Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part I

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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, et al. *Ann Thorac Surg.* 2012;94(3):922-926.

Stage IIIA—N2 NSCLC Surgery

- Invasive staging of lung cancer
- Restaging after induction therapy
- Stage IIIA-N2: Role of surgery
- Conclusion

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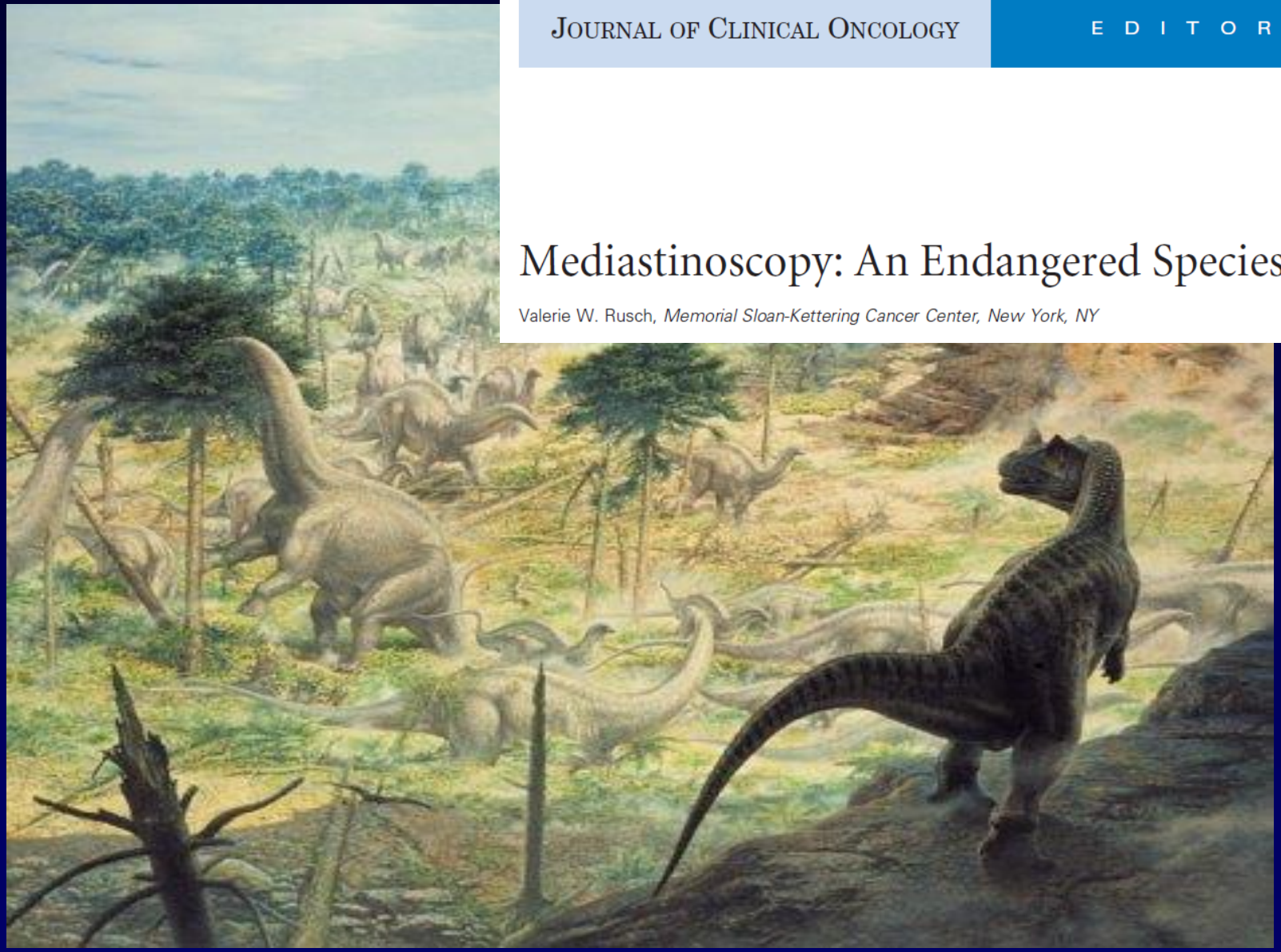
EDITORIAL

