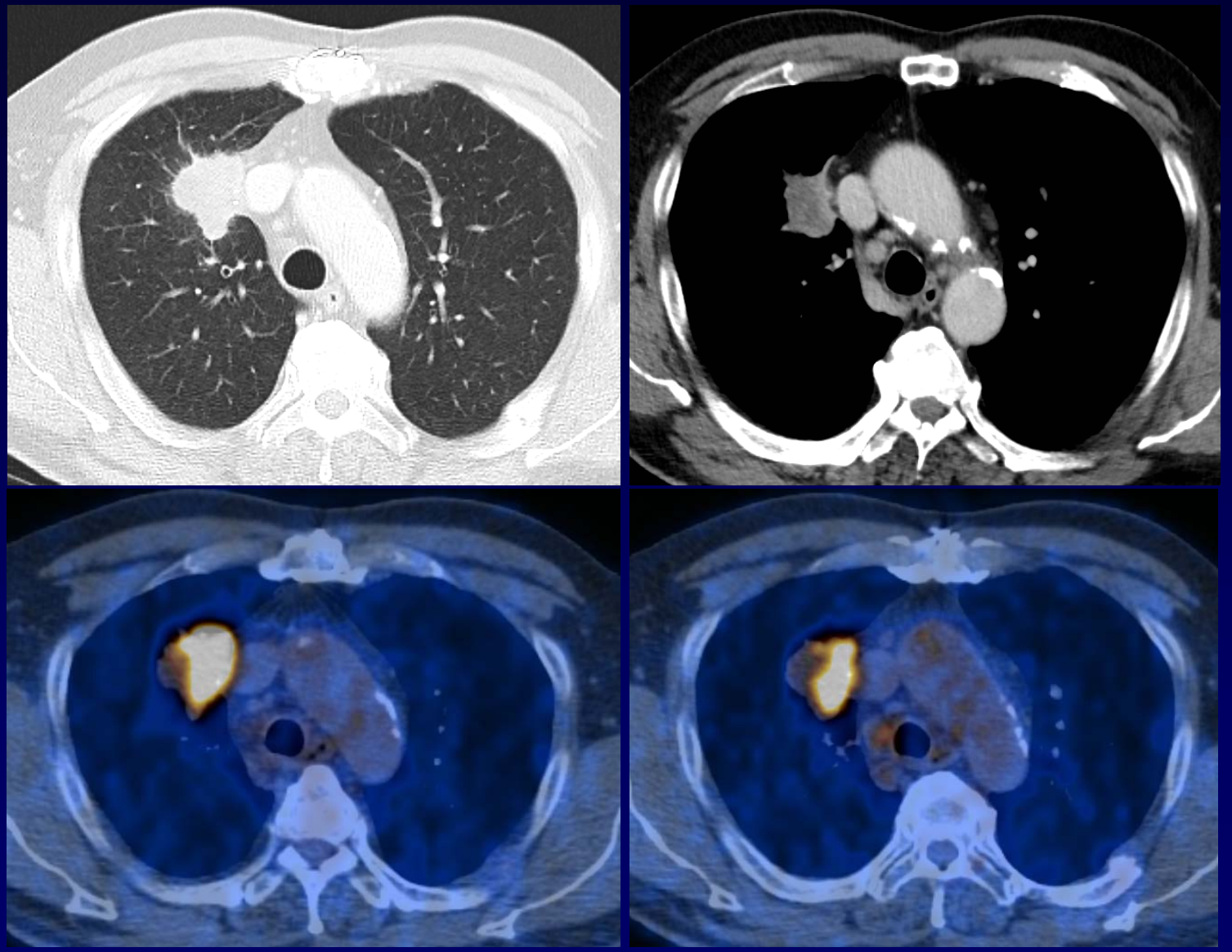
Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part I

