EVIDENCE BASED MANAGEMENT OF STAGE III NSCLC

MILIND BALDI

Overview

- Introduction
- Diagnostic work up
- Treatment
    - Group 1
    - Group 2
    - Group 3

Stage III lung cancer

- Historically was defined as
  - locoregionally advanced disease
    - attributed to primary tumor extension into extrapulmonary structures (T3 or T4)
    - Or mediastinal lymph node involvement (N2 or N3)
    - Without evidence of distant metastasis (M0)

Stage III A	T1a,b	N2	M0
	T2a,b	N2	M0
	T3	N 1, N2	M0
	T4	N 0, N1	M0
Stage III B	T1a,b	N3	M0
	T2a,b	N3	M0
	T3	N3	M0
	T4	N2	M0

- IASCLC data base

20 % patients → cIIIA → 5 year survival → 16%

3% patients → cIIIB → 5 year survival → 7%

- Stage III represents a heterogeneous population

IASLC	TNM subset	Definition	Description
III A	T1-3, N2	Occult N2	Found at surgery •Microscopic N2 •Macroscopic N2
III A	T1-3, N2	Potentially resectable	Minimal N2
III A	T1-3, N2	Potentially resectable, but at risk of incomplete resection	Pancoast subset, Centrally located III A
III A	T1-3, N2	Unresectable N2	Bulky N2
III A	T4, N0-1	Potentially resectable, but at risk of incomplete resection	Pulmonary artery, carina, spine, trachea, vena cava, right atrium

IASLC	TNM subset	Definition	Description
III B	T4 N0-1	Unresectable T4	Oesophagus, heart, aorta, pulmonary veins
III B	T1-4, N3	Unresectable N3	N3 nodes at staging

Heterogeneity

Histopathology	Squmaous, adeno, large cell
Tumor location and extension	T4N0 vs T1N3
Individual patient risk profile	Smokers vs non smokers Cardiopulmonary risks
Inter institution diversity	Expertise in •Thoracic surgery •Radiation oncology

J Clin Oncol 2005; 23: 2955–2961
J Thorac Oncol 2009; 4: 62–68
Eur Respir J 2009; 34: 17–41

CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Treatment of Stage III Non-small Cell Lung Cancer

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians

doi:10.1093/annonc/mdv187
Published online 20 April 2015

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 4.2016

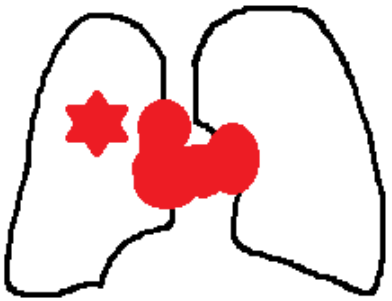
NCCN.org

Three readily identifiable groups

1. Patients with infiltrative stage III (N2/N3) tumors
2. Patients with occult N2 node involvement despite thorough preoperative staging, and
3. Patients with discrete clinically evident (by CT or CT-PET scan) N2 involvement.

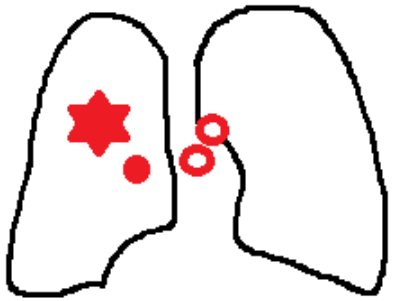
Infiltrative stage III (N2/N3) tumors

- Patients with infiltrative N2/N3 involvement have N2 or N3 disease where discrete nodes can no longer be clearly distinguished and measured
- invasive proof of mediastinal involvement is not necessary



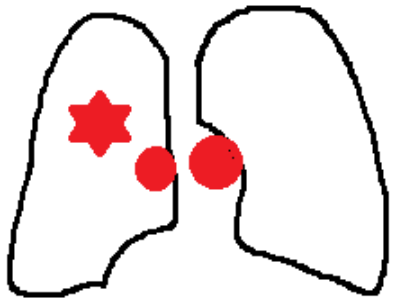
Occult N2 node involvement despite thorough preoperative staging

- Patients with occult N2 disease despite thorough preoperative staging are found intraoperatively or postoperatively to have positive N2 nodes.
- The thoroughness of the preoperative staging and intraoperative mediastinal assessment is critical.



Discrete evident (by CT or CT-PET scan) N2 involvement

- Discrete N2 involvement denotes patients in whom individual mediastinal nodes can be distinguished.
- These nodes may be enlarged or normal sized and may be suspected by PET uptake
- Mediastinal stage suggested by imaging in these patients must be confirmed thorough invasive staging



Best managed by…

- Multidisciplinary team
- High volume centers
- in a clinical trial

J Clin Oncol 2013; 31: 3141–3146
Ann Oncol 2013; 24(Suppl 6): vi89–vi98.

multidisciplinary team including

- pulmonologists
- thoracic/ medical oncologists
- radiation oncologists
- thoracic surgeons
- integrated radiologists and nuclear medicine physicians and pathologists

Ann Oncol 2013; 24(Suppl 6): vi89–vi98.

Diagnostic work up

- Positron emission tomography–computed tomography (PET-CT)
- Invasive mediastinal staging (transbronchial needle aspiration /EBUS/EUS/ mediastinoscopy)
- Brain MRI/brain CT

Positron emission tomography–computed tomography (PET-CT)

- For initial staging of stage III NSCLC patients
- Rule out extracerebral metastases
- To initiate mediastinal lymph node sampling

Lancet. 2002 Apr 20;359(9315):1388-93
J Clin Oncol. 2006 Apr 20;24(12):1800-6. Epub 2006 Mar 27

Invasive mediastinal staging

Ann Thorac Surg. 2005 Oct;80(4):1207-13; discussion 1213-4.

Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial.

Cerfolio RJ[1], Bryant AS, Ojha B, Eloubeidi M.

⊕ Author information

Abstract

BACKGROUND: Clinical stage affects the care of patients with nonsmall cell lung cancer.

METHODS: This is a prospective trial on patients with suspected resectable nonsmall cell lung cancer. All patients underwent integrated positron emission tomographic scanning and computed tomographic scanning, and all suspicious metastatic sites were investigated. A, T, N, and M status was assigned. If N2, N3 and M1 were negative, patients underwent thoracotomy and complete thoracic lymphadenectomy.

RESULTS: There were 383 patients. The accuracy of clinical staging using positron emission tomographic scanning and computed tomographic scanning was 68% and 66% for stage I, 84% and 82% for stage II, 74% and 69% for stage III, and 93% and 92% for stage IV, respectively. N2 disease was discovered in 115 patients (30%) and was most common in the subcarinal lymph node (30%). Unsuspected N2 disease occurred in 28 patients (14%) and was most common in the posterior mediastinal lymph nodes (subcarinal, 38%; posterior aortopulmonary, 15%). It was found in 9% of patients who were clinically staged I (58% in the posterior mediastinal lymph nodes) and in 26% of patients clinically staged II (86% in posterior mediastinal lymph nodes).

CONCLUSIONS: Despite integrated positron emission tomographic scanning and computed tomographic scanning, clinical staging remains relatively inaccurate for patients with nonsmall cell lung cancer. Recent studies suggest adjuvant therapy for stage Ib and II nonsmall cell lung cancer; thus the impact on preoperative care is to find unsuspected N2 disease. Unsuspected N2 disease is most common in posterior mediastinal lymph nodes inaccessible by mediastinoscopy. Thus one should consider endoscopic ultrasound fine-needle aspiration, especially for patients clinically staged as I and II, even if the nodes are negative on positron emission tomographic scanning and computed tomographic scanning.

PMID: 16181842 [PubMed - indexed for MEDLINE]

Invasive mediastinal staging

- In case of suspicious lesions invasive mediastinal staging may still be indicated despite PET negativity
  - primary tumour of >3 cm large axis,
  - central tumours,
  - CT-enlarged lymph nodes with small axis >1 cm

Eur J Cardiothorac Surg. 2014 May;45(5):787-98

- Endoscopic methods should be preferred as

Table 1. Characteristics of the Studies Included in the Present Meta-Analysis[a]

First Author	Year	Patients (No.)	Average Age (y)	Study Design	Patient Enrollment	Confirmation of EBUS-TBNA–Positive Results	Stations Examined by EBUS-TBNA	Sensitivity (%)	Specificity (%)
Yasufuku [16]	2004	108	65.3	Prospective	ND	Open thoracotomy, thoracoscopy, or clinical follow-up	2, 3, 4, 7	94.6	100
Yasufuku [17]	2006	102	67.8	Prospective	ND	Thoracotomy with complete mediastinal lymph node dissection	1, 2, 4, 5, 7	92.3	100
Yasufuku [18]	2011	153	66.8	Prospective	ND	Mediastinoscopy	2, 4, 7	81	100
Lee [15]	2008	102	64.3	Prospective	ND	...	2, 4, 7	69.8	100
Jhun [12]	2012	151	65	Retrospective	ND	Operation	1, 2, 3, 4, 7	91.9	98.4
Ye [19]	2011	101	57.4	Prospective	ND	Cytology, surgical results, and/or clinical follow-up	2, 4, 7, 8	95.08	100
Herth [13]	2006	100	58.9	Prospective	Consecutive	Mediastinoscopy or thoracotomy	2, 4, 7	92.3	100
Herth [14]	2008	97	52.9	Prospective	Consecutive	Mediastinoscopy or thoracotomy	4, 7	89	100
Vincent [10]	2008	152	59.9	Retrospective	Consecutive	Mediastinoscopy or lung resection	2, 3, 4, 7	99.1	100

[a] All of the studies had patients selected on the basis of positive results on computed tomography or positron emission tomography.

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; ND = not defined.

Ann Thorac Surg 2013;96:1502–7

- In case of negative endoscopic findings, and high suspicion of mediastinal node involvement, surgical staging is indicated

Ann Thorac Surg 2013;96:1502–7

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European Journal of Cardio-thoracic Surgery 32 (2007) 1–8

EUROPEAN JOURNAL OF
CARDIO-THORACIC
SURGERY

www.elsevier.com/locate/ejcts

ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

Paul De Leyn [a,*], Didier Lardinois [b], Paul E. Van Schil [c], Ramon Rami-Porta [d], Bernward Passlick [e], Marcin Zielinski [f], David A. Waller [g], Tony Lerut [a], Walter Weder [b]