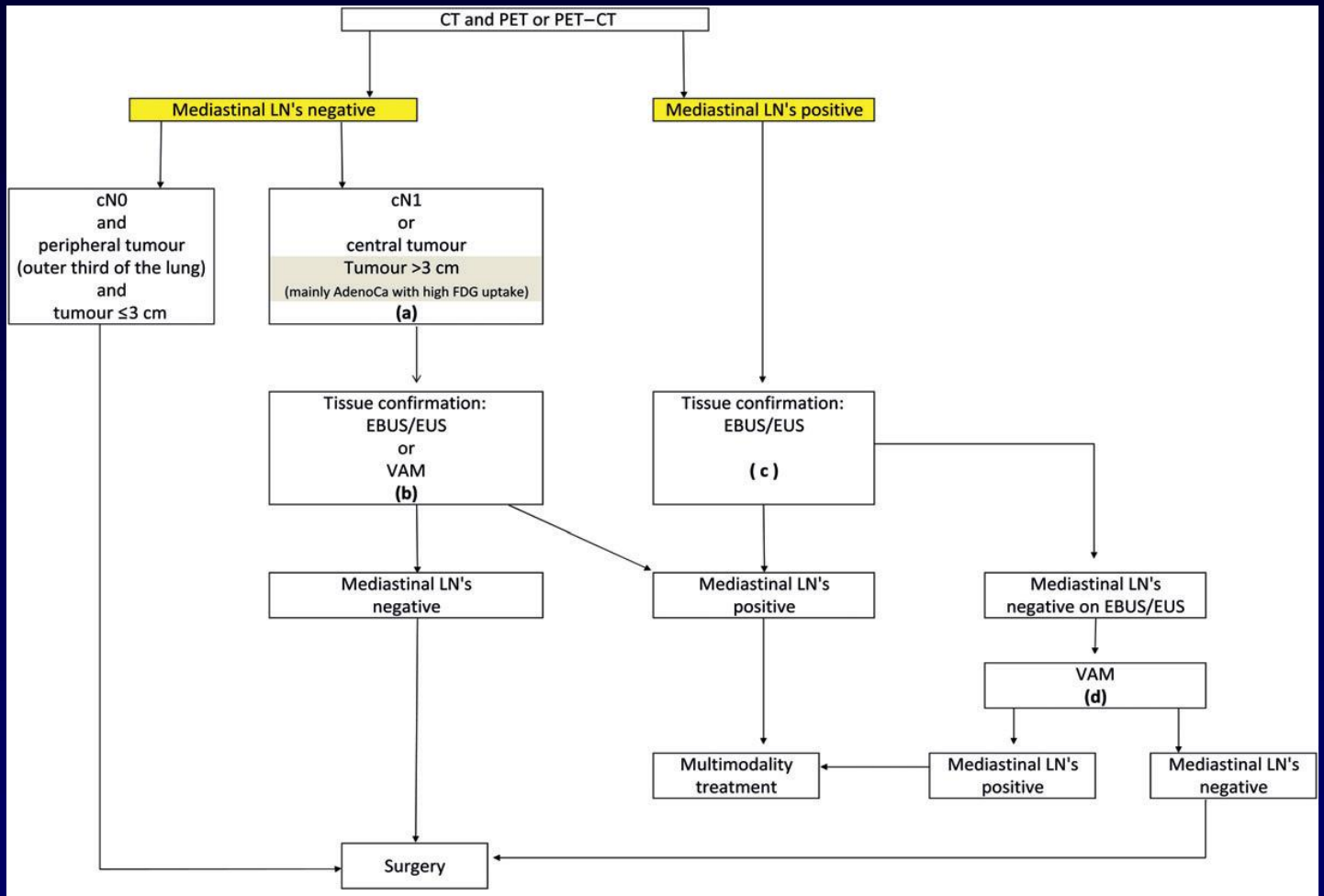
Mediastinoscopy: An Endangered Species?

Valerie W. Rusch, *Memorial Sloan-Kettering Cancer Center, New York, NY*



Rusch VW. *J Clin Oncol.* 2005;23(33):8283-8285

ESTS Guidelines for Preoperative Mediastinal Lymph Node Staging for NSCLC: PET Available