Wolfgang Jungraithmayr, MD, PhD
University Hospital Zurich
Zurich, Switzerland

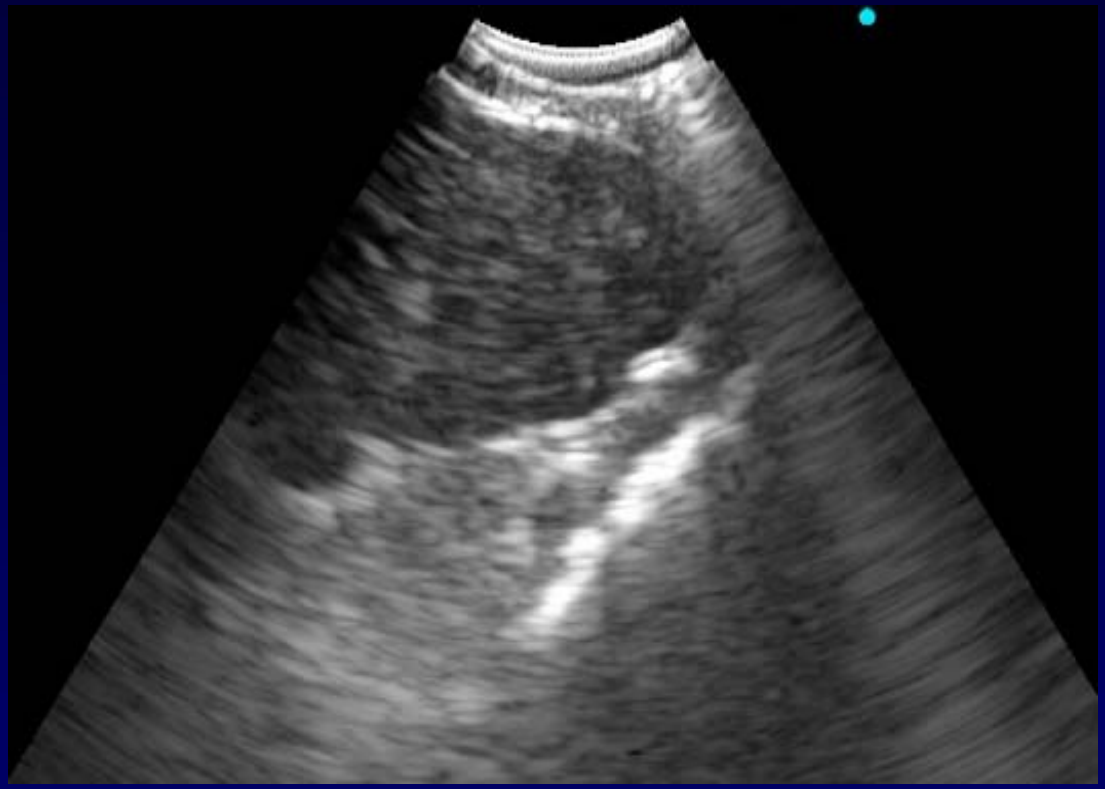
Our Patient

Our Patient



Our Patient

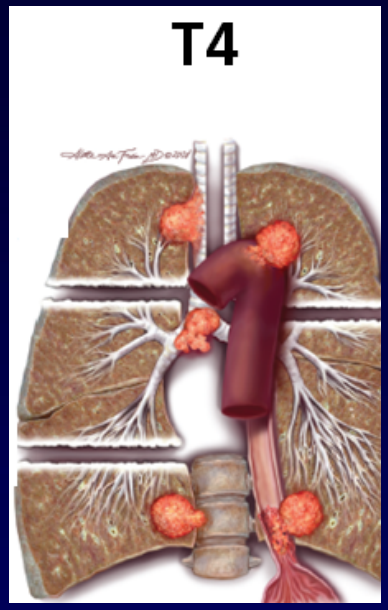
Clinical Stage: T2aN2M0 (IIIA-N2)



MULTIDISCIPLINARY THORACIC TUMOR BOARD

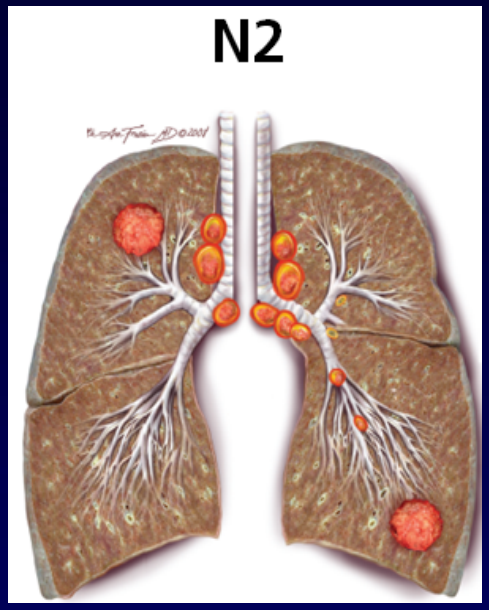
Stage III NSCLC

T4



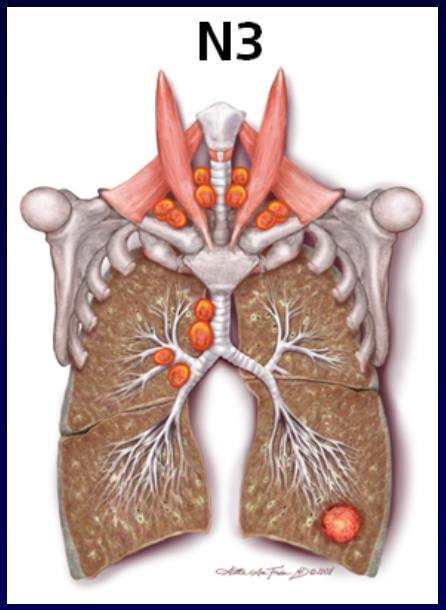
T_4, N_{0-1}

N2



T_{1-3}, N_2

N3



any T, N_3

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 $_{>7}$	IIb	IIIa	IIIa	IIIb
	T3 $_{Inv}$	IIb	IIIa	IIIa	IIIb
	T3 $_{Satell}$	IIb	IIIa	IIIa	IIIb
T4	T4 $_{Inv}$	IIIa	IIIa	IIIb	IIIb
	T4 $_{Ipsi\ Nod}$	IIIa	IIIa	IIIb	IIIb
M1	M1a $_{Contra\ Nod}$	IV	IV	IV	IV
	M1a $_{Pl\ Disem}$	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Stage groups according to TNM descriptor and subgroups

Question 1: What treatment approach would you suggest for this patient with clinical stage IIIA-N2 (single node 1.7-cm) NSCLC?

1. Surgical resection with mediastinal LN dissection → chemotherapy +/- radiotherapy
2. Neoadjuvant systemic therapy → surgery if no progression
3. Induction chemoradiotherapy (CRT) → surgery if no progression
4. Definitive concurrent CRT

Which Patients Are Candidates for Surgery?

- Is a complete resection possible?
- Does the patient tolerate pulmonary resection?
- What is the mortality/morbidity?

