity is tolerated and reversible, death rate from treatment is fortunately low.
- 5 year survival are still low (20%)
- The role of surgery after concurrent treatment is controversial, there is DFS advantage but no OS advantage.
- Rates of recurrence are still high, especially distant relapse
- ? Role of new/novel/advanced systemic therapy, radiation therapy and surgical techniques.

Thank You

Immune Checkpoint Therapy for Stage III NSCLC

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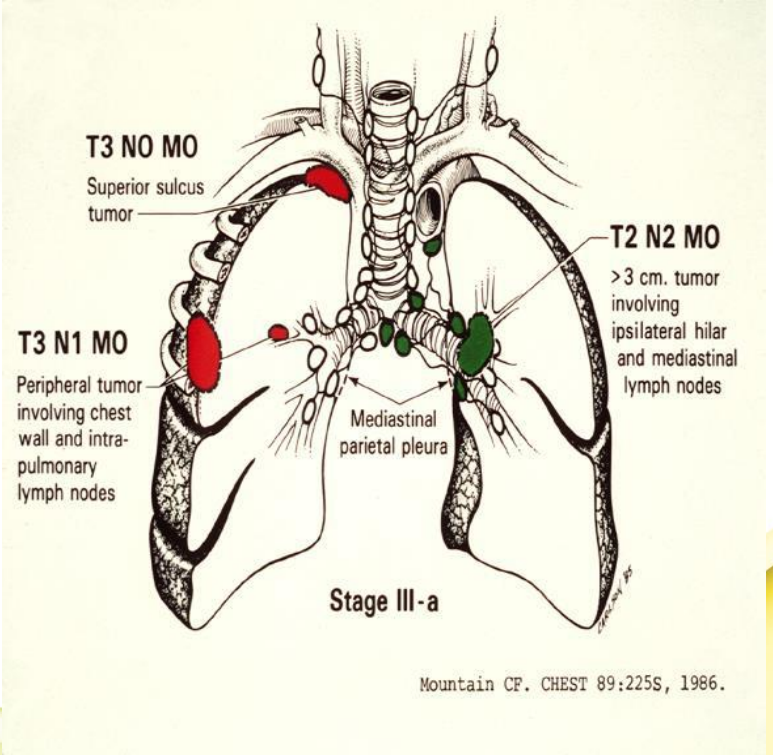
Stage 3 Disease

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b



Unmet Needs in Locally Advanced Stage III Unresectable NSCLC

Approximately, **28,600 patients in Canada** will develop lung cancer in 2017

Nearly 85-90% of lung cancers are classified as non-small cell lung cancer (NSCLC)

25-40% of patients with NSCLC will present with locally advanced disease

Approximately 30% of these patients have unresectable tumors.

Options for Treatment of Stage III Disease

- Surgery alone
- Surgery → chemotherapy
- Chemotherapy → radiotherapy
- Chemotherapy → surgery
- Chemo/radiotherapy → surgery
- Chemo/radiotherapy
- Chemotherapy → chemo/radiotherapy
- Chemotherapy / radiotherapy → chemotherapy

Cancer Care Ontario: Treatment of Patients with Stage III (N2 or N3) Non-Small Cell Lung Cancer

- Concurrent chemoradiation should be used for curative-intent treatment of patients with unresectable, lymph node-positive (N2 or N3) stage III NSCLC followed by active surveillance.
- In patients with potentially resectable (single-station, micro metastatic disease to N2) NSCLC, either definitive chemoradiation therapy or induction therapy followed by surgery (preferably lobectomy) is recommended and should be discussed at a multidisciplinary case conference.

Prognosis

- Median progression-free survival (PFS) is 10.5 months after completing Chemo-radiation.
- Five-year survival is between 15% and 20%.
- There have been no major advances in locally advanced NSCLC for several years; thus, there is significant unmet need for novel therapeutic approaches to boost survival beyond cCRT
- PACIFIC is the first randomized phase III study to evaluate immune checkpoint blockade in patients with stage III, locally advanced, unresectable NSCLC

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

Durvalumab 10 mg/kg q2w for up to 12 months N=476

2:1 randomization, stratified by age, sex, and smoking history N=713

Placebo 10 mg/kg q2w for up to 12 months N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.

ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

PACIFIC: Baseline Characteristics

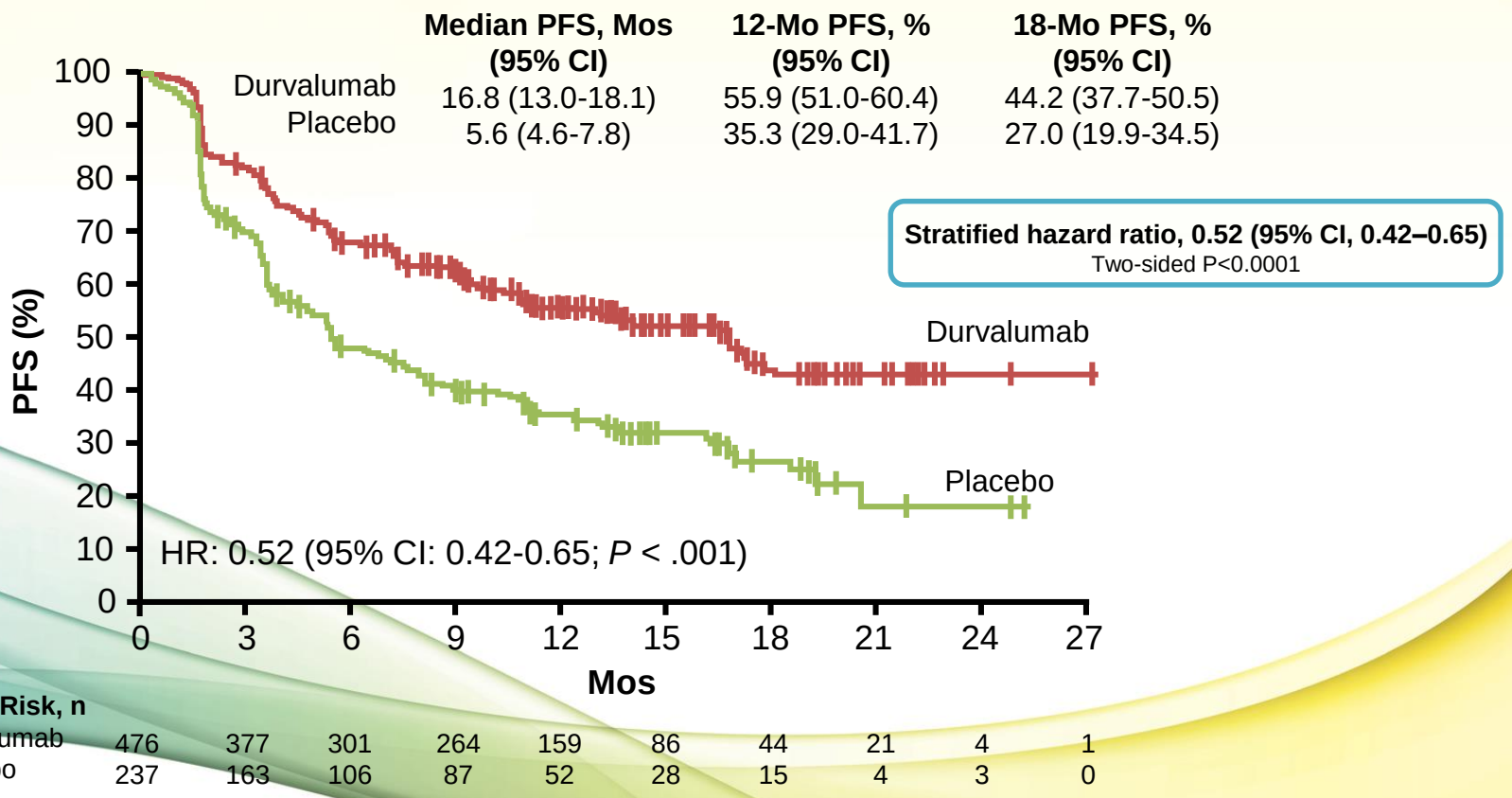
- Small number of never-smokers enrolled on study

Characteristic, %	Durvalumab (n = 476)	Placebo (n = 237)
Median age, yrs (range)	64 (31-84)	64 (23-90)
▪ Age ≥ 65 yrs, %	45.2	45.1
Male sex	70.2	70.0
WHO PS 0/1	49.2/50.4	48.1/51.5
Smoking status		
▪ Current	16.6	16.0
▪ Former	74.4	75.1
▪ Never	9.0	8.9
Disease stage		
▪ IIIA	52.9	52.7
▪ IIIB	44.5	45.1
▪ Other	2.5	2.1
Histology, squamous/ nonsquamous	47.1/52.9	43.0/57.0