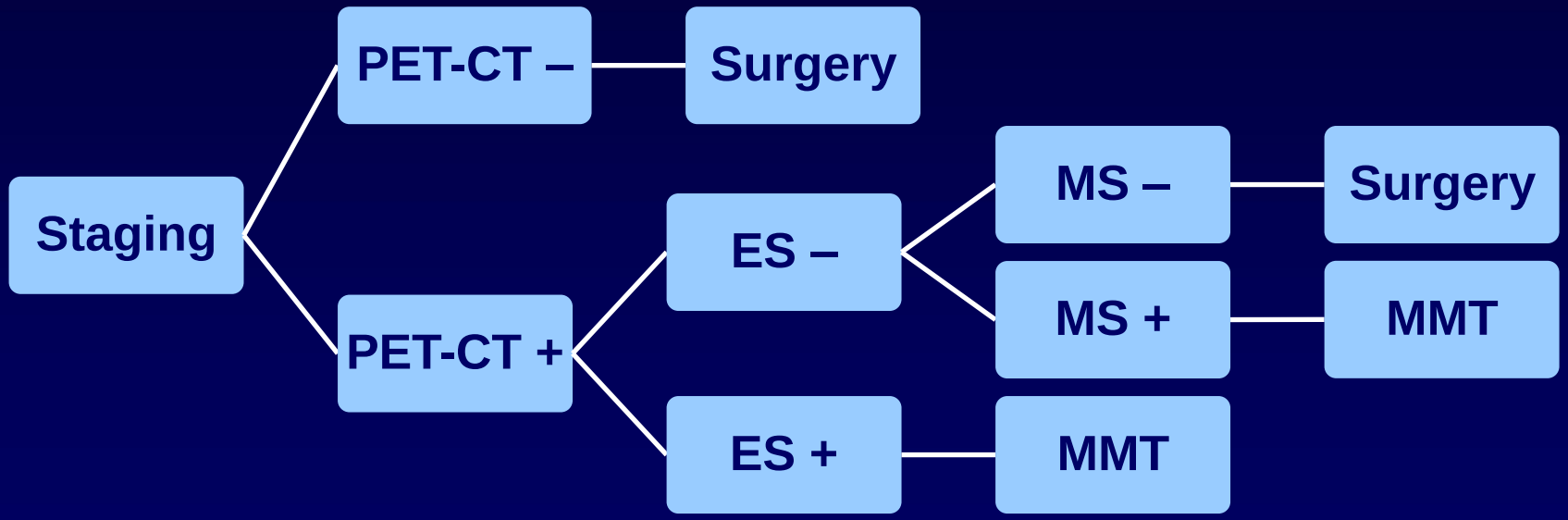


(a) : In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered
(b) : Depending on local expertise to adhere to minimal requirements for staging
(c) : Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available
(d) : Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy

ESTS, European Society of Thoracic Surgeons; VAM, video-assisted mediastinoscopy

De Leyn P, et al. *Eur J Cardiothorac Surg.* 2014;45(5):787-798.

Staging Lung Cancer
Antwerp University Hospital



ES, endosonographic technique (EBUS-EUS); MS, mediastinoscopy; MMT, multimodality therapy

Stage IIIA—N2 NSCLC Surgery

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Why Is Downstaging Important?

- Prognostic factors after induction therapy
  - Complete surgical resection
  - Clearance mediastinal lymph nodes

Detterbeck FC, et al. Diagnosis and treatment of lung cancer. An evidence-based guide for the practicing clinician. Philadelphia, PA: WB Saunders Co. 2001; p 267-282.