→ Risk-benefit ratio

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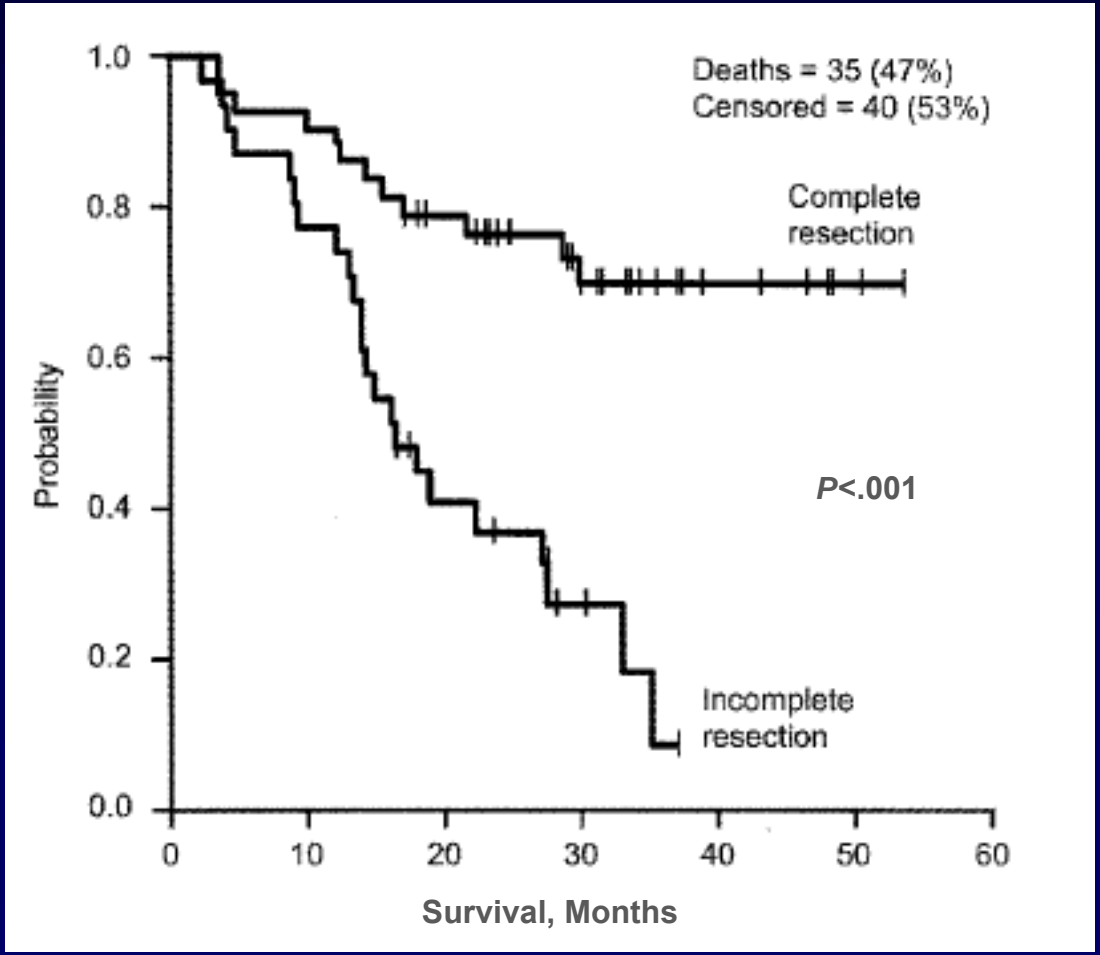
Individualized Treatment

Complete Resection in Lung Cancer Surgery

- Free resection margins (proved microscopically)
- No extra capsular nodal extension
- Highest mediastinal LN removed is negative

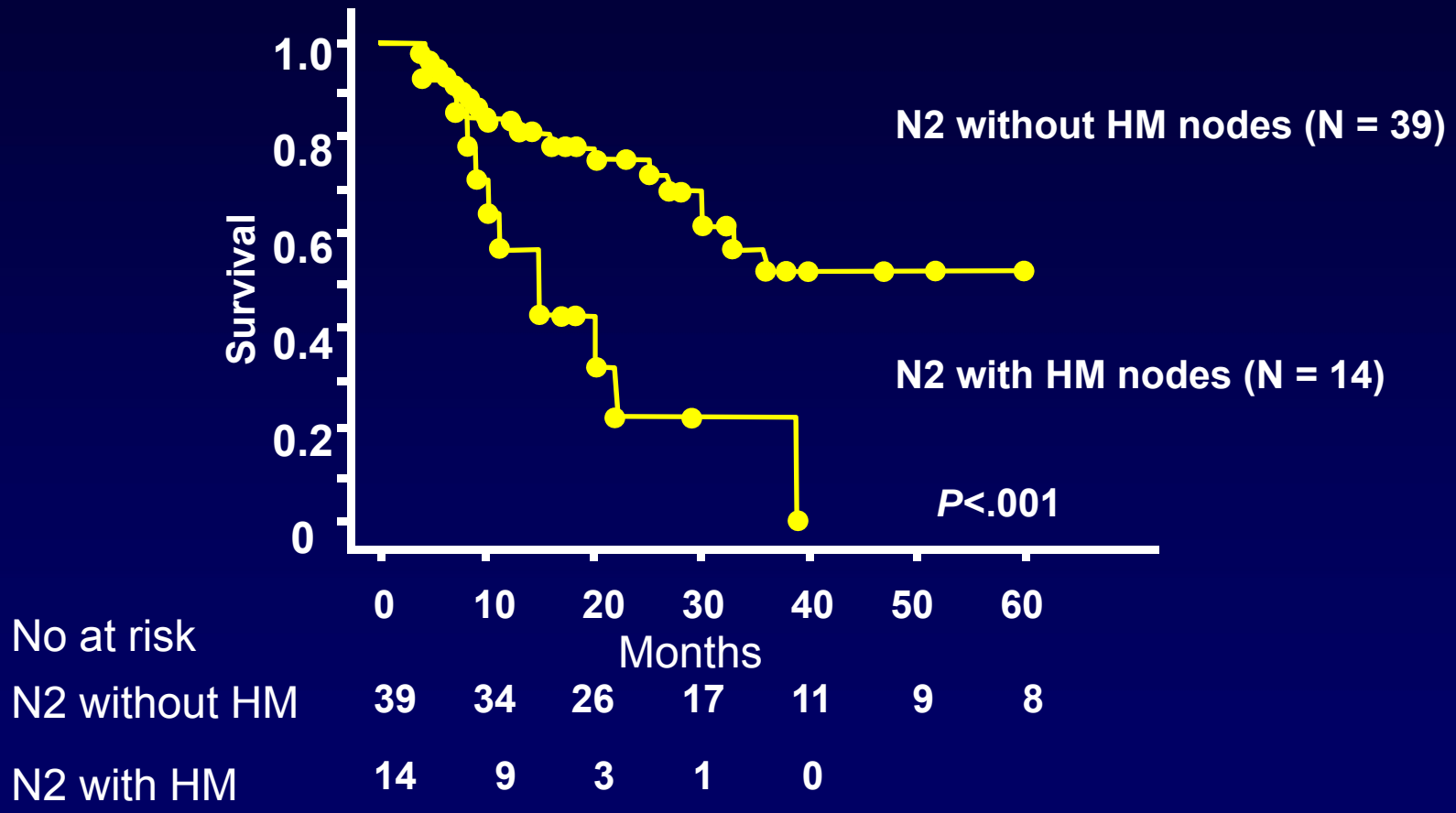
Rami-Porta R, et al. (IASLC Staging Committee). *Lung Cancer.* 2005;49(1):25-33.