Characteristic, %	Durvalumab (n = 476)	Placebo (n = 237)
PD-L1		
▪ < 25%	39.3	44.3
▪ ≥ 25%	24.2	18.6
▪ Unknown	36.6	37.1
Prior CT, induction/cCRT	25.8/99.8	28.7/99.6
Prior RT		
▪ < 54 Gy	0.6	0
▪ ≥ 54 to ≤ 66 Gy	92.9	91.6
▪ > 66 to ≤ 74 Gy	6.3	8.0
Best response to prior cCRT		
▪ CR	1.9	3.0
▪ PR	48.7	46.8
▪ SD	46.6	48.1

Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

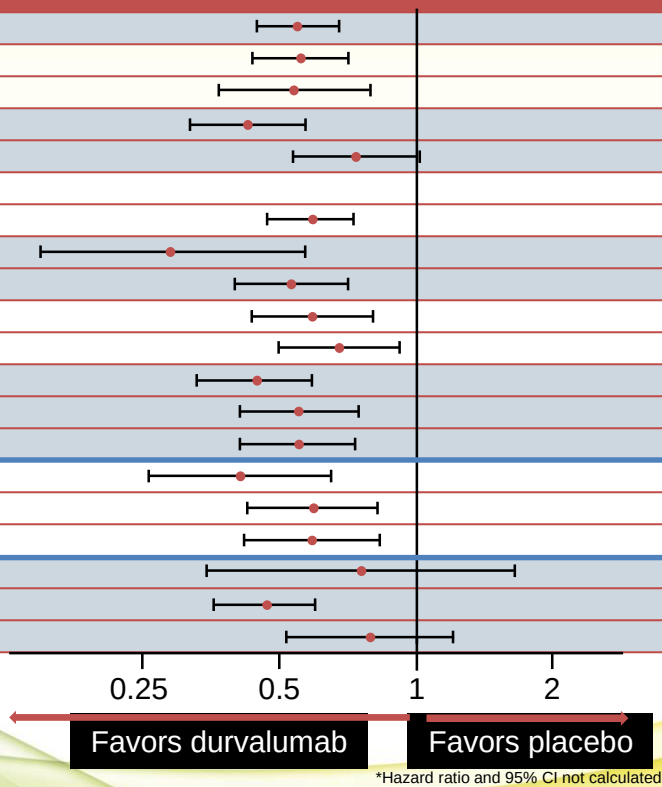
PACIFIC: PFS in ITT Population (Primary Endpoint)



Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

PFS Subgroup Analysis

		Durvalumab No. of patients	Placebo No. of patients	Unstratified HR* (95% CI)
	All patients	476	237	0.55 (0.45–0.68)
Sex	Male	334	166	0.56 (0.44–0.71)
	Female	142	71	0.54 (0.37–0.79)
Age at randomization	<65 years	261	130	0.43 (0.32–0.57)
	≥65 years	215	107	0.74 (0.54–1.01)
Smoking status	Smoker	433	216	0.59 (0.47–0.73)
	Non-smoker	43	21	0.29 (0.15–0.57)
Disease stage	Stage IIIA	252	125	0.53 (0.40–0.71)
	Stage IIIB	212	107	0.59 (0.44–0.80)
Histology	Squamous	224	102	0.68 (0.50–0.92)
	Non-squamous	252	135	0.45 (0.33–0.59)
Best response to cCRT	CR	9	7	–
	PR	232	111	0.55 (0.41–0.75)
	SD	222	114	0.55 (0.41–0.74)
PD-L1 status	≥25%	115	44	0.41 (0.26–0.65)
	<25%	187	105	0.59 (0.43–0.82)
	Unknown	174	88	0.59 (0.42–0.83)
EGFR status	Mutant	29	14	0.76 (0.35–1.64)
	Wild-type	315	165	0.47 (0.36–0.60)
	Unknown	132	58	0.79 (0.52–1.20)



*Hazard ratio and 95% CI not calculated if the subgroup has less than 20 events.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; EGFR, epidermal growth factor receptor

PACIFIC: Durvalumab Safety Summary

AE, n (%)	Durvalumab* (n = 475)	Placebo (n = 234)
Any-grade all-cause AEs	460 (96.8)	222 (94.9)
▪ Grade 3/4	142 (29.9)	61 (26.1)
▪ Grade 5	21 (4.4)	13 (5.6)
▪ Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs	322 (67.8)	125 (53.4)
Serious AEs	136 (28.6)	53 (22.6)
Any-grade immune-mediated AEs	115 (24.2)	19 (8.1)
▪ Grade 3/4	16 (3.4)	6 (2.6)

*Included 2 pts randomized to placebo but who received ≥ 1 dose of durvalumab.

Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929. Paz-Ares L, et al. ESMO 2017. Abstract LBA1_PR.

Slide credit: clinicaloptions.com

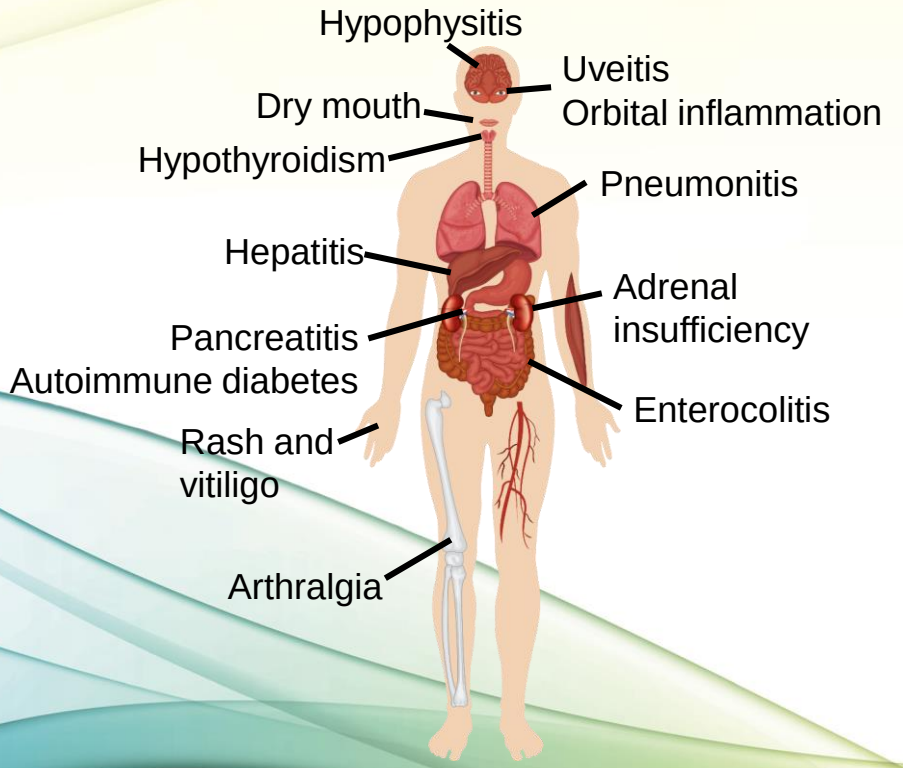
PACIFIC: Most Frequent AEs

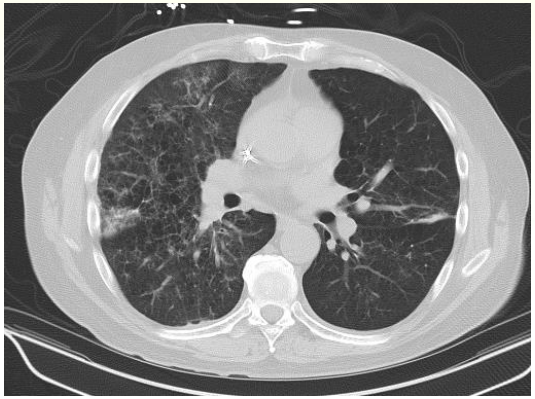
Any-Cause AEs in ≥ 10% of Pts in Either Arm,* n (%)	Durvalumab† (n = 475)		Placebo (n = 234)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis‡	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0

*Additional AEs in ≥ 10% of pts in either arm included: pruritus, rash, upper respiratory tract infection, constipation, hypothyroidism, headache, asthenia, back pain, musculoskeletal pain, anemia. †Included 2 pts randomized to placebo but who received ≥ 1 dose of durvalumab. ‡Assessed by investigators with sponsor review and adjudication.