Restaging After Induction Therapy: Systematic Review

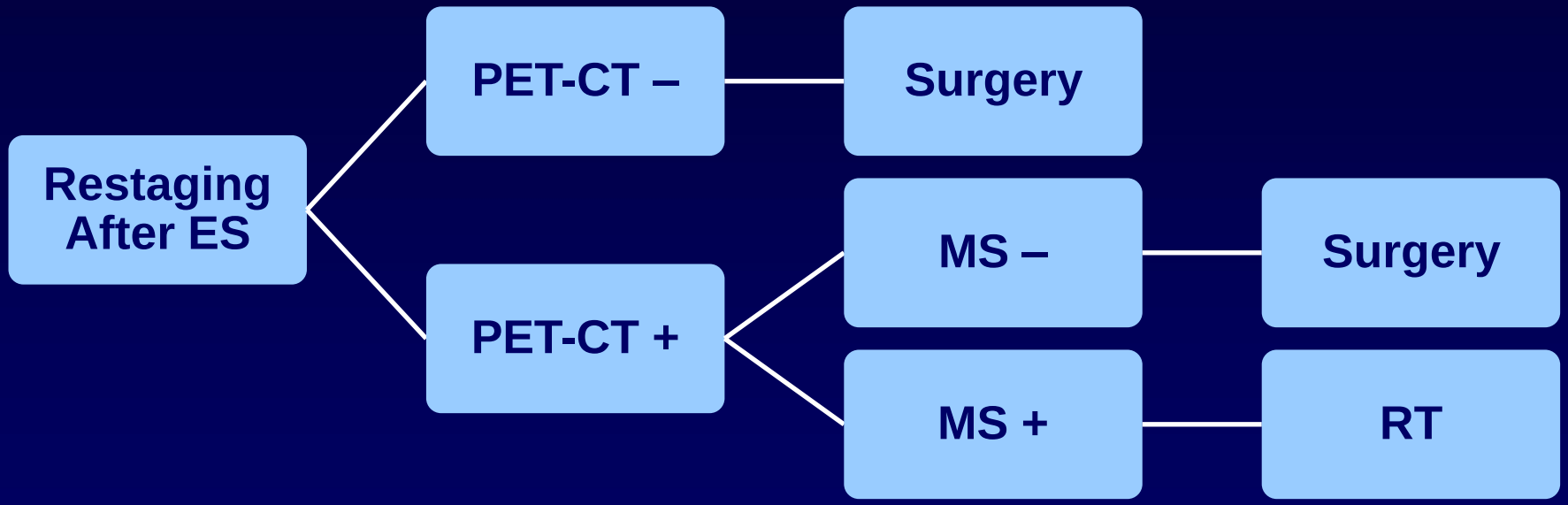
- Systematic review: Reliability of restaging after induction therapy for stage IIIA-N2 NSCLC
- Mediastinal node involvement

	N	FN Rate (FN/TN+FN), %	FP Rate (FP/TP+FP), %
CT scan	190	33	33
PET scan	453	25	33
reMS	515	22	
EUS	56	15	Expert hands!
EBUS	135	Not enough data	
Primary MS	85	9	Most accurate!

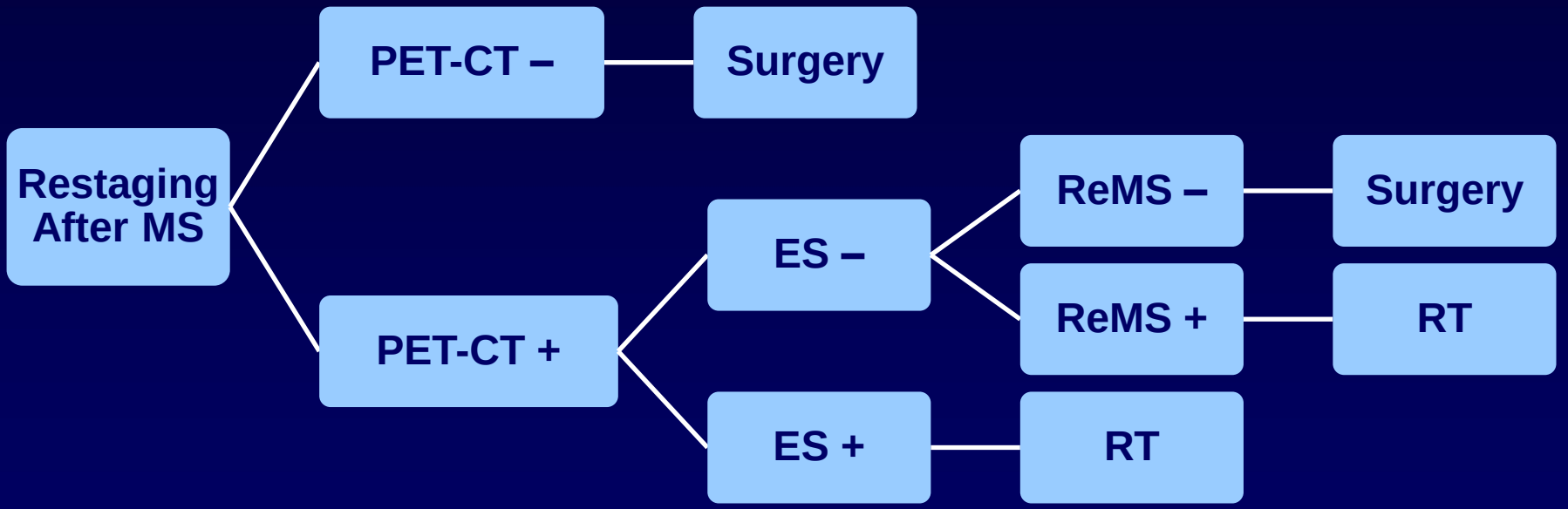
EBUS, endobronchial ultrasound; EUS, esophageal ultrasound and needle aspiration; FN, false negative; FP, false positive; MS, mediastinoscopy; reMS, repeat mediastinoscopy; TN, true negative; TP, true positive

de Cabanyes Candela S, et al. *J Thorac Oncol.* 2010;5(3):389-398.

