NON SURGICAL RADICAL TREATMENT FOR LOCALLY **ADVANCED NSCLC** NEOADJUVANT CT, CONCURRENT CT RT PROF S.N.SENAPATI, PROF & HOD. DEPT OF RADIATION ONCOLOGY AH REGIONAL CANCER CENTRE, CUTTACK

- 60 years Male
- History of Smoking
- Clinical presentn : Cough & Hemoptysis 6 months Chest Pain – 4 months
- CT Scan Thorax : Mass of size 4 cm x 3.6 x 3 cm at Lt Lower lobe with inv of subcarinal and Rt Mediastinal Lymph nodes
- No evidence of distant Metastasis
- CT Guided Biopsy: Adenocarcinoma
- Patient has EGFR deletion

What is the stage of the disease STAGE :-

What is the most appropriate treatment

- 1. Surgery followed by adjuvant treatment :-
- 2. Radiation alone :-
- 3. CT followed by RT
- 4. Concurrent CT, RT
- 5. Concurrent CT, RT followed by consolidation CT
- 6. Concurrent CT,RT followed by maintenance CT



T1 is defined as a tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). T1a is defined as a tumor 2 cm or less in greatest dimension (upper left). T1a is also defined as a superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus (lower left). T1b is defined as a tumor more than 2 cm but 3 cm or less in greatest dimension (right).



T2 is defined as a tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); involves main bronchus, 2 cm or more distal to the carina (middle left and middle right); invades visceral pleura (PL1 or PL2) (upper right); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung (bottom left). T2a is defined as tumor more than 3 cm but 5 cm or less in greatest dimension (upper left). T2b is defined as tumor more than 5 cm but 7 cm or less in greatest dimension (bottom right).



T3 is defined as a tumor more than 7 cm (upper middle left) or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors) (upper left), diaphragm (lower left), phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina but without involvement of the carina) (lower middle left); or associated atelectasis or obstructive pneumonitis of the entire lung (right) or separate tumor nodule(s) in the same lobe.



T3 includes separate tumor nodule(s) in the same lobe. T4 includes separate tumor nodule(s) in a different ipsilateral lobe.



T4 is defined as tumor of any size that invades any of the following: mediastinum, heart, great vessels (upper right), trachea (upper left), recurrent laryngeal nerve, esophagus (lower right), vertebral body (lower left), carina (middle left and right), separate tumor nodule(s) in a different ipsilateral lobe.

T4



T4 includes tumor invasion of the superior vena cava and heart.



T4 includes tumor invasion of the aorta, esophagus, and vertebral body.



N1 is defined as metastasis in ipsilateral peribronchial (left side of diagram) and/or ipsilateral hilar lymph nodes (right side of diagram) and intrapulmonary nodes, including involvement by direct extension of the primary tumor.



N2 is defined as metastasis in ipsilateral mediastinal (left side of diagram) and/or subcarinal lymph node(s) (right side of diagram).



N3 is defined as metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s), whereas M1b is defined as distant metastasis (in extrathoracic organs), and this would include distant lymph nodes.

M1a



M1a is defined as separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion. This is an image of tumor with malignant pleural effusion.lymph nodes.

THIS PT HAVING



Therapeutic Classification of NSCLC

Resectable NSCLC

Stage I, II, IIIA

Advanced/Unresectable NSCLC Stage ?III A/III B

Metastatic NSCLC T4 any N, N3 any T

INOPERABILITY IN NSCLC

- 1. N3 CONTRALATERAL LYMPHNODE MET.
- 2. T4- INVASION OF CARINA,HEART,GREAT VESSELS
- 3. M1a :- MALIGNANT PLEURAL EFFUSION
- 4. M1b:- DIST MET.
- 5. N2:- CONTROVERSIAL ??
- 6. POST OP PREDICTED FEV1/DLCO VALUE LESS THAN 40%, VO 2 15mL/kg

RADIATION IN ADVANCED NSCLC



- LARGER
 UNRESECTABLE
 LESION
- T4 N0-2
- T1-4 N2 N3

Stage III NSCLC

 Comprised of a heterogeneous group of patients with distinct clinical subsets.

