HUMANITAS
CANCER CENTER

SESSIONE II

Distretto Toracico:
il trattamento multimodale
del NSCLC stadio III

IL TRATTAMENTO MULTIMODALE

Fiorenza De Rose

Radioterapia e Radiochirurgia,

Istituto Clinico Humanitas – Rozzano (MI)

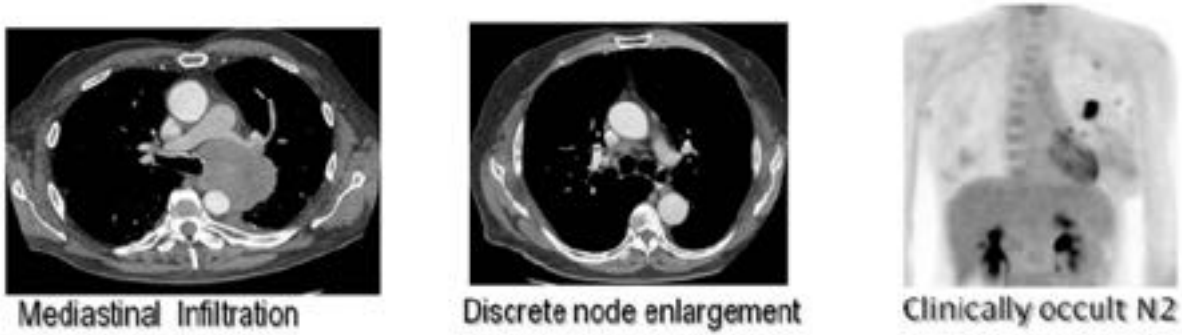
Stage and Survival

IASLC/UICC 7	Definition	TNM subsets	Description	Robinson Classification
IIIA	incidental N2 (unforeseen N2)	T1-3 N2	N2 found at surgery microscopic N2 macroscopic N2	 IIIA1 IIIA2
IIIA	potentially resectable N2	T1-3 N2	minimal N2/single station at staging	IIIA3
IIIA	potentially resectable N2 But: risk of incomplete resection	T1-3 N2	Pancoast tumour subsets, T3-4 N1, T3 N2 selective centrally located IIIA(N2)	------ IIIA3
IIIA	unresectable N2	T1-3 N2	bulky and/or multilevel N2 at staging	IIIA4
IIIA	potentially resectable T4 But: risk of incomplete resection	T4 N0-1	pulmonary artery, carina, spine, trachea, vena cava, right atrium	------
IIIB	unresectable T4	T4 N0-1 T4 N2	oesophagus, heart, aorta, pulmonary veins	------
IIIB	unresectable N3	T1-4 N3	N3 nodes at staging	

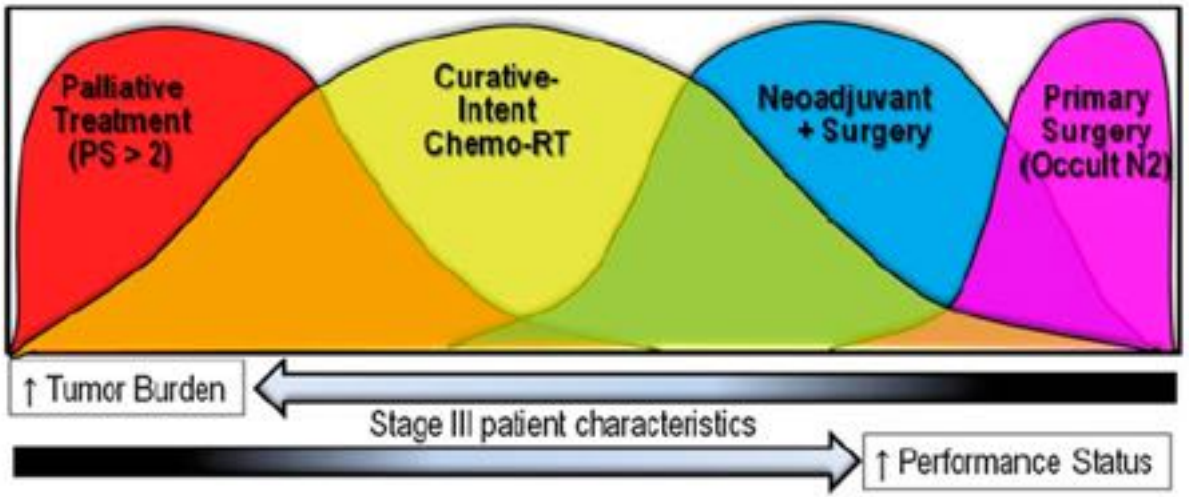
IIIA 20% of NSCLC patients
5-years SVV 15-17%

2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

General approach to treatment

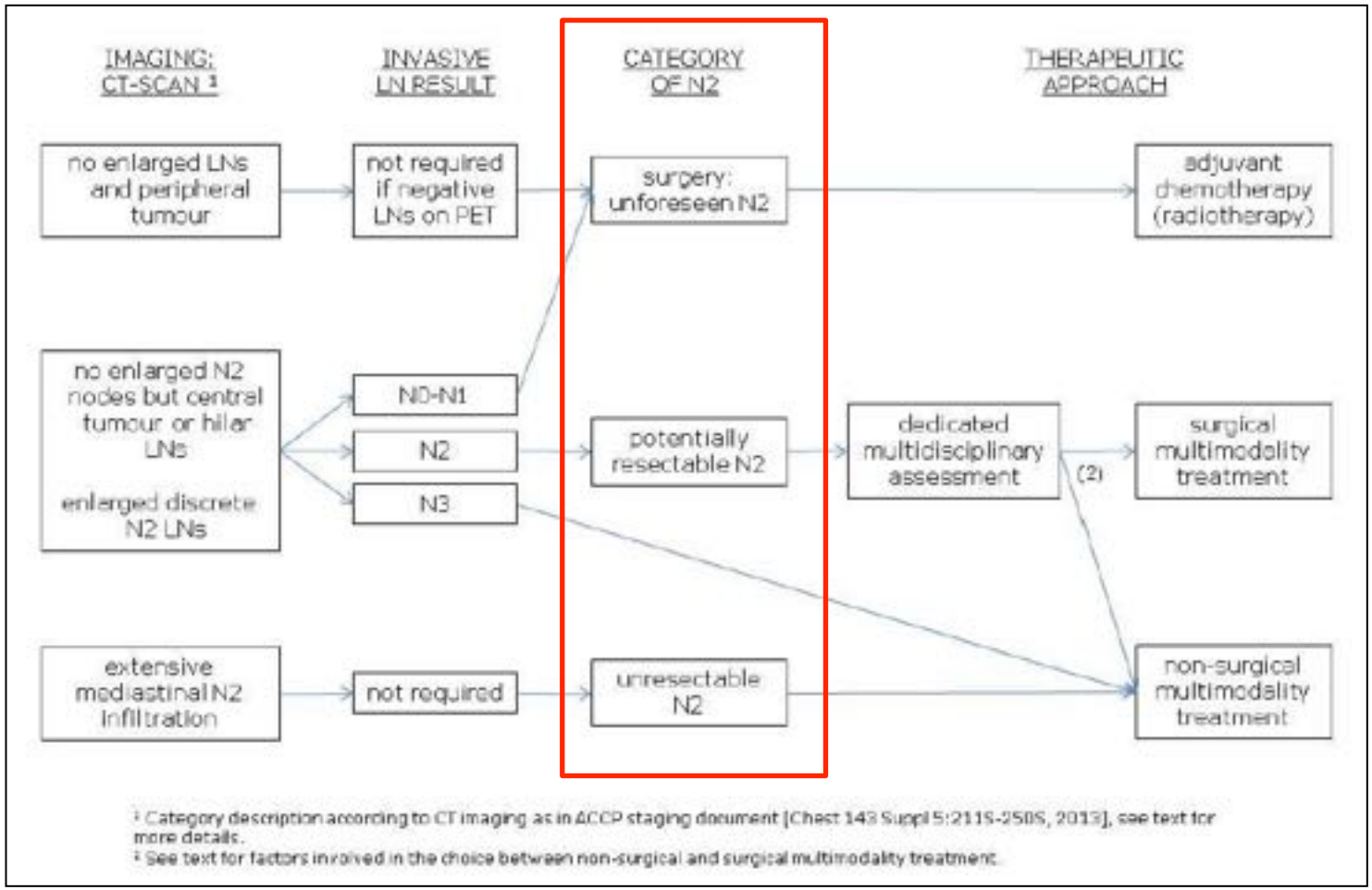


Schematic of types of patients included in studies using different treatment approaches



Ramnath N, et al. Treatment of Stage III Non-small Cell Lung Cancer. Chest 2013

General approach to treatment



2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
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Heterogeneity in disease

Identification of 3 subgroups

(1) patients with **occult N2 node involvement** despite thorough preoperative staging

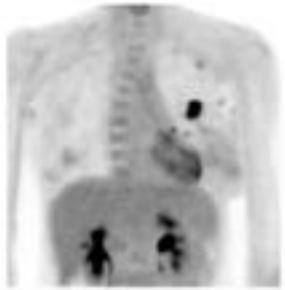
(2) patients with **discrete clinically evident** (by CT or CT-PET scan) **N2 involvement** (potentially resectable N2/T4)

(3) patients with **infiltrative stage III** (**N2/N3/T4**) tumors

Ramnath N, et al. Treatment of Stage III Non-small Cell Lung Cancer. Chest 2013

Occult N2 node involvement

T1-3 N2 found at surgery
(micro or macroscopic)



TOPIC ISSUES

- What is the optimal diagnostic work-up

- What are the optimal adjuvant treatments

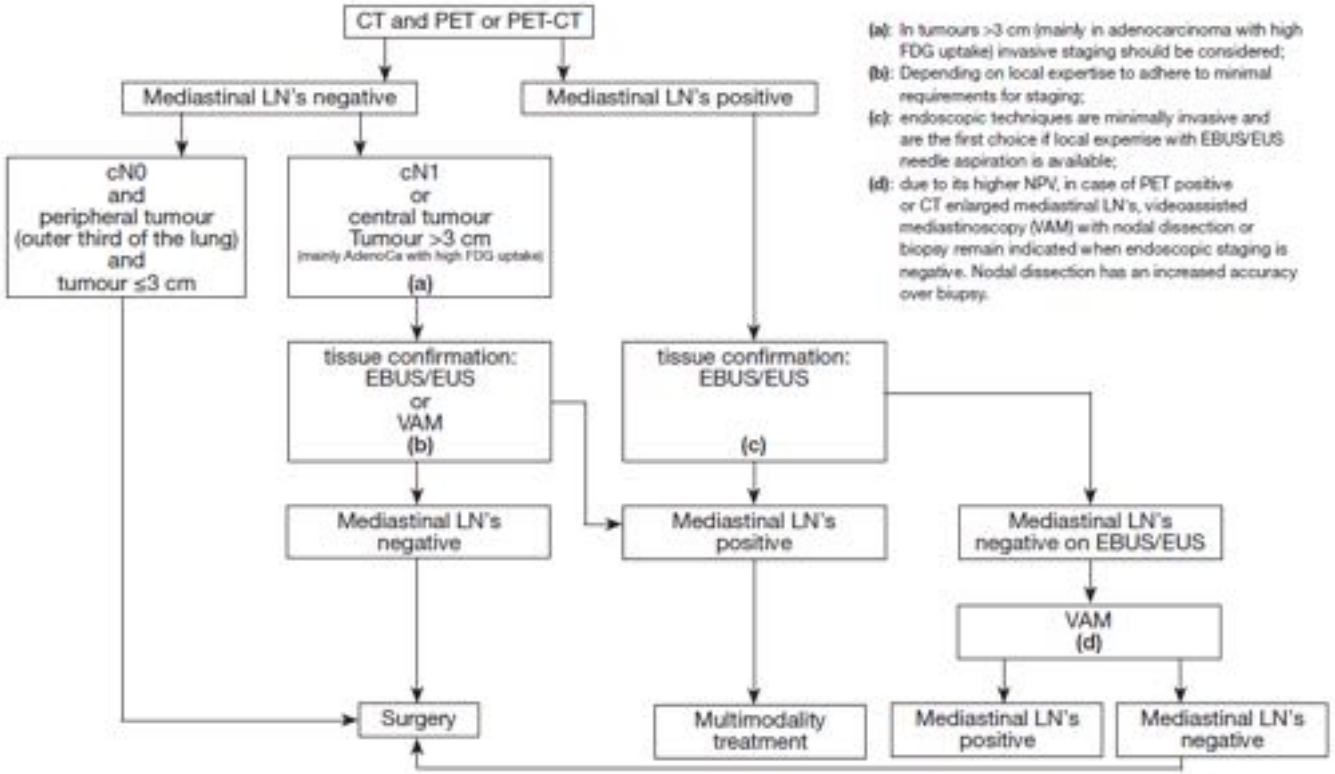
2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

