ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO PRECEPTORSHIP ON LUNG CANCER

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March 8, 2019

DISCLOSURES

PAUL VAN SCHIL, MD

- International Association for the Study of Lung Cancer (IASLC) Board member

- Lung Cancer Chair, Staging and Prognostic Factors Committee (SPFC) of IASLC

ESMO

Role of surgery for N2 disease

- surgery for N2: the problem
- randomised controlled trials
- meta-analyses N2
- recent data
- salvage surgery
- conclusions

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N2 discovered by staging

Management of stage IIIA NSCLC by thoracic surgeons in North America

web-based survey 513/2539 (20%) responded – 43% academic practice

- *microscopic N2:* 84% induction therapy + surgery
- *grossly involved N2:* 62% induction therapy + surgery (N2 downstaged)
- *bulky, single station N2, normal lung function, initially pneumonectomy*

required: 32% induction + lobectomy (N2 downstaged)
30% induction + pneumonectomy (downstaged)
12 % induction + surgery anyway
22% definitive chemoradiotherapy

Veeramachaneni NK. Ann Thorac Surg 2012; 94:922-8

Complete resection R0
IASLC

- free resection margins proved microscopically
- systematic or lobe-specific systematic nodal dissection:
  ≥ 6 nodal stations (3 mediastinal)

uncertain

- no extracapsular extension in nodes removed separately or at the margin of the lung specimen
- highest mediastinal lymph node must be negative

Rami-Porta R et al. Lung Cancer 2005; 49:25-33

Surgery for N2 disease: the problem

- it is *impossible* to identify any treatment-related predictive or prognostic factors *for selecting surgery* in the treatment of patients with stage IIIA-N2 NSCLC

  Jeremic B. Fontiers Oncol 2018; 8: article 30

- Optimal treatment of stage IIIA-N2 NSCLC: a neverending story?

  heterogeneity, imprecise definitions, Δ categories N2: N2a1, N2a2, N2b

  Van Schil P. J Thorac Oncol 2017; 12:1338-40

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Surgery for N2 disease

- **EORTC 08941**

  stage IIIA-N2 NSCLC

  phase III induction CT - in case of response: randomisation between surgery and RT

  167 pts surgery

- **Intergroup trial 0139**

  stage IIIA-N2 NSCLC

  phase III concurrent CT/RT versus induction CT/RT + surgery

  164 pts surgery

Albain KS. *Lancet* 2009; 374:379-86
Van Meerbeeck J. *JNCI* 2007; 99:442-50 Van Schil P. Eur Resp J 2005; 26:192-7

Comparison
EORTC 08941 – INT 0139

	EORTC 08941	INT 0139
induction therapy	chemotherapy	chemoradiotherapy
complete resection	50 %	71 %
definition ≠		
expl. thoracotomy	13.6 %	4.5 %
ypN0/1/2	N0/1 41.4 %	N0 46 %
	N2 56 %	N1-3 54 %
ypT0N0	5.2 %	14.4 %

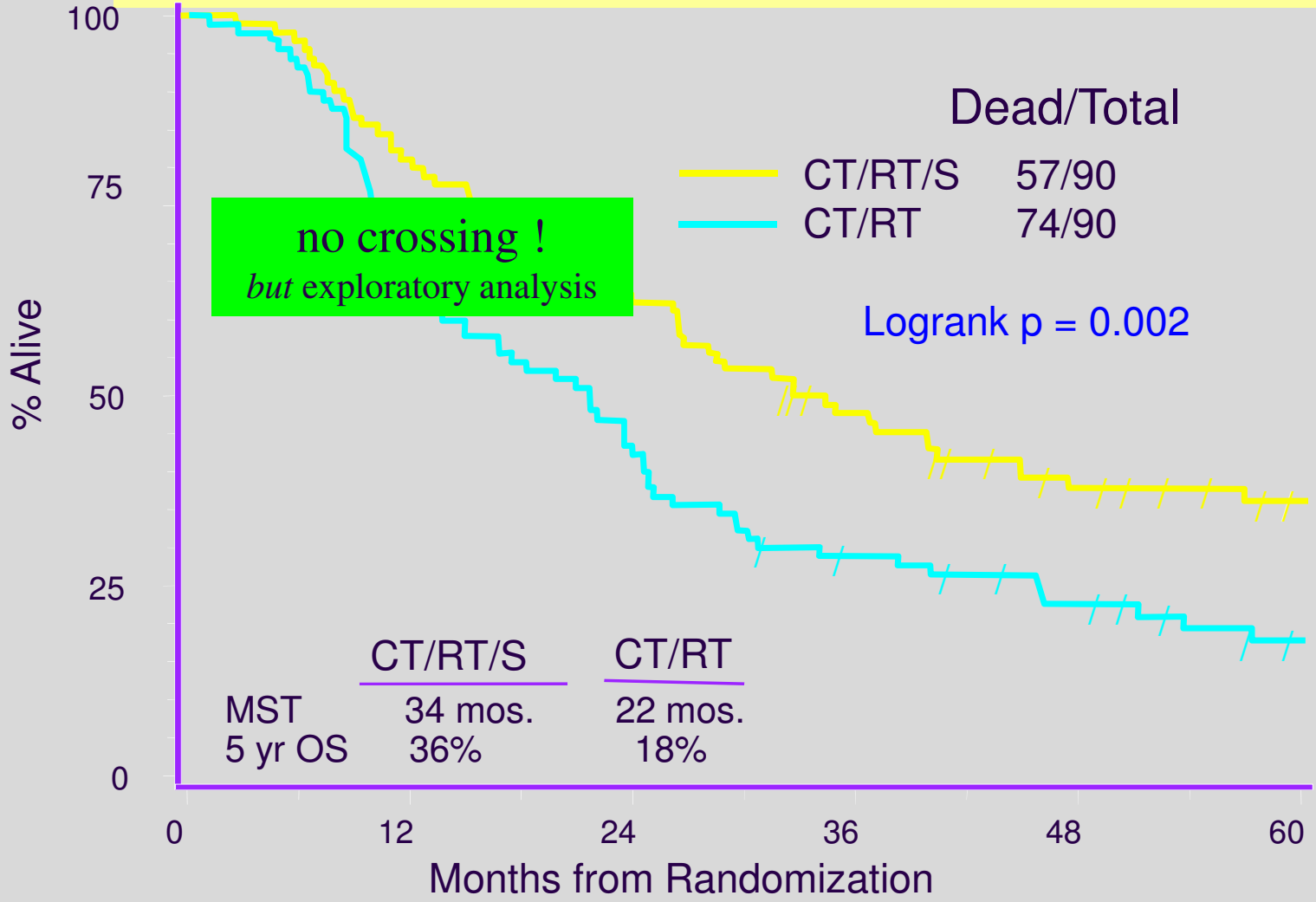
Comparison
EORTC 08941 – INT 0139

30-day mortality	EORTC 08941		INT 0139		
overall		3.9 %		5 %	
lobectomy		0 %		1 %	
pneumonectomy	6.9 %	R 5.3 %	26 %	R simple	29 %
		L 9.1 %		*R complex*	*50 %*
				L simple	0 %
				L complex	16 %
expl. thoracotomy		4.8 %		0 %	
90-day mortality		8.4 %			