RTOG 73-01: Randomized trial of various doses and schedules of TRT in inoperable NSCLC



Perez CA, et al. Cancer 45:2744-53, 1980 Perez CA, et al. Cancer 50:1091-9, 1982

CONTINUOUS RT OF 60 Gy IS BETTER THAN SPLIT COURSE 40 Gy RT

RADIATION IN ADVANCED LUNG CANCER



HOW TO IMPROVE

DOSE ESCALATION

CHEMOTHERAPY AND RADIATION

NEOADJUVANT

TECHNOLOGY

3DCRT IMRT GATING

CONCURRENT CT RT

ALTERED

CONSOLIDATION /MAINTENANCE

Strategies for the Treatment of Unresectable Stage III NSCLC



Induction Chemotherapy

Consolidation Chemotherapy

Maintenance Therapy

Maintenance or consolidation therapy: DEFINITION

 In the absence of significant toxicity, consolidation therapy is continued for a defined time & maintenance therapy until evidence of progressive disease



NEOADJUVANT CT-RT

Chemotherapy Followed by Definitive TRT

Trial	Accrual	N	Chemo	TRT	MS	1 YR OS	2 YR OS	P Value
Mattson	1982-85	119 119	CAP	30 Gy/28 Gy 30 Gy/25 Gy	322 d 311 d	42% 41%	19% 17%	p=NS
Morton ^a (NCCTG)	1983-87	56 58	MACC	50 Gy 50 Gy	313 d 317 d	46% 45%	21% 16%	p>0.2
Le Chevalier	1983-89	176 177	VCPC	65 Gy 65 Gy	12 m 10 m	50% 41%	21% 14%	p=.08
Dillman ^b (CALGB)	1984-87	78 77	VbC	60 Gy 60 Gy	13.7 m 9.7 m	55% 40%	26% 13%	p=.0066

aFYI: Original accrual 150,study closed due to slow accrual

^bFYI: Interim analysis showing OS benefit and study terminated

TRT - Thoracic Radiotherapy

CAP - Cyclophosphamide, Adriamycin, Cisplatin

MACC - Methotrexate, Doxorubicin, Cyclophosphamide, oral Lomustine (CCNU)

VCPC – Vindesine, Cisplatin, Lomustine, Cyclophosphamide

VbC - Vinblastine, Cisplatin

NS - Not significant

Mattson K, et al. Eur J Cancer Clin Oncol 24:477-82, 1988 Morton RF, et al. Ann Intern Med 115:681-6, 1991 Le Chevalier T, et al. J Natl Cancer Inst 83:417-23, 1991 Dillman RO, et al. NEJM 323:940-5, 1990

RTOG 8808/ECOG 4588/SWOG Intergroup Trial



• NEOADJUVANT CT FOLLOWED BY RT IS SUPERIOR THAN RT ALONE

CONCURRENT CT RT



INCREASED LOCAL CONTROL ORGAN PRESERVATION DECREASED DISTANT METASTASIS IMPROVED SURVIVAL

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SPATIAL COOPERATION



 Spatial cooperation refers to combining a drug that is efficacious against systemic disease with radiation, which is effective against locoregional disease. Because a full dose of radiotherapy and chemotherapy is required, and spatial cooperation does not require an interaction at the cellular level, these modalities are typically administered sequentially in an effort to reduce toxicity.



 The diverse and complex biologic processes that may be targeted by chemotherapy occurring during the interval between fractionated radiotherapy, including tumor-cell repopulation, reoxygenation, and cellular redistribution, have been collectively termed temporal modulation.

BIOLOGICAL COOPERATION additive or supra-additive RT СТ

Cytotoxic enhancement refers to the capacity of chemotherapy to interact with radiation and produce a greater effect on the local tumor than would be expected from simple additivity of cell killing.

BIOLOGICAL CO-OPERATION

✓ targeting distinct cell populations

- ✓ different mechanisms of cell killing
- ✓ inducing tumour regrowth delays.