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[b] *Department of Thoracic Surgery, University Hospital of Zurich, Switzerland*
[c] *Department of Thoracic Surgery, University Hospital of Antwerp, Belgium*
[d] *Department of Thoracic Surgery, Hopital Mutua de Terassa, Spain*
[e] *Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Germany*
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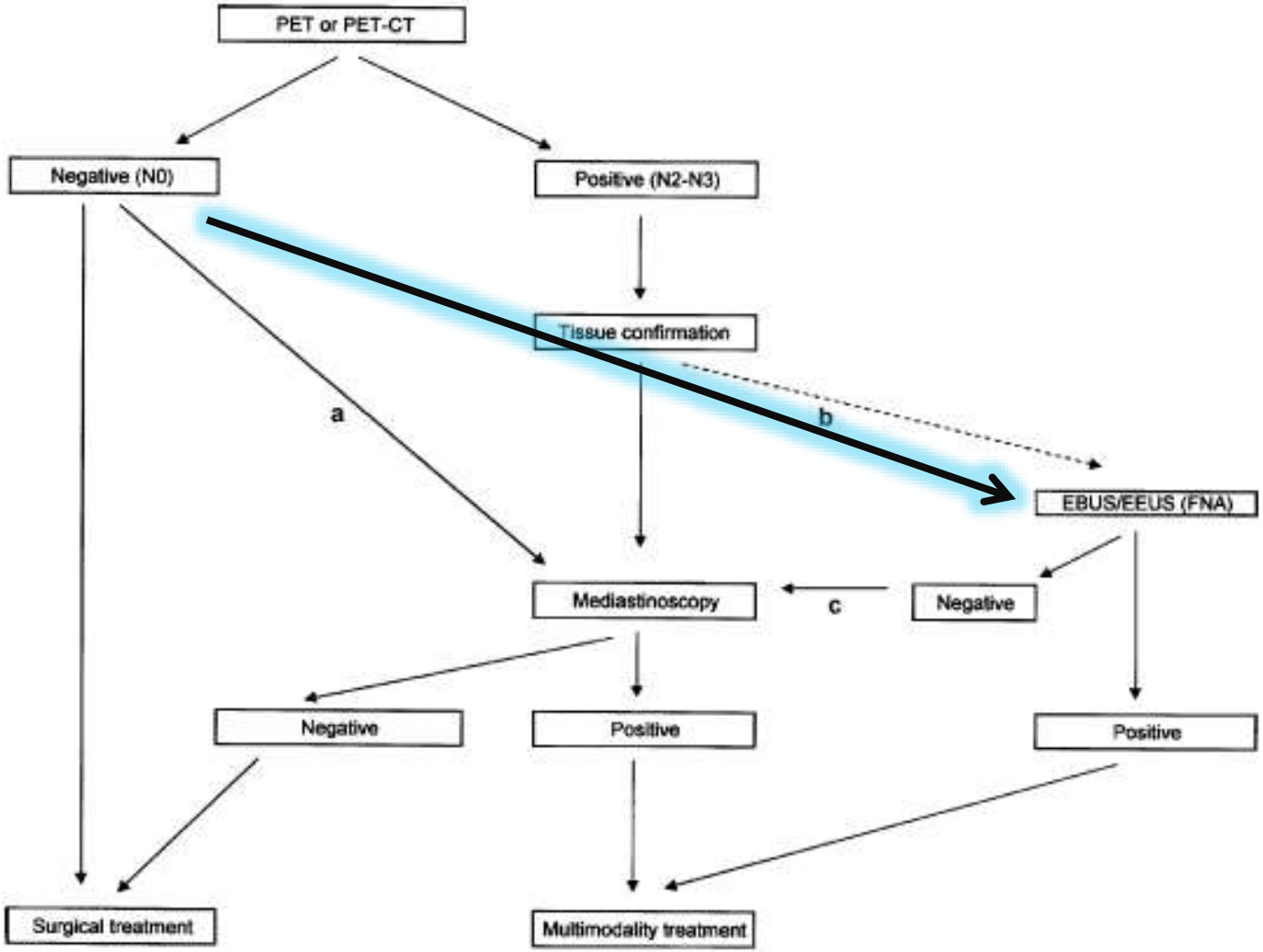
[g] *Department of Thoracic Surgery, Glenfield Hospial Leicester, United Kingdom*

Received 12 November 2006; received in revised form 28 January 2007; accepted 29 January 2007; Available online 19 April 2007



a : In central tumors, tumors with low FDG uptake, tumors with LNs ≥ 1,6 cm and/or PET N1 disease invasive staging remains indicated

b : Endoscopic techniques are minimally invasive and can be the first choice

c : Due to its higher NPV mediastinoscopy remains indicated

- If surgical staging of the mediastinum is indicated:
  - video-assisted mediastinoscopy (VAMS) is the preferred technique for upper mediastinal lymph nodes
  - video-assisted thoracoscopy (VATS) is preferred for aortopulmonary lymph nodes

Annals of Oncology 26: 1573–1588, 2015

CECT brain is a reasonable alternative.

Lung Cancer 80 (2013) 293–297

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5. Conclusion

This retrospective study of a consecutive cohort of patients suggests that there is no additive value of post contrast MRI when ^{18}FDG-PET-CT with CE-CT is performed in the diagnostic work-up of neurologically asymptomatic stage III NSCLC patients in screening for brain metastases. However, brain metastases is still an important problem as 13% of patients developed symptomatic brain metastases within 1 year after treatment with curative intent. Due to the possible impact of these findings on clinical practice a prospective trial (NTR3628) using up-to-date imaging techniques to validate these data has started.

Screening fo cell lung cancer: Is there additive value of magnetic resonance imaging above a contrast-enhanced computed tomography of the brain?

Lizza E.L. Hendriks[a,b,*], Gerben P. Bootsma[a], Dirk K.M. de Ruysscher[c,d], Nicole A.M. Scheppers[a], Paul A.M. Hofman[e], Boudewijn T. Brans[f], Anne-Marie C. Dingemans[b]

Brain MRI/Brain CT

- Patients withT4 tumours and N2 or N3 nodes
- 1RI

Table 5. Impact of limited brain MRI screening on stage determination

Stage	Before the detection of brain metastasis	After the detection of brain metastasis
I	15	13 (–2)
II	16	13 (–3)
IIIA	38	32 (–6)
IIIB	42	38 (–4)
IV	72	87 (+15)

Overall upstaging rate: 15/111 (13.5%).

Upstaging rate in patients initially considered resectable surgically: 11/69 (15.9%).

J Korean Med Sci 2005; 20: 121–126

Assessing relevant comorbidities

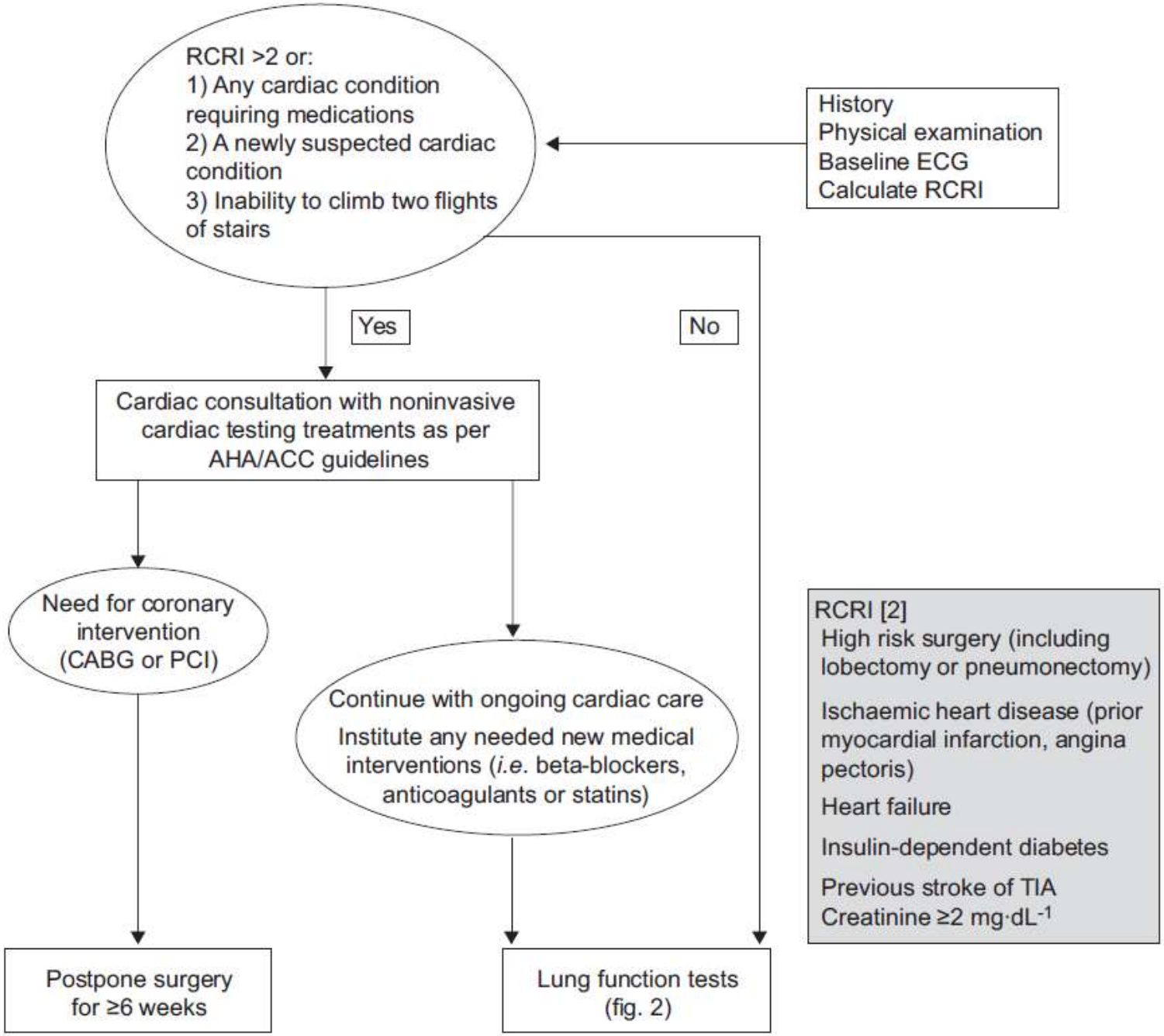
- Cardio-pulmonary functions are relevant for multidisciplinary treatment decisions.
- If surgery is planned :
  - Cardiac function: ECG, echocardiography, stress ECG, stress echocardiography or coronary angiography
  - Pulmonary function: spirometry and diffusion capacity, exercise tests (in particular, peak oxygen consumption)
- Post-radiotherapy lung function cannot be readily predicted

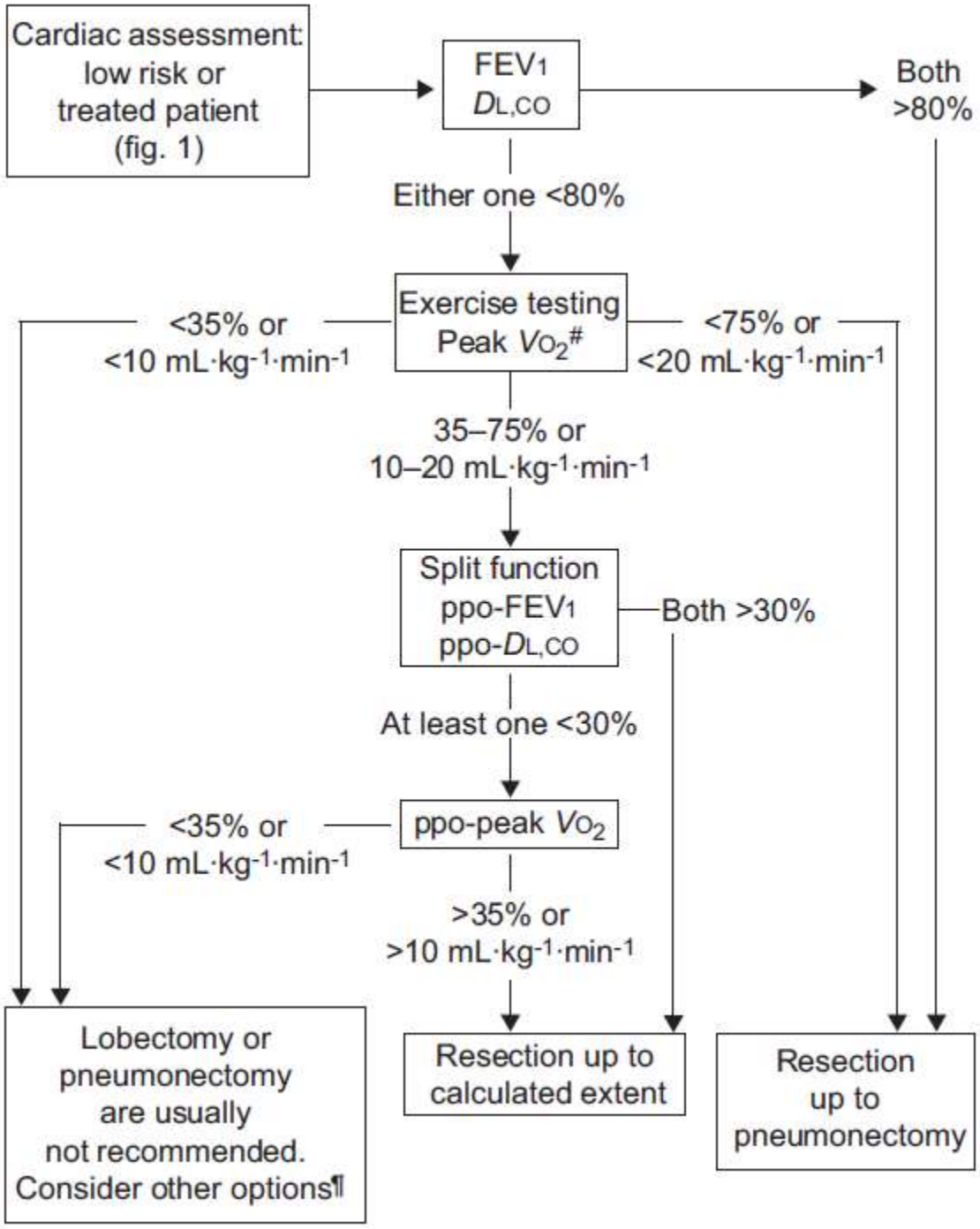
Eur Respir J 2009; 34: 17–41
DOI: 10.1183/09031936.00184308