Comparison
EORTC 08941 – INT 0139

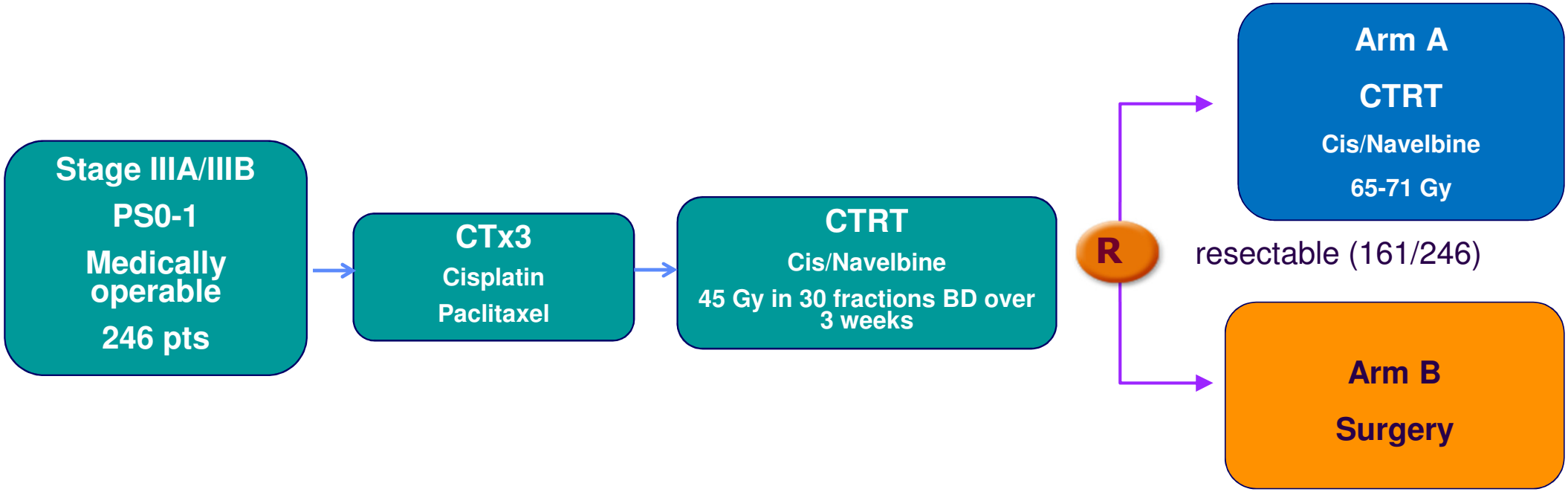
5- year survival	EORTC 08941	INT 0139
lobectomy	27 %	36 %
pneumonectomy	12 %	22 %
	p = .009	
ypN0/1/2	N0/1 29 %	N0 41 %
	N2/3 7 %	N1-3 24 %
	p = .0009	p < .0001

INT0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset



ESPATUE trial

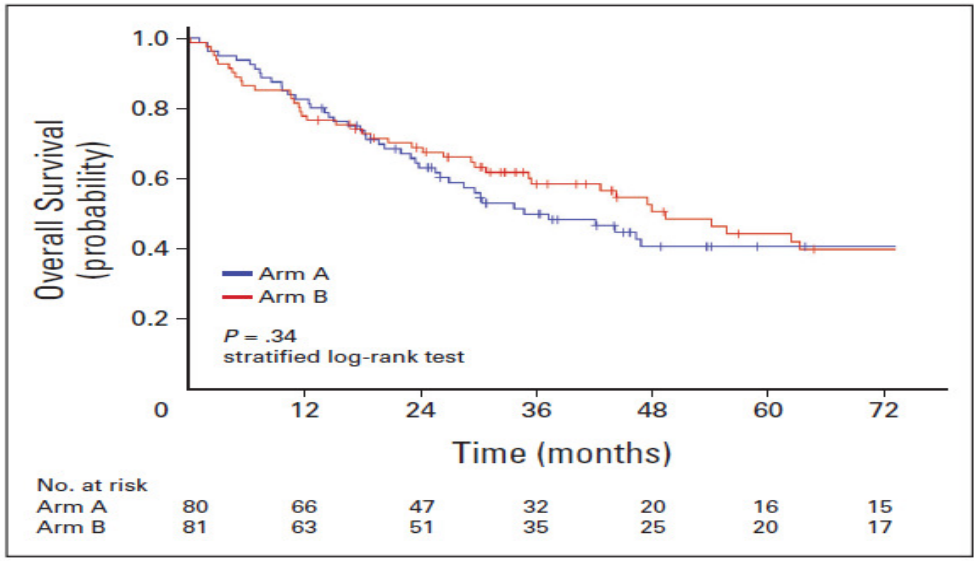
Phase III Study of Surgery Versus Definitive Concurrent CTRT Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB NSCLC After Induction Chemotherapy and Concurrent CTRT