Occult N2 node involvement: diagnostic work-up

Highlighted Reports in European Lung Cancer Conference

Preoperative mediastinal lymph node staging for non-small cell lung cancer: 2014 update of the 2007 ESTS guidelines

Paul De Leyn[1], Christophe Dooms[2], Jaroslaw Kuzdzal[3], Didier Lardinois[4], Bernward Passlick[5], Ramon Rami-Porta[6], Akif Turna[7], Paul Van Schil[8], Frederico Venuta[9], David Waller[10], Walter Weder[11], Marcin Zielinski[12]

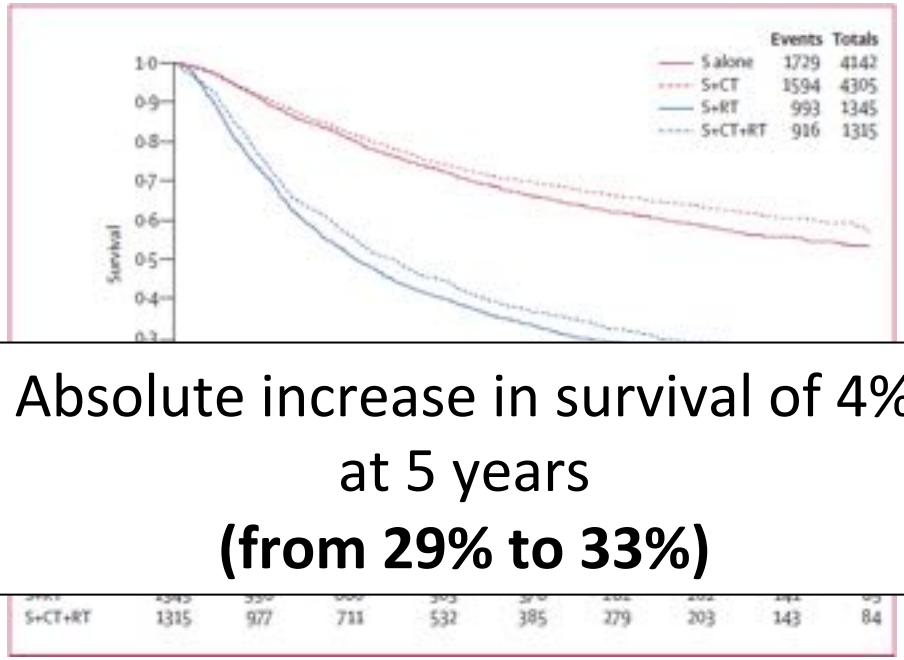


Transl Lung Cancer Res 2014;3(4):225-233

Occult N2 node involvement: Adjuvant treatment

Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

*NSCLC Meta-analyses Collaborative Group**



Absolute increase in survival of 4% at 5 years
(from 29% to 33%)

Conclusion:
The addition of adjuvant chemotherapy after surgery for patients with operable non-small-cell lung cancer improves survival, irrespective of whether chemotherapy was adjuvant to surgery alone or adjuvant to surgery plus radiotherapy.

Occult N2 node involvement: Adjuvant treatment

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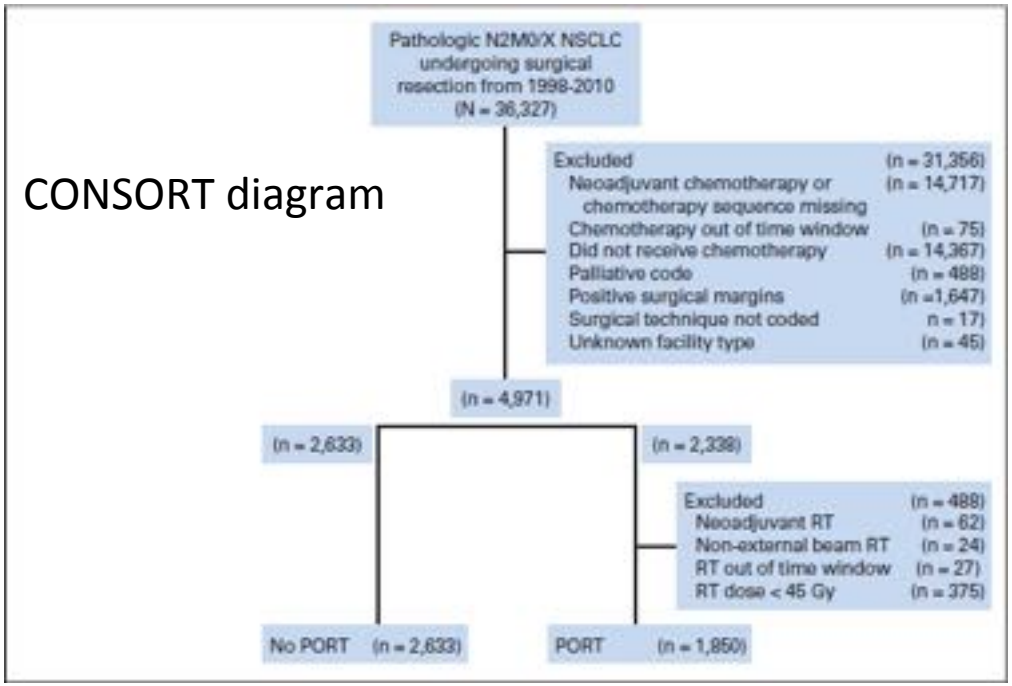
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

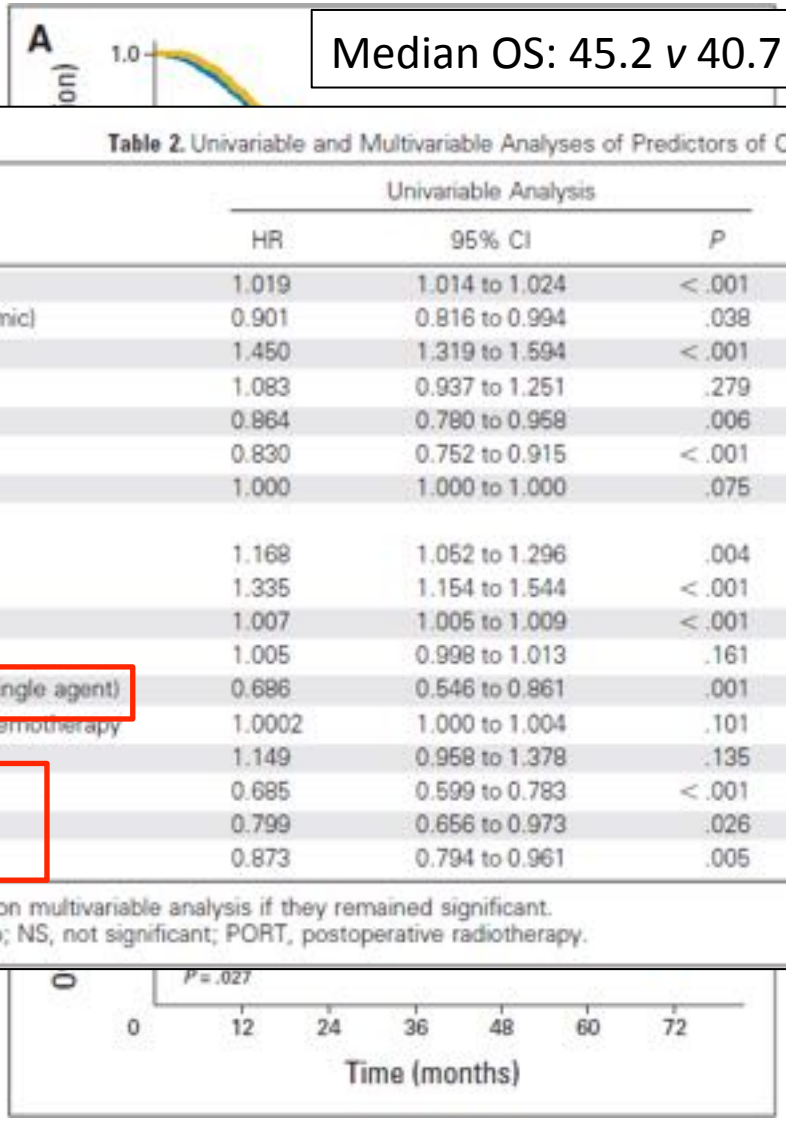
Postoperative Radiotherapy for Pathologic N2 Non–Small-Cell Lung Cancer Treated With Adjuvant Chemotherapy: A Review of the National Cancer Data Base

Cliff G. Robinson, Aalok P. Patel, Jeffrey D. Bradley, Todd DeWees, Saiama N. Waqar, Daniel Morgensztern, Maria Q. Baggstrom, Ramaswamy Govindan, Jennifer M. Bell, Tracey J. Guthrie, Graham A. Colditz, Traves D. Crabtree, Daniel Kreisel, Alexander S. Krupnick, G. Alexander Patterson, Bryan F. Meyers, and Varun Puri

CONSORT diagram



Occult N2 node involvement: Adjuvant treatment



Median OS: 45.2 *v* 40.7 months

Table 2. Univariable and Multivariable Analyses of Predictors of Overall Survival

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.019	1.014 to 1.024	< .001	1.017	1.011 to 1.022	< .001
Facility (academic *v* nonacademic)	0.901	0.816 to 0.994	.038	NS		
Sex (male *v* female)	1.450	1.319 to 1.594	< .001	1.379	1.242 to 1.531	< .001
Race (white *v* nonwhite)	1.083	0.937 to 1.251	.279			
Income (≥ *v* < $35,000)	0.864	0.780 to 0.958	.006	NS		
Population (urban *v* nonurban)	0.830	0.752 to 0.915	< .001	0.827	0.741 to 0.921	.001
Great circle distance	1.000	1.000 to 1.000	.075			
Charlson score						
1 *v* 0	1.168	1.052 to 1.296	.004	1.137	1.014 to 1.274	.028
2 *v* 0	1.335	1.154 to 1.544	< .001	1.283	1.097 to 1.502	.002
Tumor size	1.007	1.005 to 1.009	< .001	1.008	1.005 to 1.010	< .001
Surgical inpatient stay	1.005	0.998 to 1.013	.161			
Chemotherapy (multiagent *v* single agent)	0.686	0.546 to 0.861	.001	0.678	0.536 to 0.857	.001
Days between surgery and chemotherapy	1.0002	1.000 to 1.004	.101			
Readmission	1.149	0.958 to 1.378	.135			
Lobectomy *v* sublobar	0.685	0.599 to 0.783	< .001	0.581	0.501 to 0.675	< .001
Pneumonectomy *v* sublobar	0.799	0.656 to 0.973	.026	0.625	0.497 to 0.785	< .001
PORT *v* no PORT	0.873	0.794 to 0.961	.005	0.888	0.798 to 0.988	.029

NOTE. HRs are only reported on multivariable analysis if they remained significant.
Abbreviations: HR, hazard ratio; NS, not significant; PORT, postoperative radiotherapy.

