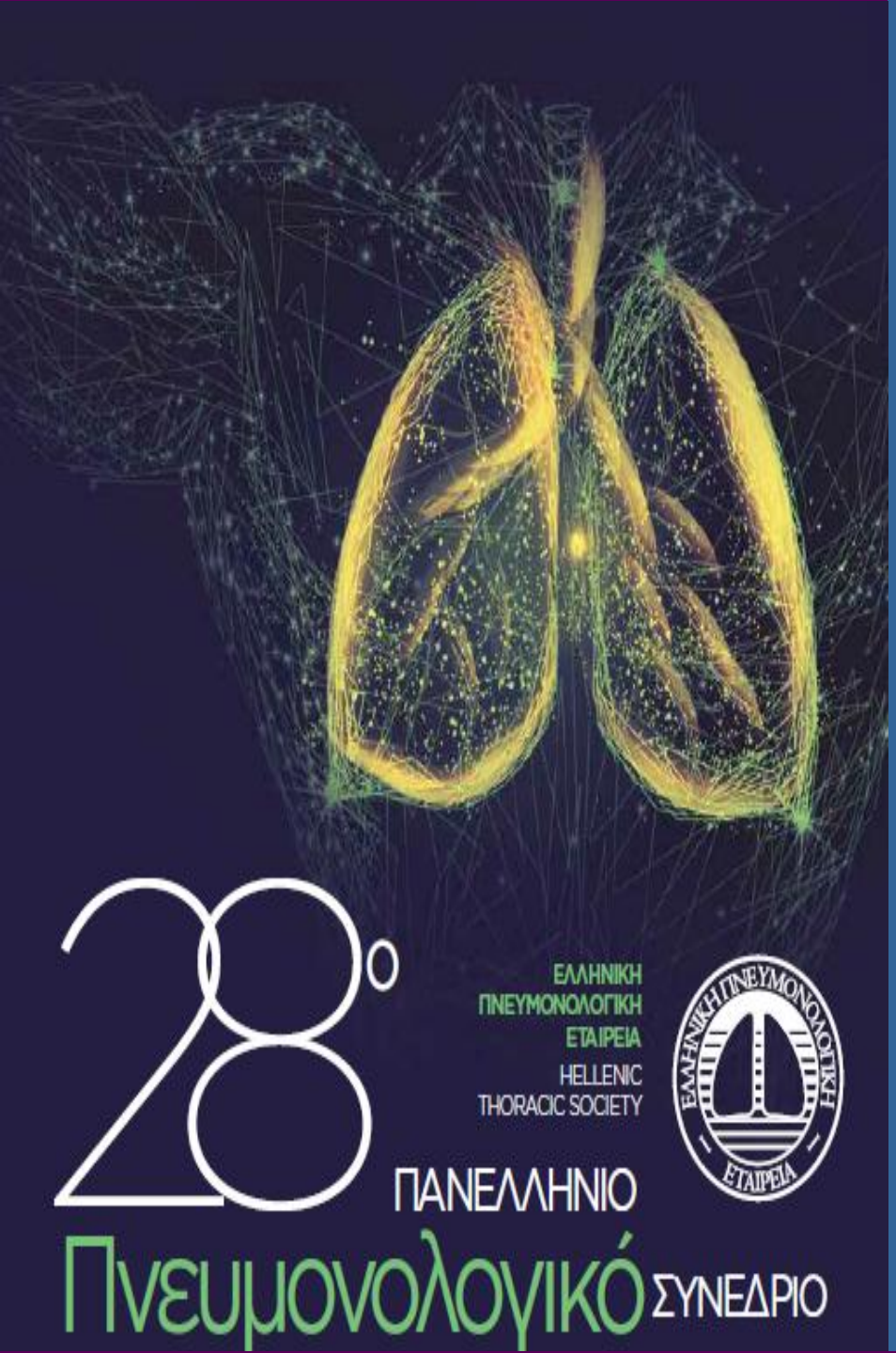


"ΜΜΚΠ σταδιου ΙΙΙ, Συνδυασμένη Θεραπευτική Προσέγγιση & Θεραπευτικοί Αλγόριθμοι στην Κλινική Πράξη"

Ιωάννης Χ. Γκιόζος
Πνευμονολόγος MD, PhD, FCCP

Επ. Συνεργάτης Πανεπιστημίου Αθηνών
Ογκολογική Μονάδα Γ'ΠΠ
ΓΝΝΘΑ "Η Σωτηρία"

Disclosures

Scientific Advisory Board: Boehringer Ingelheim

Honoraria for Lectures: ASTRA, Boehringer Ingelheim, Bristol Myers Squibb, Roche

Scientific Research: ASTRA, AbbVie

What Constitutes Stage III NSCLC?

- Heterogeneous group for which the treatment can differ dramatically based on details in disease presentation
- Treatment options include surgery, chemotherapy, radiotherapy, immunotherapy, or any combination of these depending on N descriptor, P.S. of patient, comorbidities…
- Multidisciplinary Approach is Mandatory
- Most common presentations of stage III NSCLC
  - Stage IIIA: ipsilateral mediastinal node involvement
  - Stage IIIB: contralateral mediastinal node involvement

Detterbeck. Chest. 2017;151:193. Rami-Porta. CA Cancer J Clin. 2017;67:13

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Lectus adv.

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Lectus adv.

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

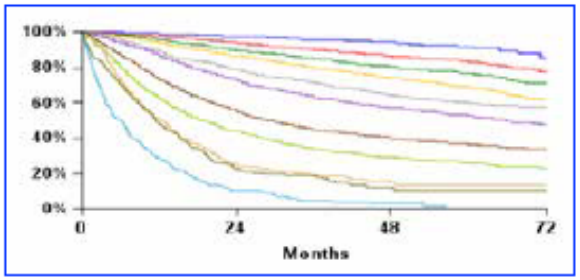
	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Lectus adv.

Proposals for stage groupings

Clinical Staging

	Events/N	MST	24 months	60 months
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	19.0	44%	26%
IIIC	831/986	12.6	24%	13%
IVA	336/484	11.5	23%	10%
IVB	328/389	6.0	10%	0%



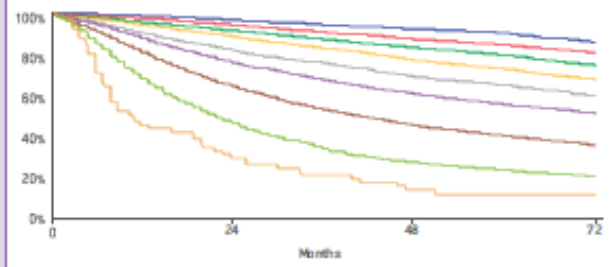
Overall survival expressed as median survival time (MST), 2-year and 5-year survival by clinical stage using the proposed International Association for the Study of Lung Cancer recommendations

Goldstraw P et al. J Thorac Oncol 2016; 11,39-51.

Proposals for stage groupings

Pathological Staging

	Events/N	MST	24 months	60 months
IA1	139/1389	NR	97%	90%
IA2	823/5633	NR	94%	85%
IA3	875/4401	NR	92%	80%
IB	1618/6095	NR	89%	73%
IIA	556/1638	NR	82%	65%
IIB	2175/5226	NR	76%	56%
IIIA	3219/5756	41.9	65%	41%
IIIB	1215/1729	22.0	47%	24%
IIIC	55/69	11.0	30%	12%



Overall survival expressed as median survival time (MST), 2-year and 5-year survival by pathologic stage using the proposed International Association for the Study of Lung Cancer recommendations

Goldstraw P et al. J Thorac Oncol 2016; 11,39-51.