Overall Survival Dependent on Complete Resection



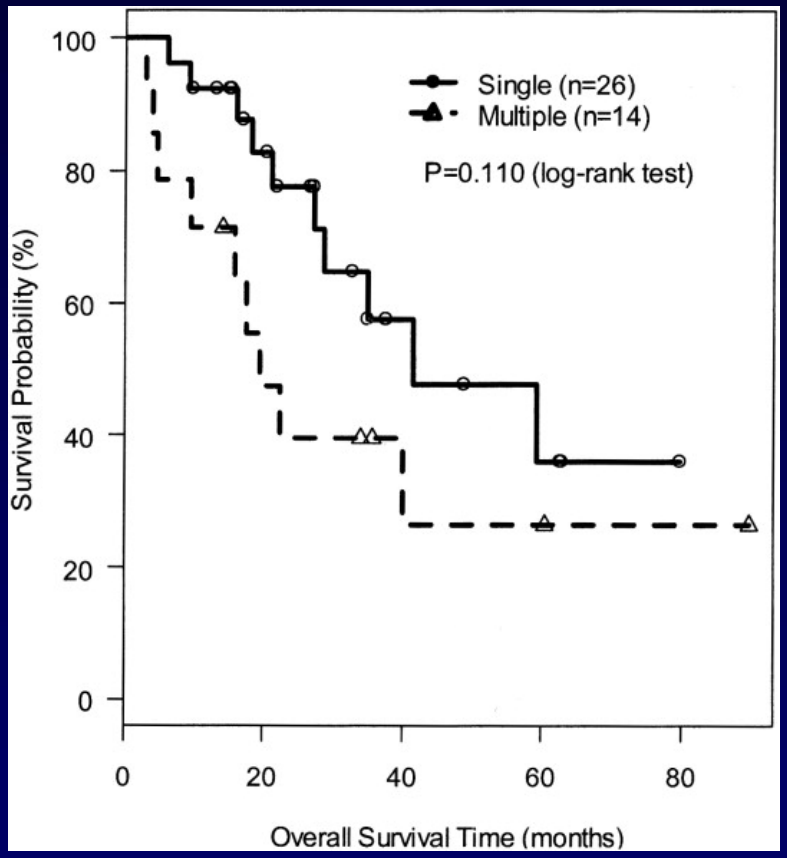
Betticher DC, et al. *J Clin Oncol.* 2003;21(9):1752-1759.

Role of Highest Level N2 Node

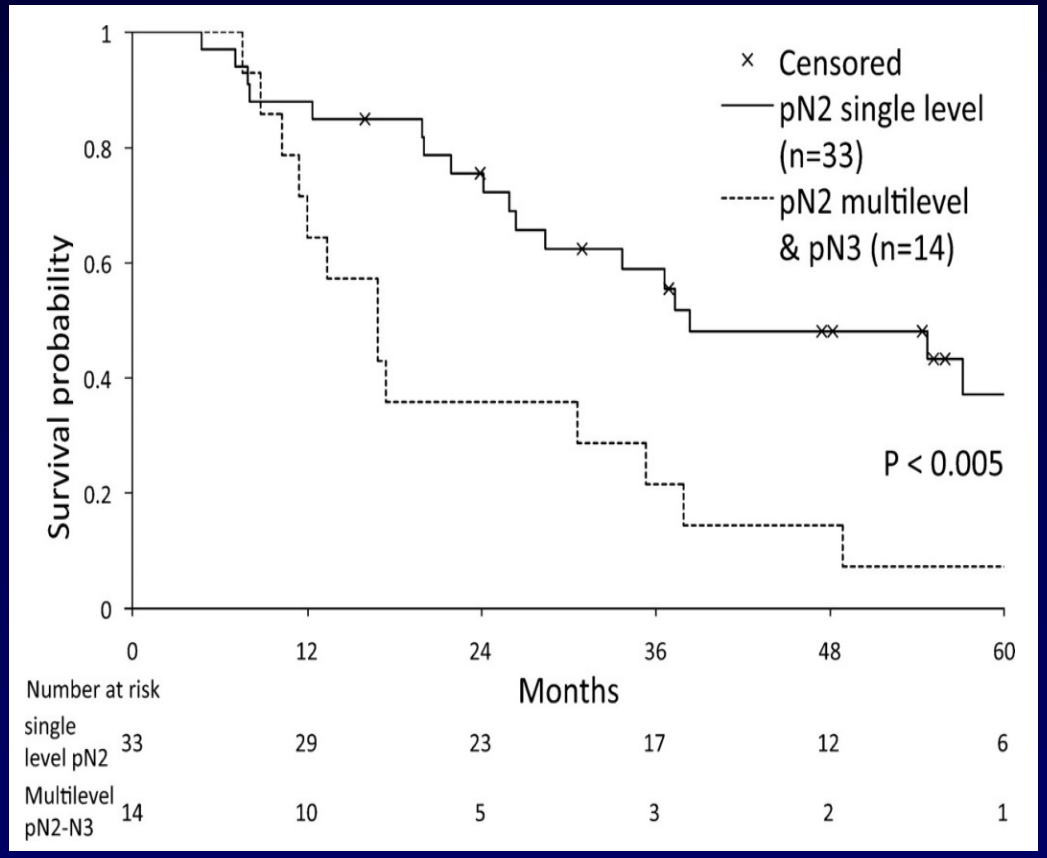


Sakao Y, et al. *Ann Thorac Surg.* 2006;81(1):292-297.

