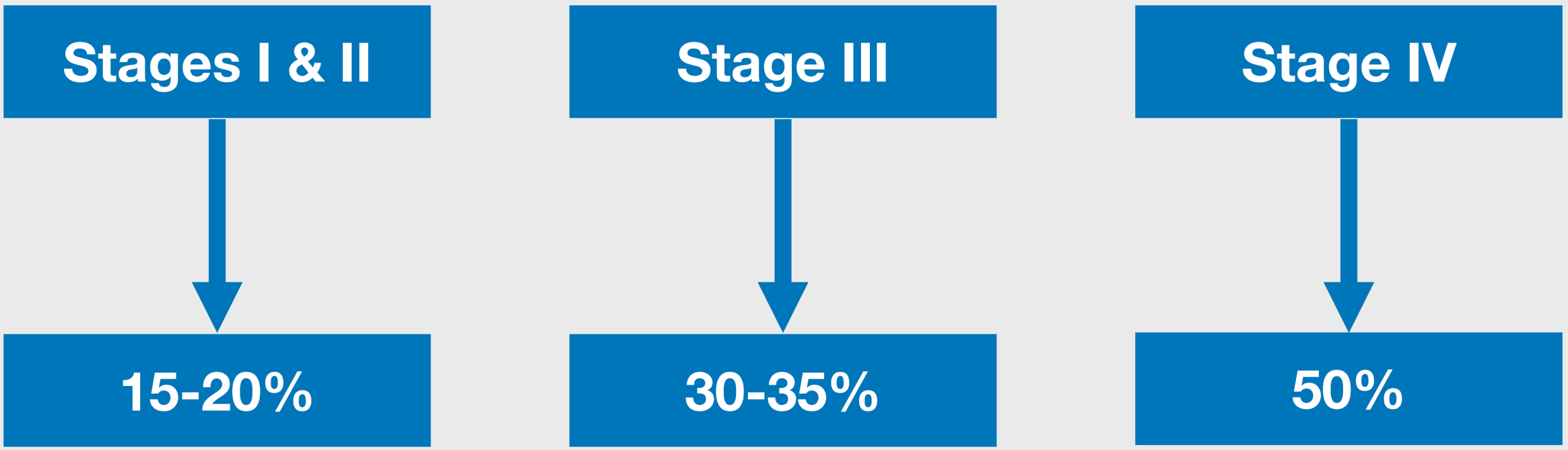
Selection of the ideal surgical candidate for stage III NSCLC

Levon Toufektzian
Thoracic Surgeon
Athens Medical Center

6th CONGRESS OF THE
MEDITERRANEAN MULTIDISCIPLINARY ONCOLOGY FORUM

Surgery for NSCLC



Surgery for NSCLC

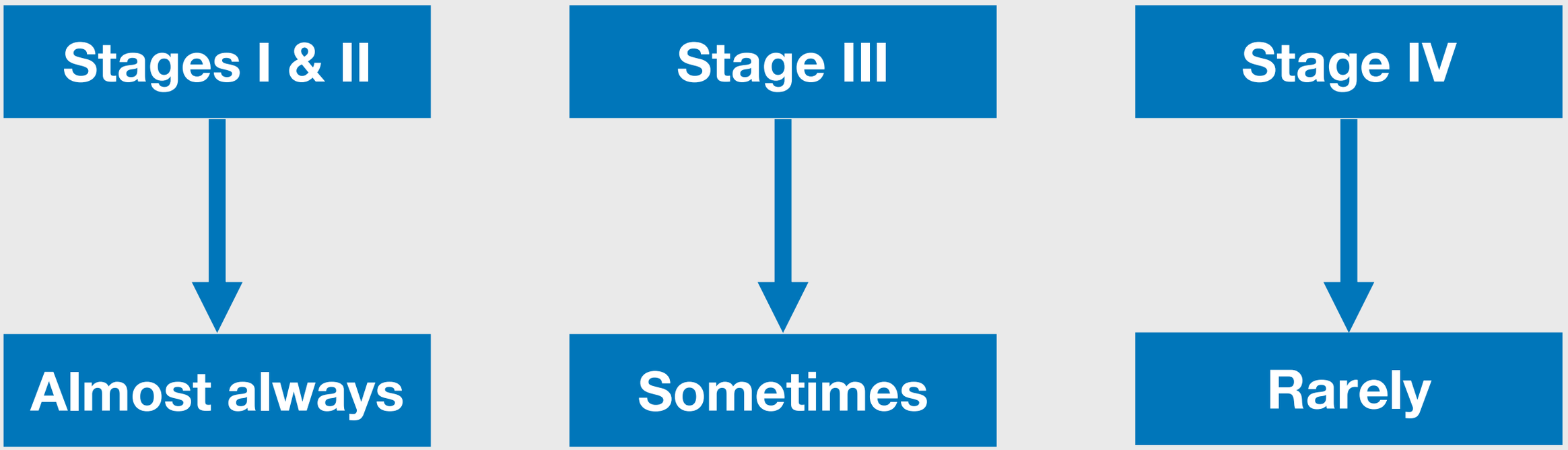
Stages I & II

Stage III

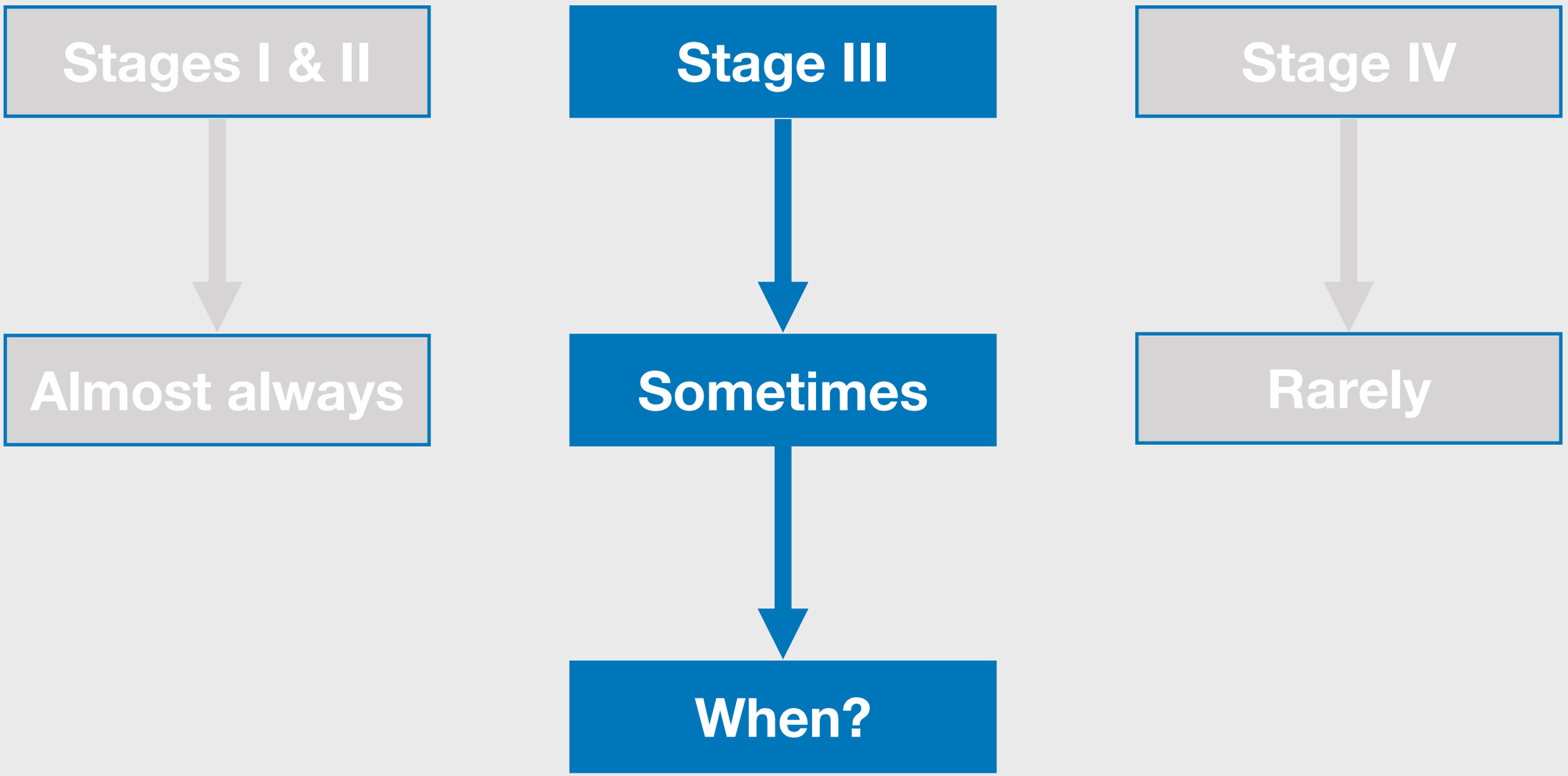
Stage IV

What is the role of surgery in the treatment?