Occult N2 node involvement: Ongoing phase III

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Radiation Therapy in Treating Patients With Non Small Cell Lung Cancer That Has Been Completely Removed by Surgery (LUNG ART)

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2014 by Gustave Roussy, Cancer Campus, Grand Paris

Sponsor:
Gustave Roussy, Cancer Campus, Grand Paris

Collaborators:
Intergroupe Francophone de Cancerologie Thoracique
Christie Hospital NHS Foundation Trust
European Organisation for Research and Treatment of Cancer - EORTC

Information provided by (Responsible Party):
Gustave Roussy, Cancer Campus, Grand Paris

ClinicalTrials.gov Identifier:
NCT00410683

First received: December 11, 2006
Last updated: September 1, 2014
Last verified: September 2014
History of Changes

Late Toxicity

No Study Results Posted on ClinicalTrials.gov for this Study

About Study Results Reporting on ClinicalTrials.gov

Study Status:	This study is currently recruiting participants.
Estimated Study Completion Date:	February 2022
Estimated Primary Completion Date:	February 2017 (Final data collection date for primary outcome measure)

Occult N2 node involvement: incompletely resected

Use of adjuvant chemotherapy (CT) and radiotherapy (RT) in incompletely resected (R1) early stage Non-Small Cell Lung Cancer (NSCLC): A European survey conducted by the European Society for Medical Oncology (ESMO) Young Oncologists Committee

R. Califano[a,b,*], M.V. Karamouzis[c], S. Banerjee[d], E. de Azambuja[e], V. Guarneri[f], M. Hutka[d], K. Jordan[g], K. Kamposioras[h], E. Martinelli[i], J. Corral[j], S. Postel-Vinay[k], M. Preusser[l], L. Porcu[m], V. Torri[m]

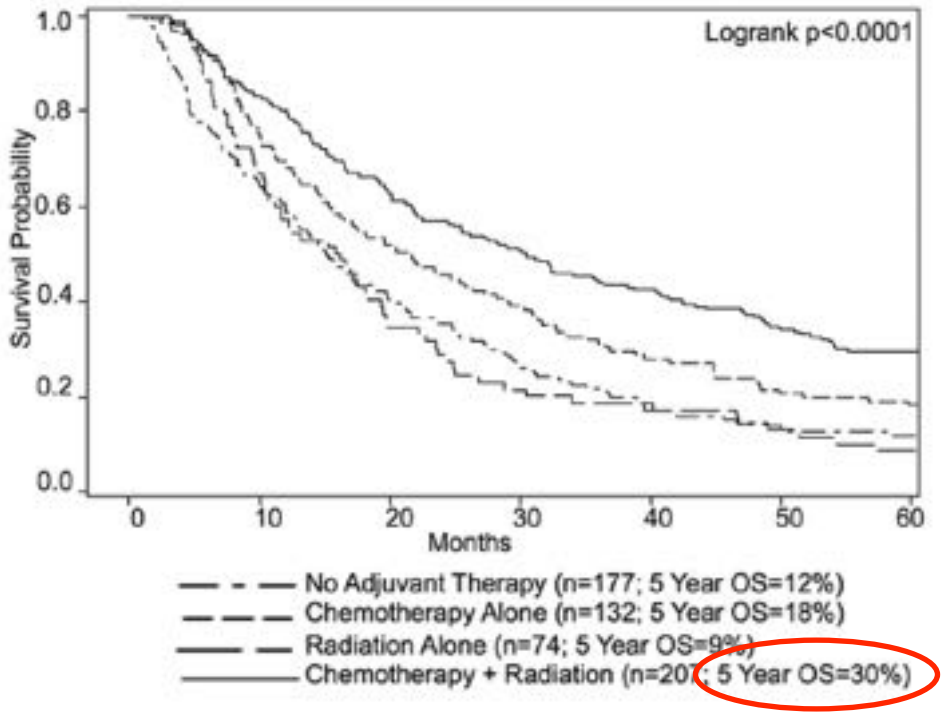
Conclusion: … the **majority** of respondents will **recommend 4 cycles of chemotherapy followed by adjuvant thoracic radiotherapy**… Prospective trials of adjuvant treatment for R1-resected NSCLC will be very difficult to conduct, but they are the only way to clarify optimal management. Until such results are available, **treatment plan needs to be discussed in a patient-to-patient basis taking into account risk of relapse, performance status, comorbidities and patient's preferences**

Occult N2 node involvement: incompletely resected

Impact of Adjuvant Treatment for Microscopic Residual Disease After Non-Small Cell Lung Cancer Surgery

Jacquelyn G. Hancock, BS, Joshua E. Rosen, BAS, Alberto Antonicelli, MD, Amy Moreno, MD, Anthony W. Kim, MD, Frank C. Detterbeck, MD, and Daniel J. Boffa, MD

pIII stage



Ann Thorac Surg 2015;99:406–13

Occult N2 node involvement: incompletely resected

- About 6% of patients are left with microscopic (R1) or macroscopic (R2) residual tumor at the surgical margin
- Prospective Trials very difficult to conduct
- Only few retrospective data

pIII stage R1: Adjuvant CT – RT (sequential)
pIII stage R2: Re-resection + Adjuvant CT
or
Adjuvant CT - RT (concomitant)

Evidence Level III

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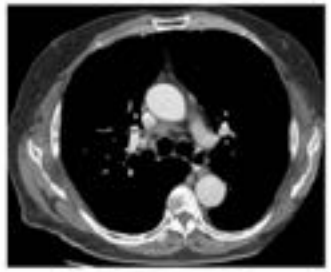
(3) patients with **infiltrative stage III** (**N2/N3/T4**) tumors

Ramnath N, et al. Treatment of Stage III Non-small Cell Lung Cancer. Chest 2013

Potentially resectable N2/T4

T1-3 N2	minimal N2/single station at staging selective centrally located
T4 N0-1	pulmonary artery, carina, spine, trachea, vena cava, right atrium



Discrete node enlargement

TOPIC ISSUES

- Possible strategies include several options
- Potentially operable patients with high risk of incomplete resection

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Annals of Oncology, First published online: April 20, 2015

CRT with or without Surgery

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, William T Sause, James D Cox

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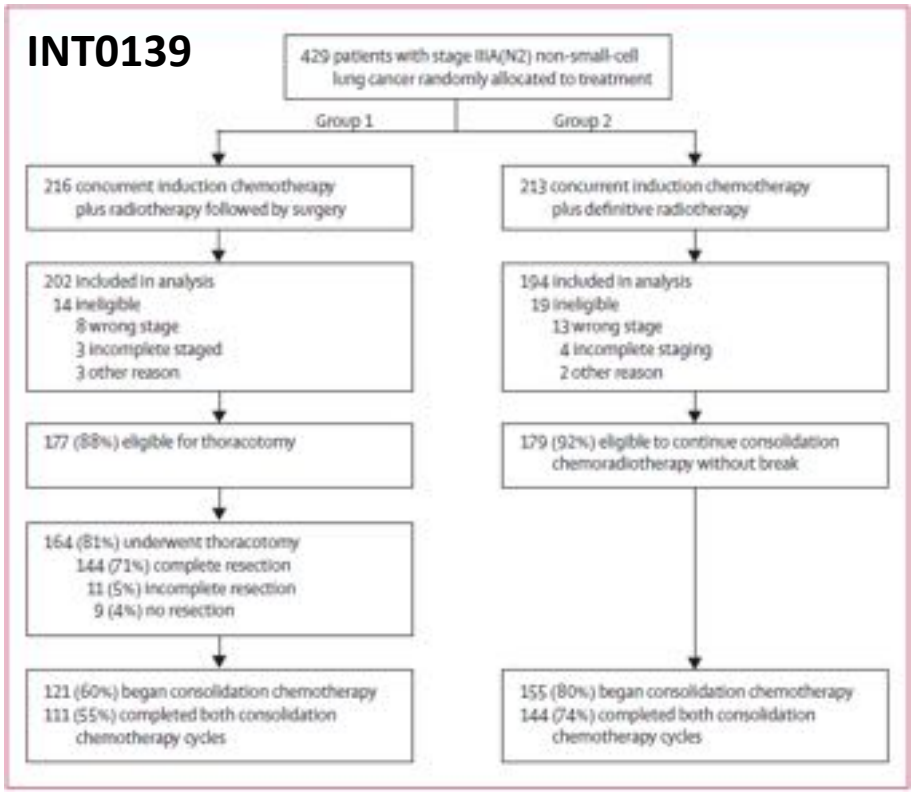
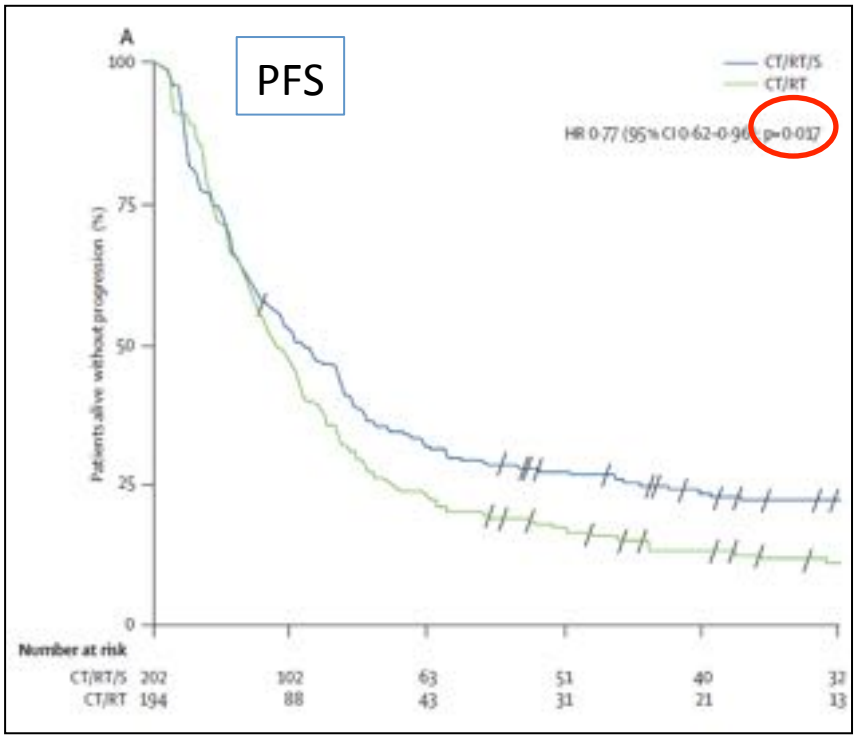
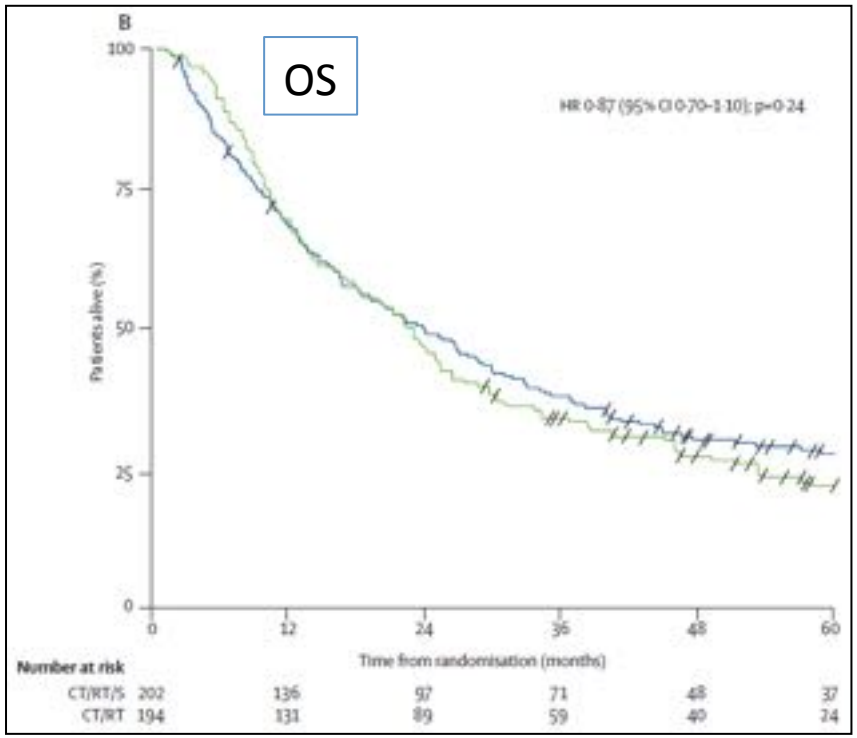