Single Versus Multilevel N2: Overall Survival



Uy KL, et al. *J Thorac Cardiovasc Surg.* 2007;134(1):188-193.



Decaluwé H, et al. *Eur J Cardiothorac Surg.* 2009;36(3):433-439.

Role of Induction Chemotherapy Followed by Surgical Resection

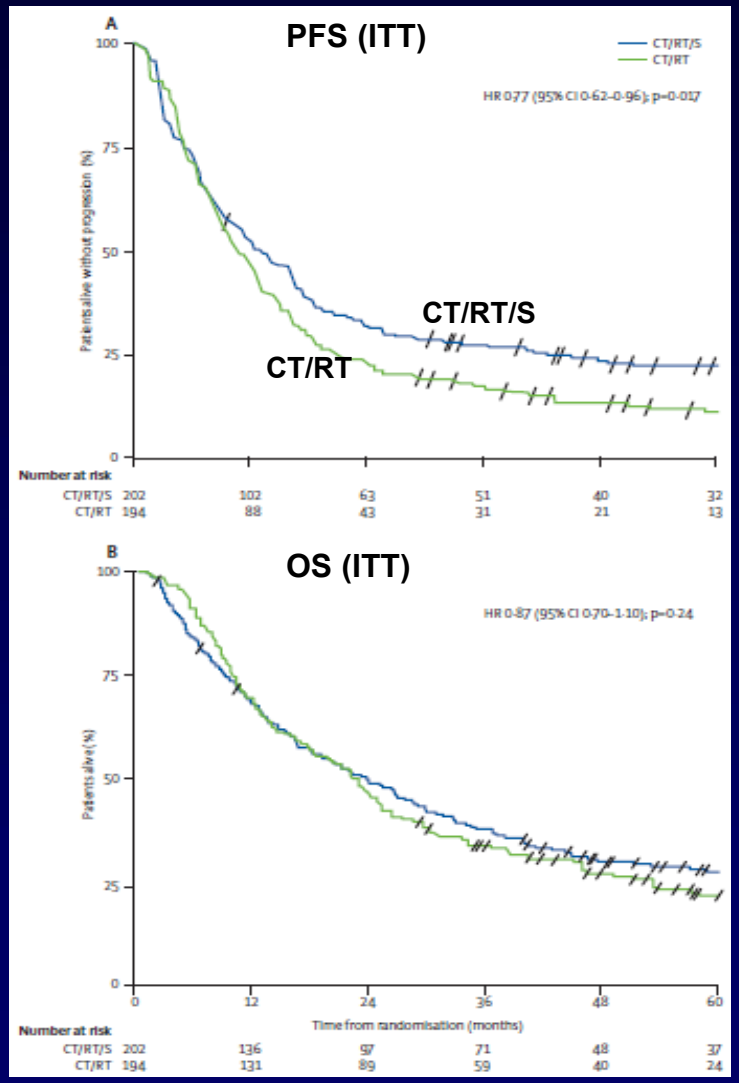
Table 1
Studies of induction chemotherapy and surgical resection for stage III (N2) disease