Surgery for NSCLC

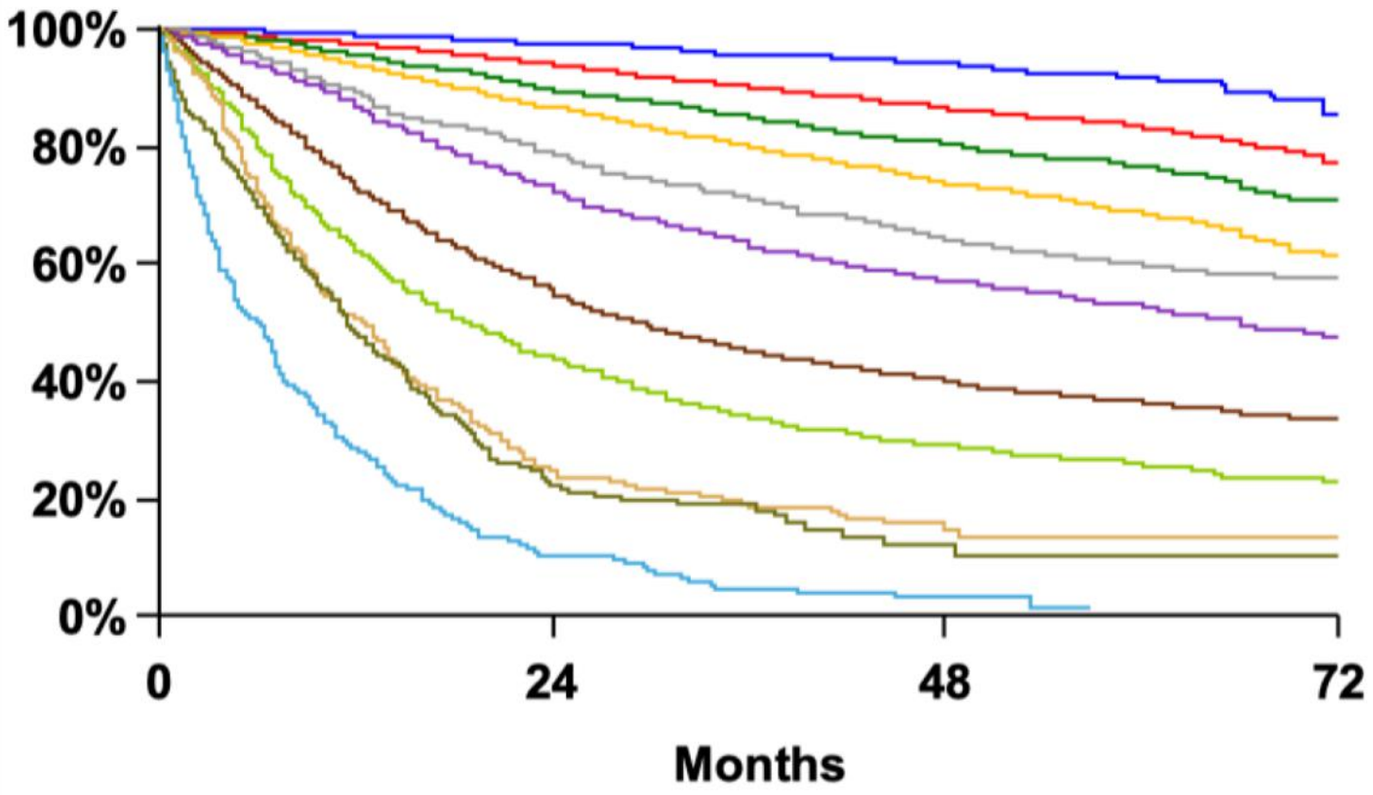


Surgery for NSCLC



Surgery for NSCLC

Why surgery?



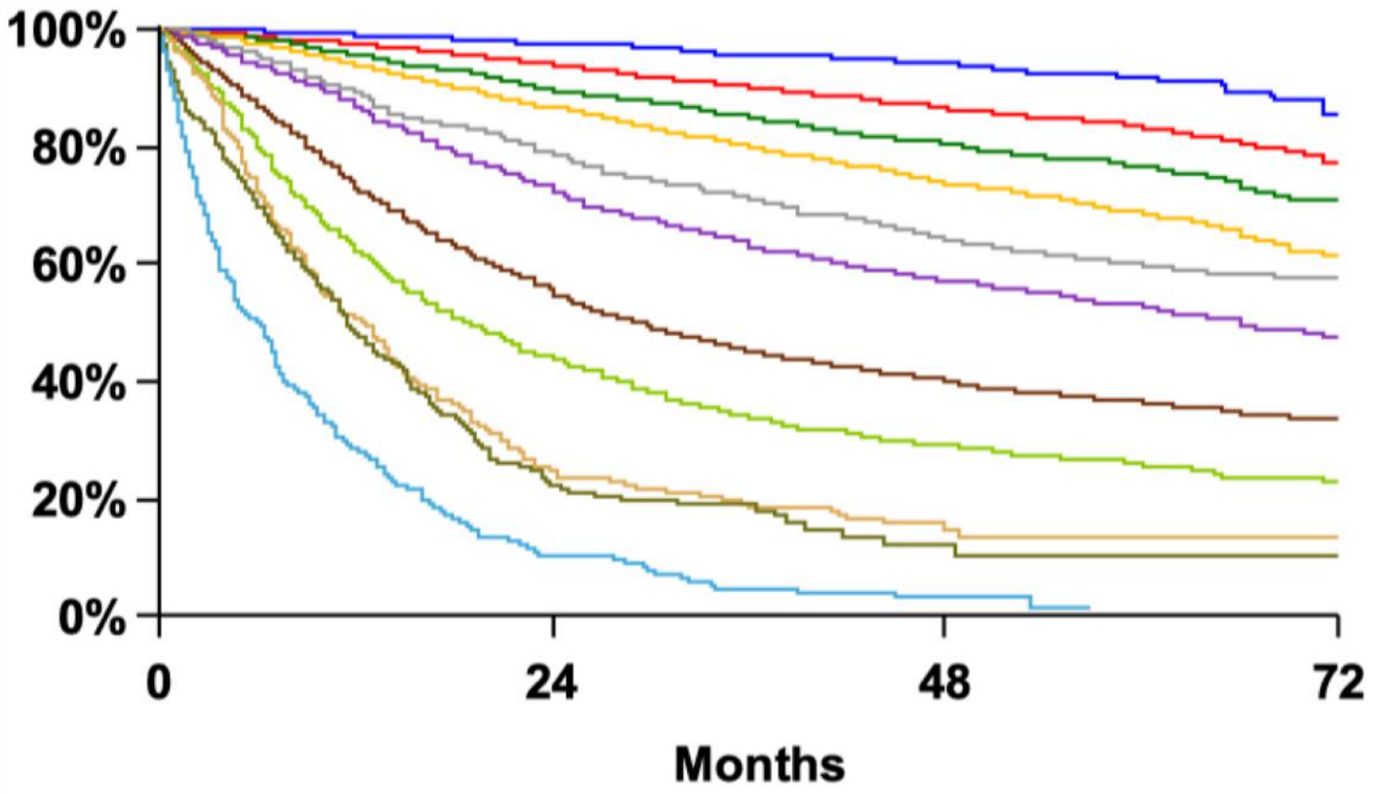
Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Goldstraw et al. J Thorac Oncol 2016
The IASLC Lung Cancer Staging Project 8th edition

87% of the entire dataset had surgery as part of their treatment

Surgery for NSCLC

Why surgery?



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Goldstraw et al. J Thorac Oncol 2016
The IASLC Lung Cancer Staging Project 8th edition

87% of the entire dataset had surgery as part of their treatment

Staging

8th edition TNM (2016)

Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0

Small Ts with big Ns, big Ts with small Ns and a combination of both

↓

Largely heterogenous group

Staging

8th edition TNM (2016)

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm*	• Tumor diameter >7cm*
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm* • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

*Changes compared with 7th edition of lung cancer staging

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

- **Oncologically appropriate**
- **Technically possible**
- **Phsysiologically fit**

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

- **Oncologically appropriate**

↓

Will the patient benefit from a surgical resection?