The 2 modalities may be given concurrently by combining radiation with bioreductive drugs mitomycin C to target hypoxic tumour cells.

MECHANISM OF ACTION

- 1. DNA damage can be induced by both chemotherapy and radiotherapy and synergy
- 2. Chemotherapy can inhibit post-radiation damage repair
- 3. Radiotherapy and chemotherapy often target different phases of the cell cycle and produce an additive effect (i.e. cytokinetic cooperation/synchronization)
- 4. Enhanced activity against hypoxic cells
- **5.** Inhibition of repopulation
- 6. Block signaling pathways that are responsible for aggressive tumor biology, poor prognosis, and radioresistance

DRUGS USED AS CHEMORADIATION IN NSCLC

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DRUGS	DOSE M g/M2	SCHEDULE
GEMCITABINE	600	D1,8.22,29
PACLITAXEL	50-125	D1,22
VINORELBINE	15	D1,8,22,29
ETOPOSIDE	50	D1-5,D29-36
CARBOPLATINUM	Auc 2	
CISPLATINUM	30-50	1,8,29,36
DOCETAXOL	40	D1,8,29,36
MITOMYCIN C	8	D1,8,29,36
VINDESINE	3	D1,8,29,36

Concurrent Weekly or Daily Chemoradiotherapy



LOCAL CONTROL AND SURVIVAL IS BETTER IN CONCURRENT DAILY CDDP ARM THAN WEEKLY CDDP

Concurrent Cyclic Chemoradiotherapy



Meta-analysis Concurrent vs Sequential Chemoradiotherapy



Decreased local regional progression	HR 0.77, 95% CI .6295; p=.01
No decrease in distant progression	HR 1.04, 95% CI .86-1.15; p=.69
Increase in acute grade 3/4 esophageal toxicity	RR 4.9, 95% CI 3.1-7.8; p≤.001

Auperin A, et al. J Clin Oncol 28:2181-90,2010

survival

Α	No. Deaths /	No. Entered				
Trial	RT + Conc CT	RT + Seq CT	0-E	Variance	Hazard Ratio	HR (95% CI)
CALGB 8831	45/46	39/45	2.4	20.9		1.12 (0.73 to 1.72)
WJLCG	131/156	142/158	-16.8	67.3	-	0.78 (0.61 to 0.99)
RTOG 9410	180/204	189/203	-20.5	91.1		0.80 (0.65 to 0.98)
GMMA Ankara 95	15/15	15/15	-1.0	7.0		0.87 (0.41 to 1.82)
GLOT-GFPC NPC	87/102	96/103	-9.9	45.0		0.80 (0.60 to 1.07)
EORTC 0897	2 63/80	66/78	-0.5	31.9		0.98 (0.69 to 1.39)
Total	521/603	547/602	-46.4	263.1	•	0.84 (0.74 to 0.95)
Test for hete	rogeneity:			0.25	1.00	4.00
$\chi^2_5 = 3.24, P$	= .66, l ² = 0%			0.25	1.00	4.00
			K	+ Conc C	I Better RI+S	Seq UT Better
RT + conc CT effect: Log-rank test = 8.19, P = .004						

C Trial	No. Events / I RT + Conc CT	No. Entered RT + Seq CT	0-E	Variance	Hazard Ratio	HR (95% CI)	
WJLCG	50/148	65/145	-10.6	28.6	-	0.69 (0.48 to 1.00)	
RTOG 9410	58/204	61/203	-2.6	29.7	-	0.92 (0.64 to 1.31)	
GMMA Ankara 95	4/15	5/15	-0.8	2.2 🗲		0.69 (0.19 to 2.57)	
glot-gfpc NPC	24/101	40/103	-8.5	15.7		0.58 (0.35 to 0.95)	
EORTC 0897	2 24/80	26/78	-0.8	12.5	i	0.93 (0.54 to 1.63)	
Total	160/548	197/544	-23.4	88.8	•	0.77 (0.62 to 0.95)	
Test for heterogeneity: $\chi^2_4 = 2.96, P = .56, P = .0\%$ RT + Conc CT Better RT + conc CT effect: Log-rank test = 6.16, P = .01							
_							