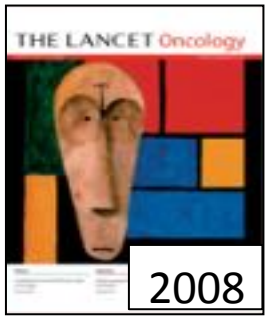
CRT with or without Surgery





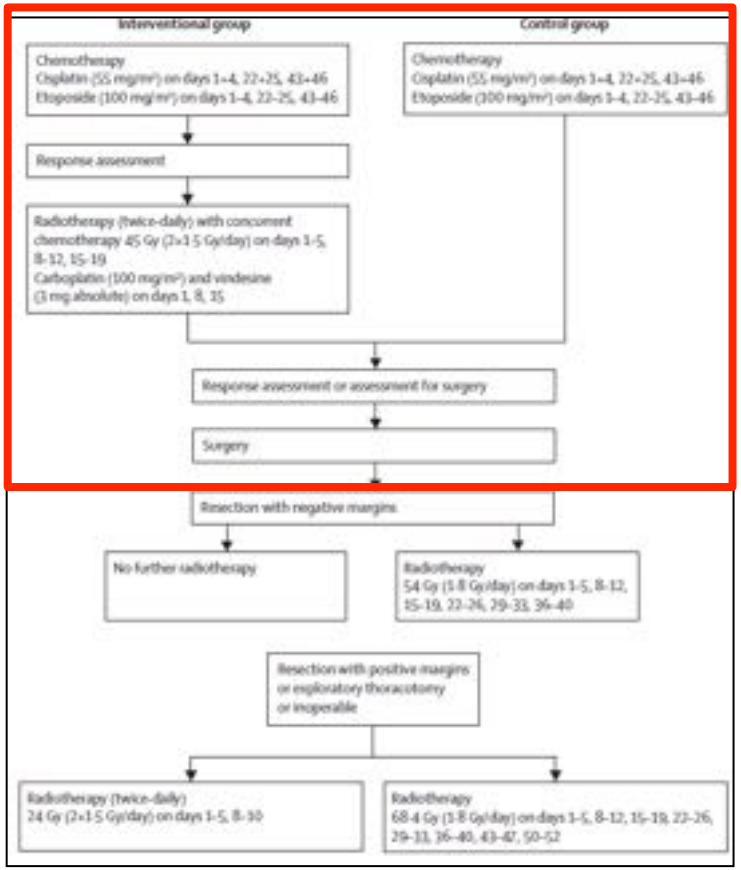
… medically healthy patients with stage IIIA(N2) non-small-cell lung cancer should be **assessed by a team skilled in multimodality treatment**, and treatment options can be considered during assessment. On the basis of the findings of our study, **patients should be counseled about the risks and potential benefits of definitive chemotherapy plus radiotherapy with and without a surgical resection** (preferably by lobectomy).

Neoadjuvant approach: CT vs CRT



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***



Neoadjuvant approach: CT vs CRT

	Interventional group (95% CI) (n=131)	Control group (95% CI) (n=141)	Hazard ratio (95% CI)	p
All patients with resection (n=272)				
Median, months	19·6 (14·8–27·1)	21·3 (14·7–29·9)	1·07 (0·81–1·42)	0·64
1-year PFS, %	66 (58–74)	67 (59–74)	–	–
3-year PFS, %	36 (28–45)	37 (29–45)	–	–
5-year PFS, %	30 (22–38)		–	–
Patients with complete resection (n=182)	(n=98)			
Median, months	23·3 (16·1–37·0)			
1-year PFS, %	73 (64–82)	73 (67–85)	–	–
3-year PFS, %	41 (31–51)	51 (40–62)	–	–
5-year PFS, %	37 (27–47)	33 (21–45)	–	–

Table 4: Progression-free survival (PFS) in patients undergoing tumour resection

No differences in PFS and OS

	Interventional group (95% CI) (n=131)	Control group (95% CI) (n=141)	Hazard ratio (95% CI)	p
All patients with resection (n=272)				
Median, months	32·4 (21·3–50·0)	33·0 (25·7–44·8)	1·10 (0·81–1·47)	0·54
1-year OS, %	81 (74–88)	82 (76–89)	–	–
3-year OS, %	48 (39–57)	45 (36–53)	–	–
		31 (23–40)	–	–
		(n=84)		
		55·6 (37·5–74·1)	0·96 (0·64–1·42)	0·82
1-year OS, %	85 (77–92)	84 (77–92)	–	–
3-year OS, %	54 (44–64)	61 (50–72)	–	–
5-year OS, %	45 (34–55)	42 (30–55)	–	–

Table 5: Overall survival (OS) in patients undergoing tumour resection

	Incomplete resection (95% CI) (n=90)	Complete resection (95% CI) (n=182)	Hazard ratio (95% CI)	p
PFS				
Median, m				
1-year PFS,				
3-year PFS,				
5-year PFS,				
OS				
Median, m				
1-year OS,				
3-year OS,	24 (15–33)	57 (50–65)	–	–
5-year OS, %	17 (9–25)	44 (36–52)	–	–

Table 6: Progression-free survival (PFS) and overall survival (OS) in patients with incomplete versus complete resection

To conclude, achieving a **high number of complete resections** and a **favourable pathological response** when treating mediastinal nodes is an **important aim of induction treatment**. In our trial, induction treatment with additional chemoradiation increased mediastinal downstaging, even for patients with incomplete resection, but did not improve survival.

Neoadjuvant approach: CT vs CRT

Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial

Nicolas Girard[a,b], Françoise Mornex[a,b], Jean-Yves Douillard[b,c], Nadine Bossard[d], Elisabeth Quoix[b,e], Véronique Beckendorf[b,f], Dominique Grunenwald[b,g], Elodie Amour[b], Bernard Milleron[b,h,*]

IFCT 01-01 trial

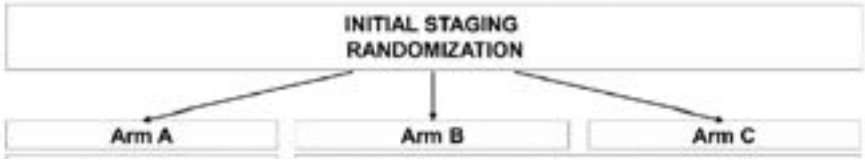
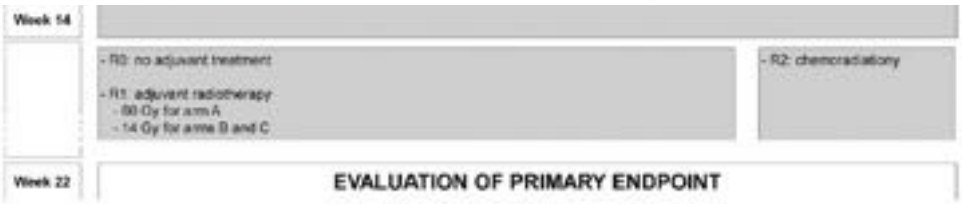


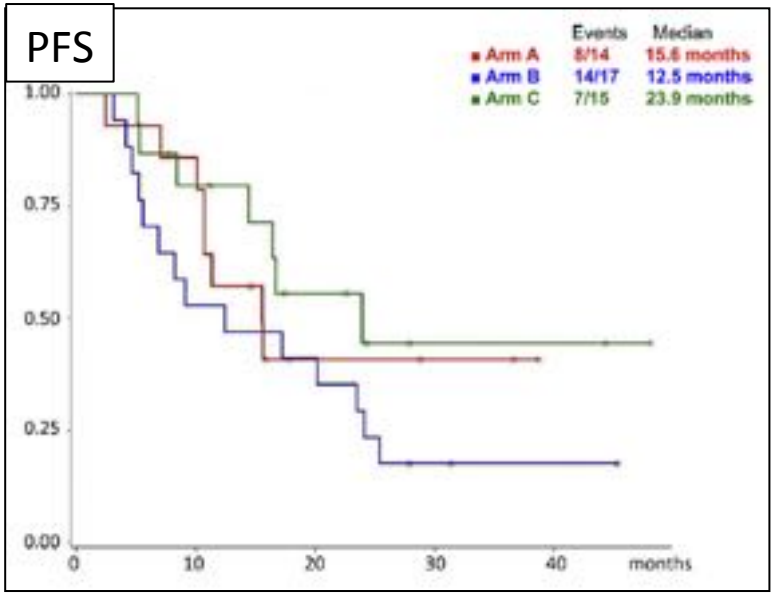
Table 4
Previously published phase II trials evaluating induction chemoradiotherapy in locally advanced NSCLC.

Author	*n*	Stage	Induction chemoradiotherapy			Surgery			Outcome	
			Chemotherapy	Radiotherapy (Gy)	Objective response rate (%)	Resectability rate (%)	Complete resection (%)	Operative mortality rate (%)	Median survival (months)	5-Year survival (%)
Initially non-resectable NSCLC										
Weiden and Piantadosi (LCSG 852) [15]	85	IIIA/IIIB	Cisplatin 5-fluorouracil	30 S	56	52	34	7	13	NR
Albain et al. (SWOG 8805) [16]	126	IIIA/IIIB	Cisplatin etoposide	45 S	59	80–85	NR	8	13–17	20
Eberhart et al. [17]	94	IIIA/IIIB	Cisplatin etoposide	45 BF	80	66	53	7	18–20	NR
Thomas et al. [18]	54	IIIA/IIIB	Carboplatin vindesine	45 BF	69	74	63	8	20	NR
Stamatis et al. [19]	56	IIIB	Cisplatin etoposide	30 S	61	59	48	5	20	26
Grunenwald et al. [38]	40	IIIB	5-Fluorouracil cisplatin vinblastine	42 BF SC	73	60	58	7	15	19
DeCamp et al. [39]	105	IIIA/IIIB	Cisplatin paclitaxel	45 BF	93	79	79	7	27	32
Trodella et al. [40]	92	IIIA/IIIB	Cisplatin 5-fluorouracil	50 S/BF	63	67	62	11	20	15
Initially resectable NSCLC										
Faber et al. [20]	85	IIIA/IIIB	Cisplatin 5-fluorouracil etoposide	40 S	NR	68	NR	4	22	NR
Strauss et al. (CALGB) [21]	41	IIIA/IIIB	Cisplatin vinblastine 5-fluorouracil	30 S	51	76	NR	15	16	NR
Deutsch et al. [22]	28	IIIA	Carboplatin etoposide	60 S	64	57	43	11	15	NR
Choi et al. [23]	42	IIIA	5-Fluorouracil cisplatin vinblastine	42 BF	74	93	87	5	25	37
IFCT-0101, 2009	*32*	*IIIA*	*cisplatin paclitaxel/vinorelbine*	*46 S*	*78*	*91*	*76*	*4*	*30*	*NR*