- **Technically possible**

↓

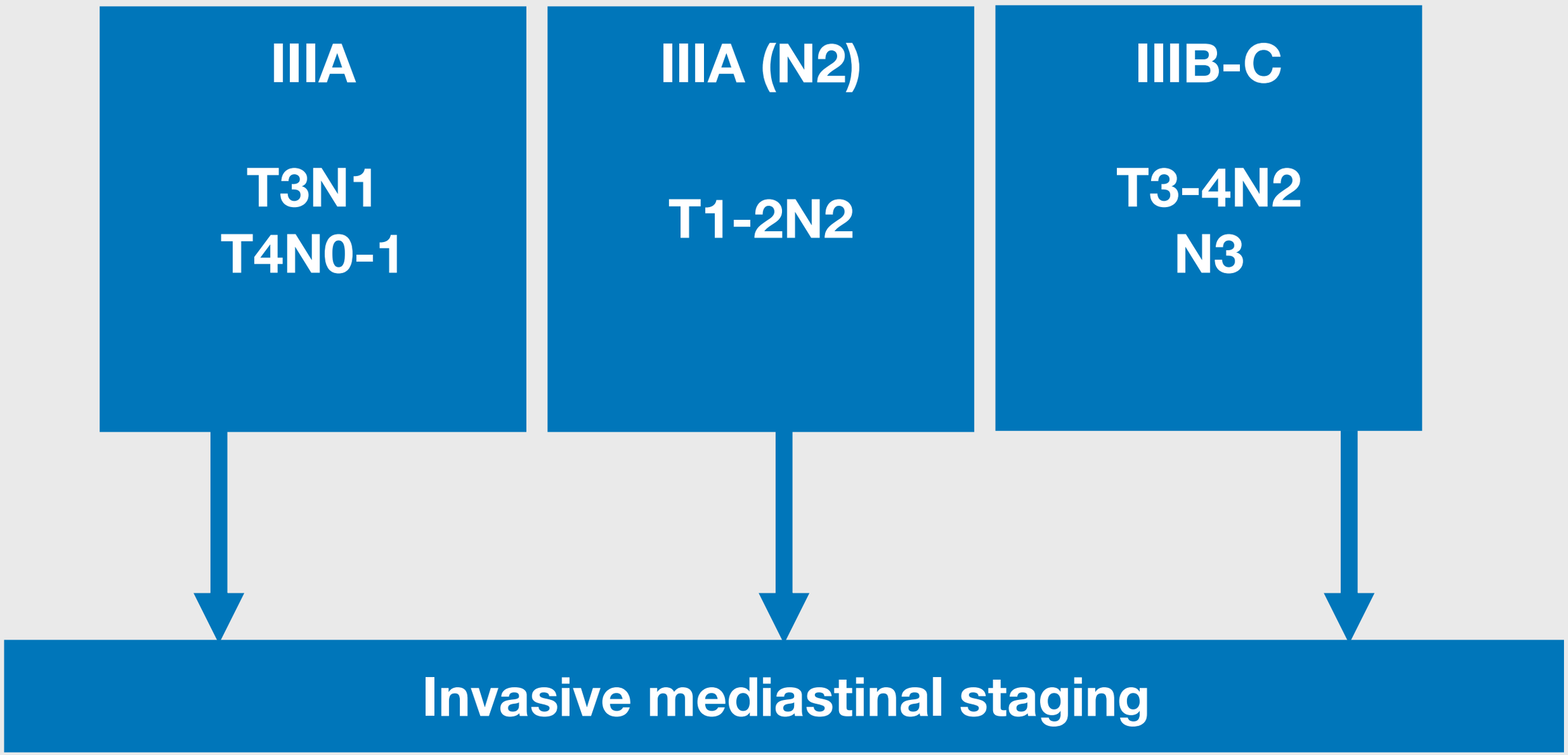
Is it possible to achieve an R0 resection?

- **Phsysiologically fit**

↓

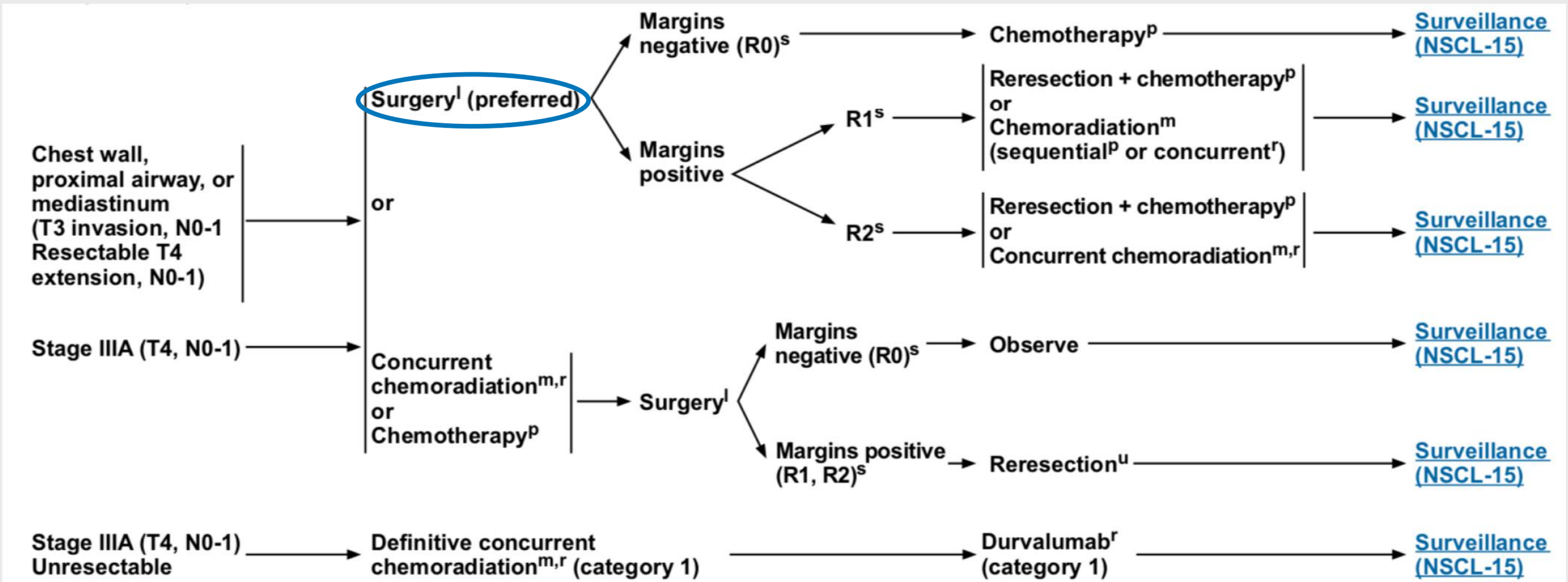
Can the patient tolerate a (extended) surgical resection?