ERS/ESTS TASK FORCE

ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy)

A. Brunelli*, A. Charloux*, C.T. Bolliger, G. Rocco, J-P. Sculier, G. Varela, M. Licker, M.K. Ferguson, C. Faivre-Finn, R.M. Huber, E.M. Clini, T. Win, D. De Ruysscher and L. Goldman on behalf of the European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy


RCRI >2 or:
1) Any cardiac condition requiring medications
2) A newly suspected cardiac condition
3) Inability to climb two flights of stairs
History
Physical examination
Baseline ECG
Calculate RCRI
Yes
No
Cardiac consultation with noninvasive cardiac testing treatments as per AHA/ACC guidelines
Need for coronary intervention (CABG or PCI)
Continue with ongoing cardiac care
Institute any needed new medical interventions (i.e. beta-blockers, anticoagulants or statins)
RCRI [2]
High risk surgery (including lobectomy or pneumonectomy)
Ischaemic heart disease (prior myocardial infarction, angina pectoris)
Heart failure
Insulin-dependent diabetes
Previous stroke of TIA
Creatinine ≥2 mg·dL-1
Postpone surgery for ≥6 weeks
Lung function tests (fig. 2)


Cardiac assessment: low risk or treated patient (fig. 1)
FEV1
DL,CO
Both >80%
Either one <80%
Exercise testing
Peak VO2#
<35% or <10 mL·kg-1·min-1
<75% or <20 mL·kg-1·min-1
35–75% or 10–20 mL·kg-1·min-1
Split function
ppo-FEV1
ppo-DL,CO
Both >30%
At least one <30%
ppo-peak VO2
<35% or <10 mL·kg-1·min-1
>35% or >10 mL·kg-1·min-1
Lobectomy or pneumonectomy are usually not recommended. Consider other options¶
Resection up to calculated extent
Resection up to pneumonectomy

- Number of preop functioning/obstructed segments should be taken into account when calculating post op predicted values.
  - T = 19 - number of obstructed segments (estimated by image techniques and/or bronchoscopy)
  - R = T - number of functioning segments to be resected
  - Pred post op values = (pre-operative value/T) x R

Eur Respir J 2009; 34: 17–41

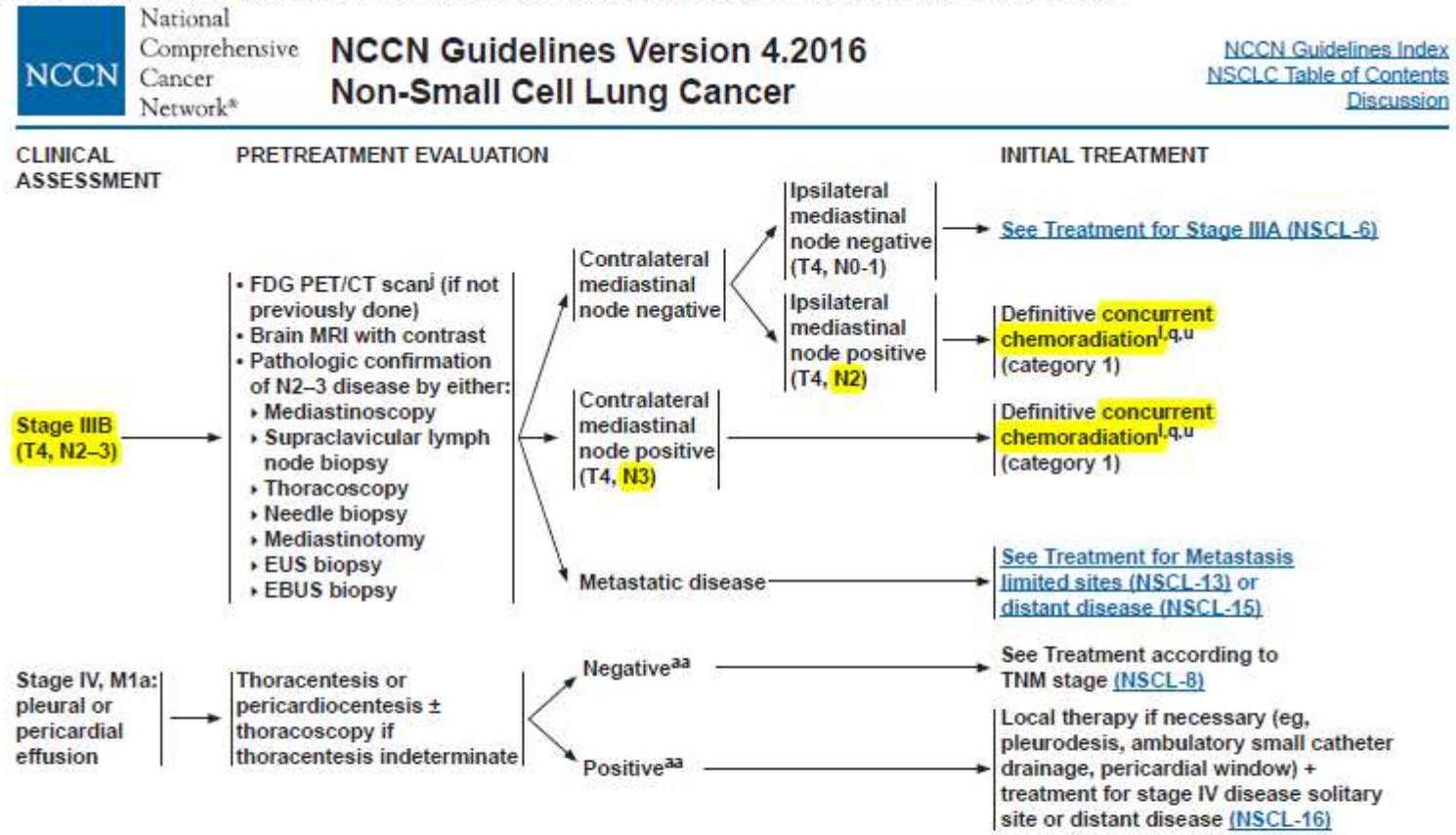
- In an obstructed right lower lobe with right pneumonectomy planned
- T= 19 – 5 = 14
- R = 14 – 5 = 9
- Post op pred = preop x 9/14

- Comorbidities are of paramount importance

The potential risk of toxicity/morbidity/mortality should be balanced with the potential benefit of any aggressive curative-intent treatment strategy

- For curative-intent management, patients should be able to undergo platinum-based chemotherapy (preferably cisplatin)
- Cisplatin can be easily administered to the majority of patients excluding only those few with significant renal failure or heart failure

Group 1: Infiltrative disease



[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

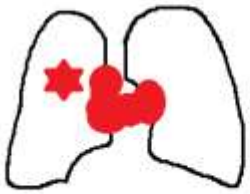
[l]See Principles of Radiation Therapy (NSCL-C).

[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

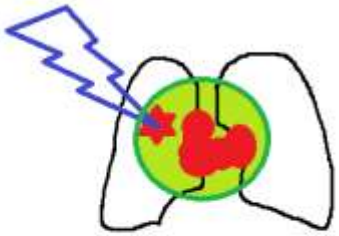
[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

[aa]While most pleural effusions associated with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



- Goal in treating the patient with stage III lung cancer seems simple:
  - to eradicate both visible, intrathoracic disease and
  - to reduce the incidence of subsequent systemic, extrathoracic metastases.



- Local control can be achieved through radiotherapy
- Systemic chemotherapy is used for two reasons:
  - As a radiosensitizing agent and
  - as a cytotoxic agent, the aim is to eradicate unsuspected or prevent de novo development of systemic metastasis

- Concurrent vs sequential ?
- Induction vs consolidative vs none ?
- Optimal dose, duration ?

Concurrent vs sequential

Author (year)	Number of patients	Result
Auperin (2010)	1,205	significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; P = .004)
O'Rourke (2010)	1,024	A significant benefit of concurrent treatment was shown in overall survival (HR 0.74, 95% CI 0.62 to 0.89;
Curran (2011)	610	Five-year survival: significantly higher for patients treated with the concurrent regimen vs sequential treatment (5-year survival: sequential: 10%; concurrent, 16% [31 patients], *P = .046*

J Clin Oncol 2010;28:2181-2190
Cochrane Database Syst Rev 2010:CD002140
J Natl Cancer Inst 2011;103:1452-1460

Analysis 2.1. Comparison 2 Concurrent vs Sequential chemoradiotherapy, Outcome 1 Overall survival.