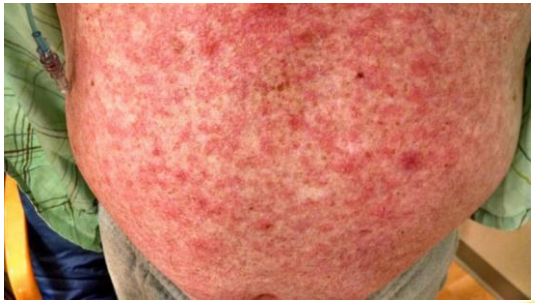
Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929. Paz-Ares L, et al. ESMO 2017. Abstract LBA1_PR.

Immune-Related AEs Seen With Immune Checkpoint Inhibitors





Pneumonitis: ground-glass opacity



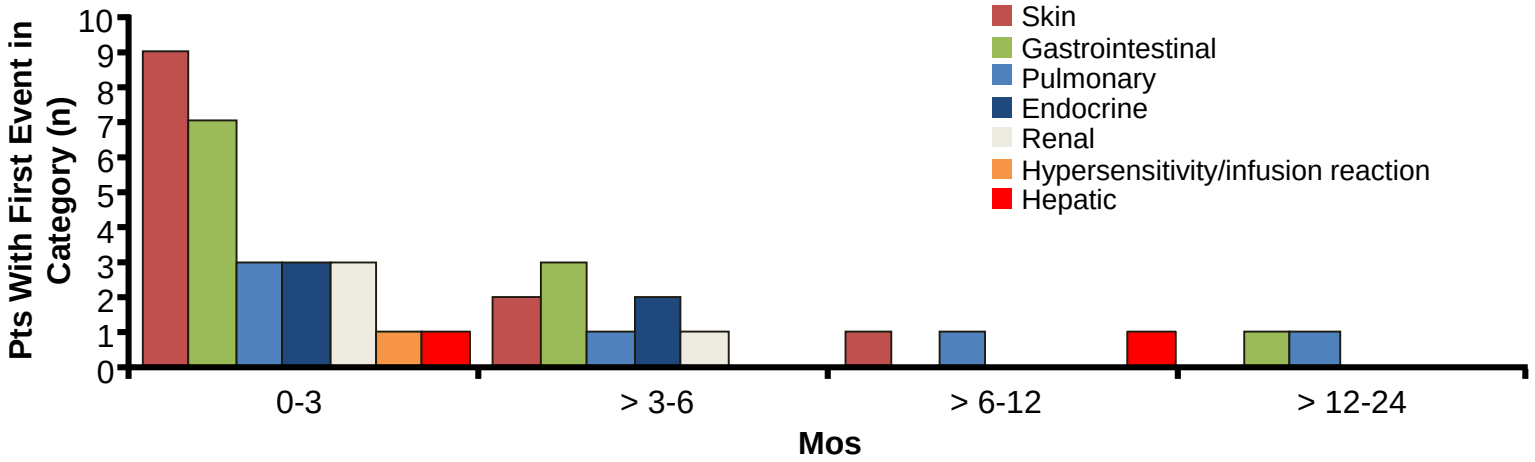
Autoimmune dermatitis

Slide credit: clinicaloptions.com

Michot JM, et al. Eur J Cancer. 2016;54:139-148. Photos courtesy of Elizabeth R. Plimack, MD, MS.

Time to Onset of First Treatment-Related AE With Nivolumab (Any Grade)

- Majority of treatment-related irAEs occurred within first 3 mos of treatment



Pts still on study, n	131	112	85	52
Pts still on treatment, n	131	73	51	25
Total pts with first event, n	24	6	2	1

Reckamp K, et al. WCLC 2015. ORAL02.01.

Slide credit: clinicaloptions.com

Durvalumab Dose Interruption Recommendations

AE	Withhold Durvalumab	Discontinue Durvalumab
Pneumonitis	Grade 2	Grade 3/4
Hepatitis	ALT/AST > 3 to ≤ 8 x ULN ***or*** total bilirubin > 1.5 to ≤ 5 x ULN	ALT/AST > 8 x ULN ***or*** total bilirubin > 5 x ULN ***or*** concurrent ALT/AST > 3 x ULN **and** total bilirubin > 2 x ULN without other cause
Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, type I diabetes mellitus	Grade 2-4	--
Nephritis	Creatinine > 1.5 to 3 x ULN	Creatinine > 3 x ULN
Rash/dermatitis	Grade 2 for > 1 wk ***or*** grade 3	Grade 4
Colitis	Grade 2	Grade 3/4
Infection	Grade 3/4	--
IRR*	--	Grade 3/4
Other	--	Persistent grade 2/3 AEs not recovering to grade ≤ 1 within 12 wks of last dose ***or*** inability to taper corticosteroid within 12 wks of last dose ***or*** recurrent grade 3/4 AE

*For grade 1/2 IRRs, interrupt or slow infusion rate.