Stage III NSCLC



Guidelines

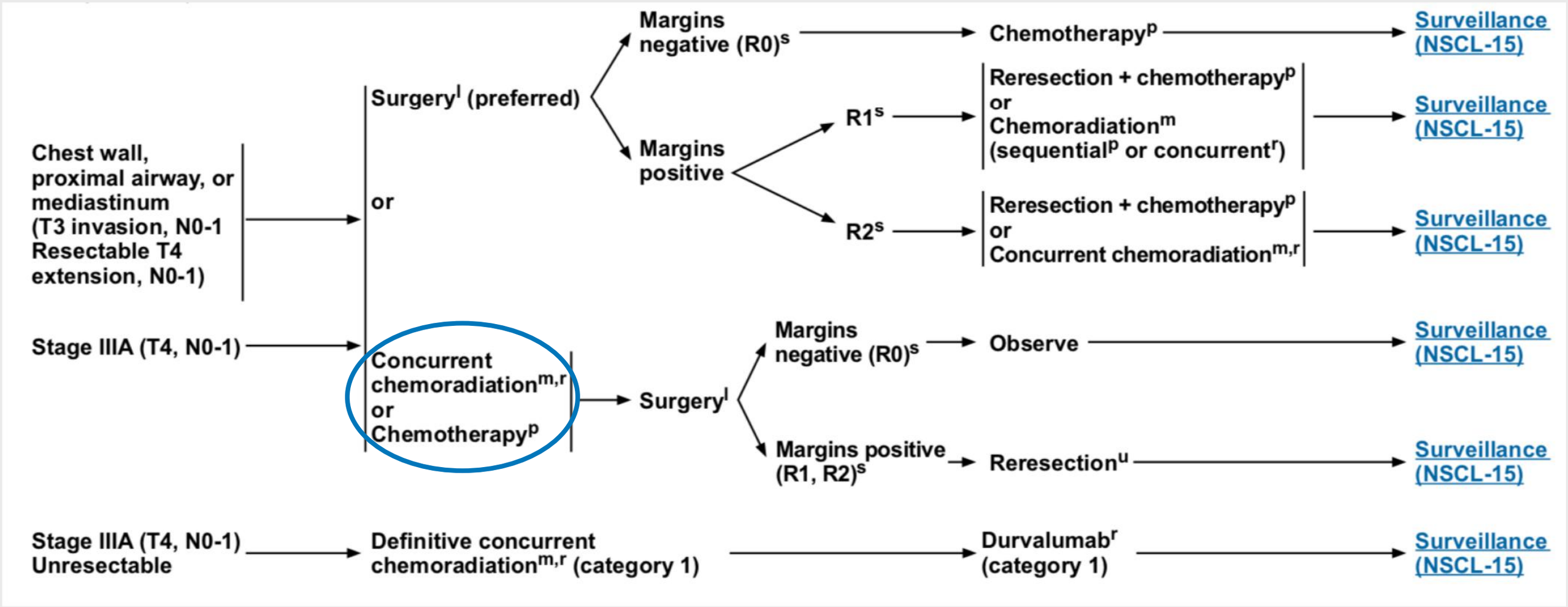
IIIA (non-N2)



- **Bottom line: Whenever a T3 or T4 tumor (N0 or N1) can be resected surgery is preferred followed by adjuvant therapy.**
- **Non-N2 stage IIIA (if resectable) is managed usually like stage II**

Guidelines

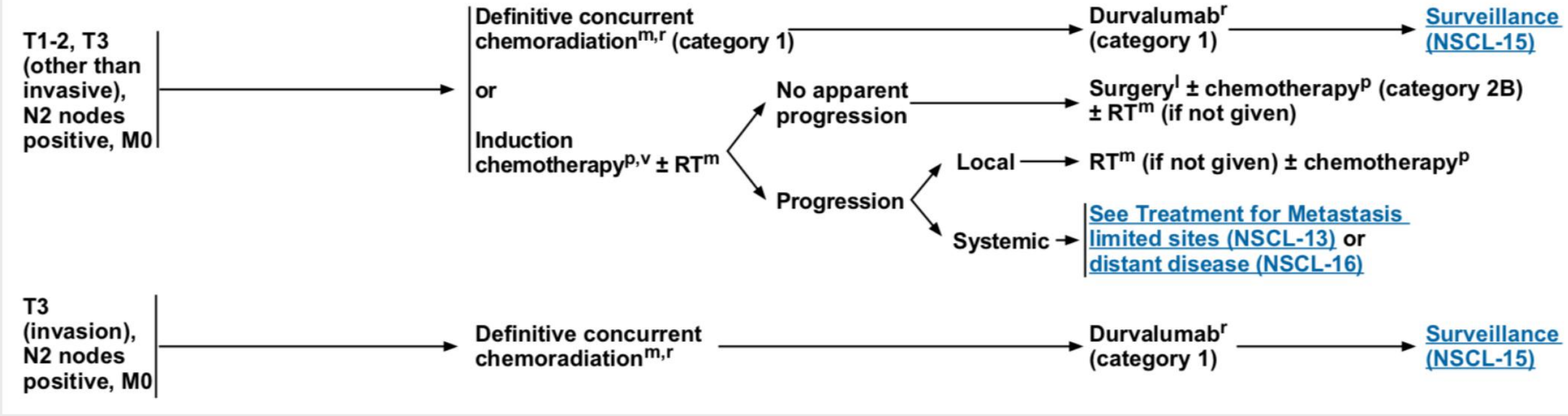
IIIA (non-N2)



- **Will induction treatment make things better?**

Guidelines

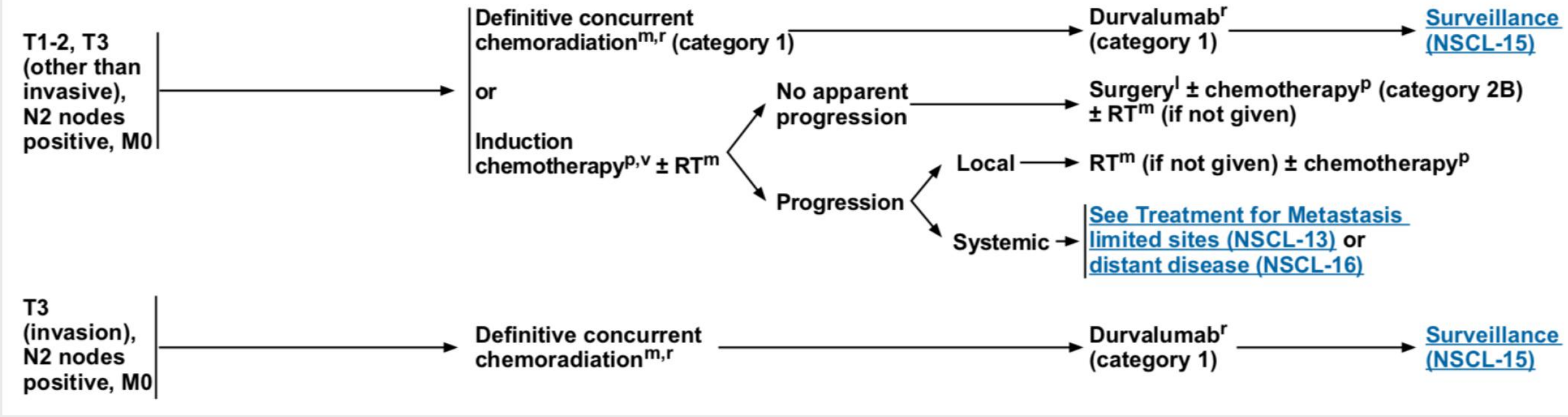
IIIA (N2), T3N2 (IIIB)



Guidelines

National Comprehensive Cancer Network®

IIIA (N2), T3N2 (IIIB)



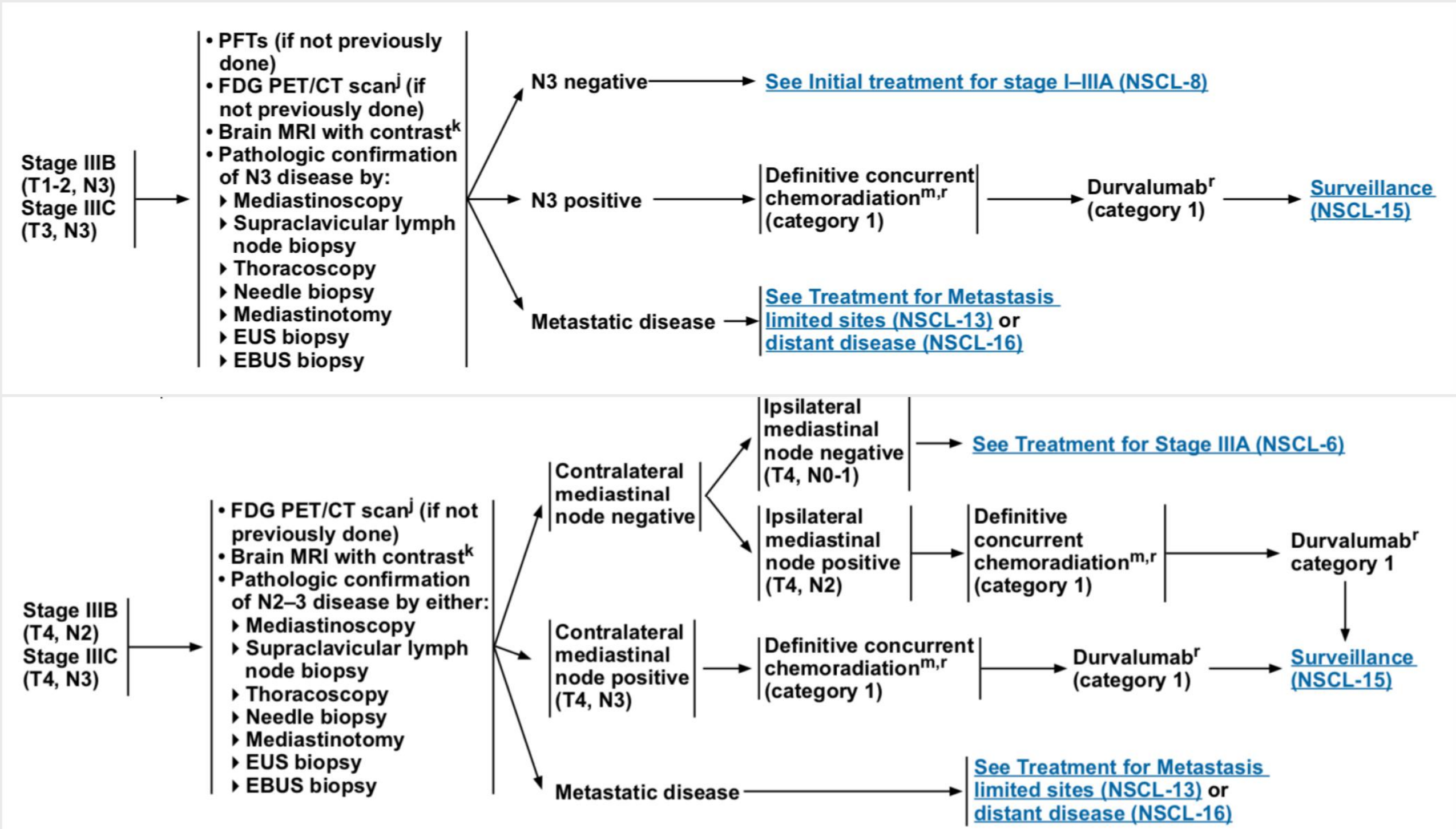
Which N2 subset?