Review: Concurrent chemoradiotherapy in non-small cell lung cancer

Comparison: 2 Concurrent vs Sequential chemoradiotherapy

Outcome: 1 Overall survival

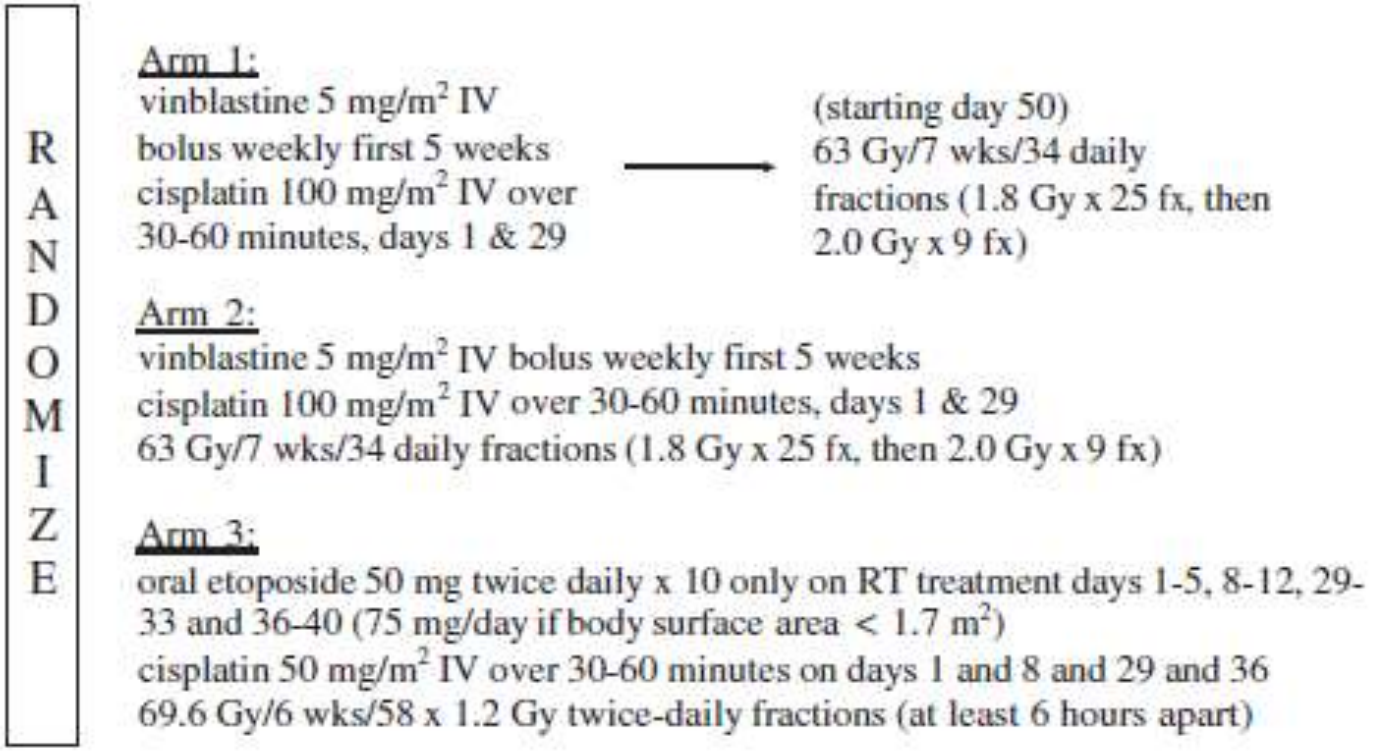
Study or subgroup	Concurrent chemoRT N	Sequential chemoRT N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Curran 2003	200	199	-0.24 (0.11)		73.8 %	0.79 [0.63, 0.98]
Fournel 2001	100	101	-0.4 (0.34)		7.7 %	0.67 [0.34, 1.31]
Zatloukal 2003	52	50	-0.49 (0.22)		18.5 %	0.61 [0.40, 0.94]
Total (95% CI)	**352**	**350**			**100.0 %**	**0.74 [0.62, 0.89]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.13$, $df = 2$ ($P = 0.57$); $I^2 = 0.0\%$

Test for overall effect: $Z = 3.16$ ($P = 0.0016$)

Test for subgroup differences: Not applicable

Cochrane Database Syst Rev 2010:CD002140



J Natl Cancer Inst 2011;103:1452-1460

Table 1. Demographics of enrolled patients*

Patient characteristic	Arm 1 (n = 195)	Arm 2 (n = 195)	Arm 3 (n = 187)	Total (n = 577)
Age, No. (%)				
<60,y	82 (42)	90 (46)	72 (39)	244 (42)
≥60,y	113 (58)	105 (54)	115 (62)	333 (58)
Median	63	60	63	62
Range	33–79	33–79	35–80	33–80
Sex, No. (%)				
Men	122 (63)	125 (64)	124 (66)	371 (64)
Women	73 (37)	70 (36)	63 (34)	206 (36)
KPS, No. (%)				
70–80	45 (23)	47 (24)	45 (24)	137 (24)
90–100	150 (77)	148 (76)	142 (76)	440 (76)
Histology, No. (%)				
Squamous	75 (38)	75 (38)	70 (37)	220 (38)
Adenocarcinoma	53 (27)	73 (37)	52 (28)	178 (31)
Large Cell	29 (15)	27 (14)	23 (12)	79 (14)
Combined	2 (1)	2 (1)	8 (4)	12 (2)
Carcinoma NOS	34 (17)	18 (9)	30 (16)	82 (14)
Other	2 (1)	0 (0)	4 (2)	6 (1)
AJCC stage, No. (%)				
II	4 (2)	3 (2)	4 (2)	11 (2)
IIIA	81 (42)	84 (43)	75 (40)	240 (42)
IIIB	110 (56)	108 (55)	108 (58)	326 (57)
Race, No. (%)				
White	167 (86)	171 (88)	161 (86)	499 (86)
Hispanic	3 (2)	2 (1)	2 (1)	7 (1)
Black or African American	20 (10)	19 (10)	17 (9)	56 (10)
Asian	3 (2)	2 (1)	5 (3)	10 (2)
Native American	0 (0)	1 (<1)	1 (<1)	2 (<1)
Other	2 (1)	0 (0)	1 (<1)	3 (1)

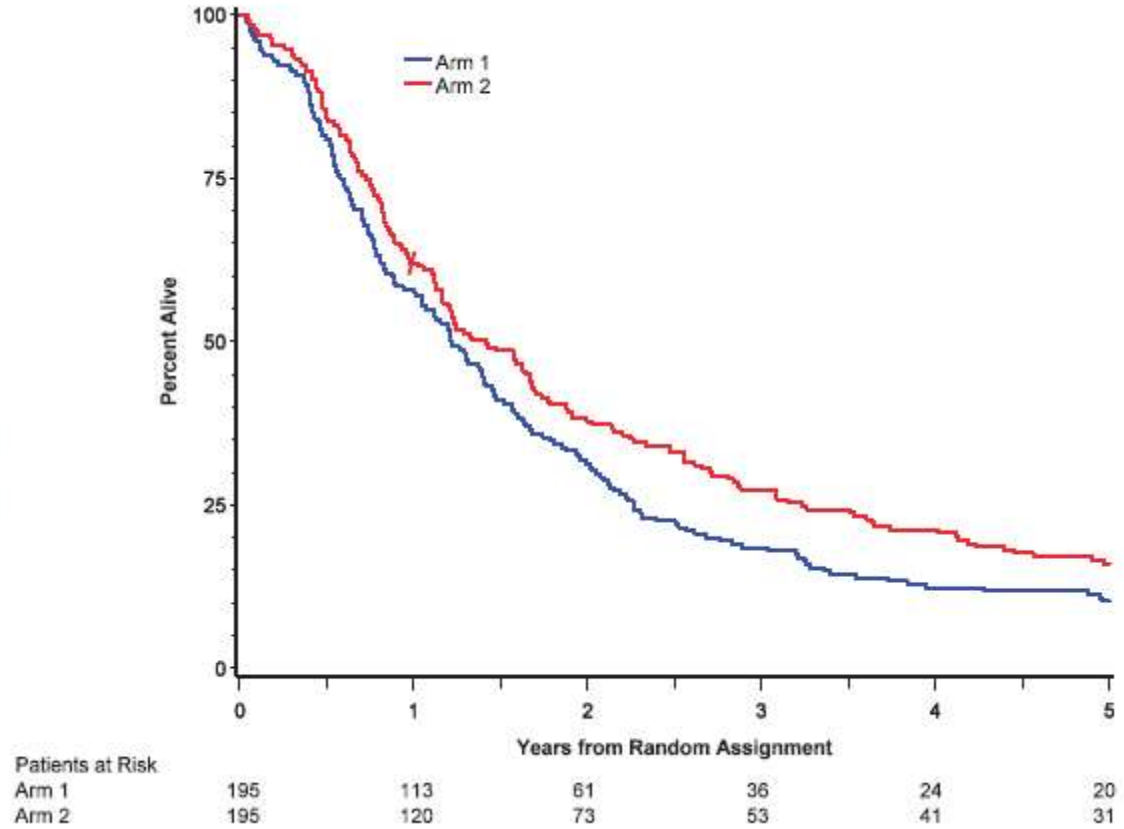


Figure 3. Five-year survival results for patients assigned to receive standard radiation with concurrent chemotherapy compared with patients assigned to receive sequential chemotherapy and radiotherapy. Hazard ratio for death = 0.812, 95% confidence interval = 0.663 to 0.996, $P = .046$, two-sided log-rank test. Total dead at any time: Arm 1 = 189 and Arm 2 = 185. **Slash marks** indicate censored observations.

- But all of the above mentioned trials have also found increased toxicity with concurrent treatment.

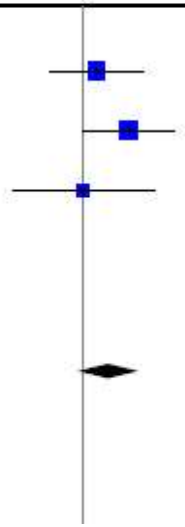
Analysis 2.6. Comparison 2 Concurrent vs Sequential chemoradiotherapy, Outcome 6 Toxicity.

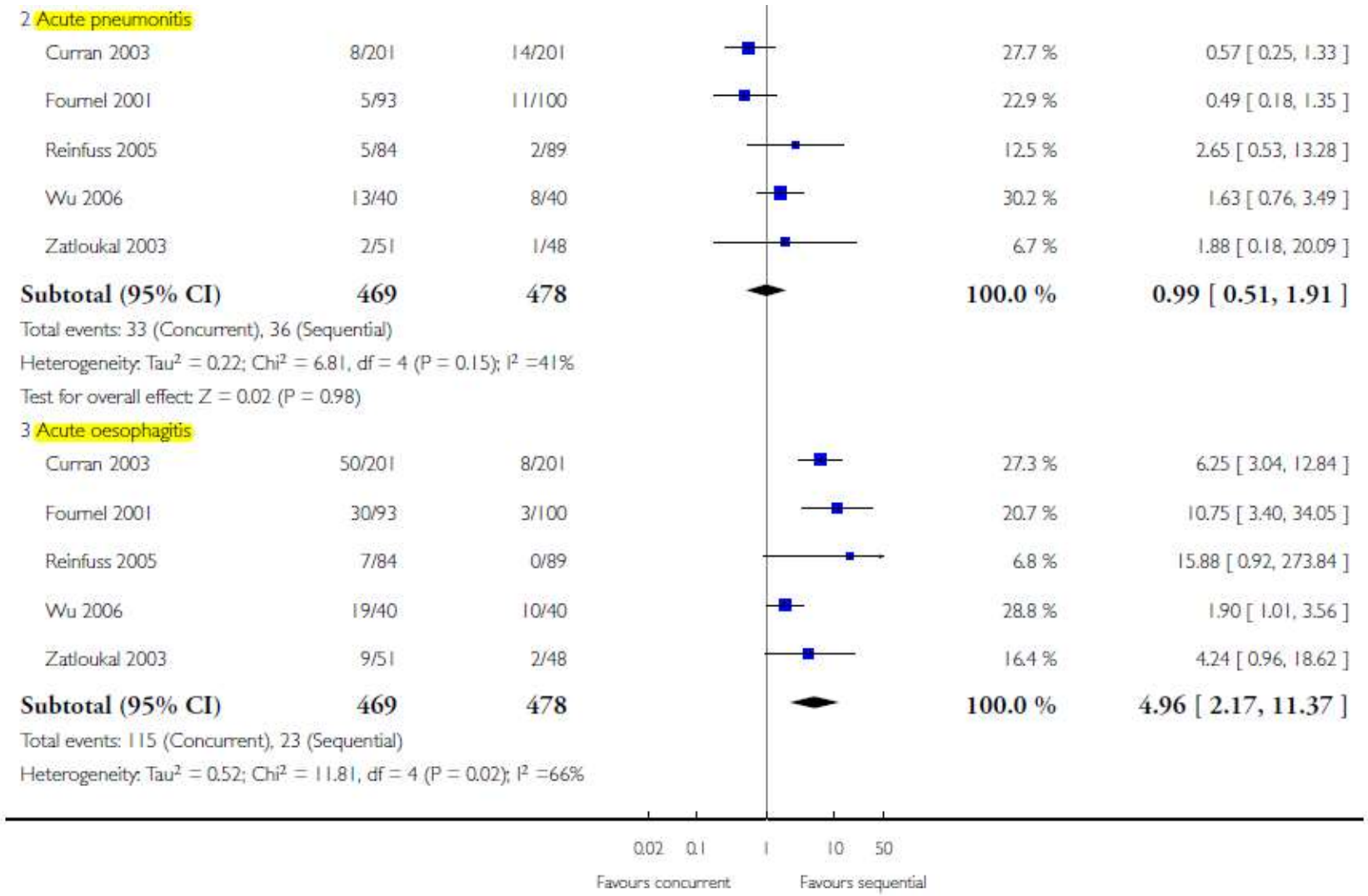
Review: Concurrent chemoradiotherapy in non-small cell lung cancer