Durvalumab [package insert]. 2018.

Slide credit: clinicaloptions.com

General Principles of Immune-Related Toxicity Management—Treatment

- Management generally based on severity of symptoms
  - Grade 1: close monitoring, symptomatic care, ± withhold drug
  - Grade 2: withhold drug, consider redose if toxicity resolves to grade ≤ 1; may administer low-dose corticosteroids (initial prednisone dose of 0.5-1 mg/kg/day or equivalent)
  - Grade 3: withhold drug, initiate high-dose corticosteroids (prednisone 1-2 mg/kg/day or methylprednisolone IV 1-2 mg/kg/day); may offer infliximab if no symptom improvement within 48-72 h of initiating corticosteroids; taper corticosteroids over at least 4-6 wks
  - Grade 4: discontinue drug
  - Exception: Adrenal insufficiency and hypothyroid require replacement hydrocortisone and levothyroxine, respectively, without use of steroids[2

Conclusions

- Durvalumab currently FDA approved for unresectable stage III NSCLC that has not progressed after concurrent platinum-based CT + RT

1. Durvalumab [package insert]. 2018. 2. Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.

RADIATION PNEUMONITIS

Javaria Sohaib

Agenda

- Prevalence
- Pathophysiology
- Risk Factors
- Phases of Radiation Injury
- Symptoms and Signs
- Investigations
- Treatment
- Prognosis

Prevalence

- Ranges by cancer, and is much more common radiographically than clinically
- Breast Ca
  - 0-10% Clinically
  - 25-40% Radiographically
- Lung Ca
  - 5-15% Clinically
  - 66% Radiographically

Pathophysiology

- Direct damage to lung tissues
- Radiation breaks chemical bonds and produces highly reactive free-radicals
- Triggers cytokines and apoptosis
- TNF Alpha, IL1 and IL-6 levels increased post-radiation. Increased IL-6 levels are predictive of radiation-induced lung injury. Fibrosis can be induced via the TGFB.
- A hypersensitivity CD4 alveolitis can be induced inside and outside the radiation field. This is usually an early reaction.

Risk Factors

- Radiation
- Chemo
- Younger age
- Female
- Smoking history (but active smoking may be protective!)
- COPD
- Steroid withdrawal during XRT
- Prior thoracic radiation
- Poor lung function (pre-treatment)
- Volume loss due to lung collapse
- Poor performance status

Radiation Risk Factors

- **Method:** Conformational (IMRT/stereotactic) < large beam
- **Volume of irradiated lung** – Risk increases if > 10% of lung in field
- **Dose of radiation**
  - V20 = Volume of lung that gets > 20 Gy
  - V20 > 22% increases risk, max recommended is 30-35%
- **Time-dose factor – dose fractionation** – BID is lower risk than same total dose in OD XRT

Chemotherapy Risk Factors

- Some drugs are **radiation sensitizers** and increase risk
  - Doxorubicin
  - Taxanes
  - Bleomycin
  - Cyclophosphamide
  - Vincristine

- **Concurrent** or **induction chemotherapy** is higher risk than sequential

Radiation Injury – 5 Phases

- Immediate Phase
- Latent Phase
- Acute Exudative Phase
- Intermediate Phase
- Fibrotic Phase

Radiation Injury: Immediate Phase

- Starts hours to days after radiation
- Patient is asymptomatic
- Pathology shows
  - Congested mucosa with leukocytic infiltration
  - Increased capillary permeability and pulmonary edema

Radiation Injury: Latent Phase

- Ciliary dysfunction and increased number of goblet cells
- Thick secretions accumulate

Radiation Injury: Acute Exudative Phase

- Occurs **3 – 12 weeks** after exposure
- Clinical “radiation pneumonitis”
- Due to sloughing of endothelial and epithelial cells with microvascular thrombosis

Radiation Injury: Intermediate Phase

- Usually occurs **3 – 6 months** after XRT
- Resolution of alveolar exudate and deposition of fibroblasts