- Single-station
- Multi-station
- Bulky

Guidelines

National Comprehensive Cancer Network®

Stages IIIB & IIIC



Guidelines

- Intraoperative incidental non-bulky N2 disease is resected followed by adjuvant chemotherapy ± PORT

- Single station N2 disease can be managed either with surgical resection followed by adjuvant therapy, or with induction therapy followed by surgical resection

- Superior sulcus tumors are managed with induction CRT followed, if technically resectable, by surgery. A similar treatment strategy can be applied for central T3 or T4 tumors.

Postmus PE, et al.
Ann Oncol 2017

Stage III NSCLC

IIIA	IIIA (N2)	IIIB-C
T3N1 T4N0-1	T1-2N2	T3-4N2 N3 *T3N2
↓	↓	↓
Surgery + CT CT + Surgery	CT + Surgery Surgery + CT ± RT	CT RT + Durvalumab

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

- Oncologically appropriate

↓

Will the patient benefit from a surgical resection?

- Technically possible

↓

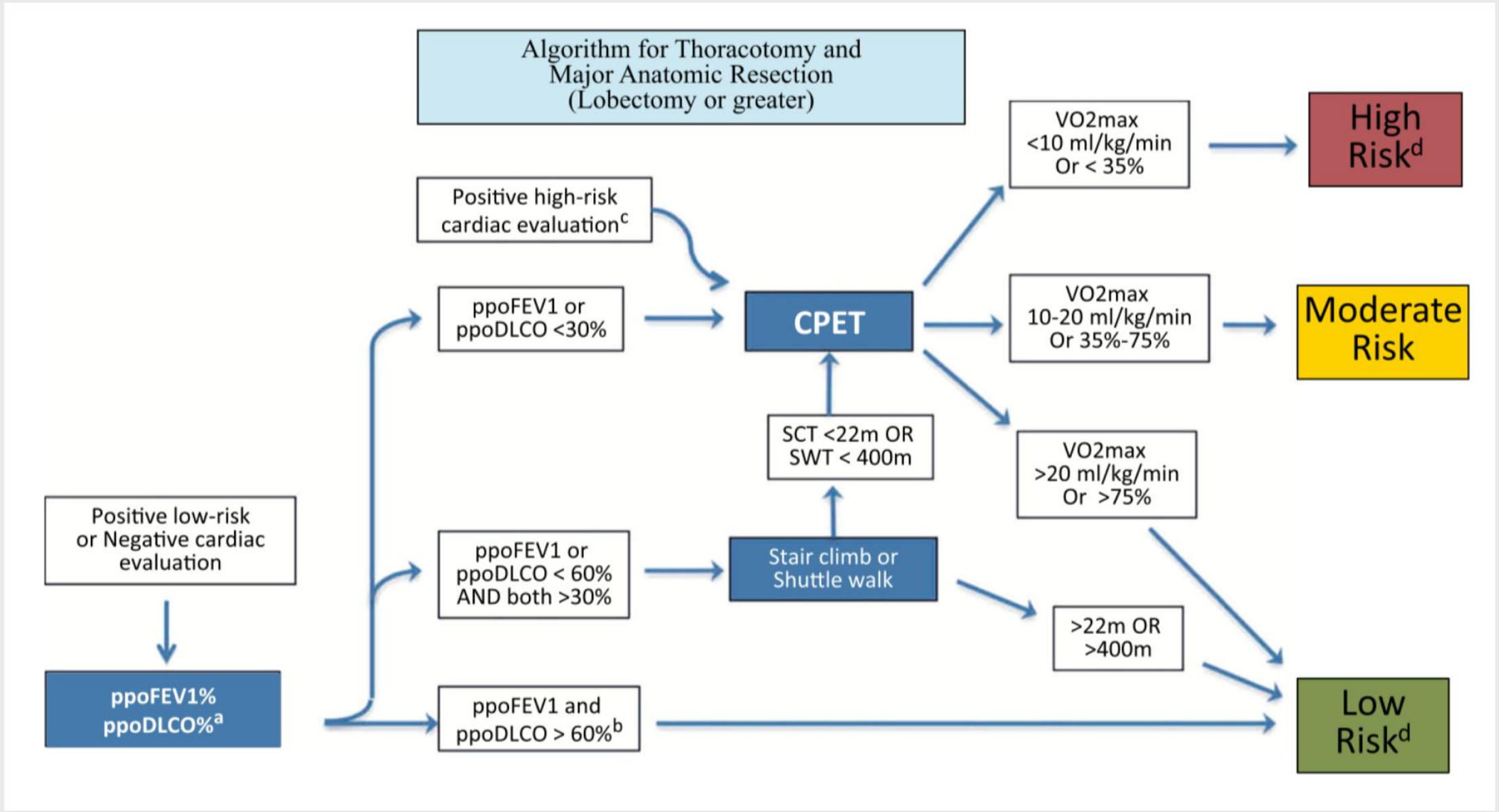
Is it possible to achieve an R0 resection?

- **Phsysiologically fit**

↓

Can the patient tolerate a (extended) surgical resection?

Preoperative respiratory workup



ACCP Evidence-Based Clinical Practice Guidelines, 3rd ed, 2013

ThRCRI (Thoracic Revised Cardiac Risk Index)

- Coronary artery disease: 1,5
- Cerbrovascular disease: 1,5
- Serum creatinine > 2mg/dl: 1
- Pneumonectomy: 1,5

- Group A: 0 point: Cardiovascular complications 1,5%
- Group B: 1-1,5 points: Cardiovascular complications 5,8%
- Group C: 2-2,5 points: Cardiovascular complications 19%
- Group D: > 2,5 points: Cardiovascular complications 23%