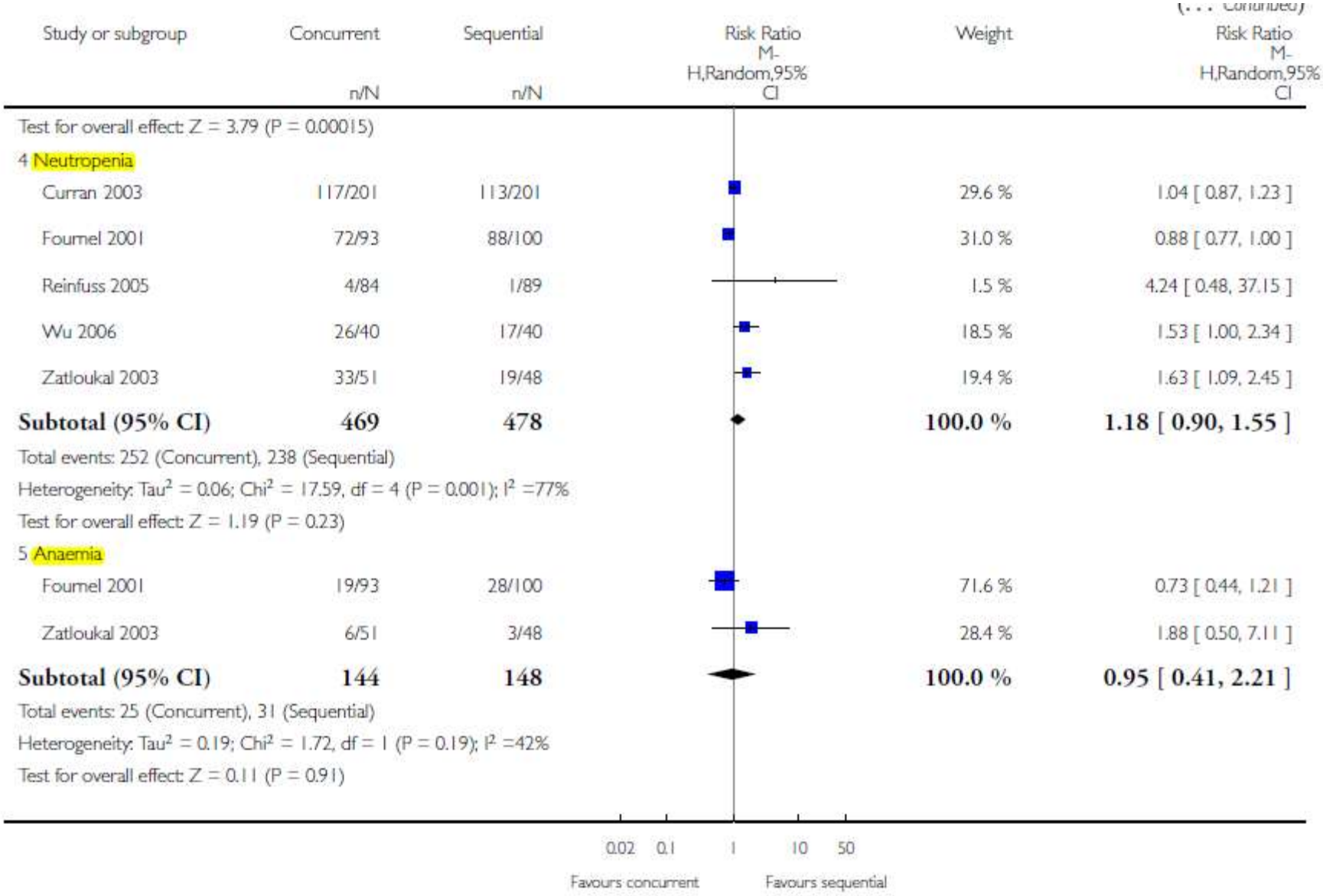
Comparison: 2 Concurrent vs Sequential chemoradiotherapy

Outcome: 6 Toxicity

Study or subgroup	Concurrent n/N	Sequential n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Treatment-related deaths					
Curran 2003	6/201	4/201		41.6 %	1.50 [0.43, 5.24]
Fournel 2001	10/93	3/100		41.0 %	3.58 [1.02, 12.62]
Reinfuss 2005	2/84	2/89		17.3 %	1.06 [0.15, 7.35]
Wu 2006	0/40	0/40			Not estimable
Zatloukal 2003	0/52	0/50			Not estimable
Subtotal (95% CI)	**470**	**480**		**100.0 %**	**2.02 [0.90, 4.52]**
Total events: 18 (Concurrent), 9 (Sequential)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.45$, df = 2 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.71 (P = 0.088)					




2 Acute pneumonitis
Curran 2003 8/201 14/201 27.7 % 0.57 [0.25, 1.33]
Fournel 2001 5/93 11/100 22.9 % 0.49 [0.18, 1.35]
Reinfuss 2005 5/84 2/89 12.5 % 2.65 [0.53, 13.28]
Wu 2006 13/40 8/40 30.2 % 1.63 [0.76, 3.49]
Zatloukal 2003 2/51 1/48 6.7 % 1.88 [0.18, 20.09]
Subtotal (95% CI) 469 478 100.0 % 0.99 [0.51, 1.91]
Total events: 33 (Concurrent), 36 (Sequential)
Heterogeneity: Tau² = 0.22; Chi² = 6.81, df = 4 (P = 0.15); I² =41%
Test for overall effect: Z = 0.02 (P = 0.98)
3 Acute oesophagitis
Curran 2003 50/201 8/201 27.3 % 6.25 [3.04, 12.84]
Fournel 2001 30/93 3/100 20.7 % 10.75 [3.40, 34.05]
Reinfuss 2005 7/84 0/89 6.8 % 15.88 [0.92, 273.84]
Wu 2006 19/40 10/40 28.8 % 1.90 [1.01, 3.56]
Zatloukal 2003 9/51 2/48 16.4 % 4.24 [0.96, 18.62]
Subtotal (95% CI) 469 478 100.0 % 4.96 [2.17, 11.37]
Total events: 115 (Concurrent), 23 (Sequential)
Heterogeneity: Tau² = 0.52; Chi² = 11.81, df = 4 (P = 0.02); I² =66%
0.02 0.1 1 10 50
Favours concurrent
Favours sequential


(... Continued)
Study or subgroup
Concurrent
n/N
Sequential
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 3.79 (P = 0.00015)
4 Neutropenia
Curran 2003 117/201 113/201 29.6 % 1.04 [0.87, 1.23]
Fournel 2001 72/93 88/100 31.0 % 0.88 [0.77, 1.00]
Reinfuss 2005 4/84 1/89 1.5 % 4.24 [0.48, 37.15]
Wu 2006 26/40 17/40 18.5 % 1.53 [1.00, 2.34]
Zatloukal 2003 33/51 19/48 19.4 % 1.63 [1.09, 2.45]
Subtotal (95% CI) 469 478 100.0 % 1.18 [0.90, 1.55]
Total events: 252 (Concurrent), 238 (Sequential)
Heterogeneity: Tau² = 0.06; Chi² = 17.59, df = 4 (P = 0.001); I² =77%
Test for overall effect: Z = 1.19 (P = 0.23)
5 Anaemia
Fournel 2001 19/93 28/100 71.6 % 0.73 [0.44, 1.21]
Zatloukal 2003 6/51 3/48 28.4 % 1.88 [0.50, 7.11]
Subtotal (95% CI) 144 148 100.0 % 0.95 [0.41, 2.21]
Total events: 25 (Concurrent), 31 (Sequential)
Heterogeneity: Tau² = 0.19; Chi² = 1.72, df = 1 (P = 0.19); I² =42%
Test for overall effect: Z = 0.11 (P = 0.91)
0.02 0.1 1 10 50
Favours concurrent
Favours sequential

Guidelines

unresectable IIIA (N2) disease and IIIB disease patients

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2016
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY (2 of 10)

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II (node positive) and stage III is concurrent chemotherapy/RT.[16-18] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf) RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemotherapy/RT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.[19,20] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/OncologyNonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf) Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).[21,22]
- RT has a role before or after surgery.
  http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf
  - Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[23] and is recommended for resectable superior sulcus tumors.[24,25]
  - Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.[26,27] The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.[28,29]
  - The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Up front multidisciplinary consultation is particularly important when considering surgical treatment of stage III NSCLC.
  - In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.[30,31] Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients[32-34] and is

Induction vs consolidation chemotherapy

treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A).

Remark: We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question.

- GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a setup margin for positioning and mechanical variability

- Commonly used dose for conventionally fractionated RT with or without chemotherapy is 60-70 Gy with a fraction size of 2 Gy over 6-7 weeks
- Dose escalation in RT alone, sequential chemoRT, or concurrent chemoRT is associated with better survival in non-randomized comparisons

Int J Radiat Oncol Biol Phys 2005;63:324-333
Int J Radiat Oncol Biol Phys 2012;82:425-434.

- Improved survival was demonstrated with accelerated fractionation RT regimens
- In PET-CT staged patients omitting elective nodal irradiation has been shown to improve survival, probably because of escalated dose.

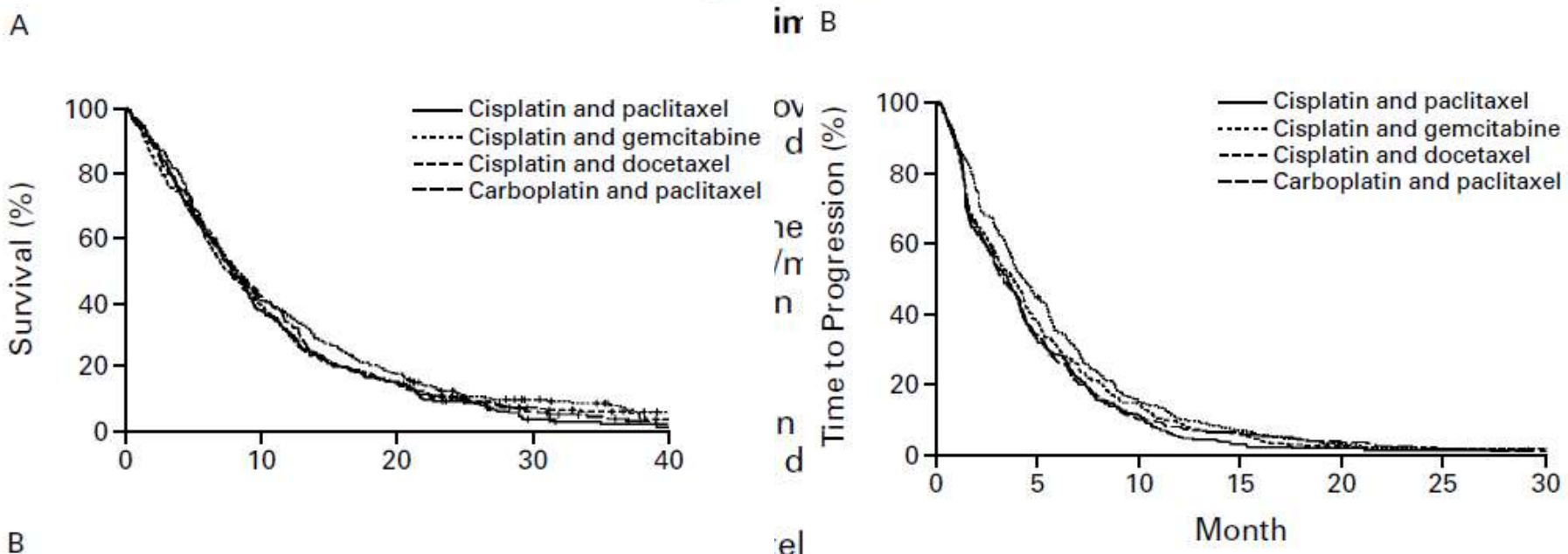
J Clin Oncol 2012;30:2788-2797

Chemotherapy vs no chemotherapy

- Objective:
  - To evaluate the effect of cytotoxic chemotherapy on survival in patients with non-small cell lung cancer
- Selection criteria:
  - Trials comparing primary treatments of surgery, surgery + radiotherapy, radical radiotherapy or supportive care versus the same primary treatment, plus chemotherapy were eligible
- Results:
  - Data from 52 trials and 9387 patients were included. The results for modern regimens containing cisplatin favoured chemotherapy in all comparisons and reached conventional levels of significance when used with radical radiotherapy and with supportive care.
- **Plain language summary**
  - **Chemotherapy can improve survival rates for non-small cell lung cancer**

Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD002139

What agent ?