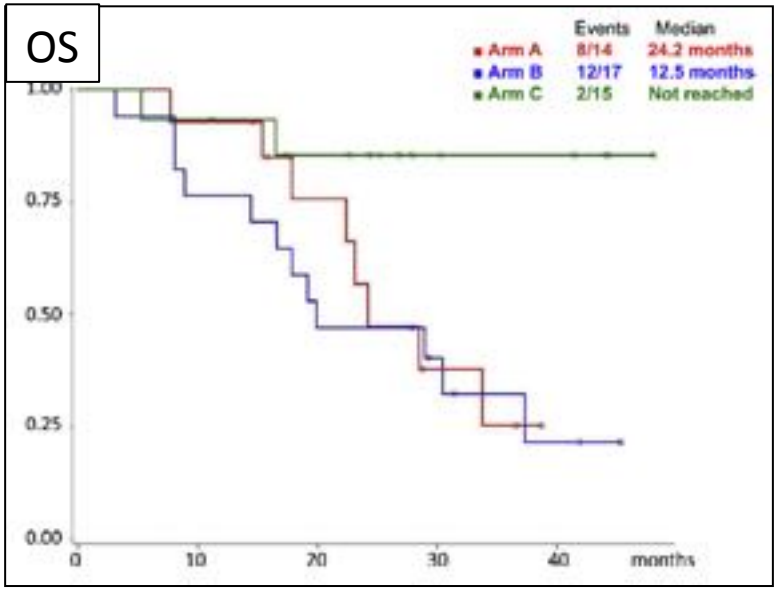


Neoadjuvant approach: CT vs CRT

PFS



OS



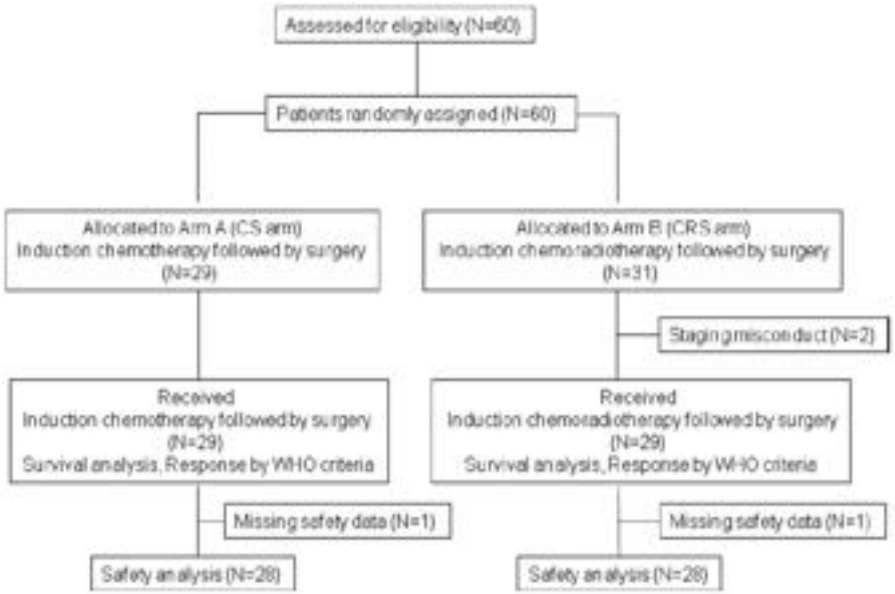
To conclude, mature results of the IFCT-0101 demonstrate that, using modern treatment schemes, **induction chemoradiotherapy followed by surgery is highly feasible in highly selected patients with stage IIIA-N2 NSCLC**. Induction chemoradiotherapy even achieved higher response rates than induction chemotherapy.

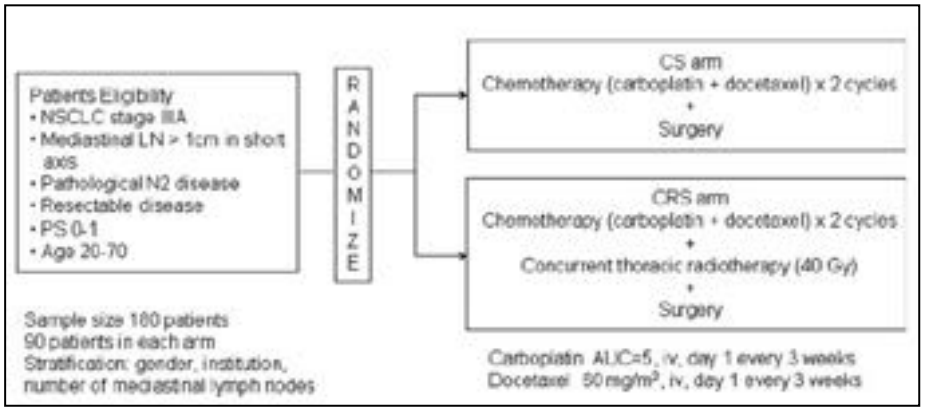
Neoadjuvant approach: CT vs CRT

Original Article

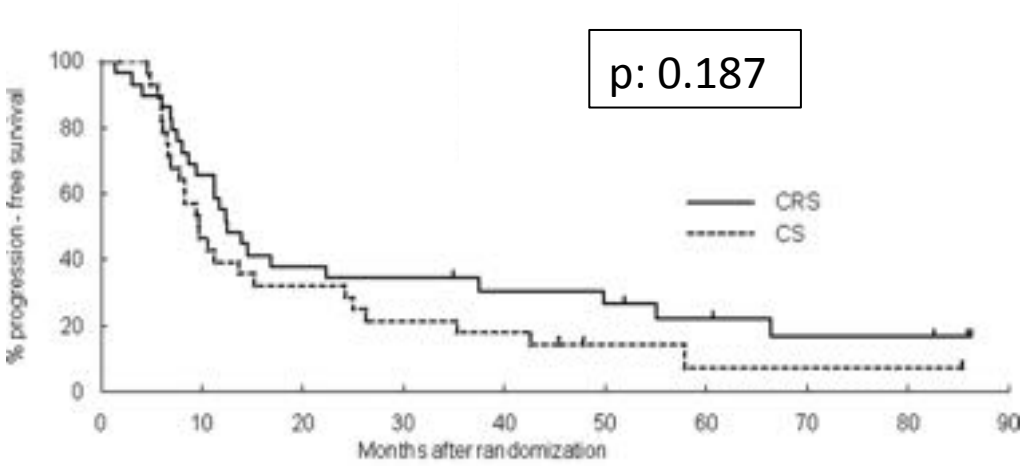
A Phase 3 Study of Induction Treatment With Concurrent Chemoradiotherapy Versus Chemotherapy Before Surgery in Patients With Pathologically Confirmed N2 Stage IIIA Nonsmall Cell Lung Cancer (WJTOG9903)

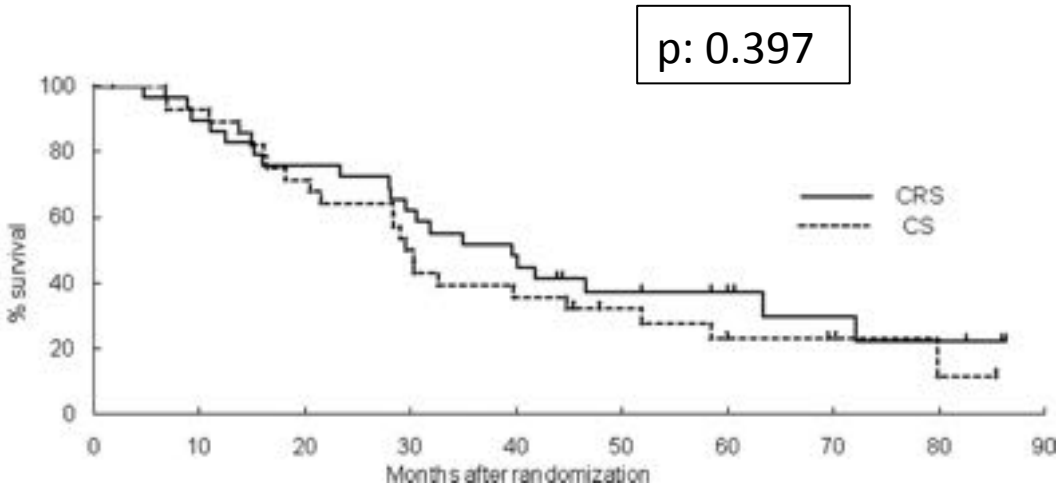
Nobuyuki Katakami, MD[1]; Hirohito Tada, MD[2]; Tetsuya Mitsudomi, MD[3]; Shinzoh Kudoh, MD[4]; Hiroshi Senba, MD[5]; Kaoru Matsui, MD[6]; Hideo Saka, MD[7]; Takayasu Kurata, MD[8]; Yasumasa Nishimura, MD[9]; and Masahiro Fukuoka, MD[10]





Neoadjuvant approach: CT vs CRT





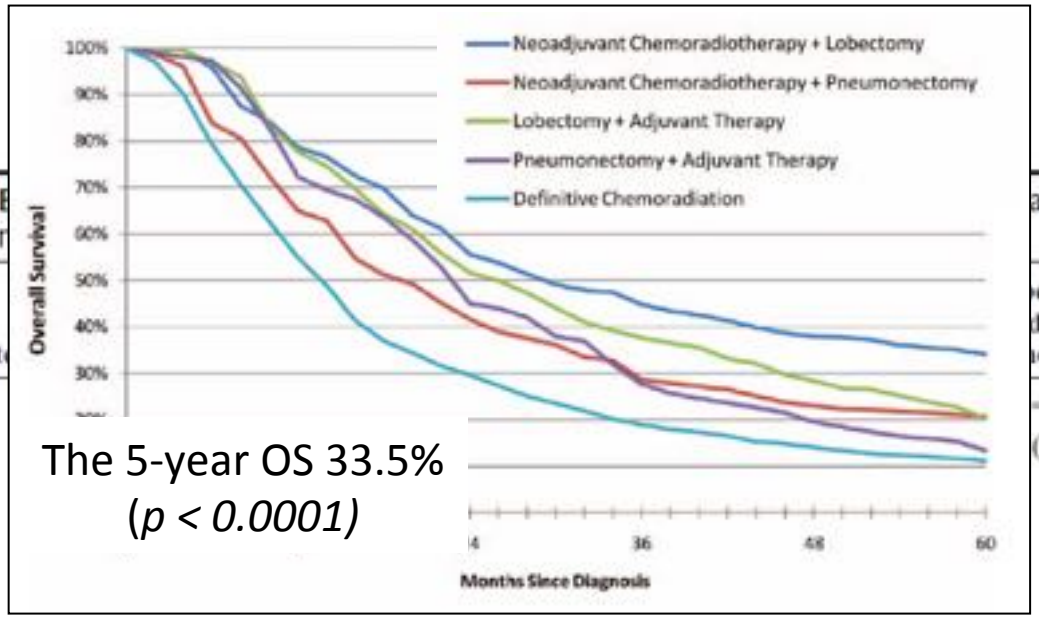
Conclusion

The addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse events. **The favorable local control in this CRS arm did not translate to a significant survival difference. We consider this was due to the small sample size.**

Neoadjuvant approach: Observational study

Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

Matthew Koshy, MD,† Stacey A. Fedewa, MPH,‡ Renu Malik, MD,† Mark K. Ferguson, MD,§¶ Wickii T. Vigneswaran, MD,§ Lawrence Feldman, MD,‖ Andrew Howard, MD,*† Khaled Abdelhady, MD,# Ralph R. Weichselbaum, MD,*† and Katherine S. Virgo, PhD, MBA‡***



The 5-year OS 33.5%
(*p* < *0.0001)*

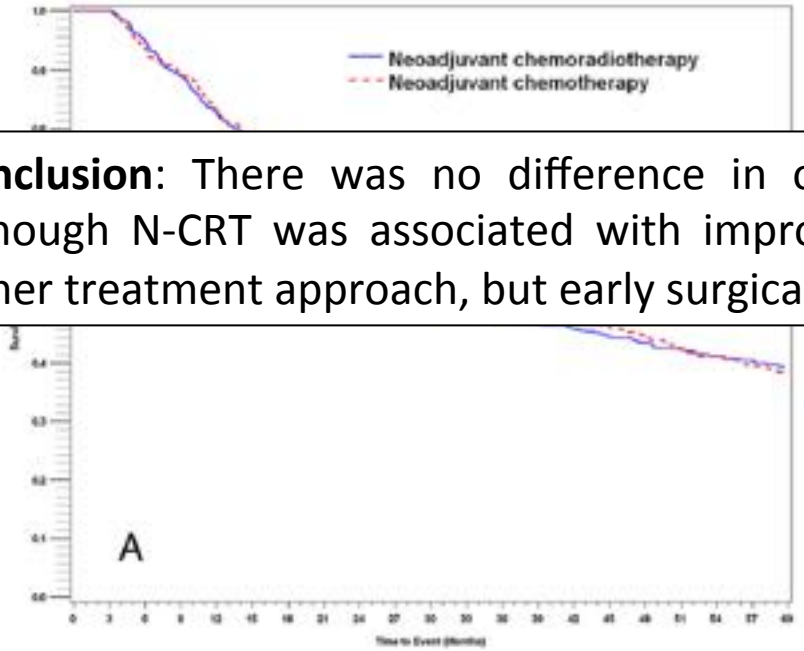
Appropriate candidates for neoadjuvant chemoradiation followed by surgery include those with **T1–T3 disease and ipsilateral positive mediastinal lymph nodes (maximum diameter <3 cm)**. Furthermore, **they should have resectable disease** as determined by a thoracic surgeon **and have adequate pulmonary function.**

Neoadjuvant approach: Observational study

Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer

David J. Sher[a,*], Mary Jo Fidler[b], Michael J. Liptay[c], Matthew Koshy[d]

[a] Department of Radiation Oncology, Rush University Medical Center, Chicago, IL, United States
[b] Section of Medical Oncology, Rush University Medical Center, Chicago, IL, United States
[c] Department of Cardiothoracic Surgery, Rush University Medical Center, Chicago, IL, United States
[d] Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL, United States



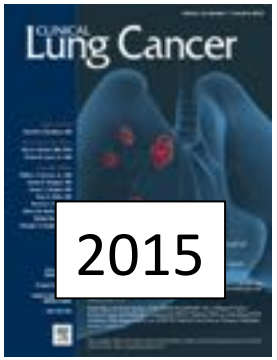
1076 patients: **700 (65%) underwent N-CRT**.
The 5-year OS for the entire cohort was 39%

Conclusion: There was no difference in overall survival between these two strategies, although N-CRT was associated with improved pathologic outcomes. These data support either treatment approach, but early surgical consultation is critical to ensure operability

CTX (p = 0.70)

N-CRT was associated with a lower independent risk of RND (p = 0.02) **and a lower risk of APF** (p = 0.0023).