If ThRCRI > 2 further cardiac risk assessment and intervention

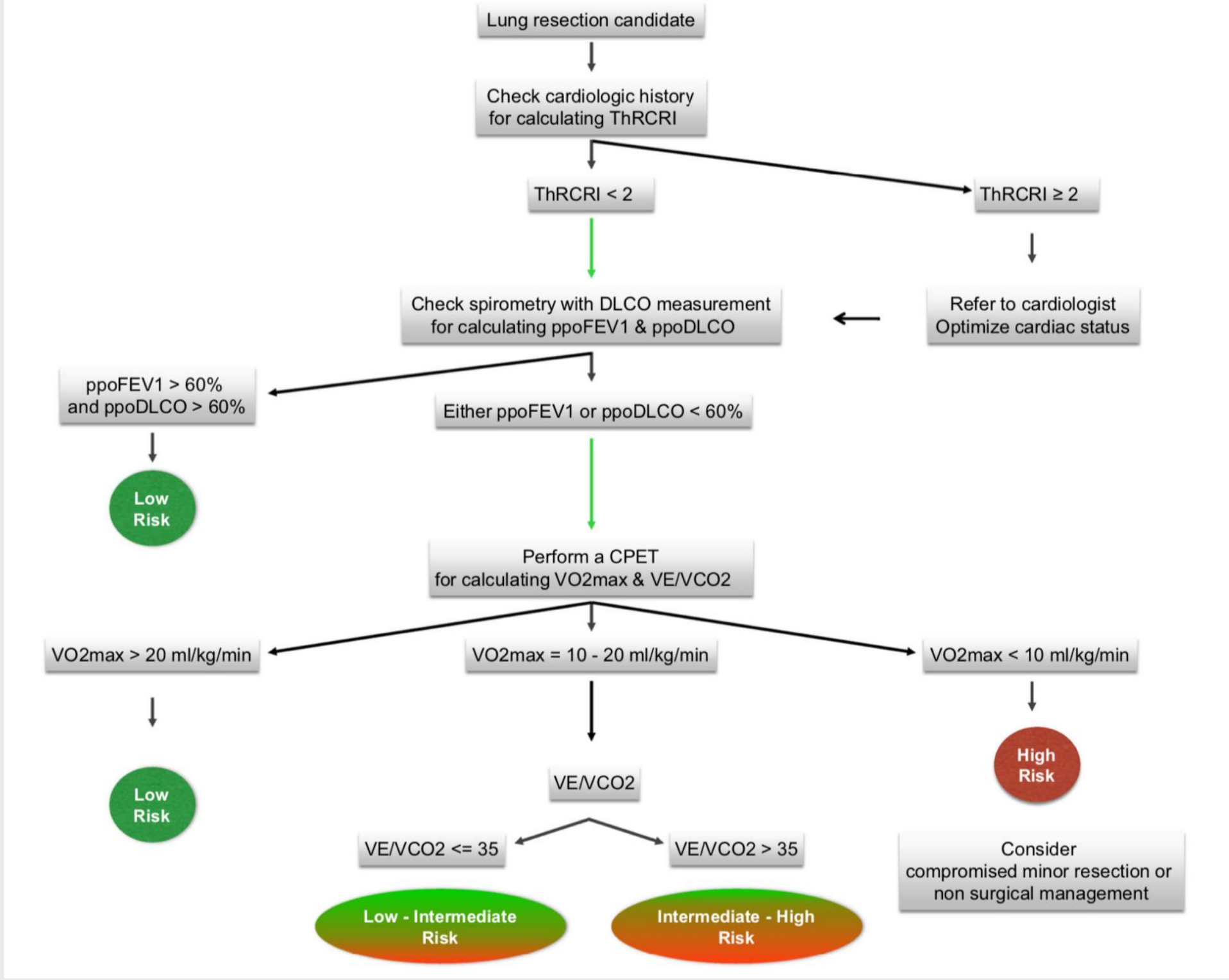
Bruneli et al.
Ann Thor Surg 2010

Preoperative further workup

- If pneumonectomy is required lung perfusion scan
- Cardiovascular assessment
    - Echocardiography (watch for signs of pulmonary hypertension)
    - Stress testing (as indicated)
- Nutritional assessment (weight loss, serum albumin)
- Performance status (ECOG scale, Karnofsky index)

Bottom line: for T3 and T4 tumors were an extended resection will be required fitness is essential for reducing postoperative complications

Risk stratification



Salati et al.
Curr Surg Rep 2016;4:37

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

- Oncologically appropriate

↓

Will the patient benefit from a surgical resection?

- Technically possible

↓

Is it possible to achieve an R0 resection?

- Phsysiologically fit

↓

Can the patient tolerate a (extended) surgical resection?

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

Position of the additional nodule will define the extent of the resection

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body
	Usually yes	Sometimes yes

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body
	Usually yes	• It is the surgeon's decision • Depends on extent of invasion and available expertise

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

Will induction treatment improve resectability?

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

- CT/RT might shrink the tumor
- But will also cause local inflammation and scarring
- Which makes resection and possible reconstructions even more difficult

T3s & T4s

Can we achieve an R0 resection?

	T3	T4
SIZE	• Tumor diameter >5cm ≤7cm	• Tumor diameter >7cm
NODULE	• Separate nodule in the same lobe	• Separate nodule in other lobe
INVASION	• Chest wall • Phrenic nerve • Parietal pleura	• Diaphragm • Mediastinum • Heart and great vessels • Trachea and carina • Recurrent laryngeal nerve • Esophagus • Vertebral body

- If a tumor can be completely resected upfront this should be preferred (surgeon's view)
- Induction treatment more often than not will not reduce the extent of the required procedure

Surgery for stage III NSCLC

Ideal surgical candidate means 3 things:

- **Oncologically appropriate**

↓

Will the patient benefit from a surgical resection?

- **Technically possible**

↓

Is it possible to achieve an R0 resection?

- **Phsysiologically fit**

↓

Can the patient tolerate a (extended) surgical resection?

Surgery for stage IIIA

IIIA	IIIA (N2)	IIIB-C
T3N1 T4N0-1	T1-2N2	T3-4N2 N3 *T3N2

Surgery for stage IIIA (T3s & T4s)

Table 1
Selected summary of extended resections of T4 NSCLC

Reference	T4 Sites of Disease	Patients	Morbidity (%)	Mortality (%)	Overall Survival (% at 5 y)
Burt et al,[6] 1987	Aorta, pulmonary artery, esophagus	225	NR	2.7	9
Tsuchiya et al,[7] 1994	Aorta, left atrium, pulmonary artery, SVC	101	NR	NR	13
Martini et al,[8] 1994	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, spine	102	NR	6	19
Bernard et al,[9] 2001	Aorta, left atrium, pulmonary artery, SVC, esophagus, carina, spine	77	NR	NR	21[a]
Pitz et al,[10] 2003	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, carina, spine	89	NR	19	19
Ratto et al,[11] 2004	Left atrium	19	37	0	14
Ohta et al,[12] 2005	Aorta	16	31	12.5	48
Yildizeli et al,[13] 2008	Aorta, left atrium, pulmonary artery, SVC, esophagus, carina, spine, subclavian artery/vein, carotid artery, chest wall	271	35	4	38
Wu et al,[14] 2009	Left atrium	46	52	0	22
Yang et al,[15] 2009	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, carina, spine	146	53	3.1	23
Spaggiari et al,[16] 2013	Aorta, left atrium, SVC, carina	167	34	5	23
Galvaing et al,[17] 2014	Left atrium	19	53	11	44

Reardon et al.
Thorac Surg Clin 2014

Surgery for stage IIIA (T3s & T4s)

It is justified, as long as a complete (R0) resection is achieved

Surgery for stage IIIA

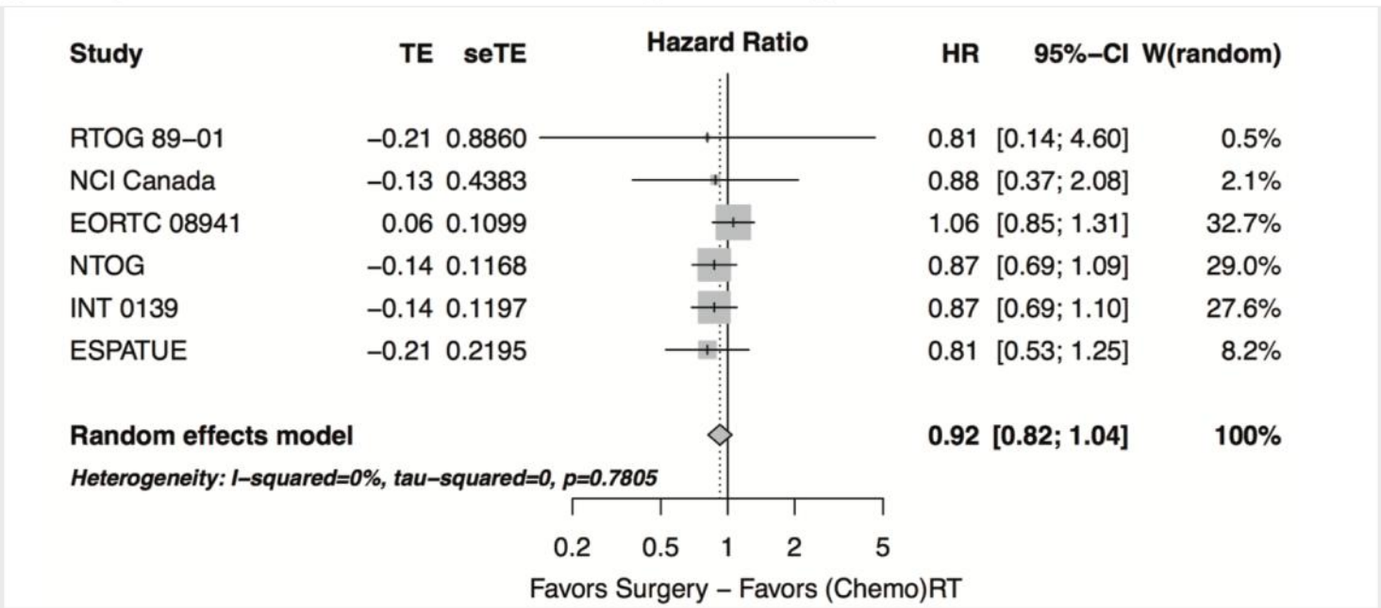
IIIA	IIIA (N2)	IIIB-C
T3N1 T4N0-1	T1-2N2	T3-4N2 N3 *T3N2