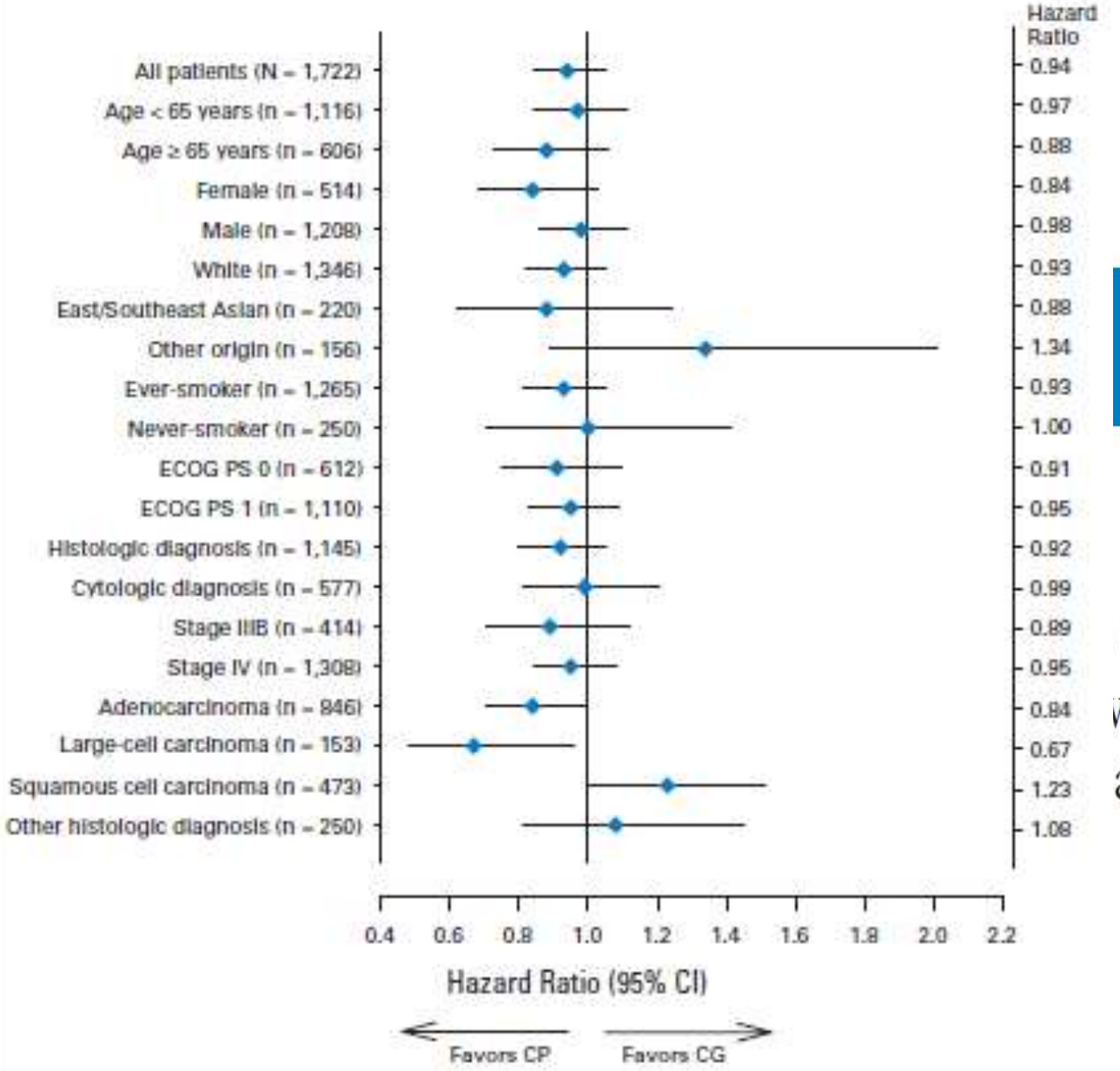
B

paclitaxel, 225 mg/m² over 3-hr period on day 1
carboplatin, AUC 6.0 mg/ml/min on day 1
3-wk cycle

N Engl J Med. 2002 Jan 10;346(2):92-8.

VOLUME 26 ·

JOURNAL OF



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J Clin Oncol. 2008 Jul 20;26(21):3543-51

A systema ess
of first-lin
with local all
cell lung c

Gerlinde Pilking drian Bagust,[1]
Rumona Dickso

Results

NSCLC population with squamous disease

In the squamous disease population, vinorelbine (oral or intravenous) doublets were shown not to be cost effective in either price scenario due to relatively poor outcomes. Paclitaxel, gemcitabine and docetaxel all lie on the efficiency frontier, but ICERs comparing interventions with better outcomes to paclitaxel exceed levels considered to be cost effective in the UK. The choice of platinum compound changes from cisplatin (base case) to carboplatin when contract drug prices are used, indicating that when drug costs are reduced, the location (and therefore cost) of administration influences cost-effectiveness estimates.

NSCLC population with non-squamous disease

In the non-squamous population, pemetrexed+cisplatin was shown to be a valid comparator to standard treatments and provides strong evidence of improved OS. However, its much higher price leads to non-competitive cost-effectiveness results.

Thorax 2015;70:359–367

National Comprehensive

NCCN Guidelines Version 4.2016

NCCN Guidelines Index

- *For curative-intent treatment of locally advanced NSCLC, concurrent chemoradiation is recommended because it* improves local contr

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chemotherapy combination

Recommendation 5.2: Most comparative studies of concurrent chemoradiotherapy versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine). There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered peri-operatively, cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].

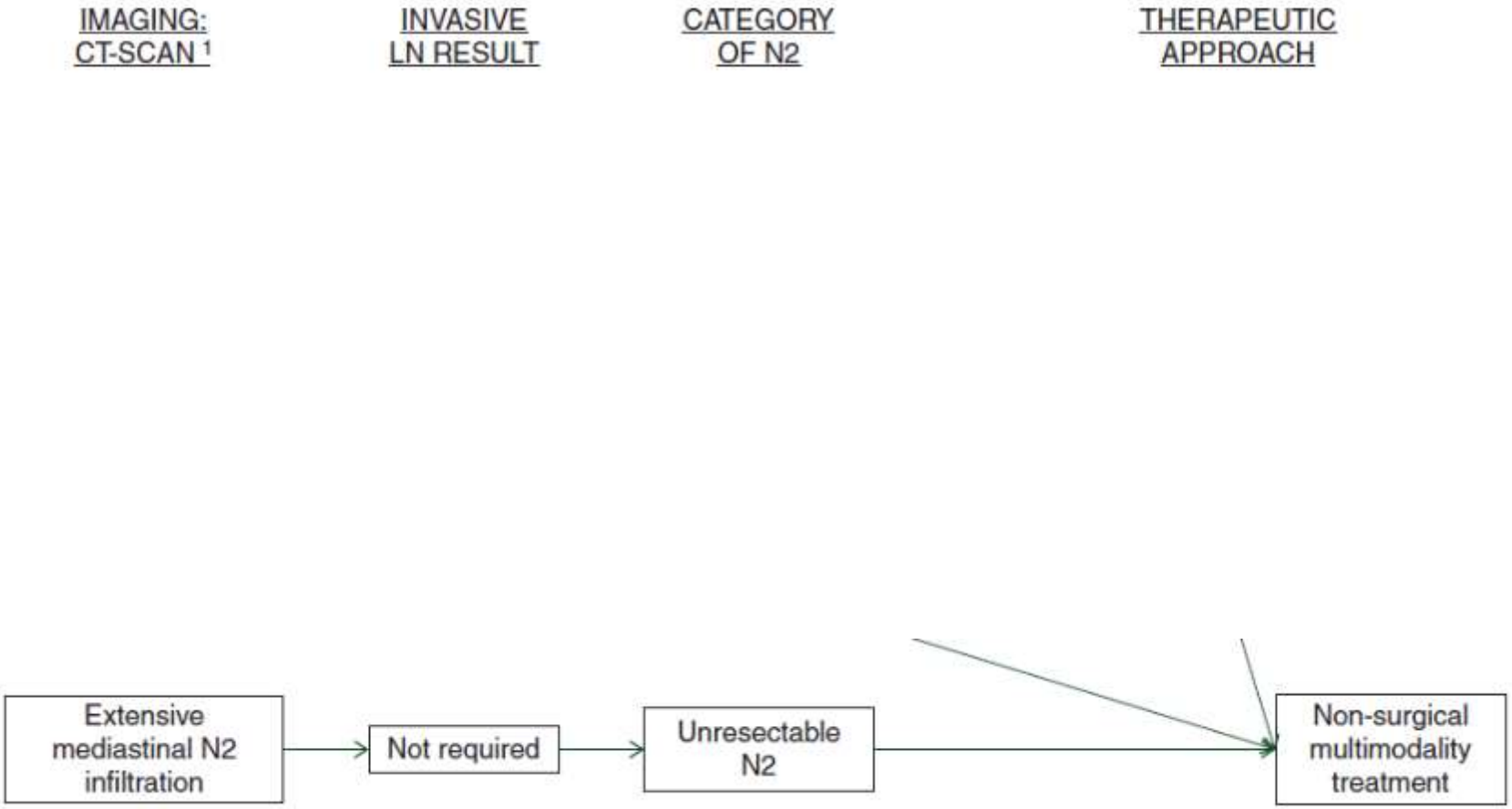
- Radiotherapy alone may be used for patients ineligible for combined modality *treatment; it may offer better* tolerability, *but poorer* survival.

- Postoperative radiotherapy *may be recommended for patients with* complete resection *of* N2 disease *to* improve local control, *but* should be delivered sequentially after *adjuvant* chemotherapy.

Number of cycles

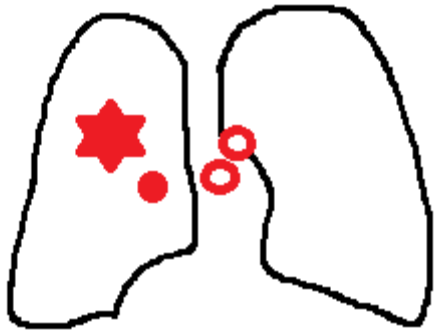
- In the stage III disease chemoradiotherapy strategy, two to four cycles of concomitant chemotherapy should be delivered.
- There is no evidence for further induction or consolidation chemotherapy.
- In the perioperative setting, three to four cycles of cisplatin-based chemotherapy are recommended
- Aim for a total cumulative dose of at least 300 mg/m2 of cisplatin in the adjuvant setting

Summary for group 1



Group 2: Occult N2 Involvement Despite Thorough Preoperative Staging

- Occult N2
- Incidental N2
- Unforeseen N2
- Unexpected N2
- Unsuspected N2



- must differentiate from
  - Ignored N2 (enlarged or PET scan positive but no biopsy specimen) or
  - underappreciated N2 (known high risk of false negative CT or PET findings but no biopsy specimen)

- True unsuspected N2
  - found intra op or post operatively
  - occurs in about 10% of surgical patients (5%-16%)

Eur J Cardiothorac Surg . 2008 ; 33 (1): 104 – 109
Ann Thorac Surg . 2006 ; 81 (3): 1013 - 1019

- If N2 nodal involvement is found at the time of surgical resection and all the involved lymph nodes and the primary tumor are technically resectable, then the surgeon should proceed with the planned lung resection along with a mediastinal lymphadenectomy.
- If a complete resection is not possible, the planned lung resection should be aborted because the average 5-year survival is < 5%.