Restaging After Induction Therapy
Antwerp University Hospital



Restaging After Induction Therapy
Antwerp University Hospital



Stage IIIA—N2 NSCLC Surgery

- Invasive staging of lung cancer
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- **Stage IIIA-N2: Role of surgery**
- Conclusion

IASLC: Complete Resection Subcommittee
Complete Resection R0

- Free resection margins proved microscopically
- Systematic or lobe-specific systematic nodal dissection:
  - ≥6 nodal stations (3 mediastinal)
- 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(1):25-33.

Surgery for N2 Disease Randomized Studies

- **EORTC 08941[1,2]**
  - **Stage IIIA-N2 NSCLC**
  - **Phase III induction CT. In case of response, randomization between surgery and RT**
    - **167 patients surgery**

- **Intergroup trial 0139[3]**
  - **Stage IIIA-N2 NSCLC**
  - **Phase III concurrent CT/RT versus CT/RT induction + surgery**
    - **164 patients surgery**

1. Van Schil P, et al. *Eur Respir J.* 2005;26(2):192-197. 2. Van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99(6):442-453. 3. Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

Comparison
EORTC 08941 – INT 0139

		EORTC 08941[1,2]		INT-139[3]
Induction therapy		Chemotherapy		Chemoradiotherapy
Complete resection definition ≠		50%		71%
Expl. thoracotomy		13.6%		4.5%
ypN0/1/2	N0/1	41.4%	N0/1	46%
	N2	56%	N2	54%
ypT0N0		5.2%		14.4%

1. Van Schil P, et al. *Eur Respir J.* 2005;26(2):192-197. 2. Van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99(6):442-453.
3. Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

Comparison
EORTC 08941 – INT 0139

30-Day Mortality	EORTC 08941[1,2]	INT-139[3]	
Overall	3.9%	5%	
Lobectomy	0%	1%	
Pneumonectomy	6.9%	26%	
	R 5.3% L 9.1%	R Simple R Complex L Simple L Complex	29% 50% 0% 16%
Expl. thoracotomy	4.8%	0%	
90-day mortality	8.4%		