Surgery for stage IIIA (N2)

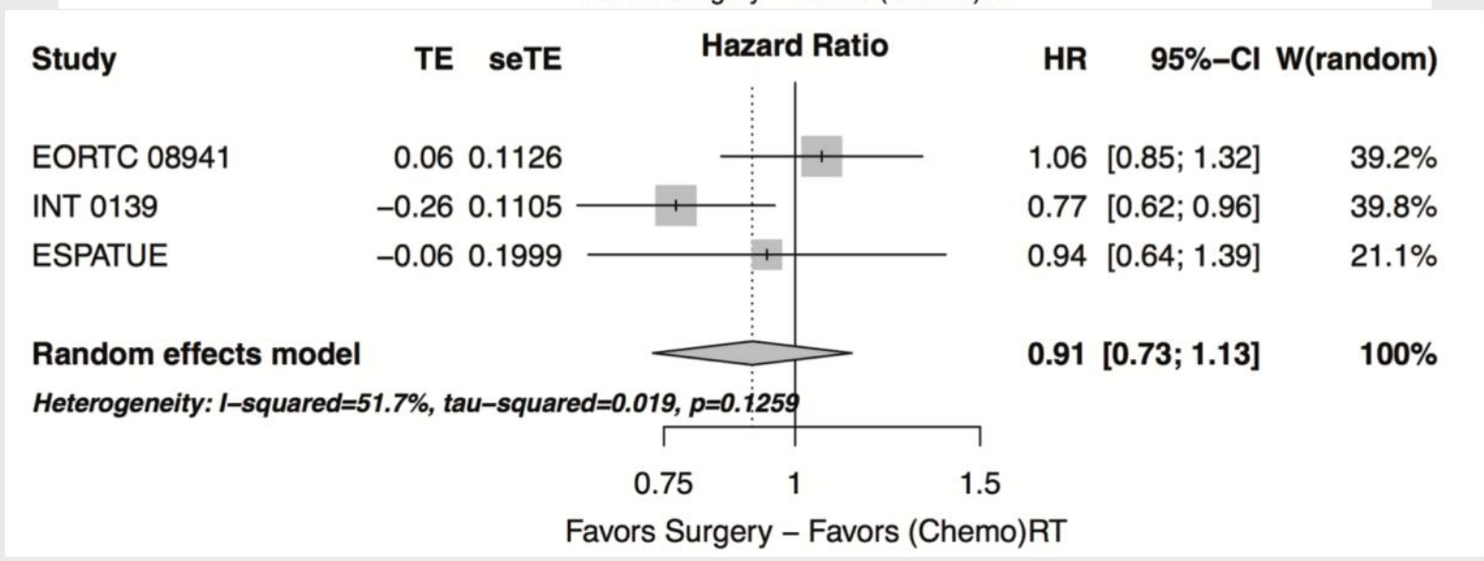
Meta-analysis 2017

Definitive radiochemotherapy *versus* surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence

Christoph Pöttgen[1], Wilfried Eberhardt[2], Georgios Stamatis[3] and Martin Stuschke[1]



Overall survival



Disease-free survival

Pöttgen et al. Oncotarget 2017

Surgery for stage IIIA (N2)

Meta-analysis 2017

Definitive radiochemotherapy *versus* surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence

Christoph Pöttgen[1], Wilfried Eberhardt[2], Georgios Stamatis[3] and Martin Stuschke[1]

Adding surgery to CT or CRT does not seem to significantly alter prognosis of N2 disease

Pöttgen et al.
Oncotarget 2017

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations

Surgery for stage IIIA (N2)

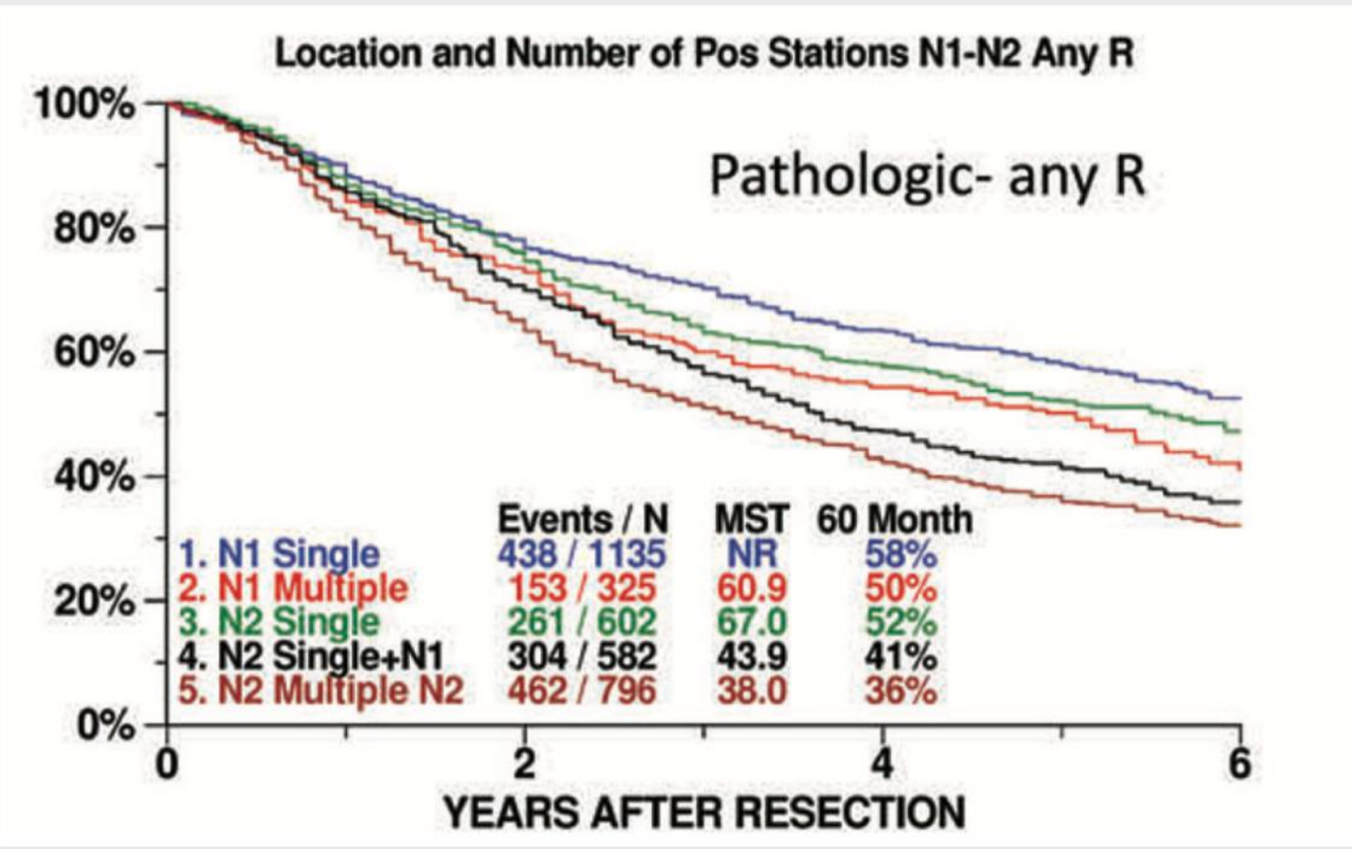
Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations
  - Lobectomy vs. Pneumonectomy
  - R0 vs. R1 vs. R2 resections
  - Multiple lymph node stations vs. single lymph node stations
  - Induction therapy: complete response vs. partial response vs. no response

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations
- N2 disease is a heterogenous population