Intraoperative handling of the mediastinum

- complete mediastinal lymph node dissection (MLND)
- systematic node sampling or
- selective sampling

- A formal MLND involves removal of all the node bearing tissues, leaving only the skeletonized trachea, phrenic nerves, aorta, and superior vena cava.
- A systematic mediastinal node sampling means that the pleura overlying each ipsilateral node station is opened and explored and representative biopsy specimens of nodes obtained.
- A selective sampling involves biopsy of only selected mediastinal nodes that are believed to be abnormal.

- Existing guidelines consistently recommend either systematic lymph node sampling or complete MLND

NSCLC adjuvant studies that included patients with stage III disease

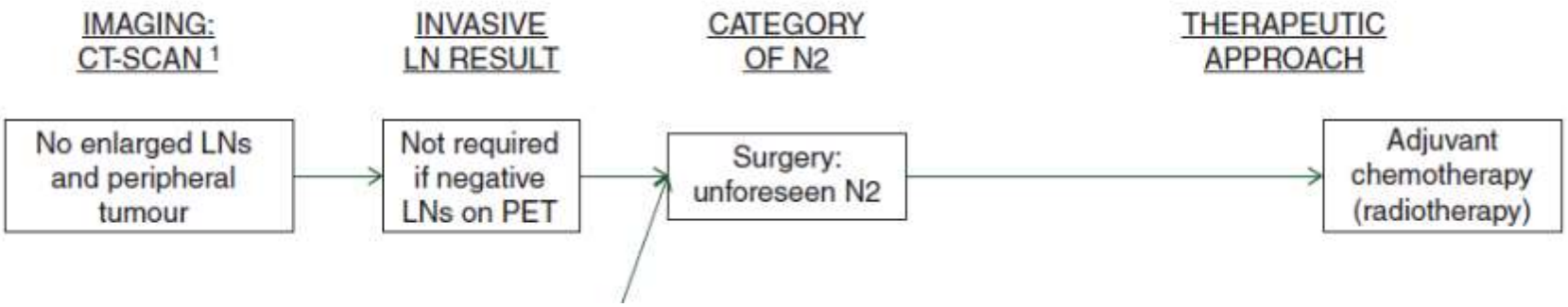
Author	Year	N	% stage III	Chemo-therapy	RT (both arms)	Survival						p
						MST (mo)		2 yr (%)		5 yr (%)		
						Adj	Cintrol	Adj	Control	Adj	Control	
Randomized trials												
IALT[102]	2004	1,867	39	PE or PV		54	45	70	67	45	40	0.03
ALPI[103]	2003	1,209	29	MVP		55	48	-	-	-	-	NS
ANITA[104]	2006	840	39	PN	+/- [x]	42*	26*	-	-	40*	19*	0.01
BLT[105]	2004	381	34	P-based		34	33	58	60	-	-	NS
Keller[106]	2000	358	59	EP	RT	38	39	60	60	39	41	NS
Dautzenberg[107]	1995	267	71	COPAC	RT	15	15	41	33	18	19	NS
Ohta[108]	1993	181	100	PVd	-	31	37	63	59	35	42	NS
Lad[109]	1988	164	92	CAP	RT	20	13	40	32	(26)	(13)	0.002
Holmes[110]	1993	130	-	CAP	-	-	-	41	30	(29)	(18)	0.03
Pisters[111]	1994	72	-	PVd	RT	16	19	31	44	17	30	NS
Kimura [132]	1996	69	78	MVdP/LAK	-	25	26	82	51	58	32	0.01
Average [y]						**33**	**30**	**54**	**48**	**36**	**32**	
Meta-analyses												
NSCLCG[113]	1995	1,394	I-III	P-based		Overall 5 year survival benefit of 5.0%						0.08
LACE[114]	2008	4,584	27	P-based	RT [z]	Overall 5 year survival benefit of 5.4%						0.005

CHEST / 143 / 5 / MAY 2013 SUPPLEMENT

- greatest effect were observed in stage III compared with stage II and stage I NSCLC
- No RCTs have addressed which chemotherapy regimen is optimal, how many cycles should be given, or when this should start
- It is suggested that adjuvant chemotherapy involving cisplatin-based doublets for three to four cycles started within 12 weeks of surgery should be given

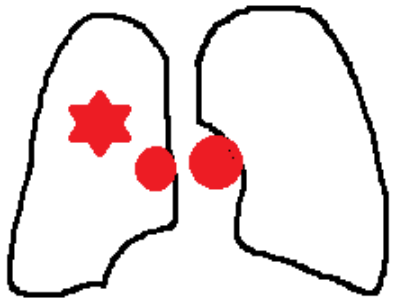
- In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.
- Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy.
- PORT with concurrent chemotherapy can be administered safely in medically fit patients and is recommended for positive resection margins

Summary for group 2



Group 3: Potentially resectable IIIA(N2) disease

- Discrete N2 involvement
- must undergo a careful staging evaluation



R[illegible]s

ARTICLE

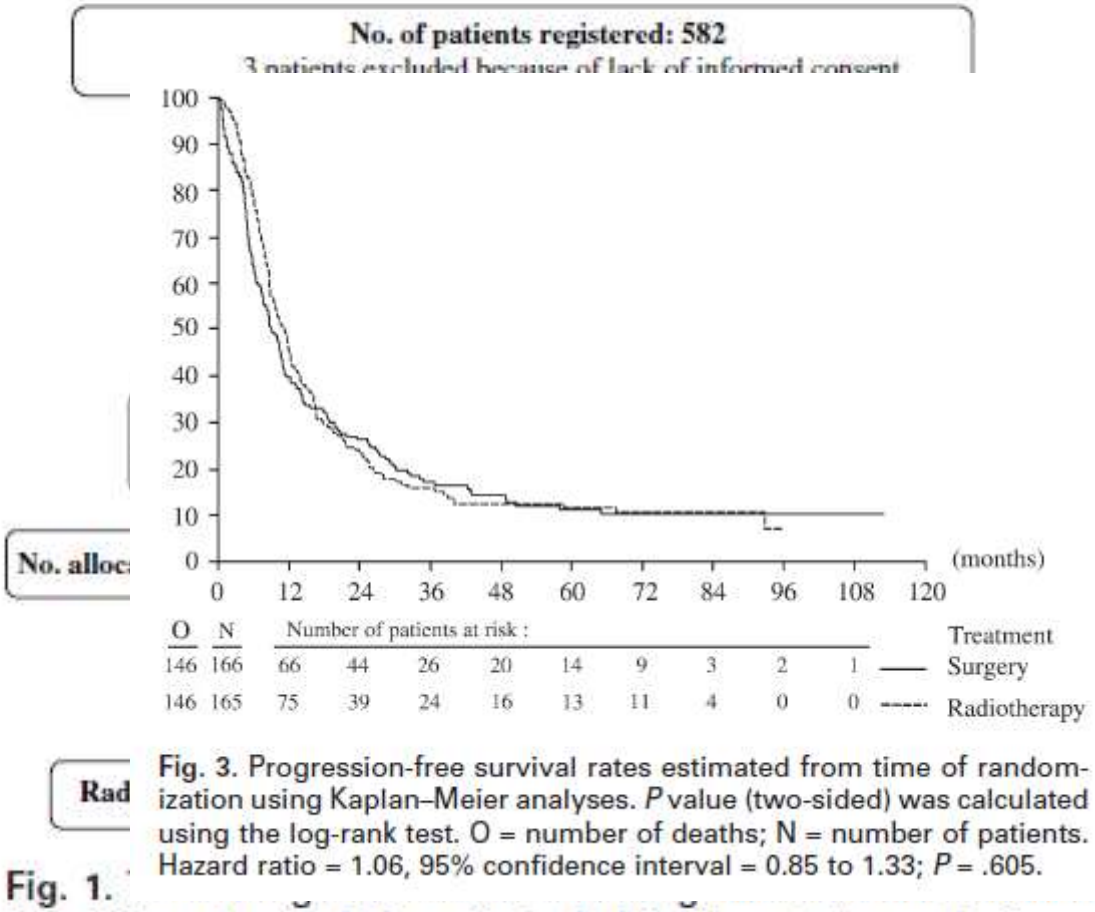


Fig. 3. Progression-free survival rates estimated from time of randomization using Kaplan–Meier analyses. *P* value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.85 to 1.33; *P* = .605.

Fig. 1. [illegible] cribes the different populations included in the study analysis: registered (n = 582), eligible (n = 579), and randomly assigned (n = 332). Patients were allocated and actually treated as per protocol with either surgery or radiotherapy.

J Natl Cancer Inst 2007;99:442-450

Abstract

Background—Concurrent chemotherapy plus radiation therapy (chemoRT) is the standard treatment for stage IIIA(N2) non-small cell lung cancer (NSCLC), a common disease entity. Phase II studies demonstrated feasibility of resection after chemoRT with encouraging survival rates. This phase III trial compared both approaches.

Methods—Patients with stage T1-3pN2M0 NSCLC were randomized before induction chemoRT (2 cycles of cisplatin and etoposide [PE] concurrent with 45 Gy RT). If no progression, arm 1 underwent resection, and arm 2 continued RT uninterrupted to 61 Gy. Two additional cycles of PE were given. The primary endpoint was overall survival (OS).

Findings—Progression-free survival for 396 eligible patients was superior in arm 1: median 12.8 versus 10.5 months, p=0.017, hazard ratio (HR) 0.77 (0.62,0.96); 5-yr 22.4% versus 11.1%. Median OS was 23.6 versus 22.2 months, p=0.24, HR 0.87 (0.70,1.10). Five-year survivals were arm 1, 27.2% and arm 2, 20.3%; odds ratio 0.63 (0.36,1.10, p=0.10). N0 status at thoracotomy predicted median OS of 33.5 months (5-year, 41.8%). Major chemoRT toxicities were neutropenia and esophagitis. Treatment-related death occurred in 16 (7.9%) patients on arm 1, of which 14 were post-pneumonectomy; and in 4 (2.1%) on arm 2. An exploratory analysis showed improved OS for patients who underwent lobectomy versus a matched cohort on chemoRT alone, but not for those undergoing pneumonectomy (matched similarly).

Interpretation—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.

Lancet 2009;374:379-386

A questionnaire was submitted to the NCCN Member Institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

a) Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
b) Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%)
c) Uses **EBUS (+/- EUS)** in the initial evaluation of the mediastinum: (80%)
d) Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
e) Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%)

- In potentially resectable superior sulcus tumors, concurrent chemoradiotherapy induction followed by definitive surgery is the treatment of choice.
- The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres.
- In both situations, surgery should be carried out within 4 weeks after the end of radiotherapy

NCCN Guidelines ver 2016.4

- Possible strategies include several options:
  - induction chemotherapy followed by surgery,
  - Induction chemoradiotherapy followed by surgery
  - concurrent definitive chemoradiotherapy.