Lung Cancer Stage Grouping (AJCC 8th Edition)

5-Yr OS,* %	IA1	IA2	IA3	IB	IIA	IIB
Clinical	92	83	77	68	60	53
Pathologic	90	85	80	73	65	56

5-Yr OS,* %	IIIA	IIIB	IIIC	IVA	IVB
Clinical	36	26	13	10	0
Pathologic	41	24	12	-	-

Locally Advanced Stage III NSCLC

*5-yr OS per IASLC global database for patients receiving NSCLC diagnoses from 1999-2010.

Detterbeck. Chest. 2017;151:193. Goldstraw. J Thorac Oncol. 2016;11:39.

T/M	Subgroup†	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 *Contra Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Disem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

†All numbers in cm.

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Lectus adv.

Treatment of T3N1 to T4N0-1

- Surgery & Adjuvant Chemotherapy
- Definitive Concurrent Chemo-Radiation and consolidation Immunotherapy
- Induction therapy & Surgery in experienced centers e.g. Pancoast tumors
- Systemic Therapy based on histology, molecular status, PD L1 score

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

cN2 disease

Heterogeneity of population

↓

Imaged N2 ≠ EBUS N2 ≠ med. N2 ≠ thoracotomy N2

↓

Difficult to compare

reported series and trial results

HETEROGENEITY OF IIIA N2 DISEASE

- If N2 found at mediastinoscopy but attempt at resection

IIIA

9% / 5y survival

- If mediastinoscopy negative but N2 found at thoracotomy

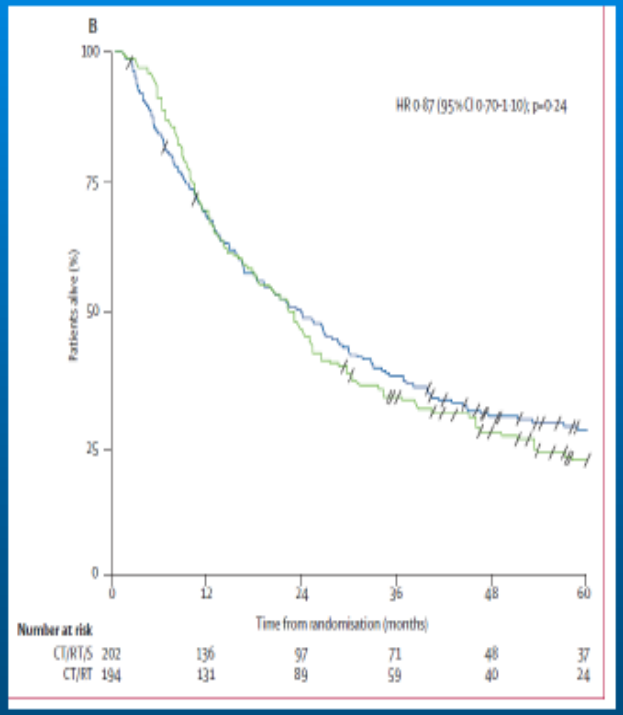
IIIA

24% / 5y survival

Pearson, J Thorac CV Surg 1982

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

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, Willliam T Sause, James D Cox



INT 0139

5 y survival C/RT/S 27% vs 20% C/RT

Op mortality of lobectomy was 1%

R pneumonectomies (n=29) or complex pneumonectomies did not do so well !

Relapse at T site 3% vs 19% (6.3 X) in favor of surgery arm

Albain KS, Lancet Oncol 2009; 374: 379-86

Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone

On behalf of the European Organisation for Research and Treatment of Cancer-Lung Cancer Group

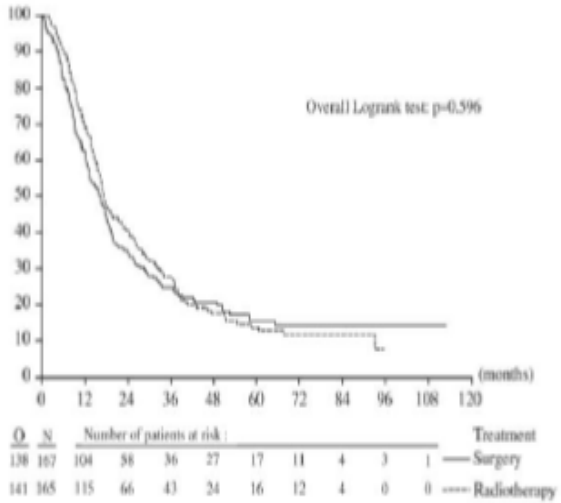


Fig. 2. Overall survival rates estimated from time of randomization using Kaplan–Meier analyses. *P* value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.84 to 1.35; *P* = .596.

EORTC

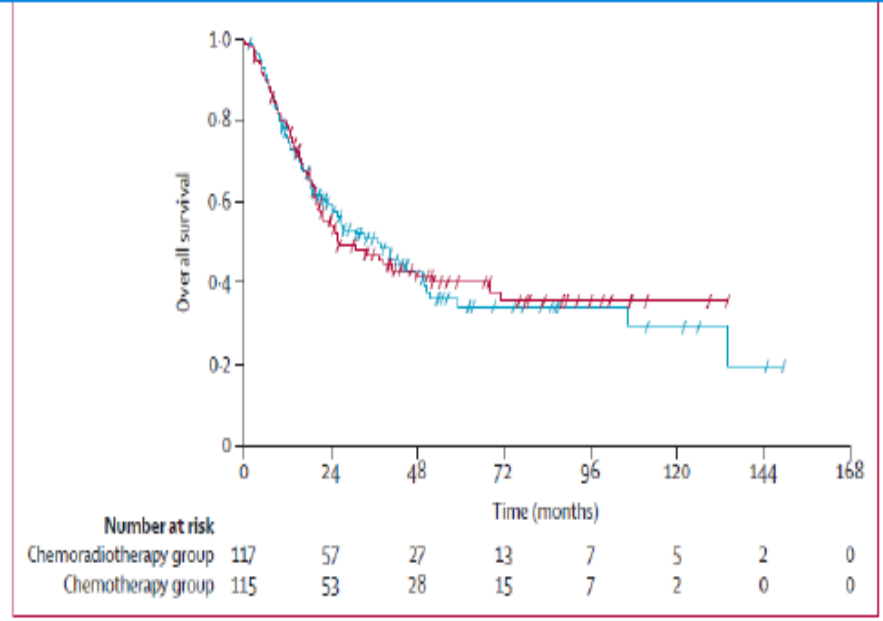
5 y survival C/S 15.7% vs 14% C/RT

Op mortality of 72 pneumonectomies was 6.9%

Van Meerbeck, J Natl Cancer Inst 2007; 99: 442-50

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

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group



SAKK 16/00

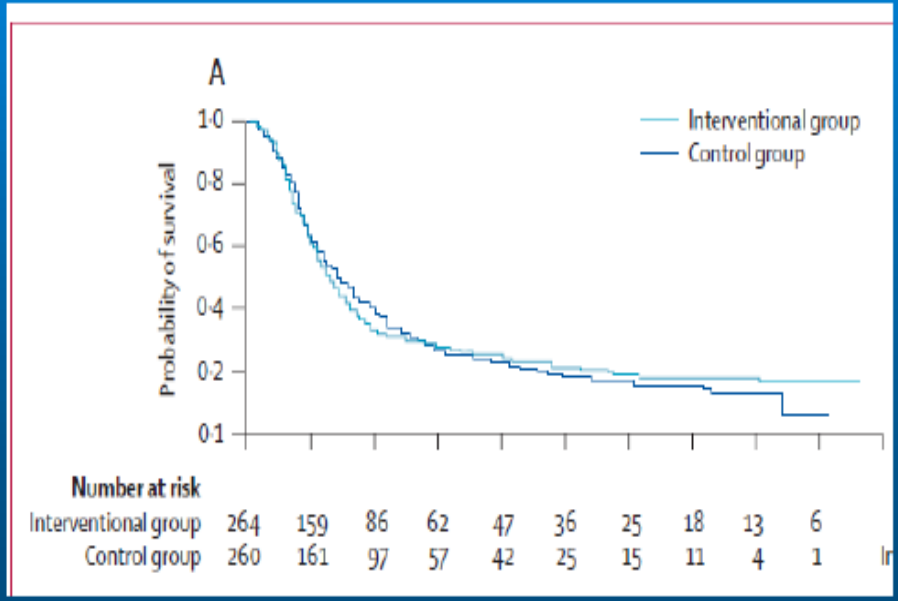
Median OS were 37 months in CRT/S and 26 months in C/S