Review article



CrossMark

Multimodality Treatment With Surgery for Locally Advanced Non–Small-Cell Lung Cancer With N2 Disease: A Review Article

Gouji Toyokawa, Mitsuhiro Takenoyama, Yukito Ichinose

- Phase II studies: inconsistent results
- Phase III studies: failed to show the survival benefit of surgery
- Large retrospective data: N-CRT + S (lobectomy) had a 49% reduced likelihood of death compared with those who underwent definitive concurrent chemoradiation.

… "what is the best way to treat patients with stage III NSCLC disease remains to be determined, which would be clarified by future studies. At present, as the ACCP guidelines recommend, **either definitive chemoradiotherapy or preoperative therapy followed by surgery might be effective for patients with discrete N2 disease**".

Strategies to improve multimodality treatment

What optimal chemoterapeutic regimen concurrently with RT?

What optimal Radiation schedule?

What risks of surgery after induction therapy?

Strategies to improve multimodality treatment

What optimal chemoterapeutic regimen concurrently with RT?

Preoperative Concurrent Chemoradiotherapy of S-1/Cisplatin for Stage III Non-Small Cell Lung Cancer

Masafumi Yamaguchi, MD, PhD, Gouji Toyokawa, MD, PhD, Taro Ohba, MD, PhD, Tomonari Sasaki, MD, PhD, Takuro Kometani, MD, PhD, Motoharu Hamatake, MD, PhD, Fumihiko Hirai, MD, PhD, Kenichi Taguchi, MD, PhD, Takeharu Yamanaka, PhD, Takashi Seto, MD, PhD, Mitsuhiro Takenoyama, MD, PhD, Kenji Sugio, MD, PhD, and Yukito Ichinose, MD, PhD

Departments of Thoracic Oncology, Radiation Oncology, and Pathology, National Kyushu Cancer Center; and Cancer Biostatistics Laboratory, Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan

Time after treatment

Ann Thorac Surg 2013

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

Annals of Oncology, First published online: April 20, 2015

Strategies to improve multimodality treatment

What optimal Radiation schedule?

"**Standard preoperative radiation doses** within chemoradiotherapy protocols **should be between 40 and 50 Gy in conventional fractionation** or **40-45 Gy** in accelerated fractionation **(bid application)** [I, B]".

Respiratory gating and tumour movement adaptations, as well as **intensity modulated radiotherapy** (IMRT), are important points for further improvement of targeting radiation delivery to the primary tumour and involved nodes

2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

Strategies to improve multimodality treatment

What risks of surgery after induction therapy?

"The optimal surgical management aims at complete resection – preserving as much non-involved parenchyma as possible, **preferably performed by lobectomy/sleeve resection** [I, A]. Complete resection necessarily **includes systematic mediastinal nodal exploration**.

In selected patients, **pneumonectomy** must be performed, but should be adequately selected and the procedure **restricted to experienced centres** [III, B]".

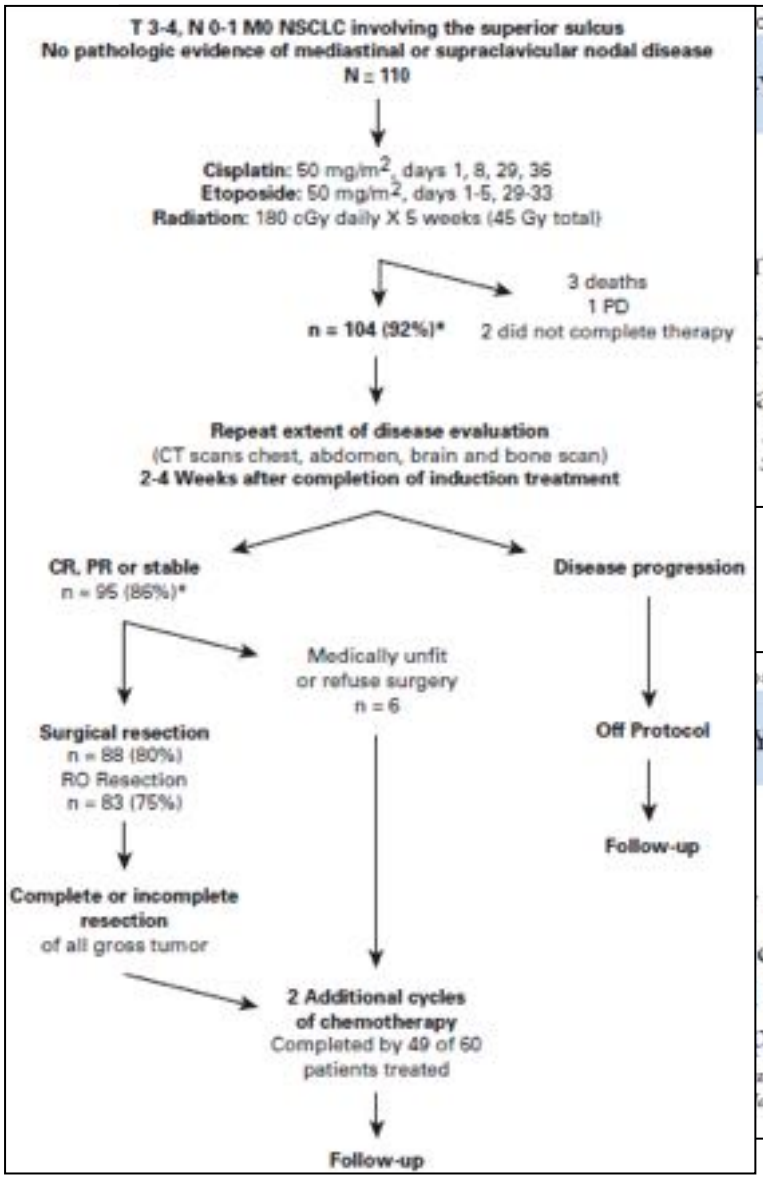
2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

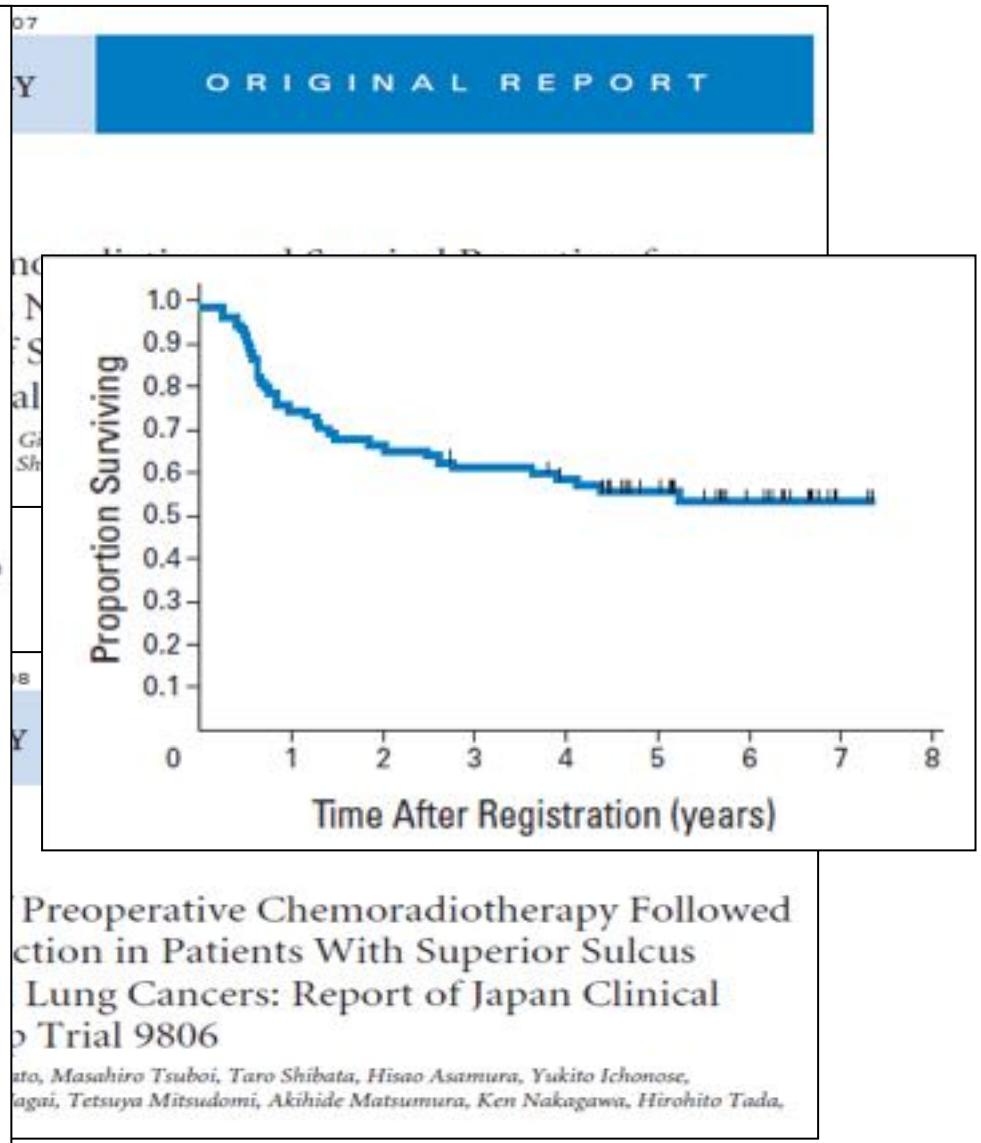
Tailored Therapy & Multidisciplinary approach

… Based on these different trials results, it is the general perception that, in these complex treatment situations, **the overall expertise of the multimodality team at the treatment centre is probably of more importance** for the overall outcome of the patient than **the exact schedule and permutation of the multimodality treatment protocol**

2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

Superior Sulcus NSCLC





Superior Sulcus NSCLC

Unresolved questions

- Management of patients with mediastinal node involvement
- No definite conclusions could be obtained from the single-arm phase II study

Heterogeneity in disease

Identification of 3 subgroups

(1) patients with **occult N2 node involvement** despite thorough preoperative staging

(2) patients with **discrete clinically evident** (by CT or CT-PET scan) **N2 involvement** (potentially resectable N2/T4)

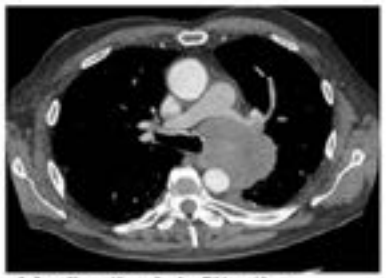
(3) patients with **infiltrative stage III** (**N2/N3/T4**) tumors