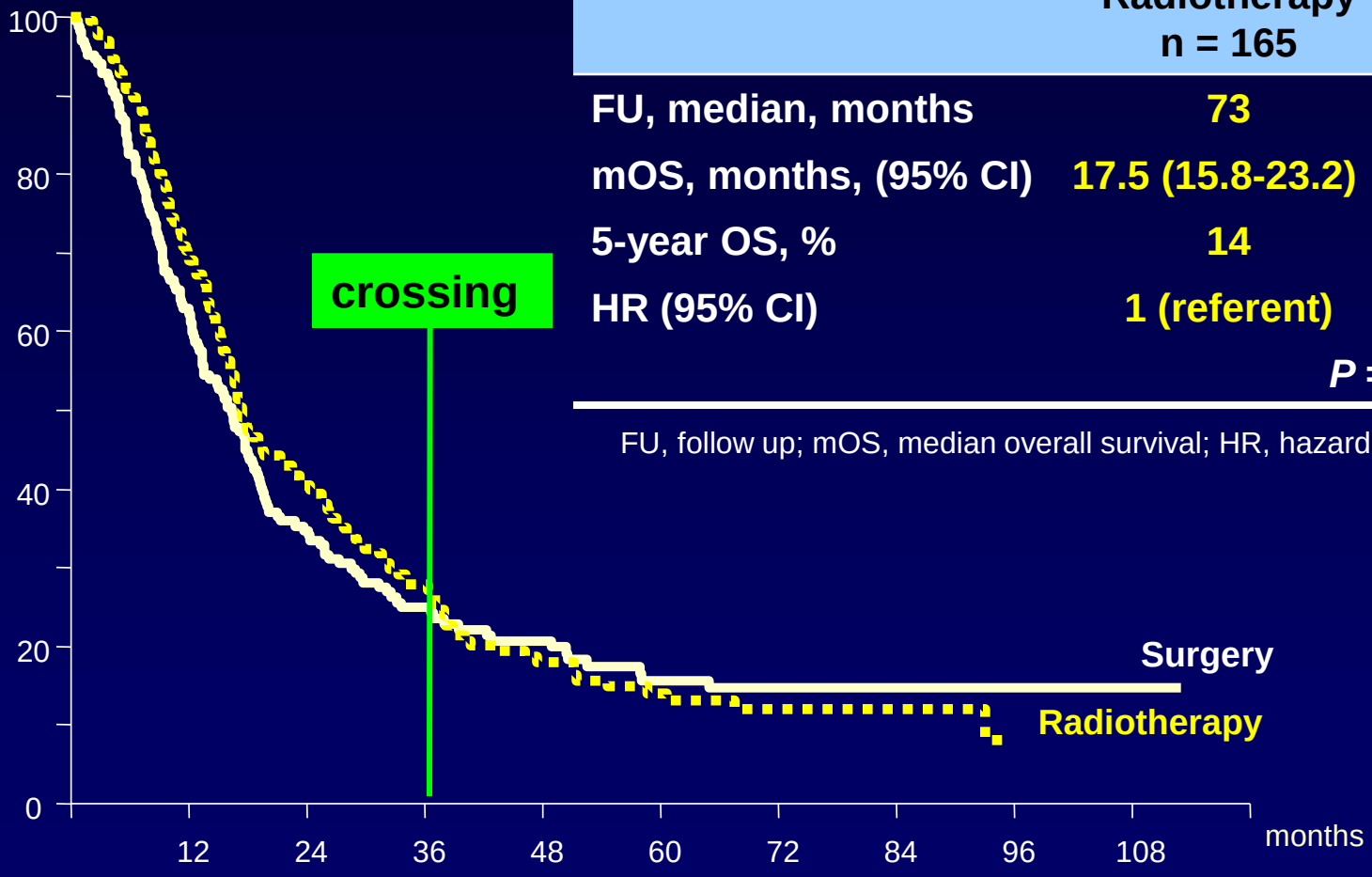
1. Van Schil P, et al. *Eur Respir J.* 2005;26(2):192-197. 2. Van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99(6):442-453.
3. Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

Comparison
EORTC 08941 – INT 0139

5-Year Survival	EORTC 08941[1,2]		INT 0139[3]	
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	

1. Van Schil P, et al. *Eur Respir J.* 2005;26(2):192-197. 2. Van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99(6):442-453.
3. Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