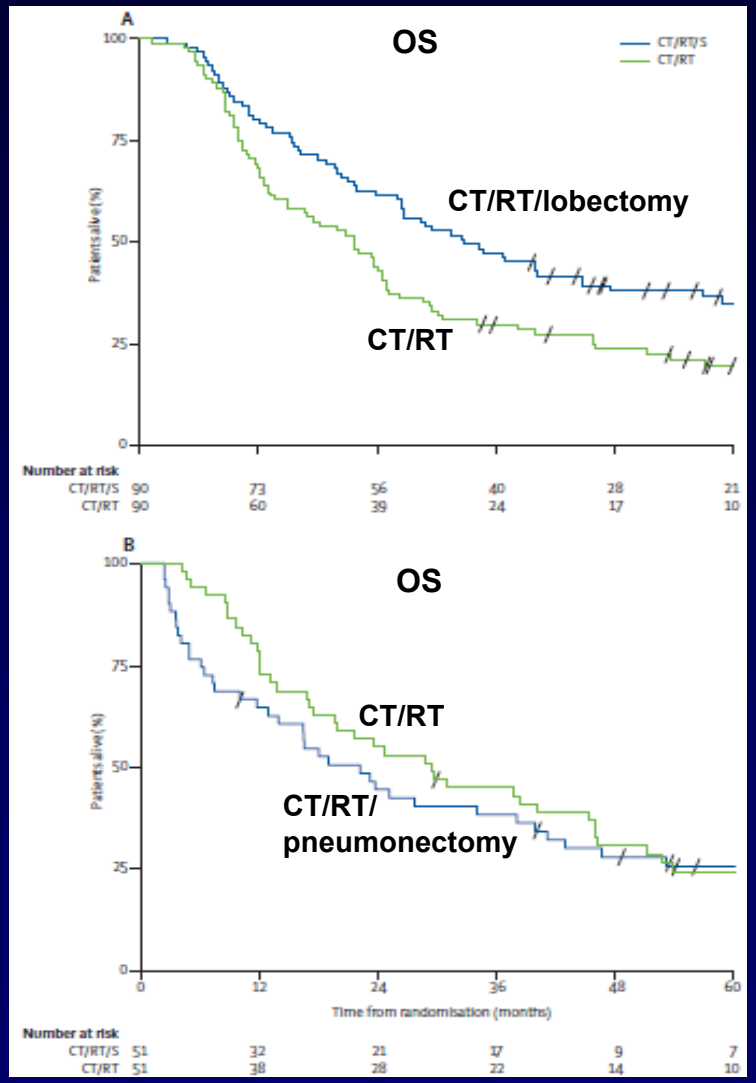
Authors,[Ref.] Year	Phase	Disease	Patients (N)	Resected (n)	Resected (%)	pCR (%)	5-y Survival (%)	N2 Downstaging
Burkes et al,[77] 1992	II	IIIA-N2	39	22	56	5	26 (3-y)	36
Sugarbaker et al,[8] 1995	II	IIIA-N2	74	46	62	NS	23 (3-y)	22
Rosell et al,[6,78] 1994, 1999	III	44/60 (N2)	60	23/27	85	3	17 (induction), 0 (no induction)	32
Roth et al,[4,5] 1994, 1998	III	IIIA	60	17/28	61	4	36 (induction), 15 (no induction)	NS
Van Zandwijk et al (EORTC),[79] 2000	II	IIIA-N2	47 (17 surgery)	16/17	94 (induction)	6 (1/17)	NS for surgical group	53
Betticher et al,[80] 2003	II	IIIA-N2	90	75	83	NS	34 (3-y)	61
Nagai et al,[81] 2003	III	IIIA-N2	62	20/31	65 (induction)	0 (0/31)	22 (induction), 10 (no Induction)	NS
O'Brien et al (EORTC),[82] 2003	II	IIIA-N2	52 (15 surgery)	12/15	80 (induction)	2	NS for surgical group	17
Garrido et al,[83] 2007	II	IIIA (N2)-B (T4N0–1)	69 (N2)	46 (N2)	67	2 (N2)	32 (N2 resected)	27

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; NS, not stated; pCR, complete pathologic response.

Ripley RT, Rusch VW. *Thorac Surg Clin.* 2013;23(3):273-285

Radiotherapy Plus Chemotherapy With or Without Surgical Resection





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

ITT, intention-to-treat population

Randomized Trials in Stage IIIA N2 NSCLC

Study (reference)	EORTC 08941 [55]		Intergroup 0139 [56]	
Treatment arm	Induction chemotherapy + surgery	Induction chemotherapy + radiotherapy	Induction chemoradiotherapy + surgery	Chemoradiotherapy
Number of patients with IIIA–N2	167	166	202	194
Chemotherapy regimen	Platinum based	–	Cisplatin–etoposide	–
Radiotherapy total dose (Gray)	–	60	45	61
Rate of pneumonectomy/ (bi-)lobectomy/exploratory thoracotomy (%)	47/38/14	–	27/49/4	–
R0 resection rate(%)	50	–	71	–
Treatment related mortality rate (%)	4	<1	8	2
Pathological nodal downstaging rate (%)	41 (pN0–1)	–	38 (pN0)	–
Pathological complete response rate (%)	5	–	15	–
Median PFS (months)	9.0	11.3	12.8	10.5
Locoregional failure rate (%)	32	55	10	22
Median OS (months) with 95% CI	16.4 (13.3–19.0)	17.5 (15.8–23.2)	23	22.2
5 year SR (%) with 95% CI	15.7 (10–22)	14 (9–20)	27.2	20.3

Crino L, et al. *Ann Oncol.* 2010;21(Suppl 5):v103-v115.

- Equivalence in overall survival between surgery and RT
- Better local control in surgery
- Choose the safest approach for each patient
  - If lobectomy is possible → surgery

Operative Risk of Pneumonectomy: Influence of Induction Therapy

- Single institution study, 1993-2007
- 183 pneumonectomy: 46 with induction chemoradiotherapy (45 Gy)
- Mortality 2/46 (4.3%) after preoperative therapy vs 9/137 (6.6%) after resection only *P* = .73
- Morbidity was not different

Gaissert HA, et al. *J Thorac Cardiovasc Surg.* 2009;138(2):289-294.

Risk of Pneumonectomy After Induction Therapy for Locally Advanced NSCLC

- Multi-institutional study 1989-2004
- 315 pneumonectomies, median age 64 years (25-82)
  - 200 right sided (63%)
  - 68 patients with induction chemotherapy (22%)
- Mortality: 9.2% and 21% after induction

d'Amato TA, et al. *Ann Thorac Surg*. 2009;88(4):1079-1085.

Mortality of Pneumonectomy After Chemotherapy or Chemo Radiotherapy for Advanced NSCLC (Stage III)

- 176 pneumonectomies (78% extended) performed after chemotherapy or chemoradiotherapy (80%) in Essen or Zurich in 1998-2007
- → Perioperative mortality 3%

  3-year and 5-year overall survival were 55% and 38%
- Meta-analyses between 1990-2010: peri-operative mortality
  - right vs left pneumonectomy, 11% vs 5%

Author	N	Induction		Mortality
		CT	CT-RT	
d'Amato '09	68	X		21%
Stamatis, '02	127	X		7%
Albain '05	24		x	27%
Sonett, '04	40		X (>59)	0%
Weder, '09	176	X	X	3%

Weder W, et al. *J Thorac CardiovascSurg.* 2010;139(6):1424-1430; Kim AW, et al. *J Thorac Cardiovasc Surg.* 2012;143(1):55-63

Conclusions

- Surgery is indicated as part of multimodality treatment in selected patients with N2 disease (nonfixed, single zone)
- N2 (bulky, fixed) or N3 disease can be considered for radical multimodality treatment preferentially in a study protocol
- Surgical resection after induction chemoradiotherapy should be limited to a lobectomy, whenever possible
- T4 tumors should be considered for multimodality treatment including surgery when complete resection can be achieved

Q2: Would you consider mediastinoscopy after preoperative therapy if evaluation PET/CT showed partial response?