Ramnath N, et al. Treatment of Stage III Non-small Cell Lung Cancer. Chest 2013

Infiltrative stage III (N2/N3/T4) tumors

IIIB

T1-3 N2	bulky and/or multilevel N2 at staging
T4 N0-1	oesophagus, heart, aorta,
T4 N2	pulmonary veins
T1-4 N3	N3 nodes at staging



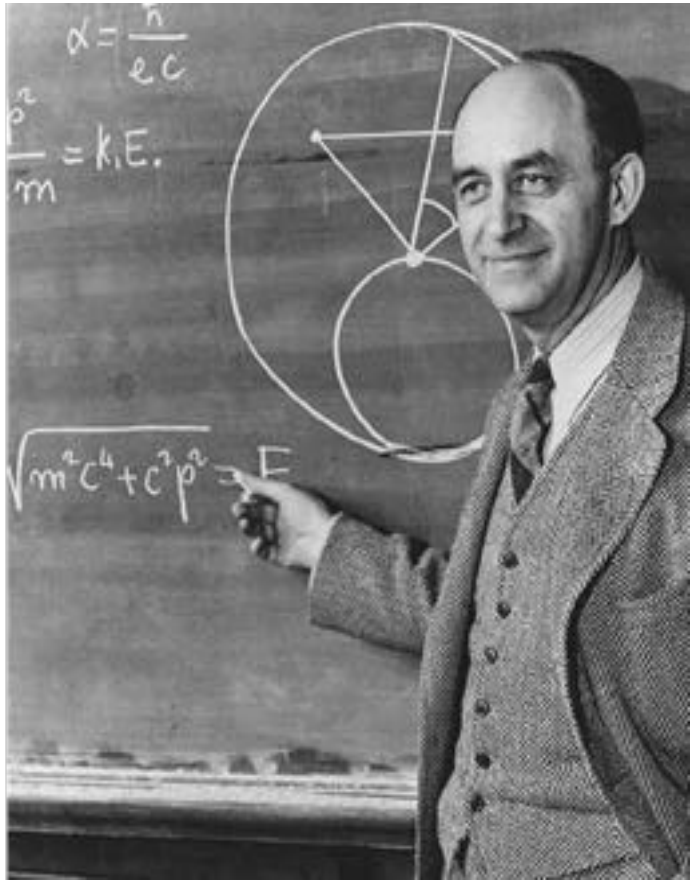
Mediastinal Infiltration

"Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible – for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A]".

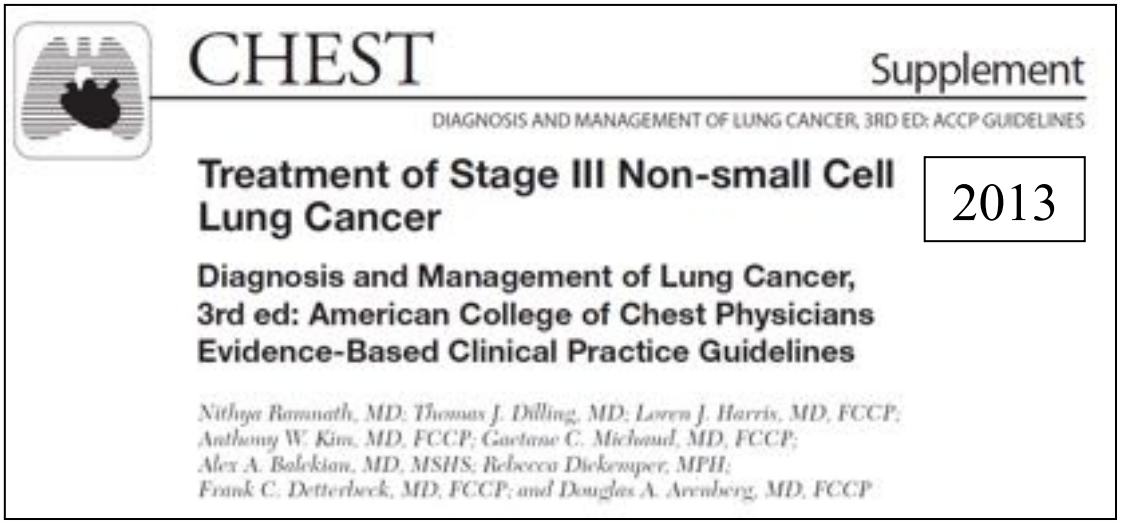
2nd ESMO Consensus Conference in Lung Cancer: locally-advanced stage III non-small-cell lung cancer (NSCLC)
Annals of Oncology, First published online: April 20, 2015

"Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level".

Enrico Fermi



Guidelines & EBM



CHEST Supplement

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

Treatment of Stage III Non-small Cell Lung Cancer

2013

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

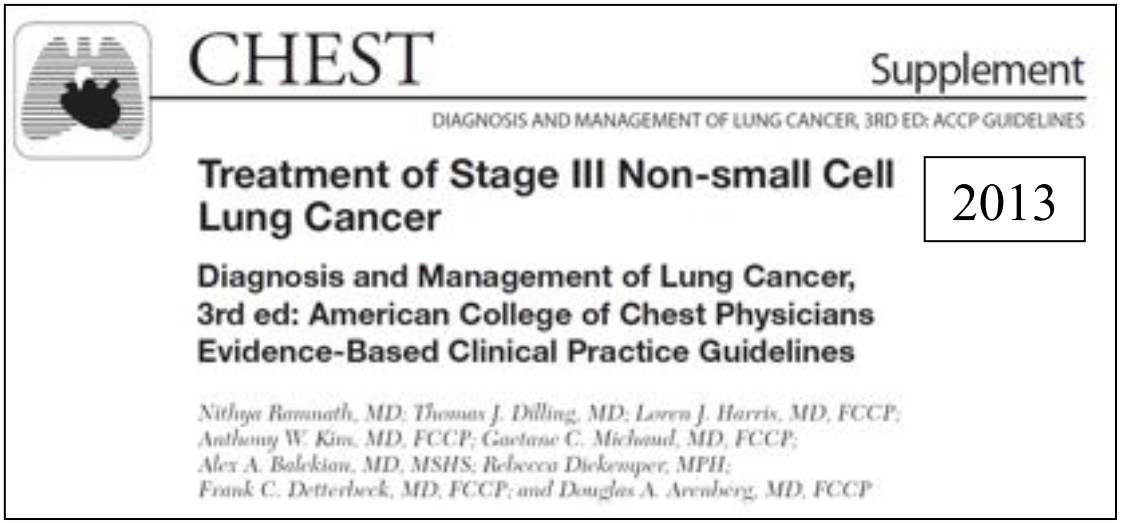
Nithya Ramnath, MD; Thomas J. Dilling, MD; Loren J. Harris, MD, FCCP; Anthony W. Kim, MD, FCCP; Gaetane C. Michaud, MD, FCCP; Alex A. Balekian, MD, MSHS; Rebecca Diekemper, MPH; Frank C. Detterbeck, MD, FCCP; and Douglas A. Arenberg, MD, FCCP

Multimodality therapy is preferable in most subsets of patients with stage III lung cancer. Variability in the patients included in randomized trials limits the ability to combine results across studies and thus limits the strength of recommendations in many scenarios. Future trials are needed to investigate the roles of individualized chemotherapy, surgery in particular cohorts or settings, prophylactic cranial radiation, and adaptive radiation.

Adjuvant Therapy

4.5.3. 4.5.4. 4.5.5. In patients with NSCLC who were found were were to have incidental (occult) N2 disease (IIIA) despite (IIIA) ease (I thorough preoperative staging and were incom- who seque pletely resected (R1,2), combined postoperative platin when concurrent chemotherapy and radiotherapy is (Grad (Grade **suggested** (Grade 2C).

Guidelines & EBM



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Discrete Mediastina

3.5.2. In patients v by NSCLC ident either definitive induction therapy f mended over eithe (Grade 1A).

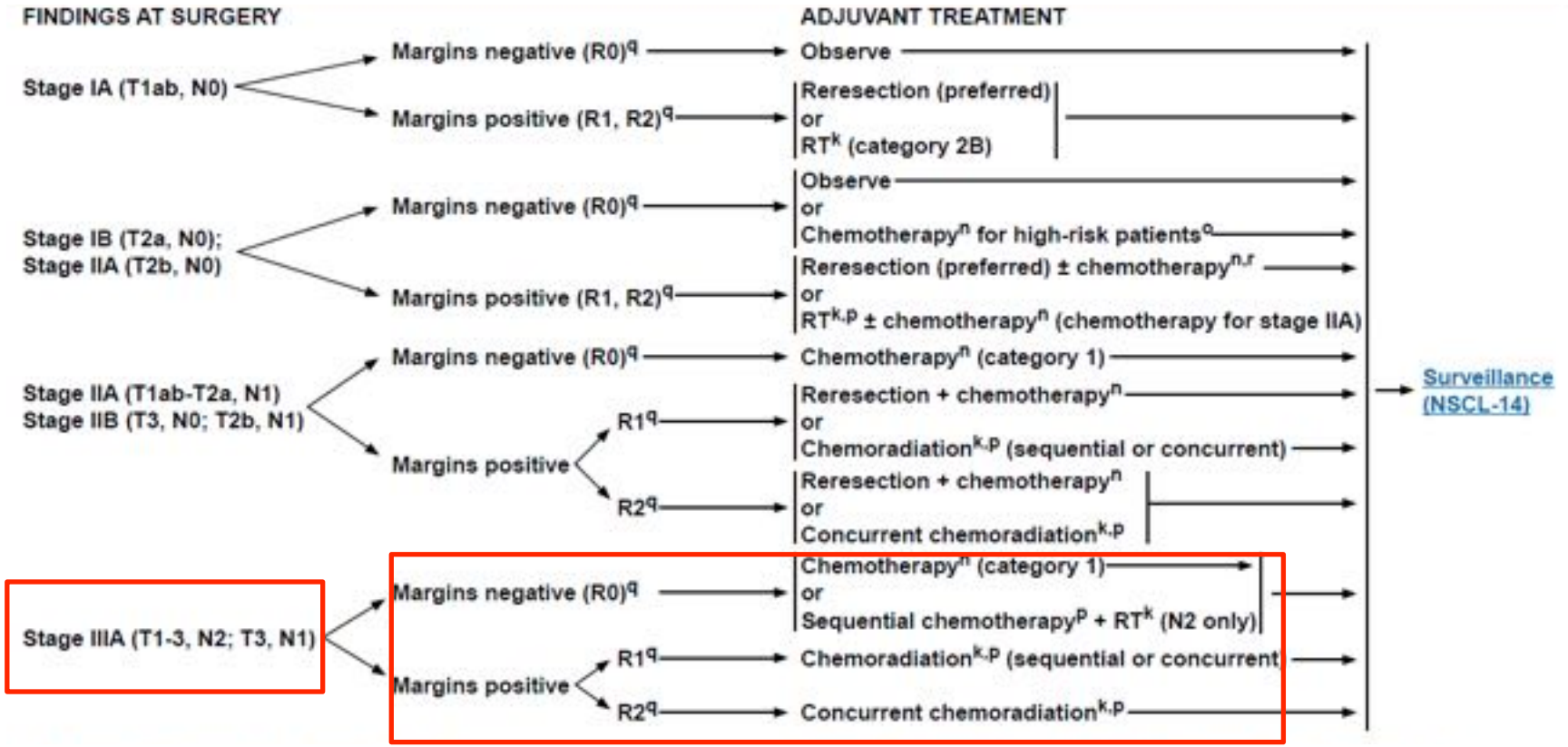
Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer

2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A).