EORTC 08941
Overall Survival in Randomized Patients

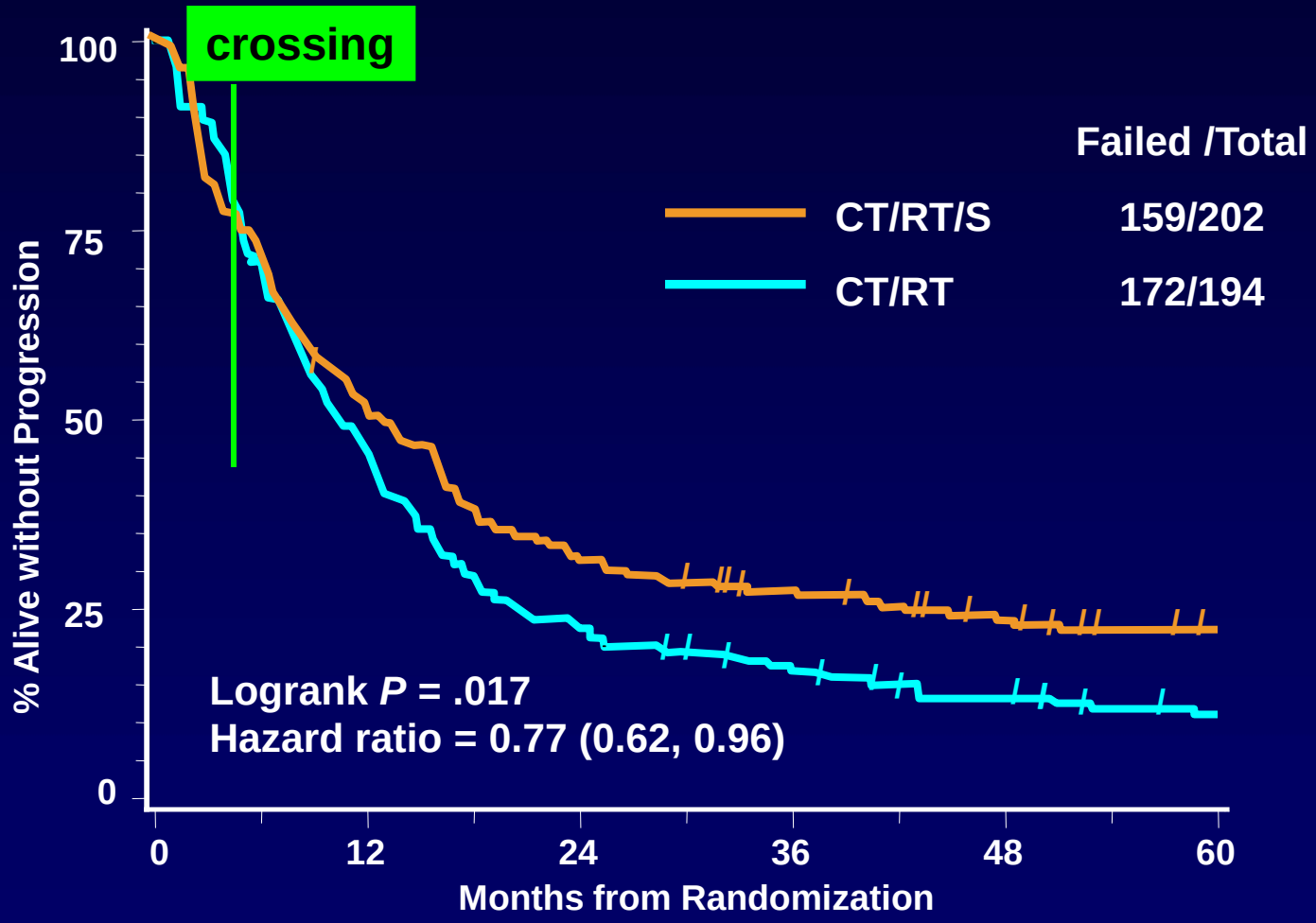


	Radiotherapy n = 165	Surgery n = 167
FU, median, months	73	67
mOS, months, (95% CI)	17.5 (15.8-23.2)	16.4 (13.3-19.0)
5-year OS, %	14	15.7
HR (95% CI)	1 (referent)	1.06 (0.84-1.35)
	P = .60	

FU, follow up; mOS, median overall survival; HR, hazard ratio

Van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99(6):442-453.

Intergroup 0139 / RTOG 9309
Progression-Free Survival by Treatment Arms



CT/RT/S, chemotherapy plus radiotherapy followed by surgery; CT/RT chemotherapy plus radiotherapy

Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

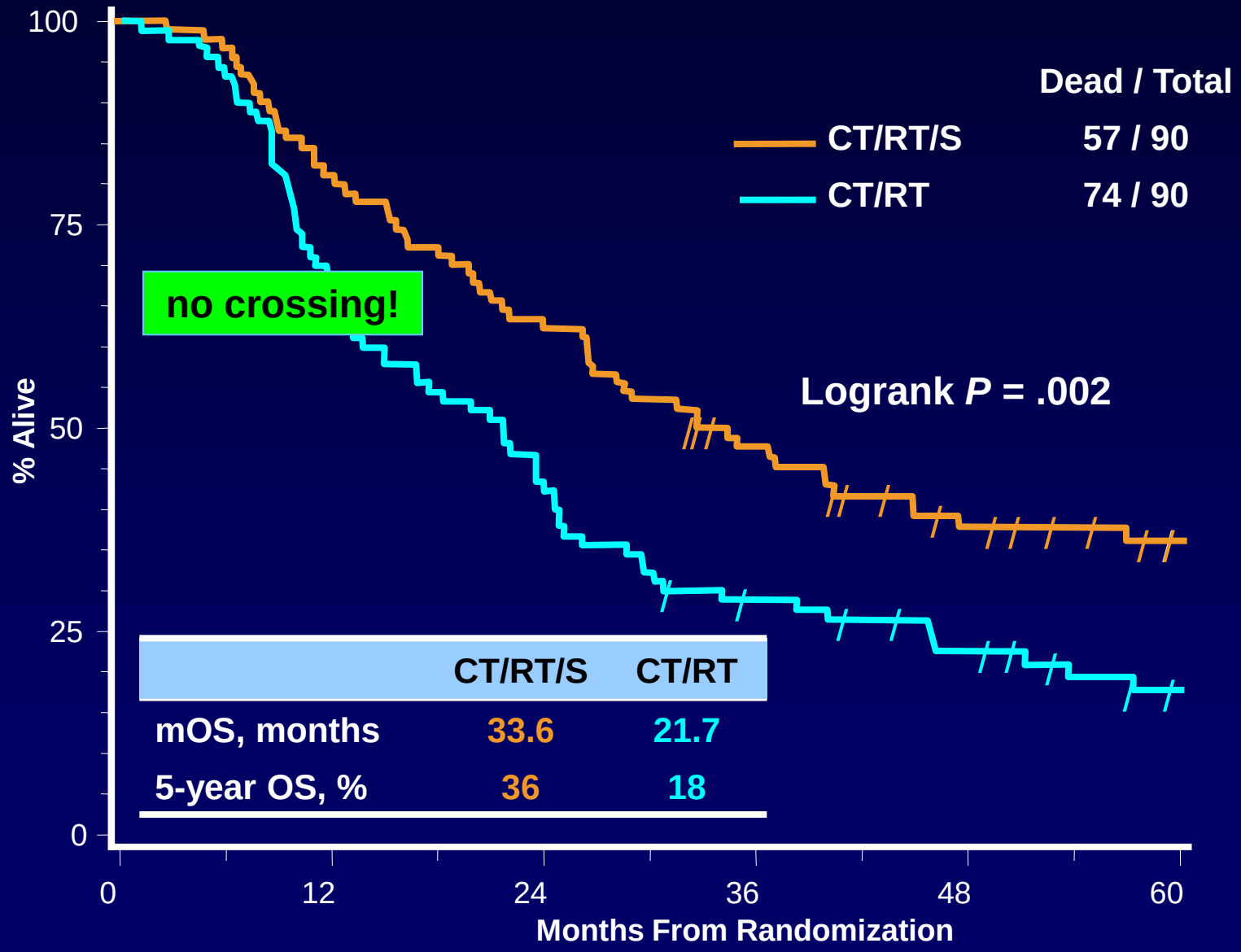
INT 0139
Exploratory Survival Analysis

- All but 1 postoperative death followed a pneumonectomy
- Hypothesized survival advantage on CT/RT/S if lobectomy performed
- Patients with lobectomy were completely matched with patients on CT/RT arm on 4 prestudy factors:
  - KPS, age, sex, T stage
  - Feasible for n = 90/98

KPS, kanorfsky performance status

Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

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



Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

EORTC – INT Trials
Lessons Learned

- **Persistent ypN2 disease after induction therapy: Poor prognosis**
- **ypN2 marker of systemic disease ≈ 50 % in both INT and EORTC trials → ↓survival**
- **Focus on *pathologic* restaging of mediastinum (EBUS, EUS, remediastinoscopy)**
- **Surgery probably beneficial; in case of mediastinal downstaging – lobectomy, complete resection**

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Restaging in Stage IIIA-N2 NSCLC

Why?

Persisting mediastinal involvement after induction therapy: Poor prognosis

Downstaging is significant prognostic factor!

How?

- **Noninvasive methods:** **CT, MRI unreliable**
  PET: FP and FN cases, metastases
- **Invasive methods:** **reMS feasible, ↓ accuracy than 1stMS**
  VATS feasible, to be explored further
- **Alternative methods:** **TBNA**
  EUS EBUS
  TTNA

Under investigation, ↑FN rate

Focus on single LN: Complete exploration?

FP, false positive; FN, false negative; reMS, repeat mediastinoscopy; 1stMS, primary mediastinoscopy; VATS, Video-assisted thoracoscopic surgery; EUS, esophageal ultrasound; TBNA, transbronchial needle aspiration; EBUS, endobronchial ultrasound; TTNA, ransthoracic needle aspiration

Surgery Stage IIIA-N2 NSCLC

- ***Surprise, unexpected N2:*** **Complete resection, adjuvant chemo ± radiotherapy**
- ***Potentially resectable N2*** **(discrete mediastinal node involvement): Induction therapy, downstaging, lobectomy**

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.
Ramnath N, et al. *Chest*. 2013;143 (5 suppl):e314S-e40S.

"Neoadjuvant therapy followed by surgery is neither clearly better nor clearly worse than definitive chemoradiation"
"Weak comparative data suggest a possible role if only lobectomy is needed in a center with low perioperative †"

→ Final goal = complete resection, irrespective of stage