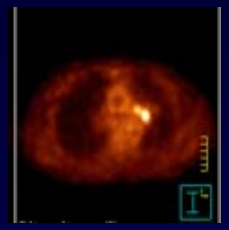
1. Yes
2. No, I would consider EBUS for restaging after neoadjuvant chemotherapy
3. No, evaluation with PET/CT is adequate
4. Uncertain

Restaging: Choices

Stage IIIA (N2) → Induction therapy → Restaging

Noninvasive

CT



PET/CT

Minimally invasive

TBNA

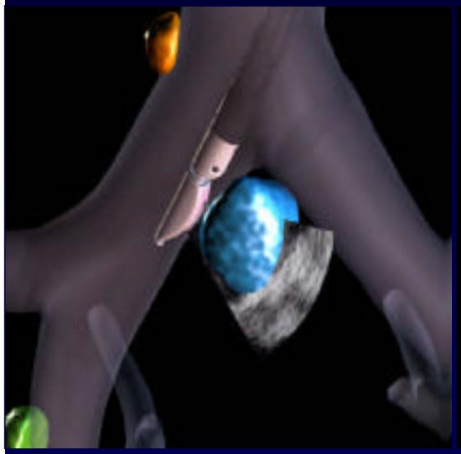
EBUS

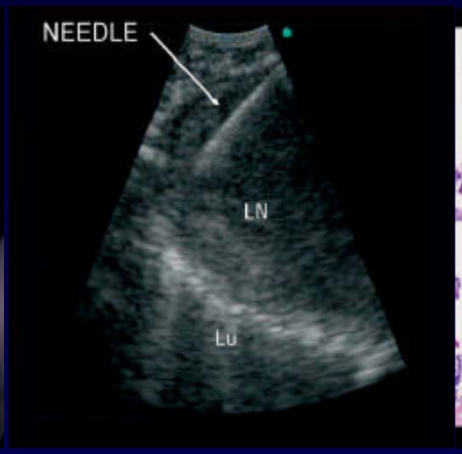
Maximally invasive

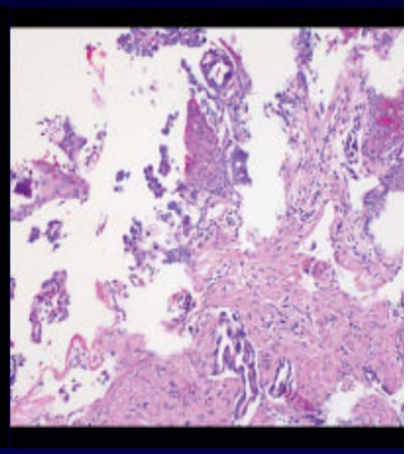
Mediastinoscopy

More accurate

(Re-) Staging Techniques



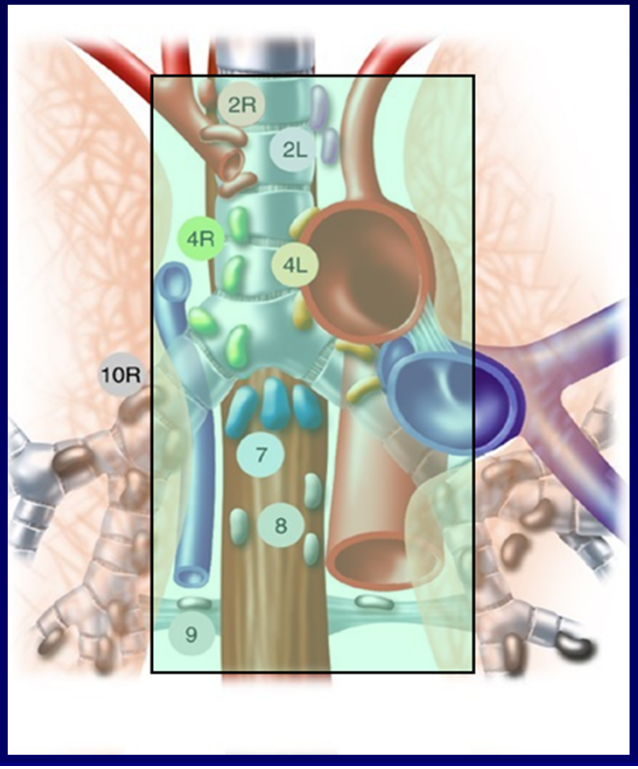




- ATS 1, 2, 3, 4, 5, 6, 7, (EUS: 8, 9), 10, 11
- Visually assisted (doppler)
- Outpatient setting possible
- Re-staging

Technique	Pat. No.	Sensitivity	Specificity
TBNA	910	0.76	0.96
EUS-FNA	215	0.88	0.91
Mediast	5.687	0.81	1.00

Toloza EM, et al. *Chest.* 2003;123(1 Suupl): 157S-166S.