pCR w IC alone was 12%

Pless M et al (SAKK), Lancet Oncol 2015

Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer

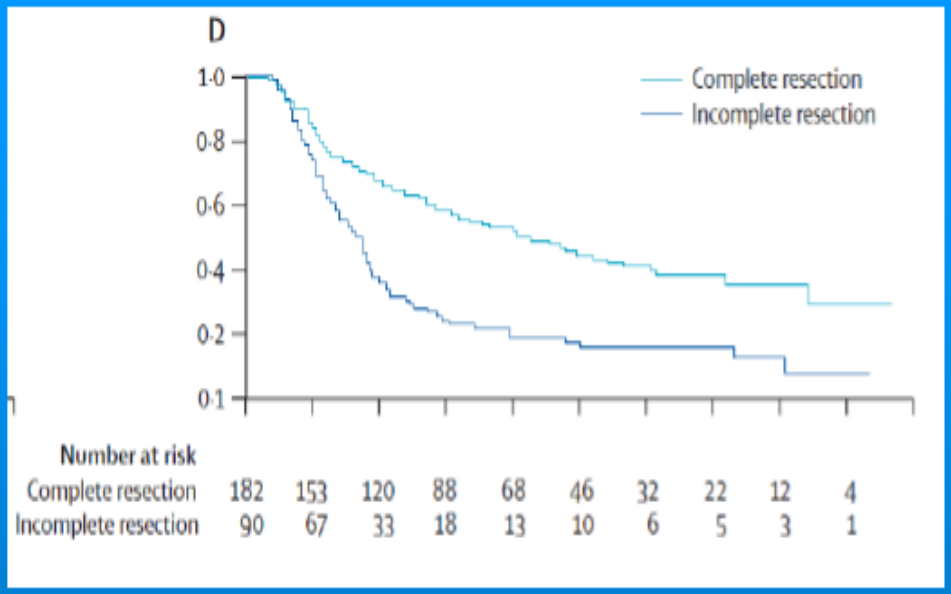
Michael Thomas, Christian Rübe, Petra Hoffknecht, Hans N Macha, Lutz Freitag, Albert Linder, Norman Willich, Michael Hamm, Gerhard W Sybrecht, Dieter Ukena, Karl-Matthias Deppermann, Cornelia Dröge, Dorothea Riesenbeck, Achim Heinecke, Cristina Sauerland, Klaus Junker, Wolfgang E Berdel*, Michael Semik*, for the German Lung Cancer Cooperative Group**

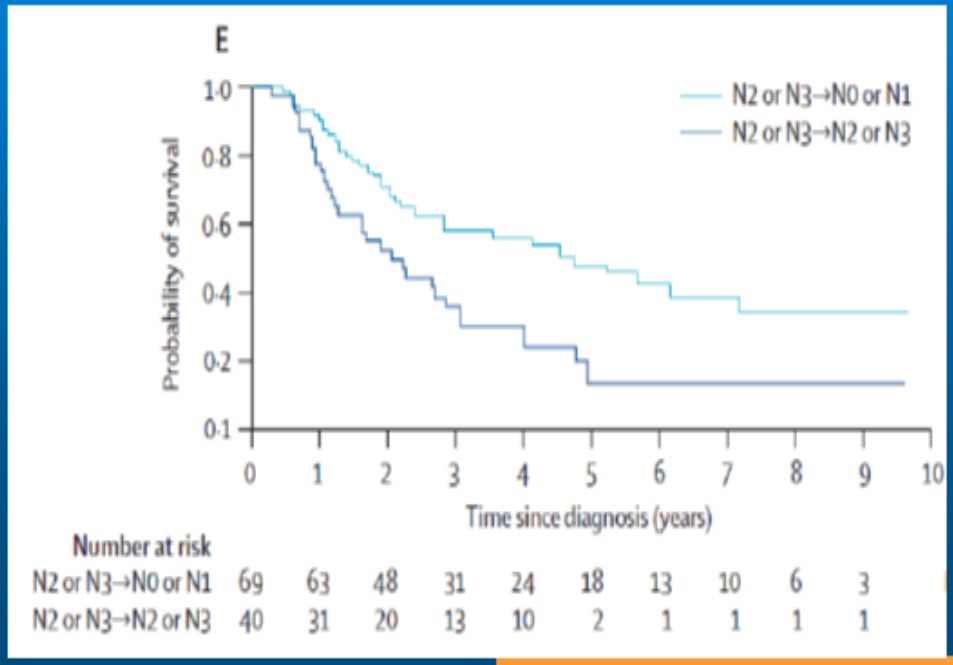


GLCGG

5 y survival C/S 21% vs 18% C/RT/S

Thomas M et al Lancet Onc 2008; 9: 636-48





Importance of R0 resection and influence of nodal downstaging

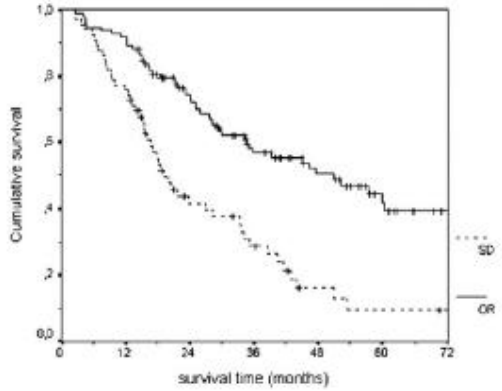
Thomas M et al Lancet Onc 2008; 9: 636-48

Which patients should be operated on after induction chemotherapy for N2 non–small cell lung cancer? Analysis of a 7-year experience in 175 patients

Alessandro Stefani, MD, Marco Alifano, MD, Antonio Bobbio, MD, Madalina Grigoroiu, MD, Rami Jouni, MD, Pierre Magdeleinat, MD, and Jean-Francois Regnard, MD

Conclusions: Surgery after chemotherapy could be effective for selected patients with N2 non–small cell lung cancer. Survival for responders is satisfactory, even in case of persistent N2 disease. Prognosis for nonresponders is disappointing. (J Thorac Cardiovasc Surg 2010;140:356-63)

Response by CT alone



VOLUME 34 · NUMBER 21 · JULY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Standardized Uptake Decrease on [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography After Neoadjuvant Chemotherapy Is a Prognostic Classifier for Long-Term Outcome After Multimodality Treatment: Secondary Analysis of a Randomized Trial for Resectable Stage IIIA/B Non–Small-Cell Lung Cancer

Christoph Pöttgen, Thomas Gauler, Alexander Bellendorf, Maja Guberina, Andreas Bockisch, Nina Schwenzer, Frank Heinzelmann, Sebastian Cordes, Martin H. Schuler, Stefan Welter, Georgios Stamatis, Godehard Friedel, Kaid Darwiche, Karl-Heinz Jöckel, Wilfried Eberhardt, and Martin Stuschke

Conclusion

$\%SUV_{remaining}$ is a predictor for survival and other end points after multimodality treatment and can serve as a parameter for treatment stratification after induction chemotherapy or for evaluation of adjuvant new systemic treatment options for high-risk patients.