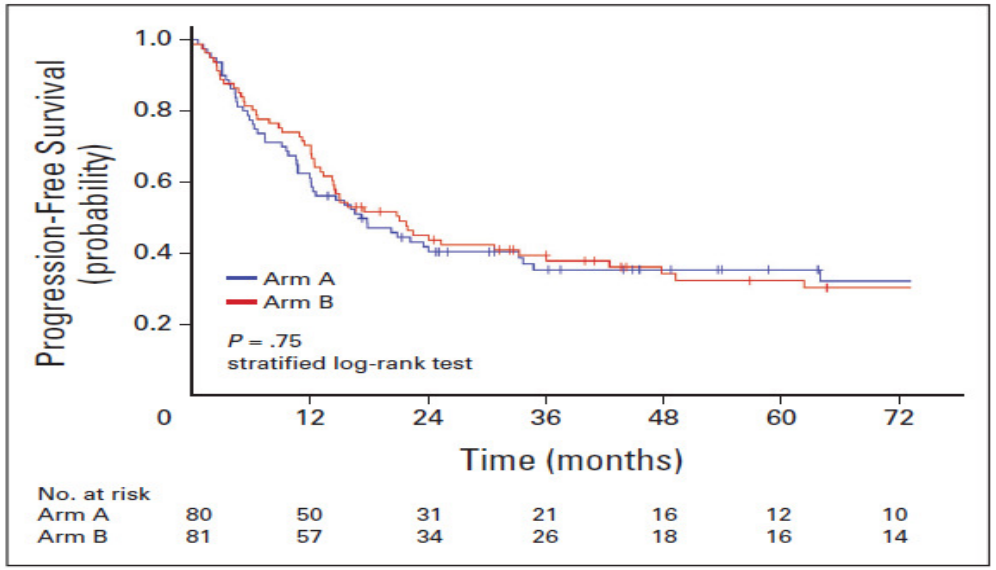


Eberhardt W. J Clin Oncol 2015; 33:4194-201

ESPATUE trial

Arm A: 5-year OS=40.6%
Arm B: 5-year OS=44.2%
log-rank: p=0.31





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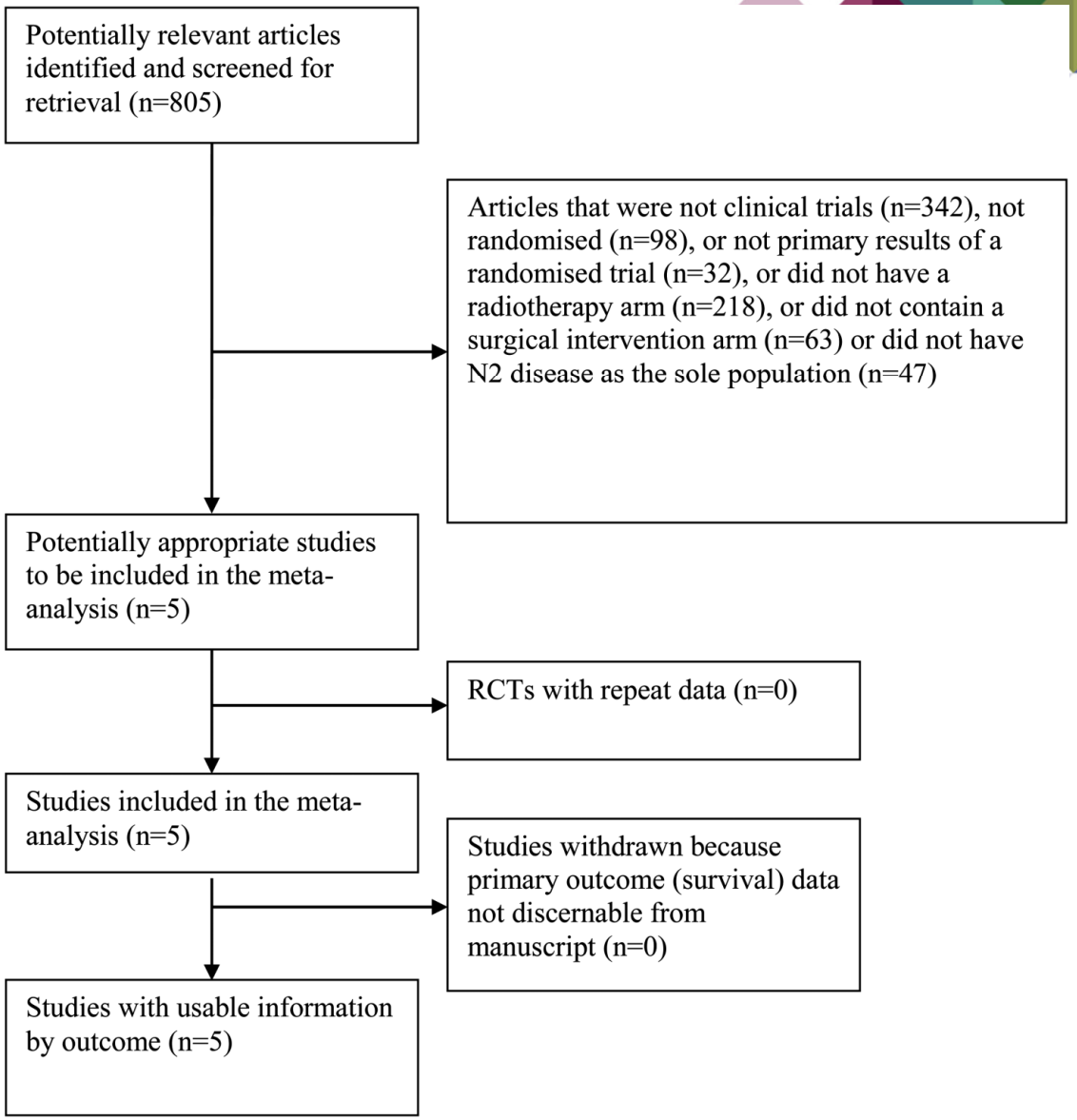
Systematic review and meta-analysis stage IIIA-N2

- outcome of patients with N2 disease in multimodality trials of chemotherapy, radiotherapy and surgery
- Medline and Embase 1980 - 2013
- pts with N2 disease who received induction chemotherapy or chemoradiotherapy and randomised to surgery or radiotherapy
- main outcome overall survival

McElnay PJ. Thorax 2015; 70:764-768

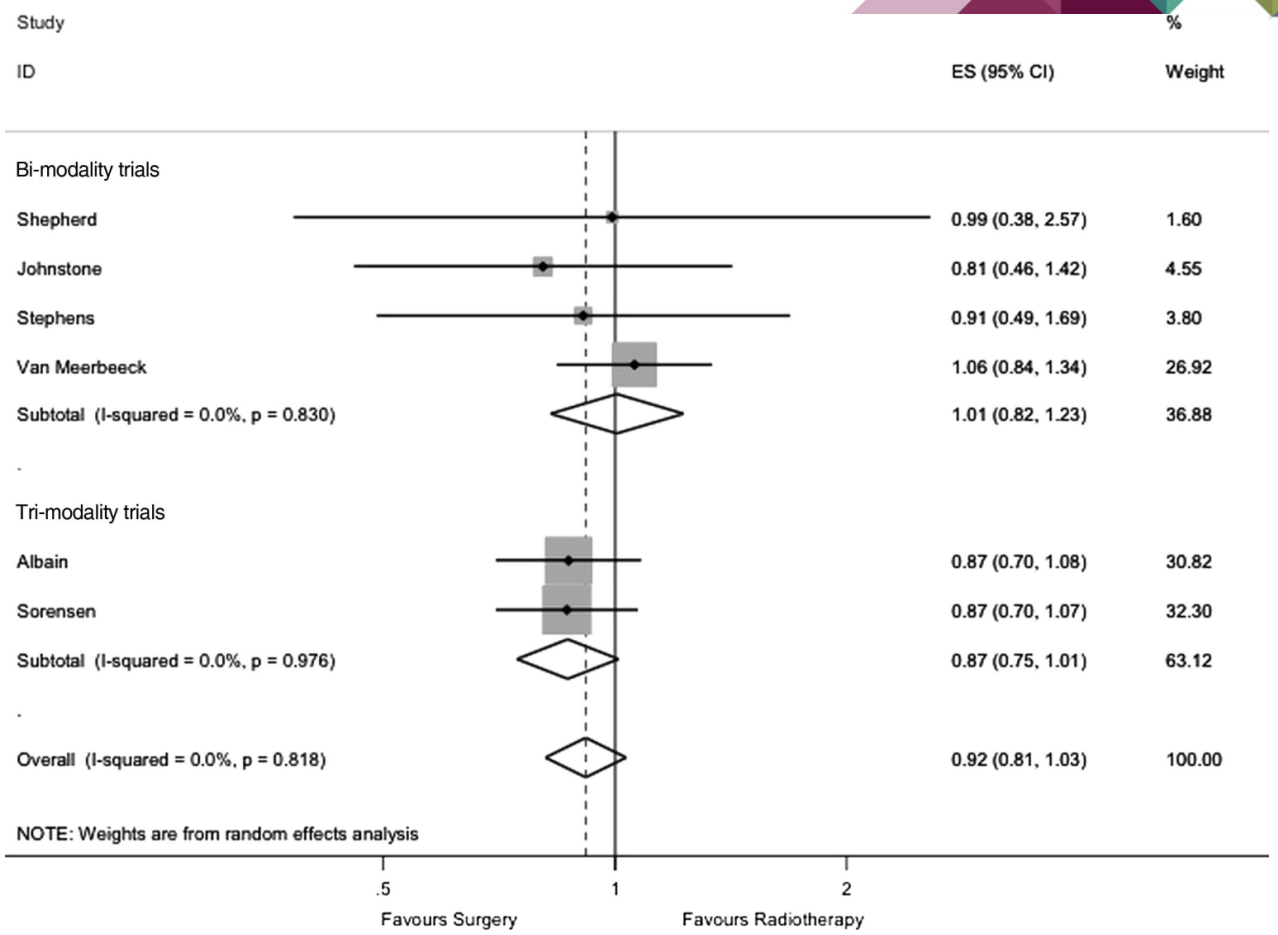
- 6 trials - 868 pts
- 4 induction chemo
  2 induction chemorad