Guidelines

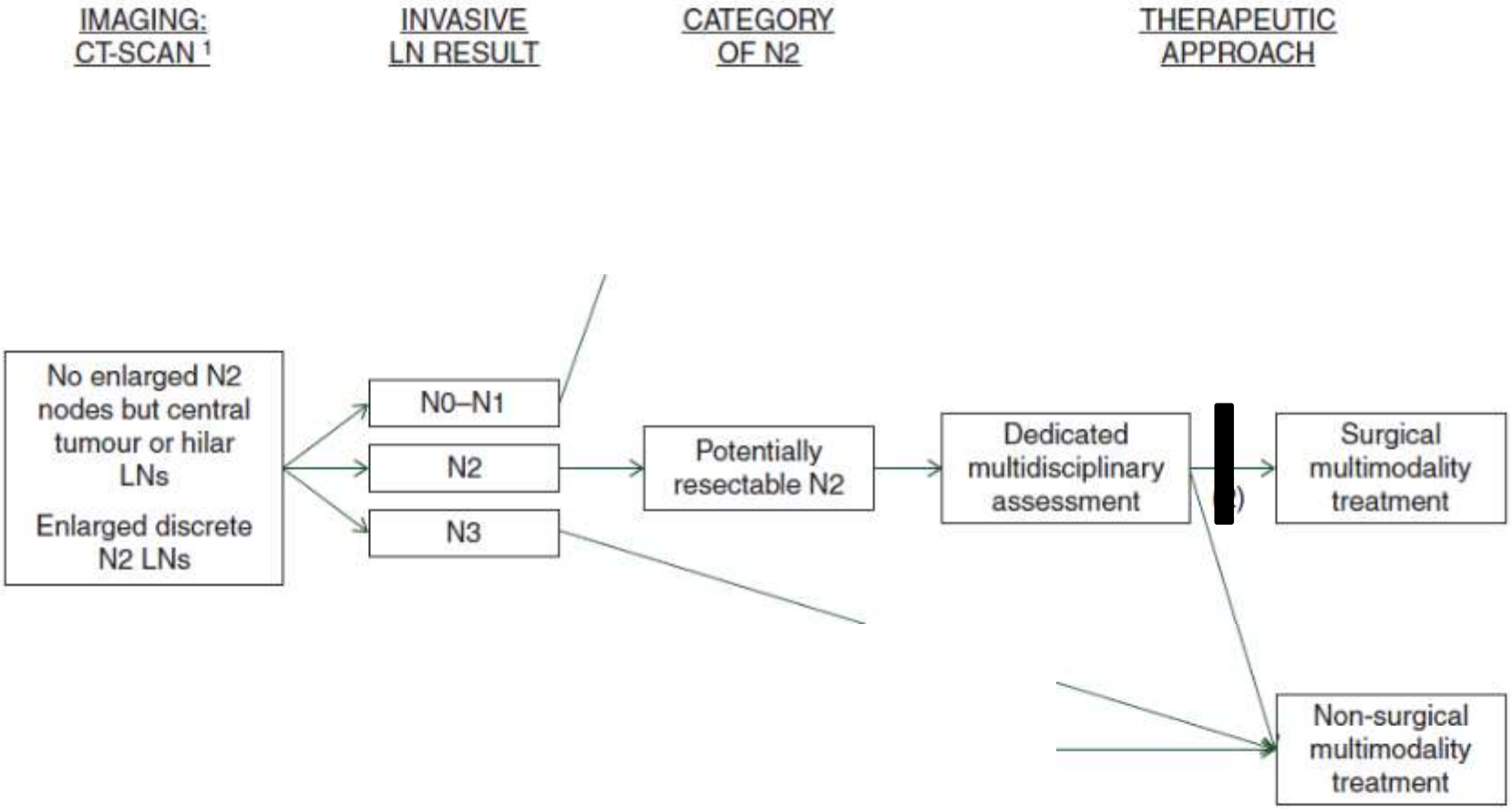
potentially resectable IIIA(N2) disease

preoperative diagnosis of IIIA(N2)

3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C).

given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].

Summary for group 3



Prophylactic cranial irradiation

- May reduce incidence of brain metastasis but none of the studies have found a survival benefit
- One of the study has shown some benefit is squamous histology
- Further studies are warranted
- No role of PCI in NSCLC

Clin Lung Cancer. 2015 Jul;16(4):292-7
PLoS One. 2014 Jul 29;9(7):e103431

Targeted therapy

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF V600E mutation*	vemurafenib[1,2] dabrafenib[2,3] dabrafenib + trametinib[4]
High level *MET* amplification or MET exon 14 skipping mutation	crizotinib[5,6,7,8]
RET rearrangements	cabozantinib[9,10]
ROS1 rearrangements	crizotinib[11]
HER2 mutations	trastuzumab[12] (category 2B) afatinib[13] (category 2B)

*Non-V600E mutations have variable kinase activity and response to these agents.

Targeted therapy in early stage NSCLC

- EGFR MUTATION-POSITIVE NSCLC
- Two trials: RADIANT and SELECT

Targeted therapy in early stage NSCLC

- SELECT
- phase II, single arm trial
- included patients with stage I to IIIA surgically resected
- standard-of-care , followed by adjuvant erlotinib at 150 mg per day.
- n = 100
- 24 patients recurred, but only 2 of them durin erlotinib treatment and the rest 22 after stop of erlotinib treatment, in time of 1 to 2 years.

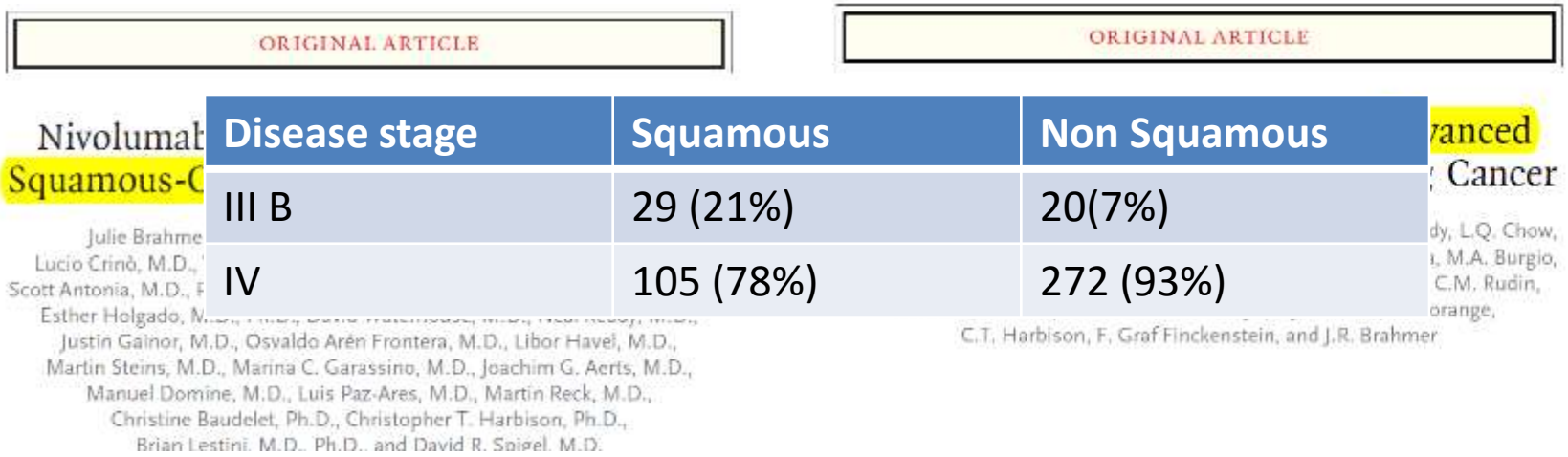
journal of the American Society of Clinical Oncology. 2014; 32 (suppl; abstr 7514)

Targeted therapy in early stage NSCLC

- The RADIANT study was a randomized study of 2 years of adjuvant erlotinib vs. placebo that enrolled a broader population of lung cancer patients among which 16% harbored EGFR mutations.
- Though the overall study was negative, the subgroup analysis of EGFR mutants suggested that erlotinib provided a disease-free survival advantage with HR = 0.61 (95% CI 0.38, 0.98) but no OS advantage in this preliminary study

official journal of the
American Society of Clinical Oncology. 2014; 32 (suppl; abstr 7501)

Targeted therapy in early stage NSCLC



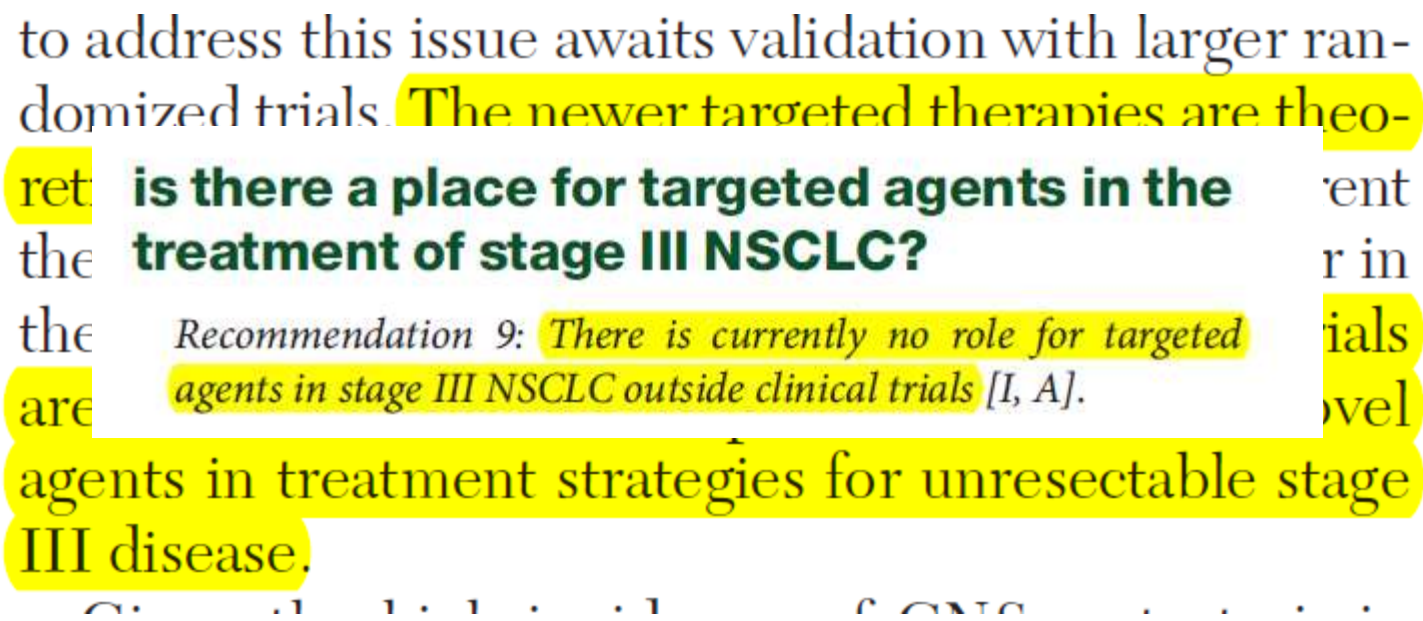
Disease stage	Squamous	Non Squamous
III B	29 (21%)	20(7%)
IV	105 (78%)	272 (93%)

Overall survival was longer in both the studies in nivolumab arm
Subgroup analysis for III B is not available

N Engl J Med 2015; 373:1627-1639
N Engl J Med 2015; 373:123-135

Targeted therapy in early stage NSCLC

- Targeted therapy are yet to find a mention in guidelines for stage III NSCLC



to address this issue awaits validation with larger randomized trials. The newer targeted therapies are theo-
ret ent
the r in
the ials
are ovel
agents in treatment strategies for unresectable stage III disease.

is there a place for targeted agents in the treatment of stage III NSCLC?

Recommendation 9: There is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A].

Take home slide