J Clin Oncol 34:2526-2533.

Factors influencing historically in operating in N2 Disease

Performance Status

Co-morbidities of the patient

ypR0 or pR0 achievement

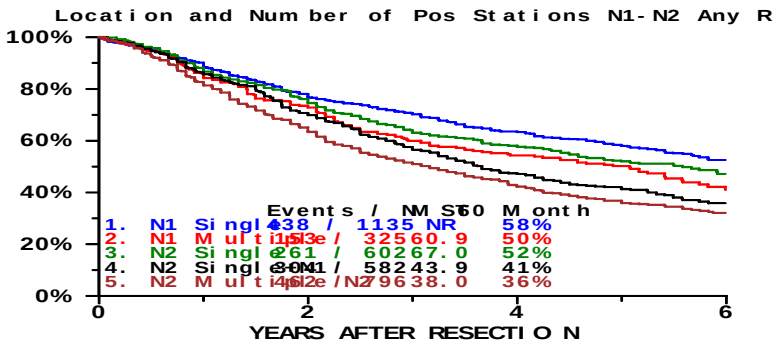
The amount of N2 disease identified by:
- number of nodes,
- extracapsular disease,
- Med vs EBUS/EUS,
- number of zones

Where is the lobe of origin in relation to N+ involvement

Need for less than a Right pneumonectomy?

Response to induction therapy

Pathological – any R



N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 (“skip mets”) = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

N1a vs N1b vs N2a1 vs N2a2 vs N2b Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+ , R0 Resection, and Region.
(Cox PH regression on All cases)

comparison	HR	P
N1b vs N1a	1.38	0.0005
N2a1 (skip) vs N1b	0.92	0.4331
N2a2 vs N2a1 (skip)	1.37	0.0002
N2b vs N2a2	1.21	0.0117
N2a2 vs N1b	1.26	0.0197

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Guidelines on the Radical Management of Patients with Lung Cancer

British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland

1.2.3 N2 disease

25. Consider radical radiotherapy or chemoradiotherapy in patients with T1–4N2 (bulky or fixed) M0 disease. **[B]**

26. Consider surgery as part of multimodality management in patients with T1–3N2 (non-fixed, non-bulky, single zone) M0 disease. **[B]**

CLINICAL PRACTICE GUIDELINES

An ESMO Product

Early and locally advanced non-small-cell lung cancer (NSCLC)

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

P. E. Postmus, K. M. Kerr, M. Oudkerk, S. Senan, D. A. Waller, J. Vansteenkiste, C. Escriu & S. Peters, on behalf of the ESMO Guidelines Committee*

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Lung-and-Chest-Tumours

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Treatment

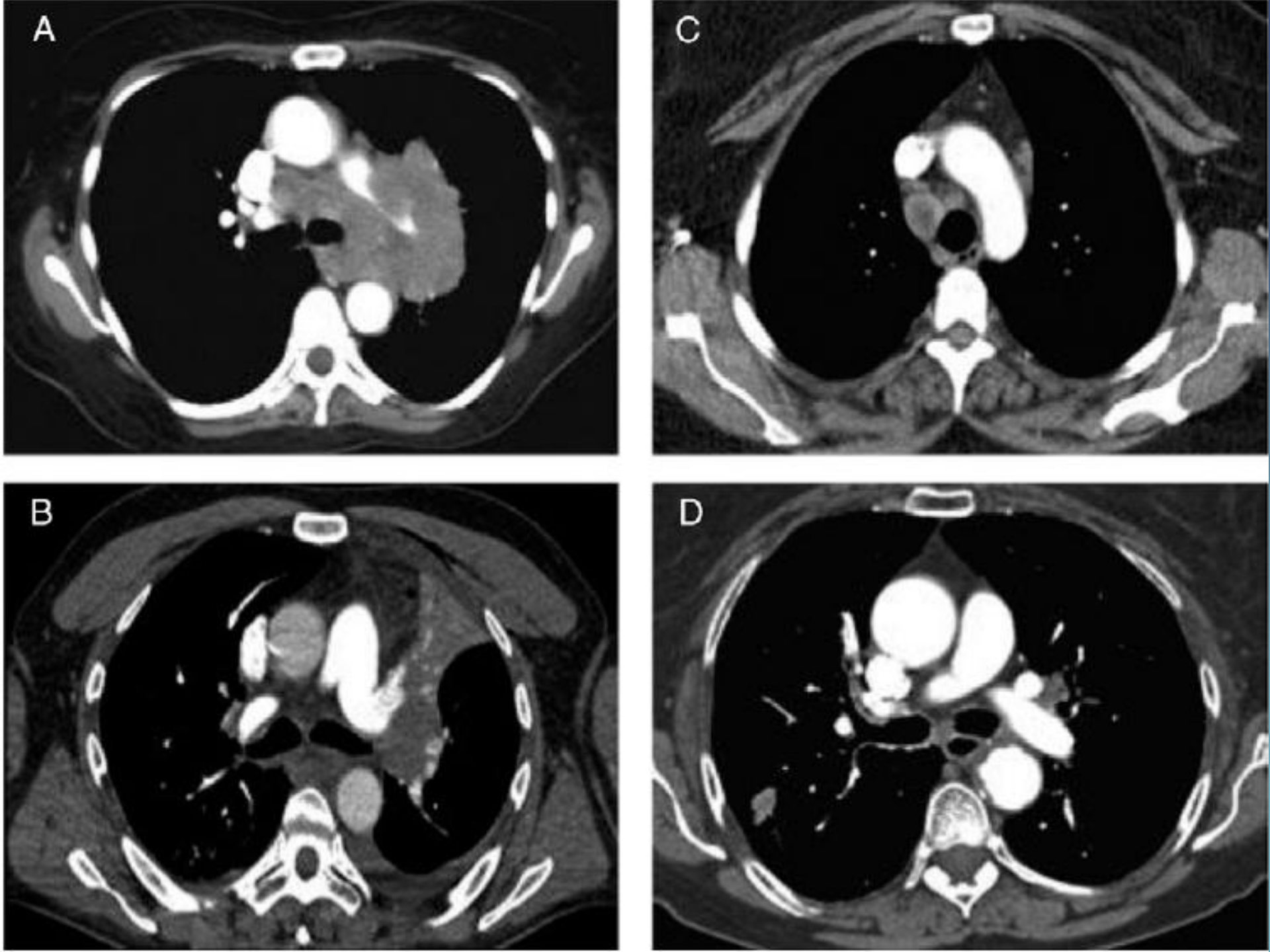
Locally advanced NSCLC (stage III) – Resectable

Summary of recommendations	LoE, GoR
Adjuvant ChT should follow after surgery for N2 disease documented only intra-operatively	I, A
PORT after complete resection may be an option after individual risk assessment	V, C
In case of single station N2 disease by preoperative pathological analysis, resection followed by ChT, induction ChT followed by surgery or CRT followed by surgery are options	IV, C
After preoperative ChT alone, PORT may be an option according to the locoregional relapse risks	IV, C
Concurrent definitive CRT is preferred in multistation N2/N3	I, A
Multimodality treatment strategy decisions should be evaluated by experienced MDT	IV, C
Concurrent CRT induction followed by definitive surgery • Treatment of choice is potentially resectable superior sulcus tumours • May be used for potentially resectable T3 or T4 central tumours in highly selected cases at experienced centres • Surgery should be carried out within 4 weeks from RT	III, A III, B III, B
There is no role for prophylactic cranial RT in stage III	II, A