Radiation Injury: Fibrotic Phase

- 6 months or later after radiation
- Can progress over years
- More likely with palliative radiation
- Develop traction bronchiectasis
- Can get recurrent infections

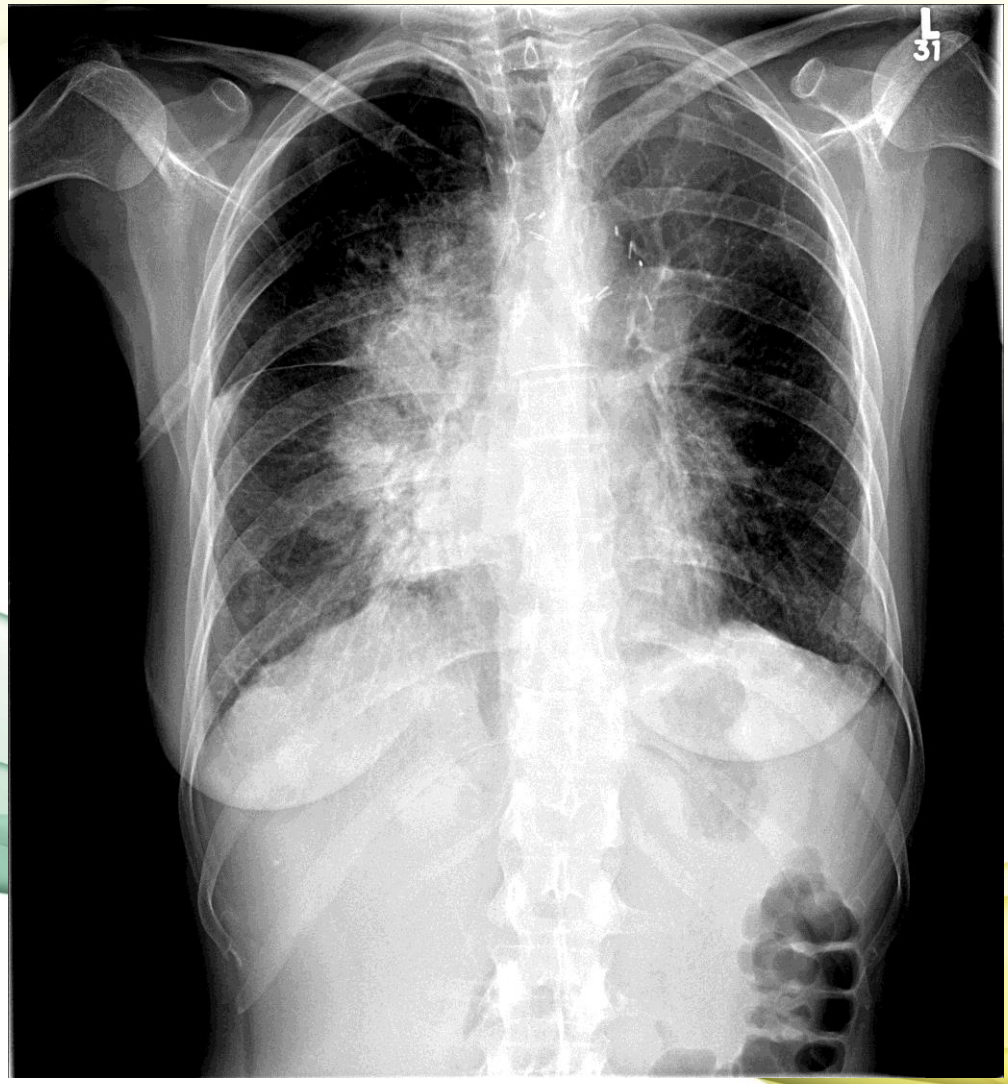
Symptoms and Signs: Radiation Pneumonitis

- Symptoms
  - Dry cough, SOBoE, pleuritic chest pain
  - Low grade fever, malaise and weight loss
- Signs
  - Crackles
  - Pleural rub
  - Pleural effusion