Restaging: CT

Study	N	CRT	CT	Sens	Spec	FN	FP
Trodella et al.	56	+	-	92	77	9	8
De Leyn et al	30	-	+	59	62	47	34
Mateu-Navarro et al.	24	-	+	42	75	44	38
Lardionois et al.	24	-	+	56	73	27	44
Ohtsuka et al	22	+	+	67	62	27	45
All sites				63	70	31	34

- Overall false negative rate of ~30%
- Generally not recommended

FN, false negative rate; FP, false positive rate

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

Restaging: PET-CT

Study	N	PET	PET/CT	Sens	Spec	FN	FP
Cerfolio et al.	93	-	+	62	88	20	25
Eschmann et al.	56	+	-	77	68	29	25
Hellwig et al.	33	+	-	50	88	15	43
Akhurst et al.	54	+	-	67	61	21	54
De Leyn et al.	30	-	+	77	92	25	7
All sites				63	70	26	34

- Overall false negative rate of ~25%
- Generally not recommended

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

Restaging: Needle Techniques

Study	N	Tech	Sens	Spec	FN	FP
Herth et al.	124	EBUS-NA	76	100	80	0
Annema et al.	17	EUS-NA	67	100	33	0
Varadarajulu et al.	14	EUS-NA	86	100	14	0
Stigt et al.	25	EUS-NA	96	100	8	0
Kunst et al.	11	TBNA	100	100	0	0
All sites			84	100	14	0

- Overall false negative rate of ~15%
- Only large study of EBUS had FN rate of 80%!
- EUS / TBNA studies very small (inconclusive)
- Not recommended given lack of solid evidence

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

Restaging: Primary Mediastinoscopy

Study	N	CRT	CT	Sens	Spec	FN	FP
Zielinski et al.	63	+	+	96	100	3	0
Lardinois et al.	22	-	+	82	100	15	0
All sites				89	100	9	0

- Overall false negative rate of ~10%
- Best option

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

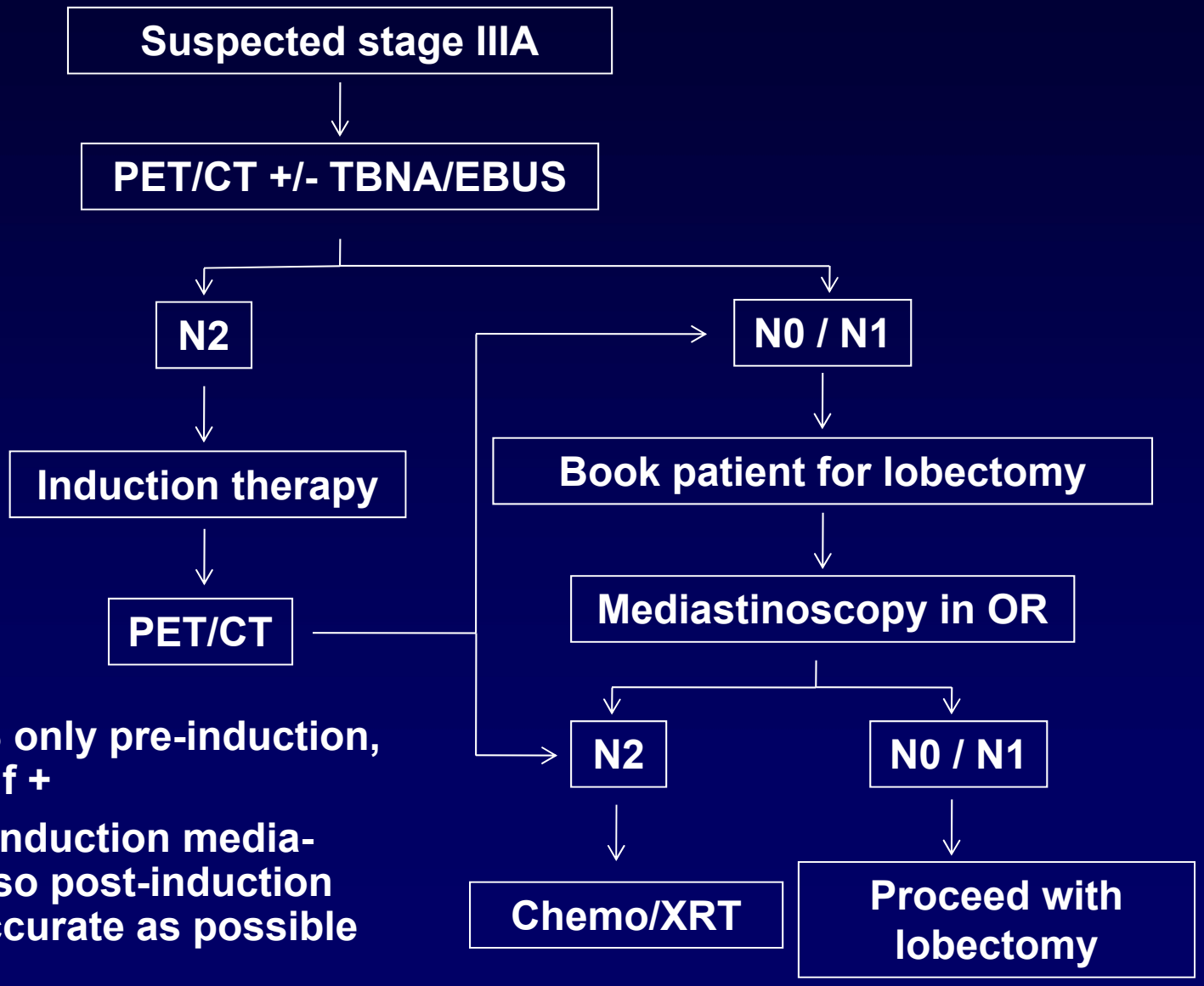
Restaging: Repeat Mediastinoscopy

Study	N	CRT	CT	Sens	Spec	FN	FP
Stamatis et al.	165	+	-	74	100	14	0
Meerschaut et al.	112	n/a	n/a	71	100	9	0
Marra et al.	104	+	-	51	100	21	0
De Waele et al.	104	+	+	70	100	27	0
De Leyn et al.	30	-	+	50	100	38	0
All sites				63	100	22	0

- Overall false negative rate of ~20%
- Technically feasible but difficult
- Recommended over noninvasive imaging

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

Stage IIIA N2 Disease: Algorithm



Features

1. TBNA/EBUS only pre-induction, only useful if +
2. Avoids pre-induction media-stinoscopy so post-induction will be as accurate as possible