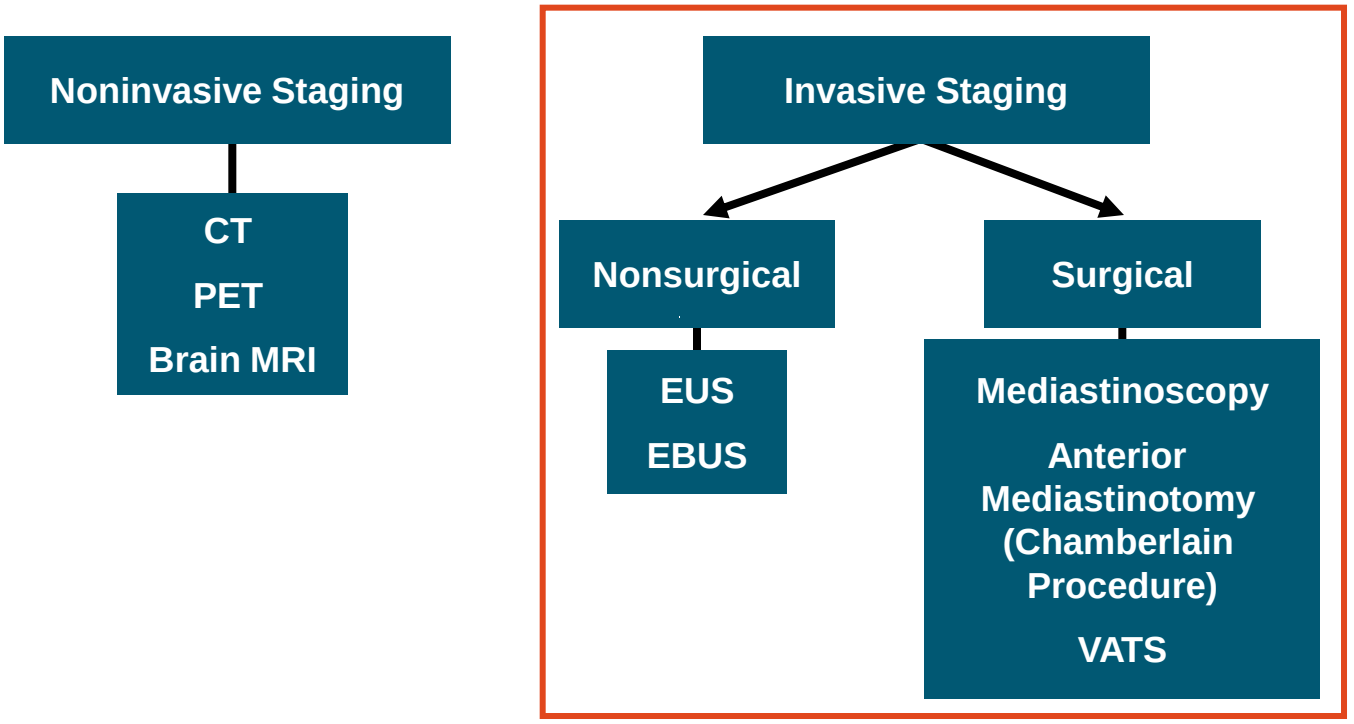
ESMO

FIGURE 4. [Sections 2.0, 4.1] Definition of intrathoracic radiographic categories of lung cancer.

Group	Description	Definition (by chest CT scan)
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured[a]
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes ≥ 1 cm in short-axis diameter on a transverse CT image
C	Clinical stage II or central stage I tumor	Normal mediastinal nodes (< 1 cm) but enlarged N1 nodes (≥ 1 cm) or a central tumor (within proximal one-third of the hemithorax)
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes (< 1 cm) and a peripheral tumor (within outer two-thirds of hemithorax)


A
C
B
D

Mediastinal Staging for Lung Cancer



Why Do Invasive Staging?

- Accuracy of CT and PET staging in mediastinal lymph nodes from
  43 CT and 45 PET trials

Modality, %	Sensitivity	Specificity
CT (N = 7368)	55	81
PET (N = 4105)	80	88

Silvestri. Chest. 2013;143(suppl):e211S.

Accuracy Comparison of Staging Tests for NSCLC

Procedure	No. of Studies	N	Sensitivity, %	Specificity, %
Mediastinoscopy	35	10,648	81	100
EUS	26	2443	89	100
EBUS	26	2756	89	100
EBUS/EUS	7	811	91	100

Silvestri. Chest. 2013;143(suppl):e211S. VanderLaan. Cancer Cytopathol. 2014;122:561.

CHEST Commentary

Classification of the Thoroughness of Mediastinal Staging of Lung Cancer

Frank Detterbeck, MD, FCCP; Jonathan Puchalski, MD; Ami Rubinowitz, MD; and David Cheng, MD

Table 1—*Classification of Type and Thoroughness of Clinical Mediastinal Staging of Lung Cancer*

Type/Name	Description	Thoroughness	Detailed Definition
1/Surgical	Mediastinoscopy, Chamberlain, VATS	A, Complete removal[a]	Complete lymphadenectomy by TEMLA or VAMLA (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor)
		B, Systematic sampling[a]	Mediastinoscopy with sampling/exploration of 2R, 2L, 4R, 4L, 7, and 5, 6 if LUL tumor
		C, Selective sampling	Mediastinoscopy with biopsy of ≥ 1 station, and must include any node suspicious by imaging
		D, Poor	Mediastinoscopy with visual assessment only; no node biopsy or no nodal tissue in samples
2/Needle-based	EUS-NA, EBUS-NA, TBNA, TTNA	A, Complete sampling[a]	Sampling of each visible node in each station (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor), ≥ 3 passes per node or ROSE[b]
		B, Systematic sampling[a]	Nodes in each station sampled (2R, 4R, 7, 4L, 2L, and 5, 6 if LUL tumor), ≥ 3 passes per node or ROSE[b]
		C, Selective sampling	Biopsy of ≥ 1 station, which must include a node suspicious by imaging or ≥ 1 cm by US if present, or < 3 passes and no ROSE
		D, Poor	Visual assessment only; no node biopsied or no lymphatic tissue in aspirates
3/Metabolic	PET	A, Complete assessment	Integrated CT/PET, glucose < 200, clear identification for each mediastinal and N1 node station whether nodes have uptake > mediastinal background or not
		B, Systematic assessment	Dedicated PET, clear identification for each mediastinal and N1 node station whether nodes have uptake > mediastinal background or not
		C, Selective assessment	Vague description of level of PET uptake or location of suspicious nodes, or PET read without CT correlation
		D, Poor	No PET uptake in primary tumor or no dedicated PET scanner
4/Radiologic	CT	A, Complete assessment	IV contrast, ≤ 5-mm slice. For each mediastinal and hilar N1 node station the size of the largest node is provided
		B, Systematic assessment	Clear identification for each mediastinal and N1 node station whether nodes are enlarged or not (≥ 1 cm[c]), ≤ 8-mm slice, ± contrast
		C, Selective assessment	Mediastinal nodes ≥ 1 cm[b] identified in report, but not by station, ± contrast
		D, Poor	Unclear definition of abnormal nodes and/or location of nodes

Recommendations

- Mediastinal nodal staging in patients with suspected or proven non-small-cell lung cancer (NSCLC) with abnormal mediastinal and/or hilar nodes at computed tomography (CT) and/or positron emission tomography (PET), endosonography is recommended over surgical staging as the initial procedure (*Recommendation grade A).*

- Subsequent surgical staging is recommended, when endosonography does not show malignant nodal involvement *(Recommendation grade B).*

*Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (**ESGE**) Guideline, in cooperation with the European Respiratory Society (**ERS**) and the European Society of Thoracic Surgeons (**ESTS**) Endoscopy 2015; 47: 545–559*

Recommendations

- For mediastinal staging in patients with centrally located suspected or proven NSCLC without mediastinal or hilar involvement at CT and/or CTPET, we suggest performance of EBUS-TBNA, with or without EUS-(B)-FNA, in preference to surgical staging

  (Recommendation grade D).