McElnay PJ. Thorax 2015; 70:764-768



Forest plot of OS comparing postinduction surgery with radiotherapy

McElnay PJ. Thorax 2015; 70:764-768



Systematic review and meta-analysis stage IIIA-N2

• OS	bimodality	pooled HR † surgery	1.01	*p=0.954*
	trimodality		0.87	*p=0.068*
	all trials		0.92	*p=0.157*

- no statistical evidence of heterogeneity
- bimodality: both surgery and radiotherapy options are valid

  trimodality: results support surgery as part of multimodality management *(13% relative improvement in OS)*

McElnay PJ. Thorax 2015; 70:764-768

Definitive radiochemotherapy versus surgery within multimodality treatment in stage III NSCLC – cumulative meta-analysis of the randomized evidence

- 6 randomized trials 1322 pts *comparing surgery with radiotherapy* as local treatment modalities within combined modality regimen for stage III NSCLC
- OS, PFS = surgery ↔ radiotherapy; excess early † surgical arm
- induction therapy followed by either resection or definitive chemoradiation are valid treatment options

Pottgen C. Oncotarget 2017; 8:41670-8

Optimal treatment for stage IIIA-N2 NSCLC: *a network meta-analysis*

- analysis RCT comparing surgery, radiotherapy, chemotherapy and their multiple combinations
- 18 eligible trials reporting 13 Δ treatments
- optimal treatment: neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy
  → ↑ OS and ↓ treatment-related ✝

Zhao Y. Ann Thorac Surg 2018; Dec. 14 [Epub]

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OA 01.05 WCLC 2018 Toronto

NEO-ADJUVANT CHEMO-IMMUNOTHERAPY FOR THE TREATMENT OF STAGE IIIA RESECTABLE NON-SMALL-CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUDY

NADIM: Neo-Adjuvant Immunotherapy

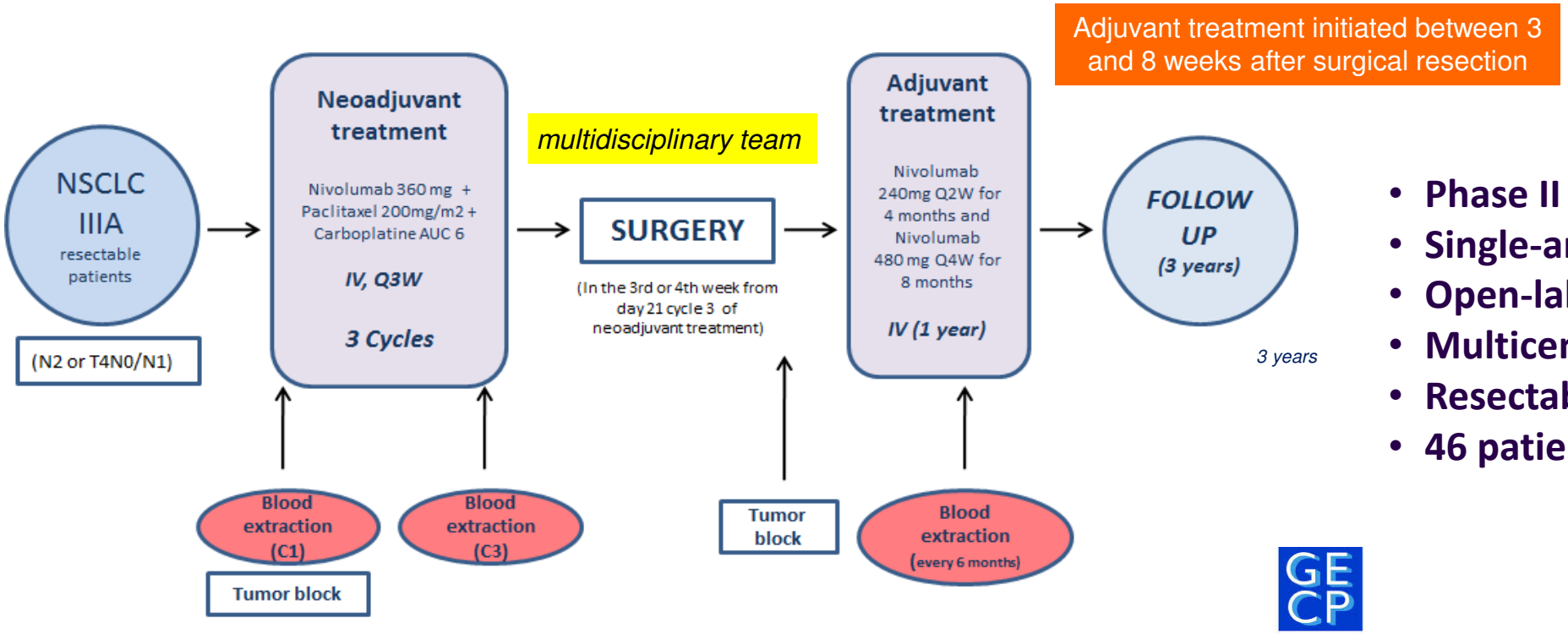
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

M. Provencio[1], E. Nadal[2], A. Insa[3], R. García-Campelo[4], G. Huidobro[5], M. Dómine[6], M. Majem[7], D. Rodríguez-Abreu[8], V. Calvo[1], A. Martínez-Martí[9], J. de Castro[10], M. Cobo[11], G. López-Vivanco[12], E. del Barco[13], R. Bernabé[14], N. Viñolas[15], I. Barneto[16], B. Massuti[17]