Guidelines & EBM

National Comprehensive Cancer Network®

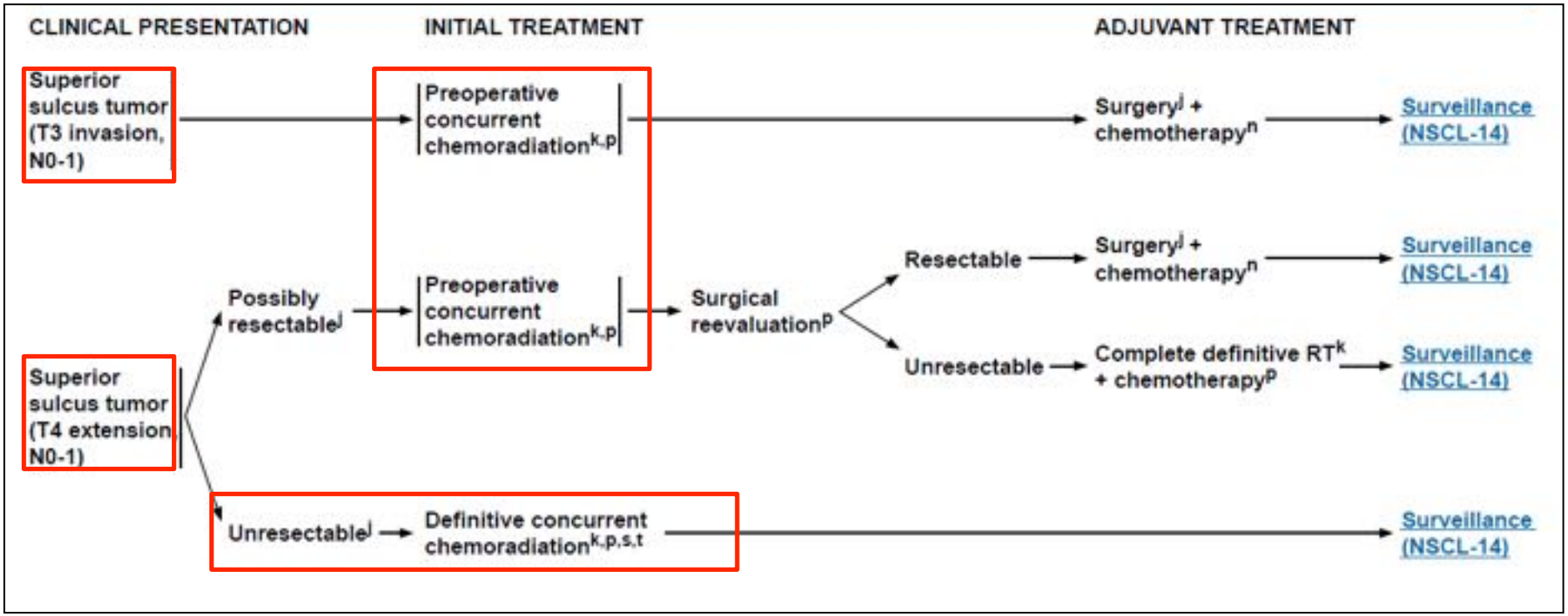
NCCN Guidelines Version 6.2015
Non-Small Cell Lung Cancer



Guidelines & EBM

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2015
Non-Small Cell Lung Cancer



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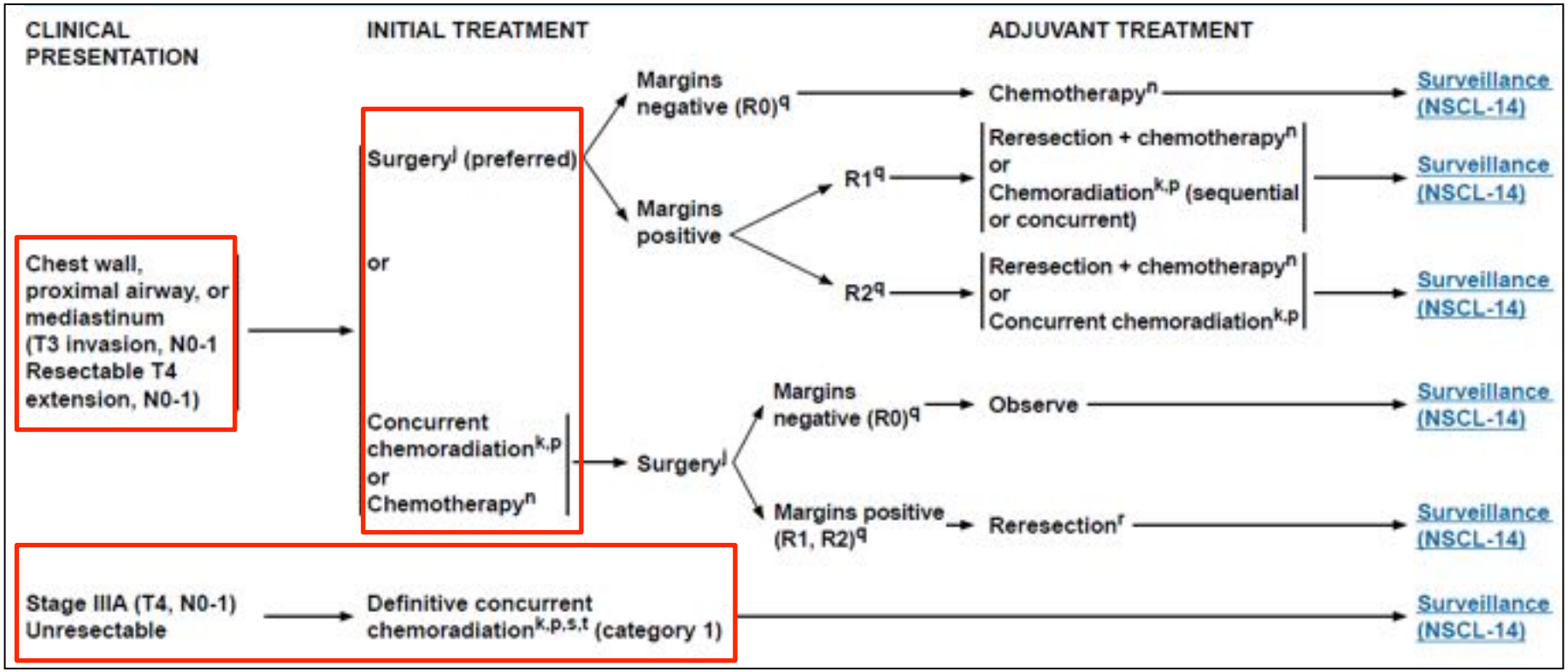

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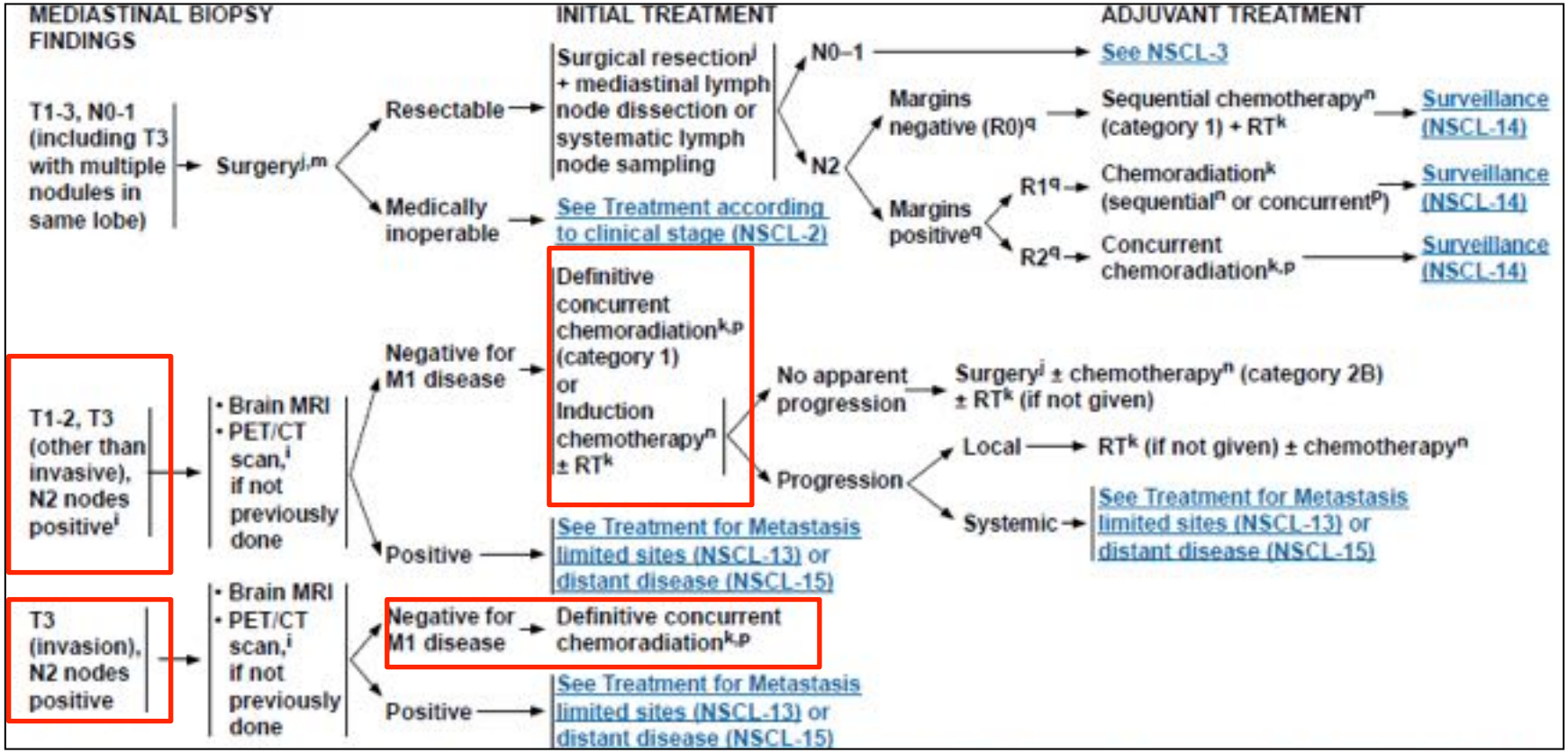

Guidelines & EBM

ASCO Key Recommendations (extracted from ASTRO recommendations [with ASCO qualifying language in italics]; see Data Supplement 1 for reprint of all ASTRO recommendations)

- *For curative-intent treatment of locally advanced NSCLC,* concurrent chemoradiation *is recommended because it* improves local control and overall survival compared *with* sequential chemotherapy followed by radiation or radiation therapy alone.
- The standard dose-fractiona… …tions *of 2 Gy once per day* over 6 weeks. Dose escalation bey… …d to be *of* benefit.
- There is no role for the rou…
- There *is no* role for the rou… routine use of consolidatio… receive full systemic chemo… Current data fail to support …ion for patients who did not
- The ideal concurrent chem… …on regimens *are* cisplatin/ etoposide and carboplatin/
- For patients *who* cannot to… radiation *is recommended b*… …llowed by radical (*definitive*) …alone.
- Radiotherapy alone may be… …*ay offer better* tolerability, *but poorer* survival.
- Postoperative radiotherapy… control, *but* should be deliv… …sease *to* improve local
- Postoperative radiotherapy… gross residual disease), *to b*… …c or *gross* positive margin, or
- *Patients with resectable stag… best candidates for preopera…* pneumonectomy), no weig… …*s best surgical judgment. The* …opposed to

Relevant ASTRO Statements Concerning Role of Radiotherapy in Context of Trimodality Treatment of LA NSCLC

- There is no level I evidence recommending the use of induction radiotherapy (or chemoradiotherapy) followed by surgery for patients with resectable stage III NSCLC (HQE, "strong").
- In those patients who are selected for trimodality approach, preoperatively planned lobectomy (as opposed to pneumonectomy), based on best surgical judgment, is preferable, since it was associated with survival benefit in the exploratory posthoc North American Intergroup study INT 0139 analysis (MQE, "strong").
- No definitive statement can be made about best patient selection criteria for the trimodality therapy, although no weight loss, female gender, and one (*v* more) involved nodal stations were associated with improved outcome in INT 0139 (MQE, "strong").

ASCO comments. We agree and have summarized these statements as follows: *Patients with resectable stage III NSCLC should be managed by a multidisciplinary team that uses best surgical judgment. The best candidates for preoperative chemoradiotherapy have preoperatively planned lobectomy (as opposed to pneumonectomy), no weight loss, female sex, and only one involved nodal station.*

Multidisciplinary approach

MEDICAL ONCOLOGIST

RADIOLOGIST and NUCLEAR MEDICINE

PATIENT

THORACIC SURGEON

PULMONOLOGIST

RADIATION ONCOLOGIST