- For mediastinal nodal staging in patients with suspected or proven non-small-cell peripheral lung cancer without mediastinal involvement at CT or CT-PET, we suggest that EBUS-TBNA and/or EUS-(B)-FNA should be performed before therapy, provided that one or more of the following conditions is present:
  (i) enlarged or FDG-PET(+) ipsilateral hilar nodes;
  (ii) primary tumor without FDG uptake;
  (iii) tumor size ≥3cm

  (Recommendation grade C).

*Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (**ESGE**) Guideline, in cooperation with the European Respiratory Society (**ERS**) and the European Society of Thoracic Surgeons (**ESTS**) Endoscopy 2015; 47: 545–559*

UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

TNM Classification according to the IASLC Proposals

TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB

Lectus adv.

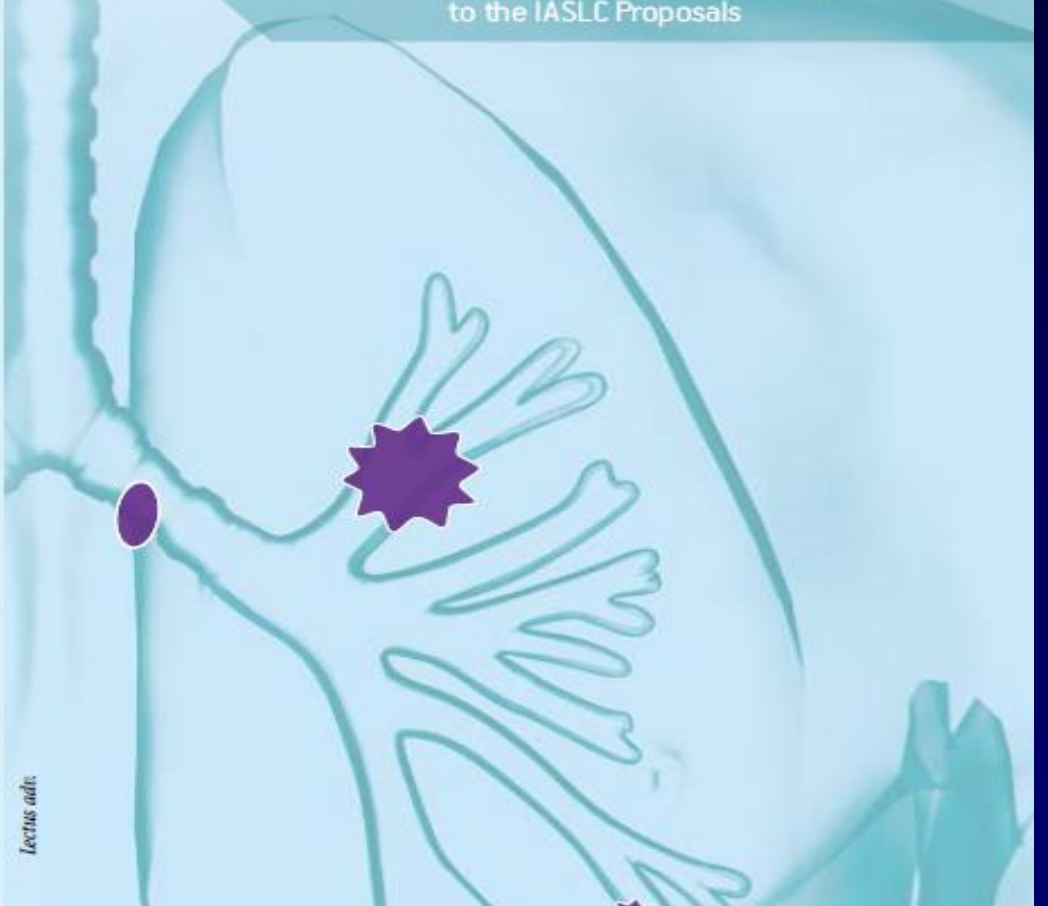
UPDATED
2016

Non-Small Cell Lung Cancer Staging Atlas

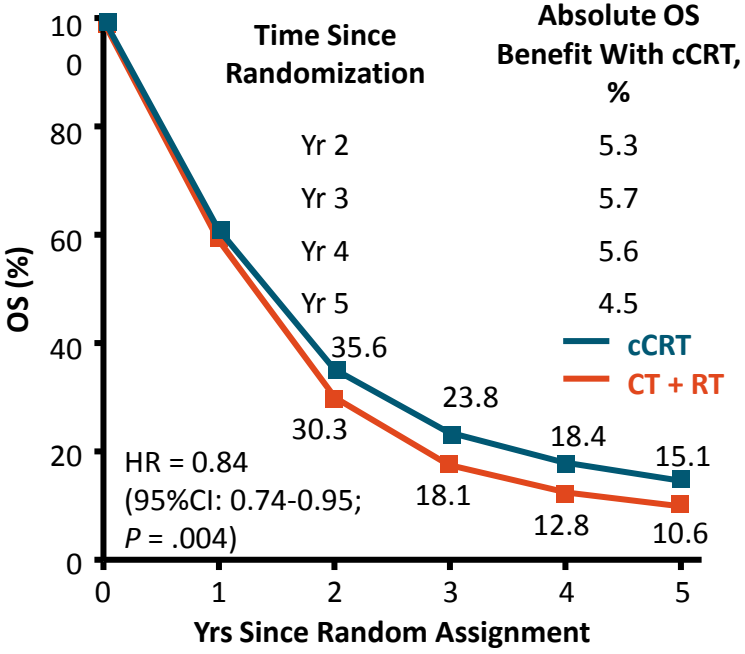
TNM Classification according to the IASLC Proposals

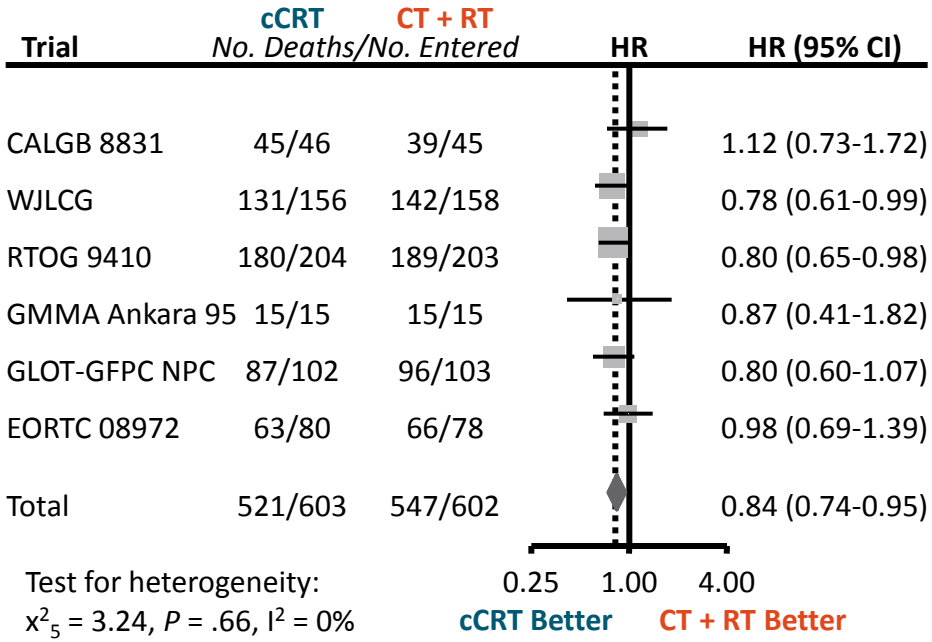
TNM Classification according to the IASLC Proposals, updated 2016

	N0	N1	N2	N3	M1a-1b any N	M1c any N
T1a	IA1	IIB	IIIA	IIIB	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVB



Meta-analysis of Concurrent CRT vs Sequential CT + RT in Locally Advanced NSCLC: OS





Median follow-up: 6 yrs
cCRT effect: *P* = .004

Auperin. J Clin Oncol. 2010;28:2181.