Progression free survival

в	No. Events / I	No. Entered				
Trial	RT + Conc CT	RT + Seq CT	0-E	Varian	ce Hazard Ratio	HR (95% CI)
CALGB 8831	45/46	39/45	1.7	20.8		1.08 (0.70 to 1.66)
WJLCG	128/148	132/145	-11.0	64.0	-	0.84 (0.66 to 1.08)
RTOG 9410	189/204	192/203	-18.8	94.0		0.82 (0.67 to 1.00)
GMMA Ankara 95	13/15	14/15	-1.3	6.6		0.82 (0.38 to 1.76)
GLOT-GFPC NPC	88/102	97/103	-8.0	44.9	-	0.84 (0.63 to 1.12)
EORTC 0897	2 70/80	67/78	8.4	33.8	-	1.28 (0.92 to 1.80)
Total	533/595	541/589	-29.0	264.2	•	0.90 (0.79 to 1.01)
Test for hete $\chi^2_5 = 6.37$, P	erogeneity: = .27, I² = 22%		F		0.25 1.00 In CT Better RT + Seq	4.00 CT Better
RT + conc CT effect: Log-rank test = 3.18, P = .07						

					r enect. Log-rank test = 0.	10, 7 = .01
D Trial	No. Events / N RT + Conc CT	lo. Entered RT + Seq CT	0-E	Variance	Hazard Ratio	HR (95% CI)
WJLCG	67/148	55/145	7.0	30.5		1.26 (0.88 to 1.79)
RTOG 9410	85/204	88/203	-3.1	43.2		0.93 (0.69 to 1.25)
GMMA Ankara 95	8/14	8/14	0.5	4.0	-	- 1.15 (0.43 to 3.08)
glot-gfpc NPC	34/101	36/103	-0.5	17.0		0.97 (0.60 to 1.56)
EORTC 0897	2 32/80	32/78	0.3	16.0		1.02 (0.63 to 1.67)
Total	226/547	219/543	4.2	110.6	•	1.04 (0.86 to 1.25)
Test for heterogeneity: 0.25 1.00 4.00 $\chi^2_4 = 1.76, P = .78, I^2 = 0\%$ RT + Conc CT BetterRT + Seq CT BetterRT + conc CT effect: Log-rank test = 0.16, $P = .69$						4.00 q CT Better 16, P = .69

Distant progression

Local progression

CONCURRENT CT RT IS BETTER THAN SEQUENTIAL CT RT

The Role of Induction Chemotherapy CALGB 39801



Vokes EE et al. JCO 25:1698-1704, 2007

Induction Strategy

Study	Year	Strategy	No.	MST	3 yr
CALGB 39801	2006	Induction>Concurrent	184	14 m o	23%
		Concurrent alone	182	12 mo	19%
Korea	2007	Induction>Concurrent	67	13 m o	<25%
		Concurrent alone	67	18 m o	NR
CALGB 9431	2002	Induction>Concurrent	62	18 m o	28%
		Induction>Concurrent	58	15 m o	19%
		Induction>Concurrent	55	18 m o	23%
RTOG 9801	2007	Induction>Concurrent	118	17 mo	27%
		Induction>Concurrent	121	18 m o	28%
NCI/RTOG/MDA	2007	Induction>Concurrent	188	14 m o	~25%
		Induction>Concurrent	191	16 m o	~25%

PRESENTED AT:

ASCO

50 MEETING

SCIENCE & SOCIETY

Induction Strategy

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CALGB 9431	2002	Induction>Concurrent	62	18 m o	28%
		Induction>Concurrent	58	15 m o	19%
		Induction>Concurrent	55	18 m o	23%
RTOG 9801	2007	Induction>Concurrent	118	17 mo	27%
		Induction>Concurrent	121	18 m o	28%
NCI/RTOG/MDA	2007	Induction>Concurrent	188	14 m o	~25%
		Induction>Concurrent	191	16 mo	-25%