[1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, [2]Institut Catalá de Oncología-Hospitalet, Barcelona, [3]Hospital Clínico Universitario, Valencia, [4]Hospital Universitario de la Coruña, La Coruña, [5]Hospital Universitario de Vigo, Pontevedra, [6]Fundación Jiménez Díaz, Madrid,[7]Hospital de la Santa Creu i Sant Pau, Barcelona, [8]Hospital Insular de Gran Canaria, Las Palmas, [9]Hospital Universitario Vall Hebrón, Barcelona, [10]Hospital Universitario la Paz, Madrid, [11]Hospital Provincial de Málaga, Málaga, [12]Hospital de Cruces, Bilbao, [13]Hospital Universitario de Salamanca, Salamanca, [14]Hospital Universitario Virgen del Rocío, Sevilla, [15]Hospital Clínic de Barcelona, Barcelona, [16]Hospital Universitario Reina Sofía, Córdoba, [17]Hospital General de Alicante

Mariano Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

NADIM: Study design & Flow-chart



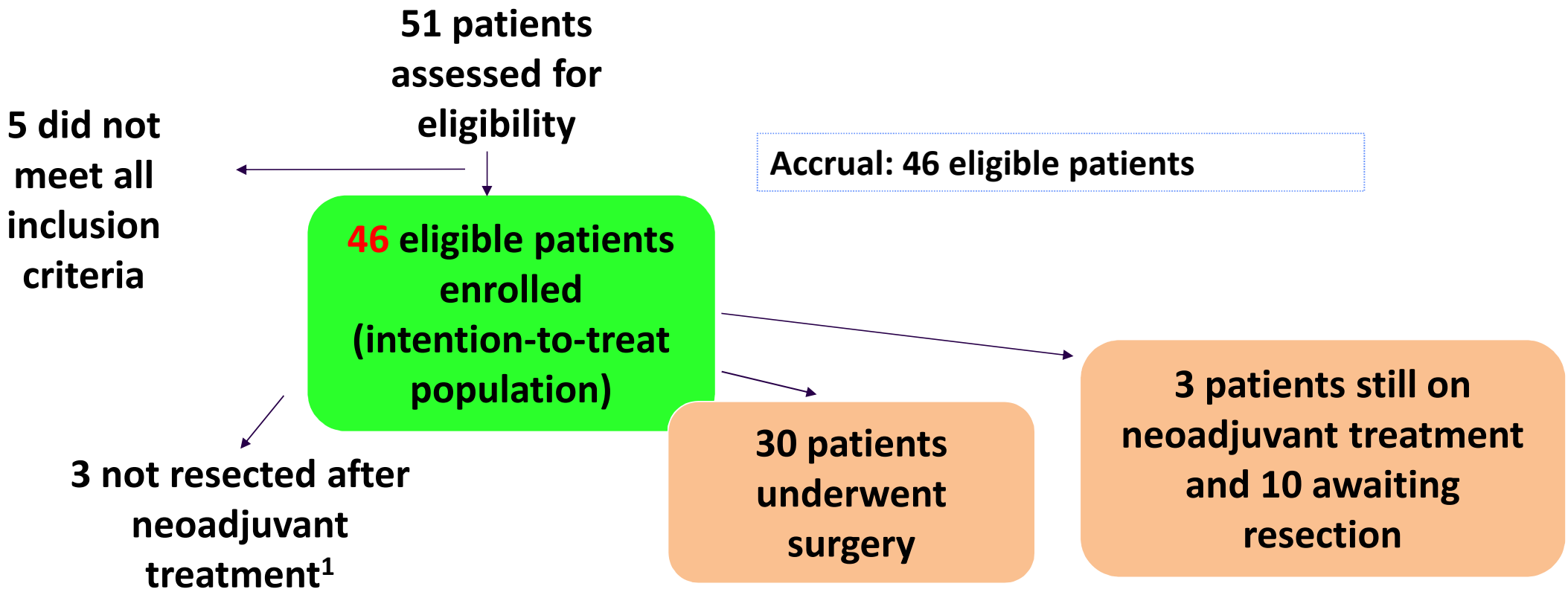
- **Phase II**
- **Single-arm**
- **Open-label**
- **Multicenter**
- **Resectable IIIA NSCLC**
- **46 patients**

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

RECRUITMENT AND FOLLOW-UP



[1] 2 patients decided not to undergo resection, one patient did not fulfill surgical criteria for resectability

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Neoadjuvant treatment

	N	Median	Range
Cycles	45	3.0	(1.0-3.0)

CYCLES	N	%
1	3	5
3	43	95
Total	46	100.0

All patients received three neoadjuvant cycles except for the three patients still being treated.

Clinical response

	N	%
Complete response (CR)	3	10.0
Partial response (PR)	18	60.0
Stable disease (SD)	9	30.0
Total	30	100.0

No PD has been observed.

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

Pathological response

	N	%
Major response[1]	24	80.0
Complete response	18	75.0
Less < 90%	6	20.0
Total	30	100.0

[1]Major pathological response defined as <10% viable tumor cells in the resected specimen.

The following factors were considered to identify factors that potentially influence pathological response (complete and major):

- *Age*
- *Gender*
- *Performance status*
- *Smoking status*
- *Comorbidities*
- *Clinical stage*
- *Clinical response*
- *Primary tumor site (right vs left)*
- *Histology (adenocarcinoma vs squamous)*
- *Nodes involvement (yes/no)*
- *Nodes resected and hematological toxicities grade 3-4*

Each factor was compared between patients with pathological response (complete and major) vs those with no response. Factors with p<0.1 were considered potential factors for a logistic regression analysis (N=30).

No significant logistic regression models were obtained.

- *median patient follow-up = 4.1 months, range 0.2-14.6 months.*
- *none of the patients have suffered recurrence*

- *promising treatment but preliminary results!*

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Neoadjuvant PD-1 blockade in resectable lung cancer
Forde PM et al. NEJM 2018; Apr. 16

- 21 pts NSCLC stage I-IIIA 2 preop. doses nivolumab 3 mg/kg
- only 2/21 pts (9.5%) radiographic response
- 20/21 pts (95.2%) complete resection
- major pathological response 45%
- major pathological response → tumor mutational burden
- treatment → expansion of mutation-associated neoantigen-specific T-cell clones

Neoadjuvant erlotinib in EGFR – mutated stage IIIA-N2 patients

- pts stage IIIA-N2 17 Chinese centers screened
- 72 pts randomized

	neoadjuvant erlotinib *42dd pre – 1y postop*	cisplatin + gemcitabine *2 cycles pre – 2 cycles postop*	
ORR	54.1%	34.3%	*OR 2.26*
surgery	31 pts – 83.8%	24 pts – 68.6%	
LN downstaging	13%	4.2%	
PFS	21.5 mos	11.9 mos	*HR 0.42*

- no OS data
- EGFR-mutated stage IIIA-N2 erlotinib ↑ ORR and PFS

ESMO 2018 LBA48_PR - CTONG 1103. Zhong WZ et al.
Erlotinib versus gemcitabine + cisplatin as neoadjuvant treatment for stage IIIA-N2 EGFR-mutation NSCLC (EMERGING): a randomised study