Stage III Unresectable NSCLC: Survival Outcomes Using Recommended CRT Regimens

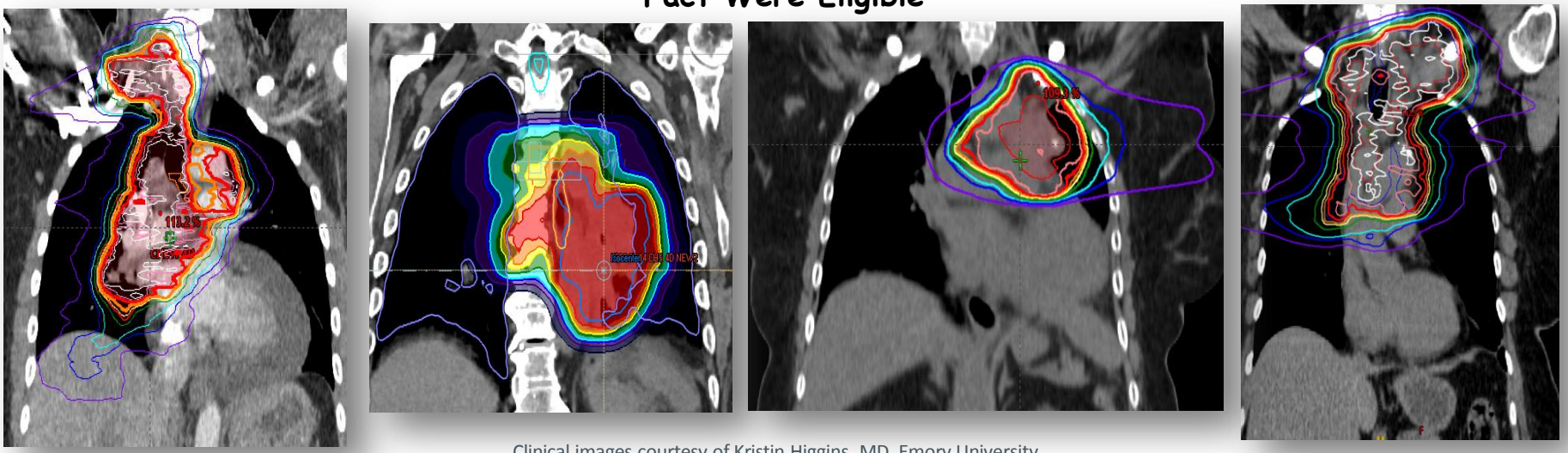
Trial	Regimen	Disease Stage	Median Survival, Mos
SWOG 9019[1]	Cisplatin/etoposide + XRT[1]	IIIB	OS: 15
LAMP[2]	Carboplatin/paclitaxel + XRT[2]	IIIA/B	OS (CT → RT): 13.0 OS (CT → CT + RT): 12.7 OS (RT + CT → CT): 16.3
PROCLAIM[3]	Cisplatin/pemetrexed + XRT[3]	IIIA/B (nonsquamous)	OS: 26.8 (vs 25.0 for cisplatin/etoposide + XRT) **PFS: 11.4 vs 9.8**

1. Albain KS, et al. J Clin Oncol. 2002;20:3454-3560. 2. Belani CP, et al. J Clin Oncol. 2005;23:5883-5891. 3. Senan S, et al. J Clin Oncol. 2016;34:953-962.

We Need to Ensure That All Eligible Patients With Stage III NSCLC Receive Concurrent Chemoradiation

- Vast majority of patients with stage III NSCLC are eligible for concurrent CRT but registry data show that 50% or fewer of these patients receive it

Selected Treatment Plans of Patients With NSCLC Who Were Deemed Not to Be Candidates for CRT but in Fact Were Eligible

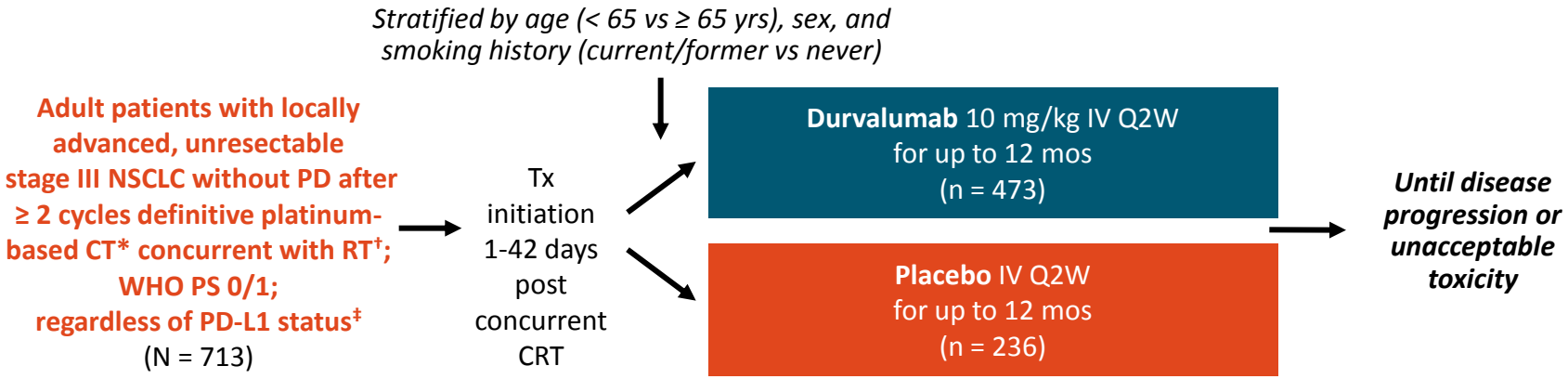


Clinical images courtesy of Kristin Higgins, MD. Emory University.

Ahmed. Clin Lung Cancer. 2017;18:706.

PACIFIC: Study Design

- Randomized, double-blind, placebo-controlled phase III trial



*Platinum-based CT contained etoposide, vinorelbine, paclitaxel, docetaxel, vinblastine, or pemetrexed.
†92% of patients received 54 Gy to 66 Gy RT dose. **‡If available, archived pre-cCRT tumor tissue tested for PD-L1.**

- Co-primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints including: ORR, DoR, TTDM by BICR, PFS2 by investigator, safety, PROs

Antonia. N Engl J Med. 2017;377:1919. Antonia. WCLC 2018. Abstract PL02.01. Antonia. N Engl J Med. 2018;379:2342.

Questions That ARE Addressed……

- Do we recommend durvalumab after sequential chemotherapy and radiation therapy in patients who are not candidates for concurrent treatment due to frailty and other comorbidities?
- Do we recommend durvalumab in patients who do not recover well from concurrent CRT and cannot start durvalumab within 2-6 wks of treatment?
- Do we recommend durvalumab in patients with driver mutations after concurrent therapy?
- Mandatory biomarkers?
- Required early Response assessment
- PET-CT scan after Chemo-RT?
- How would you treat a patient with stage III NSCLC who progresses to metastatic disease on or after durvalumab?

Questions That ARE Addressed…..

- What is the optimal treatment duration?
- When should PD-(L)1 inhibition start (induction, concurrent, maintenance)?
- The role of Surgery?
- Radiotherapy Dose?

Conclusions…….