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SCIENCE & SOCIETY

INDUCTION CT FOLLOWED BY CONCURRENT CT RT DO NOT SHOW STATISTICALLY SIGNIFICANT SURVIVAL ADVANTGES OVER **CONCURRENT CT RT**

Randomized Phase II Trial Evaluating Newer Chemotherapy Regimens: CALGB 9431

Cisplatin + Gemcitabine, Paclitaxel or Vinorelbine

Response	Cisplatin/ Gemcitibine (n=62)	Cisplatin/ Paclitaxel (n=58)	Cisplatin/ Vinorelbine (n=55)
Complete Response	0	0	2%
Partial Response	35%	31%	38%
Stable Disease	40%	45%	42%
Overall Response Rate	40%	33%	44%

TRT Cisplatin + Gemcitabine, Paclitaxel or Vinorelbine

Response	Cisplatin/ Gemcitibine (n=62)	Cisplatin/ Paclitaxel (n=58)	Cisplatin/ Vinorelbine (n=55)
Complete Response	8	19	16%
Partial Response	60%	47%	53%
Stable Disease	16%	17%	20%
Overall Response Rate	74%	67%	73%
Median OS	18.3 m	14.8 m	17.7 m
1 YR OS	68%	62%	65%
GR 3/4 ANC	51%	53%	27%
GR 3/4 Plts	56%	6%	2%
GR 3/4 Esophogitis	52%	39%	27%

Second vs Third Generation Chemotherapy Regimens + TRT

	Treatment	Ν	Med OS	5 YR OS	P Value				
WJTOG0105									
Cyclic	MVP + TRT	146	20.5 m	17.5%	NS				
Weekly	Irinotecan/CBDCA+ TRT*	147	19.5 m	17.8%	NS				
Weekly	Paclitaxel/CBDCA+ TRT*	147	22.0 m	17.9%	NS				
OLCSG 0007 1 YR OS									
Cyclic	MVP + TRT	101	23.7 m	48.1%	NS				
Cyclic	Doc/P + TRT**	99	26.8 m	60.3%	NS				

TRT - Thoracic Radiotherapy

MVP - Mitomycin, Vindesine, Cisplatin

CBDCA - Carboplatin

Doc/P - Docetaxel/Paclitaxel

*significantly less Grade 3 and 4 neutropenia, febrile neutropenia and GI toxicities with third generation agents ** significantly less febrile neutropenia with docetaxel

Arm C was equally efficacious and exhibited a more favorable toxicity profile among three arms. Arm C should be considered a standard regimen in the management of locally advanced unresectable NSCLC

Segawa Y, et al. J Clin Oncol 28:3299-3306, 2010



The Role of Consolidation Chemotherapy HOG LUN 01-24/USO 02-033



Our updated results confirm our prior conclusion that consolidation D does not improve survival following EP/XRT, is associated with significant toxicities and can no longer be considered as standard treatment for pts with inoperable stage III NSCLC.

Hanna N, et al. J Clin Oncol. 26:5755-60, 2008

A Multinational Randomized Phase III Trial with or without Consolidation Chemotherapy Using Docetaxel and Cisplatin after Concurrent Chemoradiation in Inoperable Stage III Nonsmall Cell Lung Cancer (CChelN)

Keunchil Park¹, Jin Seok Ahn¹, Myung-Ju Ahn¹, Yong Chan Ahn¹, Joo-Hang Kim², Chang Geol Lee², Eun Kyung Choi³, Kyu Chan Lee³, Ming Chen⁴, Dae Seog Heo⁵, Hoon-Kyo Kim⁸, Young Joo Min⁷, Jin-Hyoung Kang⁸, Jin Hyuck Choi⁹, Sang-We Kim¹⁰, Guangying Zhu¹¹, Yi Long Wu¹², Sung Rok Kim¹³, Kyung Hee Lee¹⁴, Hong Suk Song¹⁵

Study Design

Multinational, phase III randomized trial

Locally Advanced, Inoperable Stage III NSCLC





- The primary endpoint of increased PFS with the addition of weekly docetaxel-cisplatin consolidation chemotherapy was not met in the present study.
- Concurrent chemoradiotherapy alone should remain as the standard of care for inoperable stage III NSCLC.