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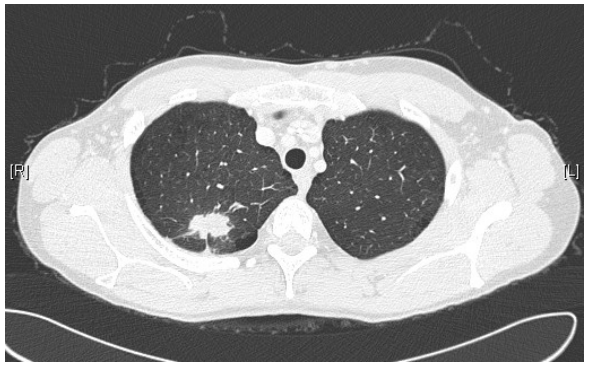
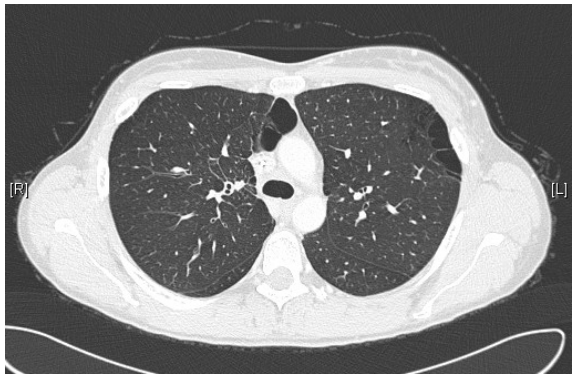
Salvage surgery

- 39-year-old ♀
- 25 pack years
- cT1N2M0 adenoca. RUL
- multilevel N2
- PET: no distant metastases
- c stage IIIA
- induction chemotherapy cisplatin-pemetrexed + RT 60 Gy 30 sessions

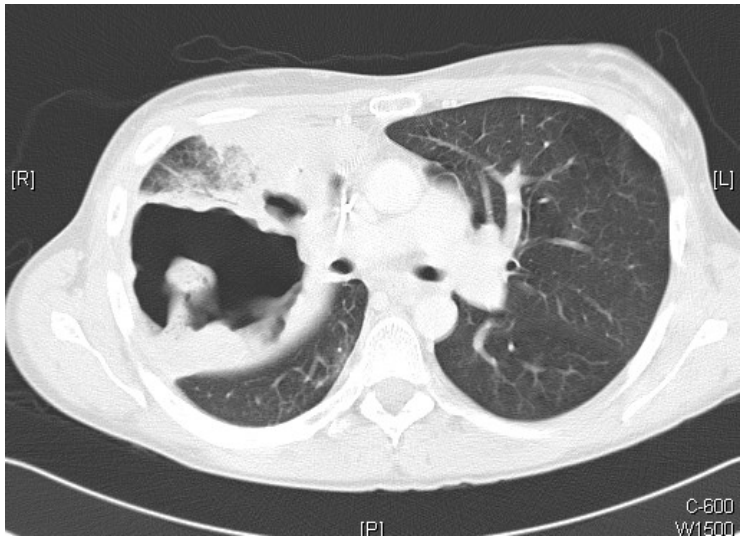
CT 170407





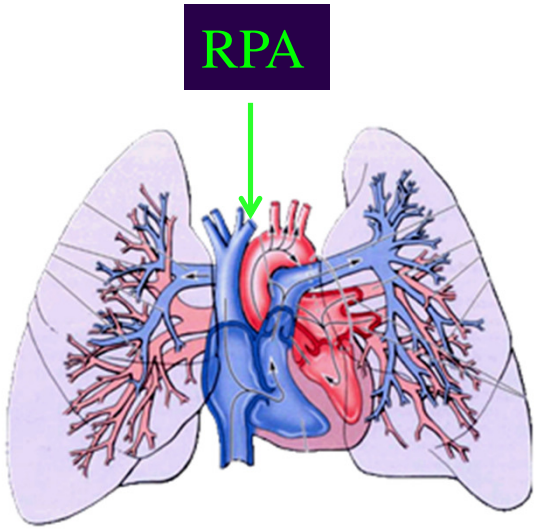
Salvage surgery

- purulent cough, haemoptysis
- infected cavity
- necrotic lung abscess



CT 091007

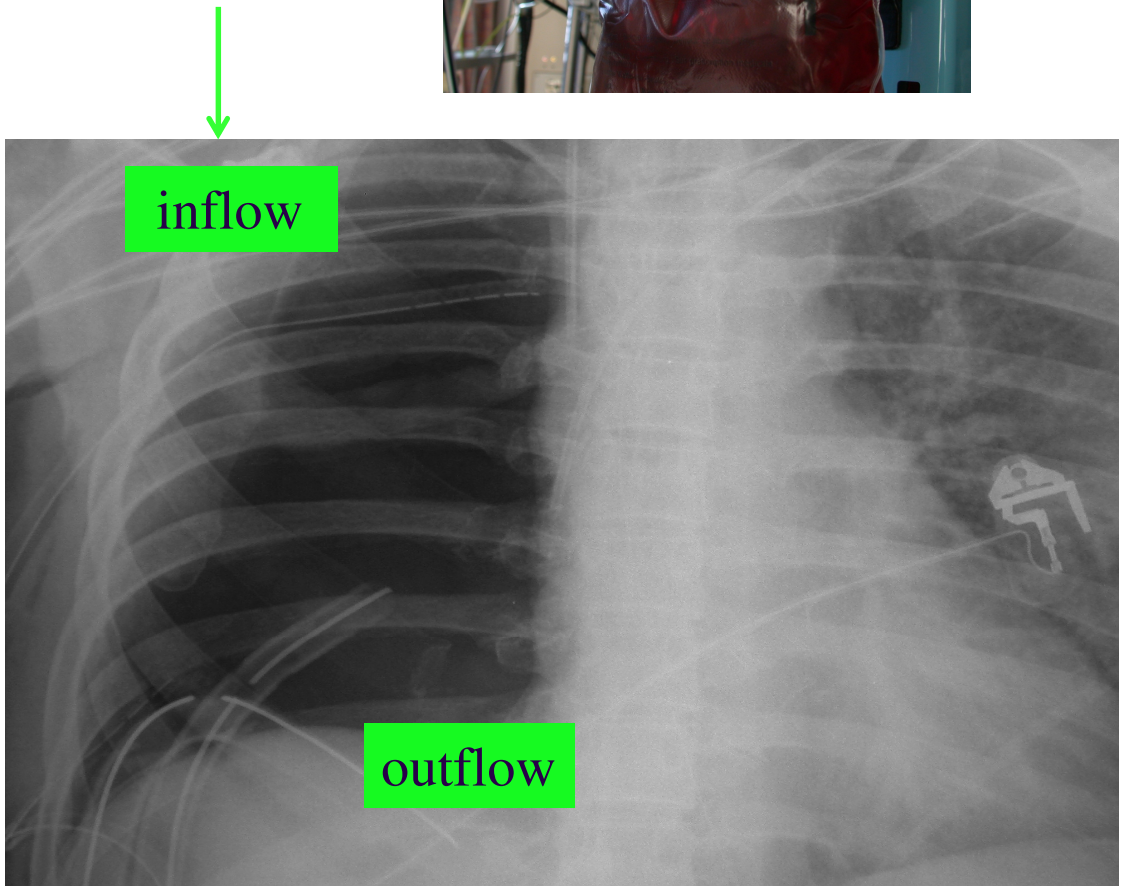
- R muscle-sparing thoracotomy
- dense hilar fibrosis, invasion fissure
- intrapericardial pneumonectomy