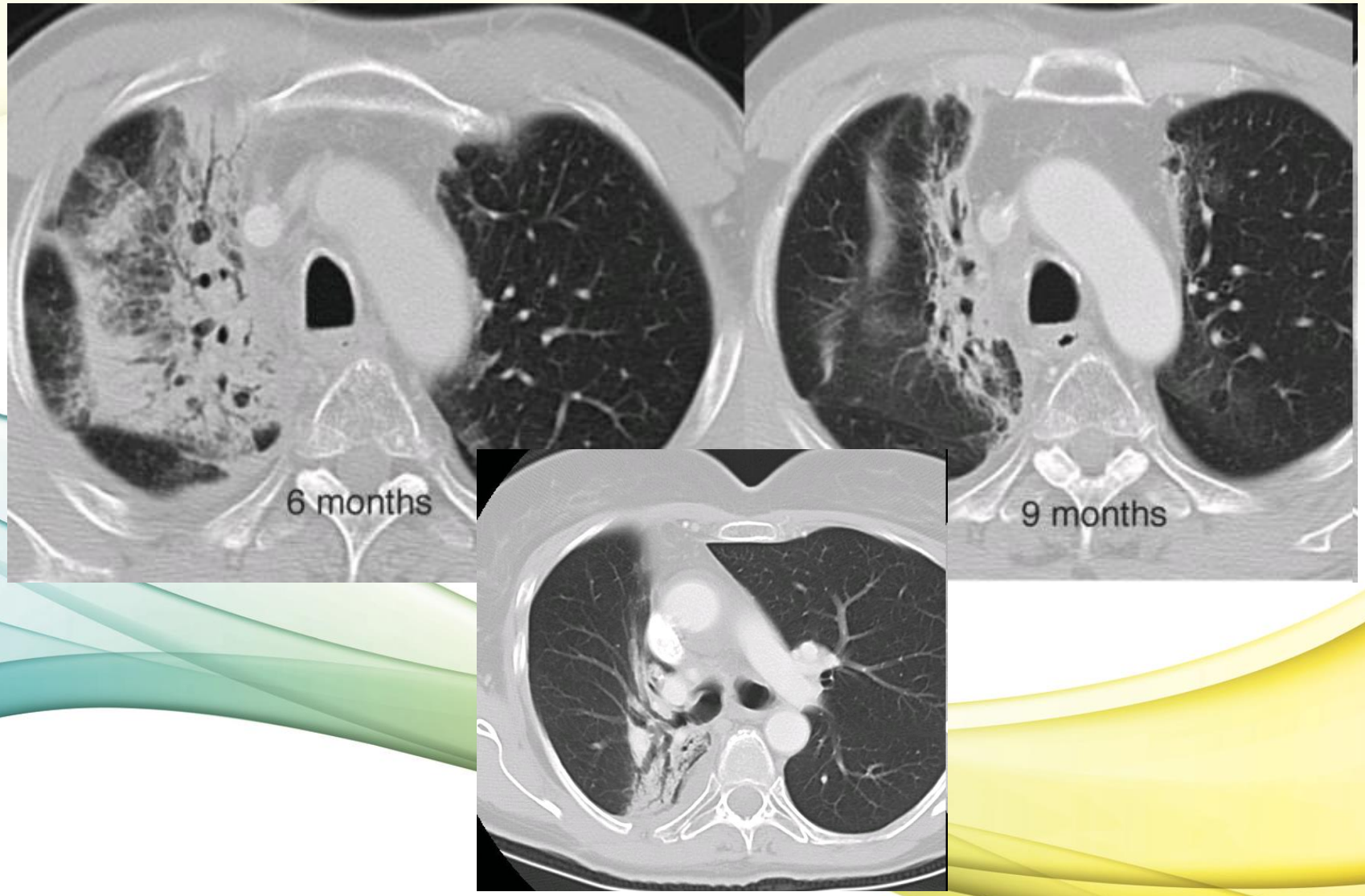
Investigations

- PFT's show restrictive pattern (low TLC/DCO)
- Radiologic abnormalities are very common
- Symptoms of radiation pneumonitis are much less common

Classic Pneumonitis and Fibrosis



Classic Pneumonitis and Fibrosis



Treatment

- Prednisone
  - At least 60mg/day x 2 weeks
  - Taper over 3 – 12 weeks
- Azathioprine and Cyclosporine A
  - Both been used in case reports
  - Consider if can’t use steroids

Prognosis

- Variable prognosis, can be mild or fatal
- Patients usually improve from 3 – 18 months after XRT
- Later improvement is unusual

Thank you!

My patient is in the office and is understandably very worried. His family is putting pressure on me. **What are the next steps?**

- Call Dr. Hirmiz
- Send patient to ER
- Send patient to Lung DAP
- Call David Musyj
- Refer the patient to the Cancer Centre and arrange a talk appointment with your patient