CONSOLIDATION CT DOES NOT IMPROVE THE SURVIVAL(PFS/OS)

Induction vs Consolidation

Study	Yr	Strategy	No	MST	3 yr
GFPC-GLOT-IFCT	2006	Induction>Concurrent	64	19	<25%
		Concurrent>Consolidation	63	16	<25%
SLCG	2005	Induction>Concurrent	68	22	~20%
		Concurrent>Consolidation	67	14	~20%
LAMP	2005	Induction>Concurrent	74	13	15%
		Concurrent>Consolidation	92	16	17%

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ANNUAL

Induction vs Consolidation

					\frown
Study	Yr	Strategy	No	MST	3 yr
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SLCG	2005	Induction>Concurrent	68	22	~20%
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LAMP	2005	Induction>Concurrent	74	13	15%
		Concurrent>Consolidation	92	16	17%

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ANNUAL

• NO DIFFERENCE IN SURVIVAL IN INDUCTION FOLLOWED BY CONCURRENT CT RT Vs

CONCURRENT CT RT FOLLOWED BY CONSOLIDATION CT

The Role of Maintenance Therapy SWOG 0023



START Trial



Butts C, et al. Lancet Oncol 15:59-68, 2014

MAINTENANCE THERAPY DID NOT IMPROVE THE SURVIVAL

Treatment Strategies for Unresectable Stage III NSCLC



60 years Male

- History of Smoking
- Clinical presentn : Cough & Hemoptysis 6 months Chest Pain – 4 months
- CT Scan Thorax : Mass of size 4 cm x 3.6 x 3 cm at Lt Lower lobe with inv of subcarinal and Rt Mediastinal Lymph nodes
- No evidence of distant Metastasis
- CT Guided Biopsy: Adenocarcinoma
- Patient has EGFR deletion

What is the stage of the disease STAGE :- IIIB

What is the most appropriate treatment

- 1. Surgery followed by adjuvant treatment :- 💥
- 2. Radiation alone :- X
- 3. CT followed by RT 💥
- 4. Concurrent CT, RT
- 5. Concurrent CT, RT followed by consolidation CT X
- 6. Concurrent CT,RT followed by maintenance CT 🐰

TAKE HOME MESSAGE

- 1. CONTINUOUS RT OF 60 Gy IS BETTER THAN SPLIT COURSE 40 Gy RT
- 2. NEOADJUVANT CT FOLLOWED BY RT IS SUPERIOR THAN RT ALONE
- 3. LOCAL CONTROL AND SURVIVAL IS BETTER IN CONCURRENT DAILY CDDP ARM THAN WEEKLY CDDP
- 4. CONCURRENT CT RT IS BETTER THAN SEQUENTIAL CT RT
- 5. INDUCTION CT FOLLOWED BY CONCURRENT CT RT DO NOT SHOW STATISTICALLY SIGNIFICANT SURVIVAL ADVANTGES OVER CONCURRENT CT RT

TAKE HOME MESSAGE

- 6. 3RD GENERATION CT IS EQUALLY EFFECTIVE BUT LIMITED TOXICITY.TAXANE + PLATINUM IS BETTER CHOICE FOR CONCURRENT CT RT.
- 7. CONSOLIDATION CT DOES NOT IMPROVE THE SURVIVAL(PFS/OS)
- 8. NO DIFFERENCE IN SURVIVAL IN INDUCTION FOLLOWED BY CONCURRENT CT RT Vs CONCURRENT CT RT FOLLOWED BY CONSOLIDATION CT
- 9. MAINTENANCE THERAPY DID NOT IMPROVE THE SURVIVAL

Treatment Strategies for Unresectable Stage III NSCLC



Conclusion

 Over the past 50 years combined modality regimens for inoperable stage III NSCLC have almost tripled the median survival of this disease.



Lung cancer does not take a vacation!

THANK YOU!