irrigation system

culture: fungi, Klebsiella ESBL + and Staph. aureus

pathology:
multiple nodules adenoca.
LN 7+ ypT3N2M0



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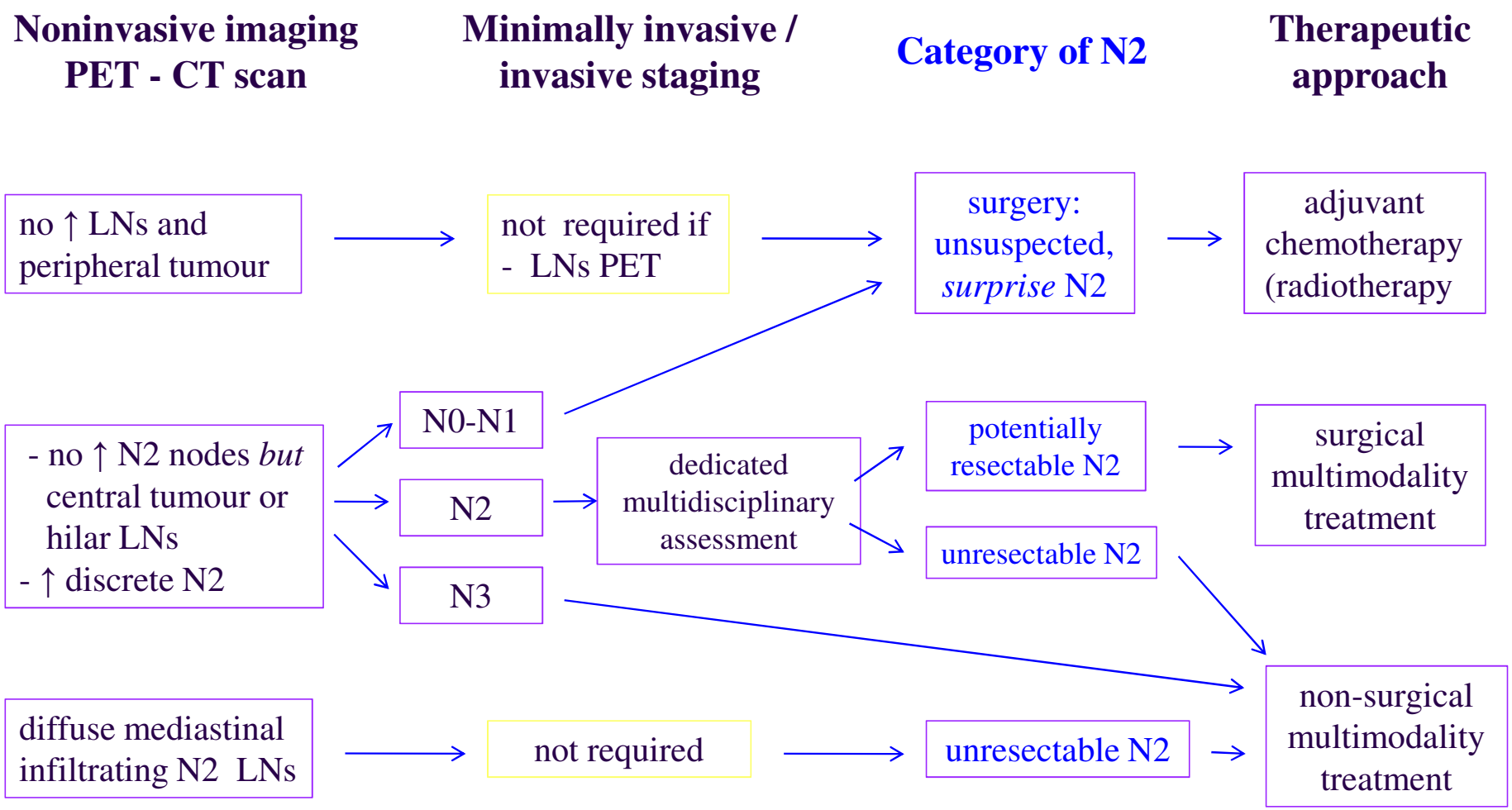
ESMO guidelines. Eberhardt W.
Ann Oncol 2015; 26:1573-88



ESMO guidelines 2017

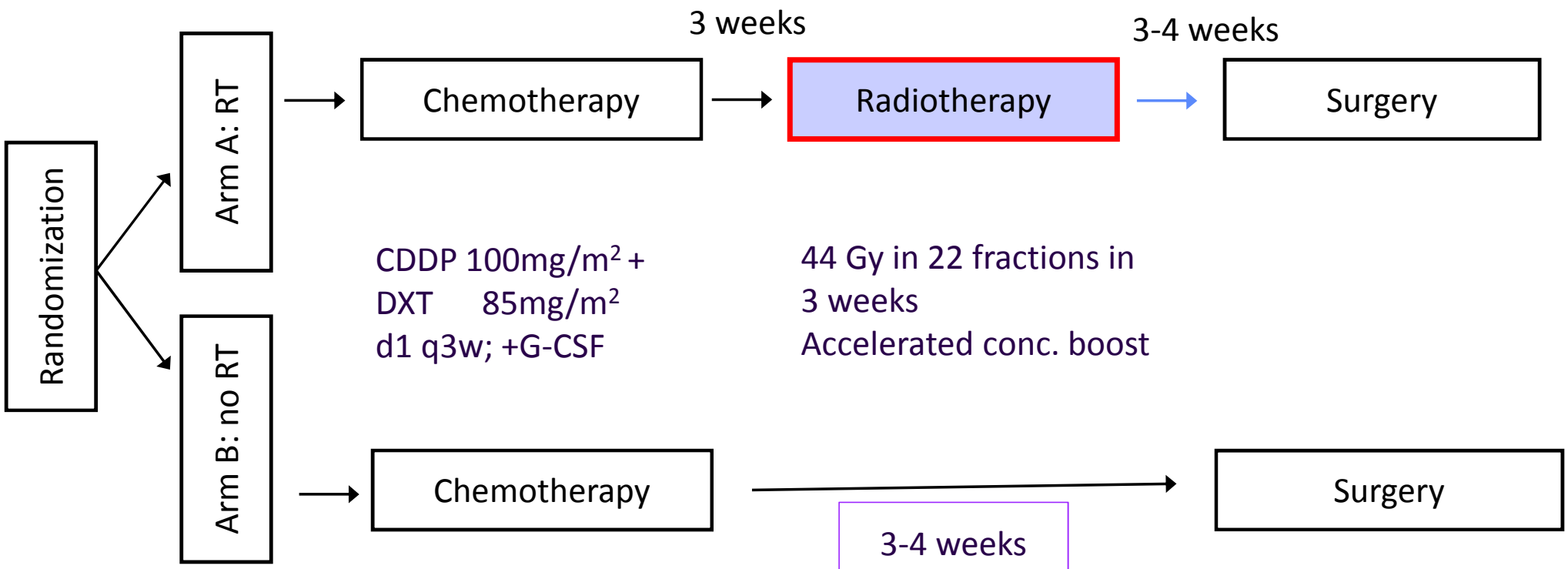
Postmus P et al. *Annals of Oncology*, Volume 28, Issue suppl_4,
1 July 2017, pages iv 1–iv 21