- Stage III, locally advanced NSCLC is heterogeneous with the majority of patients having unresectable tumors
  - 8th edition of the TNM classification for lung cancer divides stage III into 3 subgroups, stage IIIA, IIIB, and IIIC
  - Experts recommend invasive staging procedures for NSCLC
  - ***Multidisciplinary management is critical***

- Before era of immunotherapy, concurrent CRT ± induction chemotherapy demonstrated 20% to 25% "cure" rate
  - Multiple strategies to improve survival in this setting tested without success

- Advanced RT technologies have led to safer and more efficacious treatment of patients with stage III NSCLC, yet according to registry data, 50% or fewer of these patients receive concurrent CRT
  - All eligible patients with stage III NSCLC should receive concurrent CRT

Conclusions….

- RT induces multiple immunomodulatory changes that may influence immunotherapy efficacy

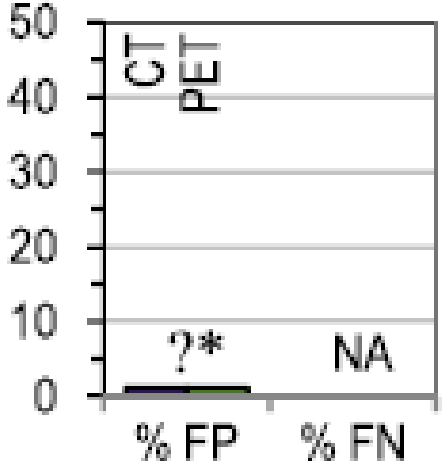
- In patients with unresectable stage III NSCLC and a good PS, concurrent platinum-based CRT followed by consolidation durvalumab is SoC
  - **PACIFIC** trial has changed the approach in unresectable stage III NSCLC

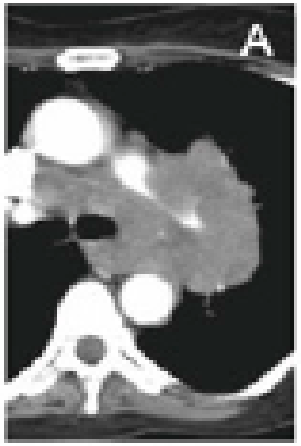
- Clinical trials should be prioritized to continue progress in this setting

"We have to use all the help that we can get"

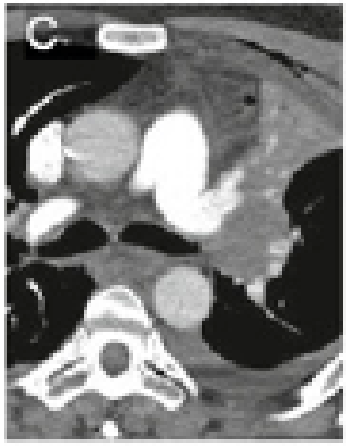
Confirmation of Intrathoracic Stage

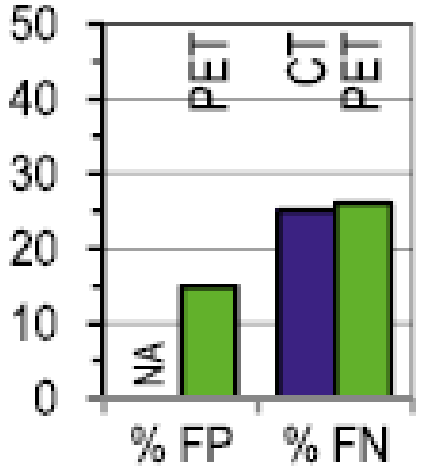
Extensive Infiltration

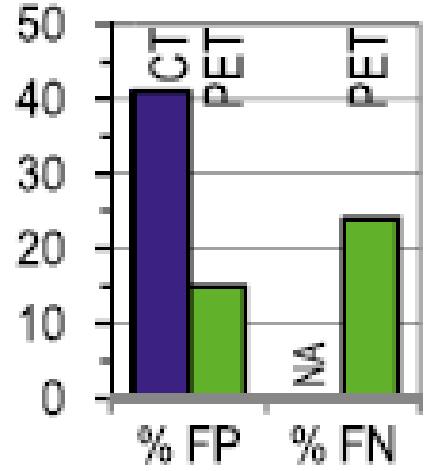


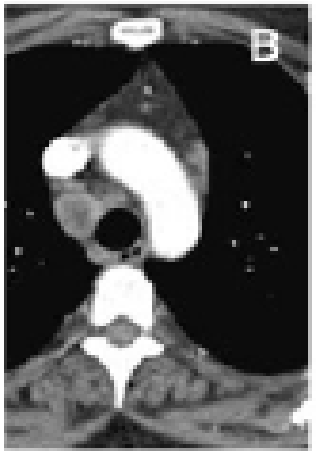


CT negative but central, N1

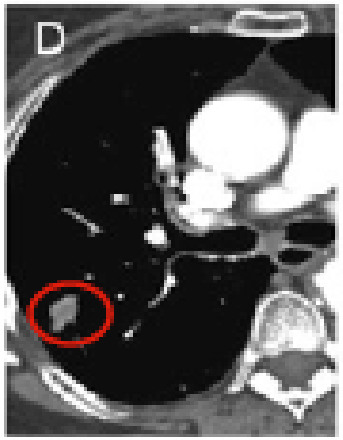


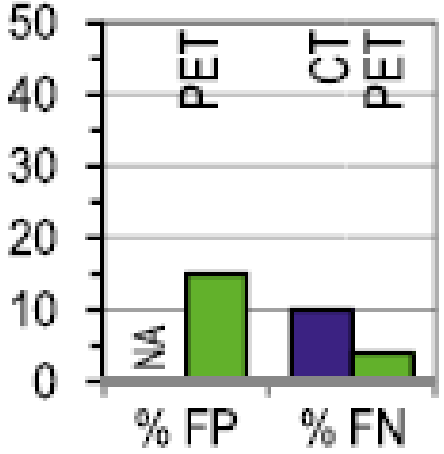






Discrete N2,3 enlargement





Peripheral stage cI

Bayes' Theorem

Prior probability of "H"

Likelihood of the evidence "E" if the hypothesis "H" is true

$$\underbrace{P(\mathrm{H}|\mathrm{E})}_{\text{Posterior}} = \frac{\overbrace{P(\mathrm{H})}^{\text{Prior}} \overbrace{P(\mathrm{E}|\mathrm{H})}^{\text{Likelihood}}}{\underbrace{P(\mathrm{E})}_{\text{Prior}}}$$

Posterior probability of "H" given the evidence

Prior probability that the evidence itself is true

Combined Modality Therapy in Stage III NSCLC: Concurrent vs Sequential Chemoradiotherapy

- Meta-analysis of **concurrent CRT** vs sequential CRT in 6 trials of locally advanced NSCLC (N = 1205)
  - ↑ OS (HR: 0.84; *P* = .004)
  - ↑ PFS (HR: 0.90; *P* = .07)
  - ↓ risk of locoregional progression (HR: 0.77; *P* = .01)
  - No difference in rates of distant progression between strategies
  - Acute esophageal toxicity (grade 3/4) increased from 4% to 18% (RR: 4.9; 95% CI: 3.1-7.8; *P* < .001)
  - No difference in acute pulmonary toxicity

Aupérin. J Clin Oncol. 2010;28:2181.

Evaluate and Sample Contralateral Mediastinal Lymph Nodes, if Present

- When performed for diagnosis and staging purposes, however, EBUS-TBNA should be performed first from N3 nodes, followed by N2 nodes and for diagnosis, when necessary N1 nodes

- If N3 nodes were found to be positive for malignancy on rapid on-site cytological evaluation, the procedure could be terminated

*Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (**ESGE**) Guideline, in cooperation with the European Respiratory Society (**ERS**) and the European Society of Thoracic Surgeons (**ESTS**) Endoscopy 2015; 47: 545–559*