- If *single station N2 disease* can be demonstrated by preoperative pathological nodal analysis:
  - *resection followed by adjuvant CT*
  - *induction CT followed by surgery*
  - *induction CRT followed by surgery* are options
- If induction CT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks

near future: role of immunotherapy ↑

- In *multistation N2 or N3*, concurrent definitive CRT is preferred.
- An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases

SAKK - phase III trial of induction chemorad vs chemo stage IIIA-N2



2001-12: 232 pts enrolled
117 chemo + RT (sequential) + surgery
115 chemo + surgery

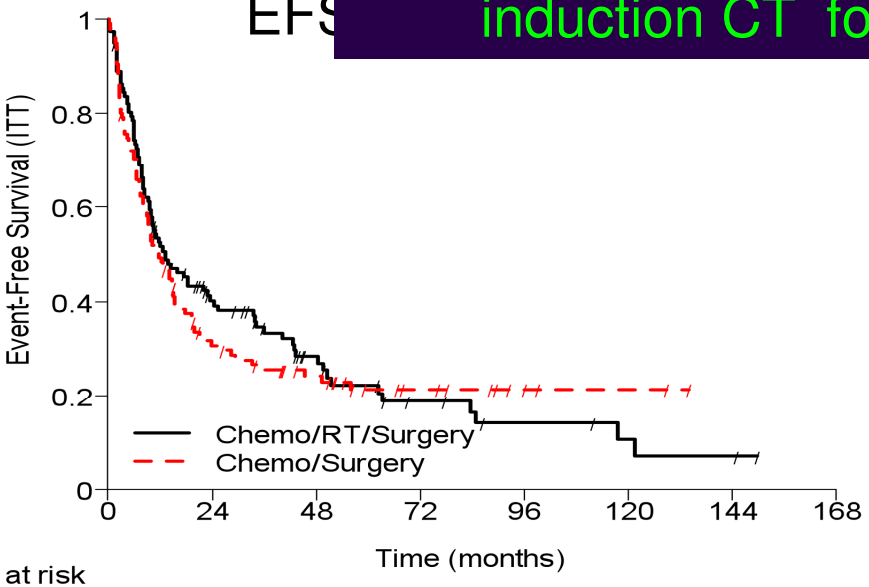
staging: (PET-) CT: PD went off study

Pless M. Lancet 2015; 386(9998):1049-56

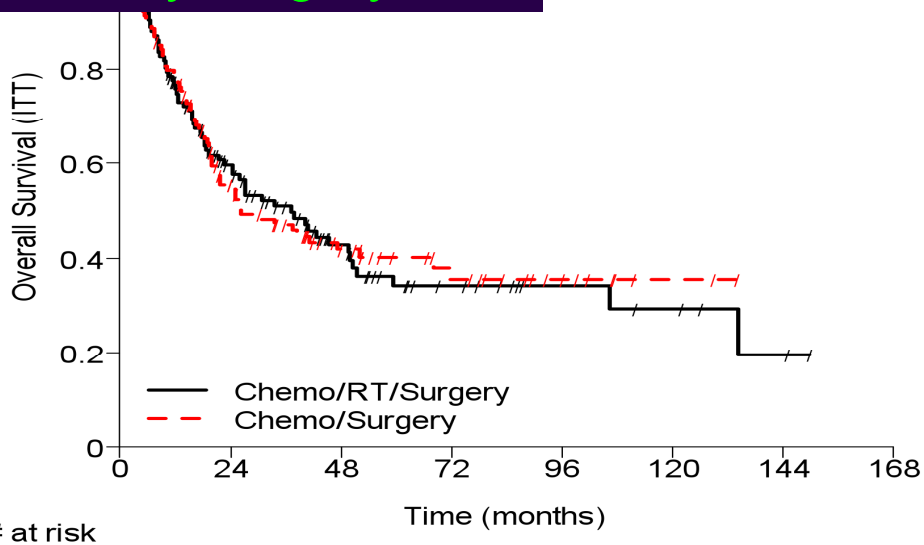
SAKK - phase III trial of induction chemorad vs chemo stage IIIA-N2

Conclusion: RT did not any benefit to induction CT followed by surgery

EFS



# at risk								
RT	117	38	19	9	5	3	2	0
no RT	115	31	19	9	3	2	0	0



# at risk								
RT	117	57	27	13	7	5	2	0
no RT	115	53	28	15	7	2	0	0

CRT 12.8 mos CT 11.6 mos p=0.67

CRT 37.1 mos CT 26.2 mos HR 1.0

Pless M. Lancet 2015; 386(9998):1049-56

Resectable clinical N2 NSCLC: what is the optimal treatment strategy?
Update by the BTS Lung Cancer Specialist Advisory Group

- complex and heterogenous patient population
- no RCT single-station N2 ↔ multistation N2
- fit patient wit potentially resectable cN2 NSCLC consider:
  trimodality therapy: chemotherapy, RT and surgery
  bimodality therapy: chemotherapy and RT or surgery
- MDT, all pts should see thoracic surgeon + oncology team

Evison M. J Thorac Oncol 2017; 12:1434-41

Salvage surgery after definitive chemoradiotherapy for NSCLC

- 2003-13 35 pts lung cancer recurrence after definitive chemoradiation (cisplatin-based – 58 Gy)
- 6 exploratory thoracotomies (17.1 %)

29 pts lung cancer resection	(bi)lobectomy	12
	pneumonectomy	17 - 7R, 10L

- 13 pts (45%) extended resections (IP, SVC, trachea, chest wall)
- R0 resection 27 pts (77.1 %)
- median time CRT → resection 7 mos (range 1-39)

Casiraghi M. Semin Thoracic Surg 2017; 29:233-41

Salvage surgery after definitive chemoradiotherapy for NSCLC

- viable tumor 26/29 pts 89.6%
- 2 pts † 30-day mortality 5.7%
- 9 pts major complications (25.7 %)
- median follow-up 13 mos
- 2- and 3-year survival after R0 resection 46% and 37%

- salvage surgery after definitive CRT:
  feasible
  acceptable complication and survival rates

Casiraghi M. Semin Thoracic Surg 2017; 29:233-41