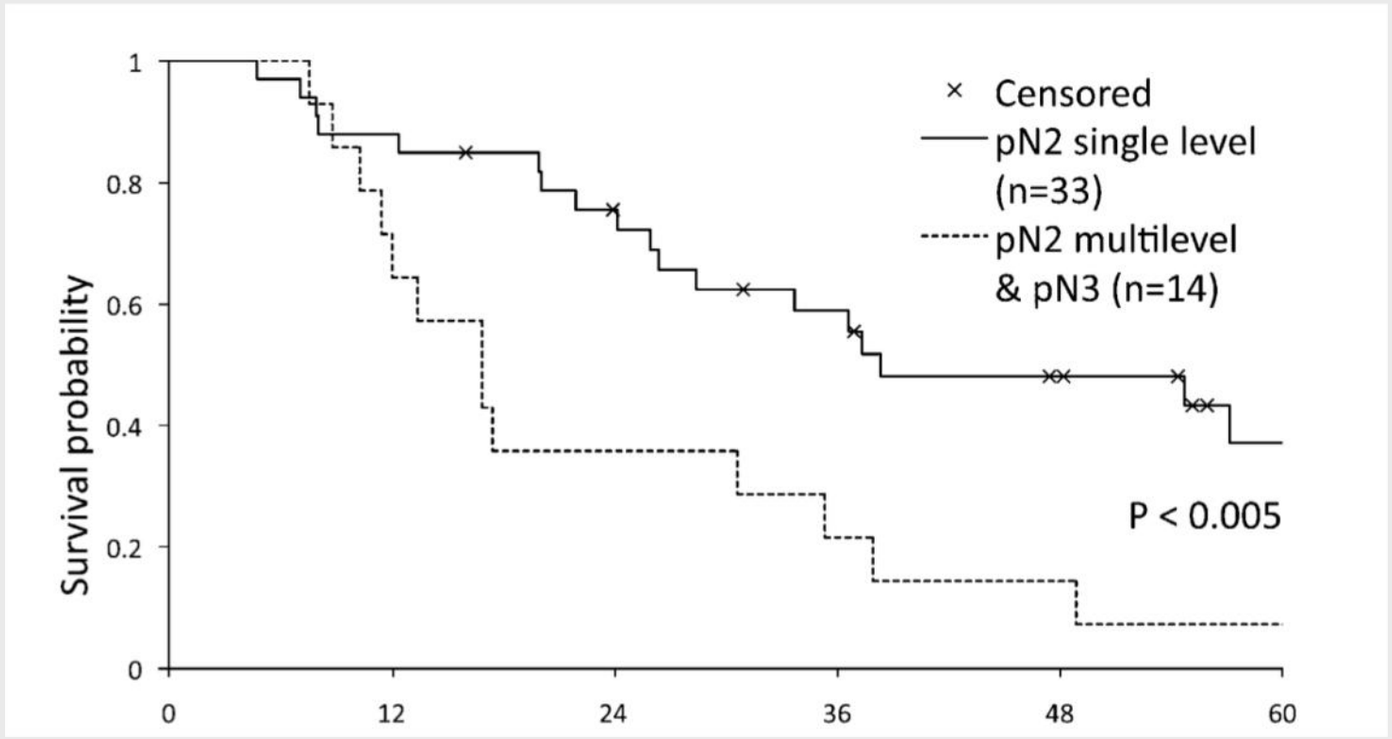
N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

Asamura H et al.
J Thorac Oncol 2015

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations
- N2 disease is a heterogenous population
- Improved induction therapy response is associated with improved survival after surgery



Decaluwé H et al.
Eur J Cardiothorac Surg 2016

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations
- N2 disease is a heterogenous population
- Improved induction therapy response is associated with improved survival after surgery
- Invasive (re)staging of the mediastinum

Decaluwé H et al.
Eur J Cardiothorac Surg 2016

Surgery for stage IIIA (N2)

Why do we persist operating N2 disease?

- Randomized studies have included significantly heterogenous populations
- N2 disease is a heterogenous population
- Improved induction therapy response is associated with improved survival after surgery
- Invasive (re)staging of the mediastinum
- Prognostic factors
  - ypN0-N1
  - R0 resection

Decaluwé H et al.
Eur J Cardiothorac Surg 2016

Surgery for stage IIIA (N2)

Given that surgery seems to be beneficial for those with good to great response after induction treatment, is it appropriate that all patients with N2 disease (non-bulky), irrespective of number of stations, undergo induction therapy followed by invasive restating of the mediastinum, followed by surgery?

Surgery for stage IIIA (N2)

Given that surgery seems to be beneficial for those with good to great response after induction treatment, is it appropriate that all patients with N2 disease (non-bulky), irrespective of number of stations, undergo induction therapy followed by invasive restating of the mediastinum, followed by surgery?

In these cases is surgery appropriate after only complete or also after partial response, or even no disease progression?

Salvage surgery

Therapeutic Advances in Medical Oncology

Salvage surgery for recurrent or persistent tumour after radical (chemo)radiotherapy for locally advanced non-small cell lung cancer: a systematic review

Chris Dickhoff, Rene H. J. Otten, Martijn W. Heymans and Max Dahele

Definition: Surgical resection following definitive CRT (usually after 3 months) for persistent or recurrent localized disease

Rationale: Attempt second localized treatment in presumed resectable disease in the absence of distant metastases

Salvage surgery

Author	Year/patients (M/F; age)	Median follow-up duration (months)	PFS post Sx (median, months)	Site of recurrence	OS post Sx (median, months)
Baumann *et al.*[5]	2008/24 (12/12; median = 60*)	n.r. (29 months for 10 survivors)	12	DP 6, LF 2, LF + DP 3	30 3 years 47%
Kuzmik *et al.*[6]	2013/14 (6/8; median = 64 at Sx)	n.r.	n.r.	n.r.	9 2 years 49%
Yang *et al.*[7]	2015/31 (18/13; median = 58 at Sx)	26 (40 months for survivors)	3 years 30% 5 years 23%	DP 7, LRF 4, LF + DP 2	32.5 3 years 42% 5 years 31%
Dickhoff *et al.*[8]	2016/15 (11/4; median = 59 at CRTx)	12.1	43.6 (EFS)	DP 2, LF + DP 1	46
Shimada *et al.*[9]	2016/18 (17/1; 63 at CRTx*)	46.2	3 years 72%	DP 2, LRF 3, LRF + DP 1	3 years 78%
Sawada *et al.*[10]	2015/8 (8/0; median = 61*)	48	n.r.	RF 1	5 years 75%
Casiraghi *et al.*[11]	2017/35 (27/8; <60 $n = 14$, 60–69 $n = 14$, ⩾70 $n = 7$*)	13	12 3 years 20% 5 years 20%	n.r.	13 3 years 32% 5 years 20%
Schreiner *et al.*[12]	2018/13 (8/5; median = 56 at Sx)	50.4	21.9 5 years 44%	DP 5, LRF 5	29.7 3 years 46% 5 years 46%

*Timepoint or mean/median specifically mentioned.
CRTx, chemoradiotherapy; DP, distant progression; EFS, event free survival; LF, local failure; LRF, locoregional failure; M/F, male/female; n.r., not reported; OS, overall survival; PFS, progression-free survival; RF, regional failure; Sx, surgery.

Dickhoff et al.
Ther Adv Med Oncol 2018

Salvage surgery

Author	Year/patients (M/F; age)	Median follow-up duration (months)	PFS post Sx (median, months)	Site of recurrence	OS post Sx (median, months)
Baumann *et al.*[5]	2008/24 (12/12; median = 60*)	n.r. (29 months for 10 survivors)	12	DP 6, LF 2, LF + DP 3	30 3 years 47%
Kuzmik *et al.*[6]	2013/14 (6/8; median = 64 at Sx)	n.r.	n.r.	n.r.	9 2 years 49%
Yang *et al.*[7]	2015/31 (18/13; median = 58 at Sx)	26 (40 months for survivors)	3 years 30% 5 years 23%	DP 7, LRF 4, LF + DP 2	32.5 3 years 42% 5 years 31%
Dickhoff *et al.*[8]	2016/15 (11/4; median = 59 at CRTx)	12.1	43.6 (EFS)	DP 2, LF + DP 1	46
Shimada *et al.*[9]	2016/18 (17/1; 63 at CRTx*)	46.2	3 years 72%	DP 2, LRF 3, LRF + DP 1	3 years 78%
Sawada *et al.*[10]	2015/8 (8/0; median = 61*)	48	n.r.	RF 1	5 years 75%
Casiraghi *et al.*[11]	2017/35 (27/8; <60 n = 14, 60–69 n = 14, ⩾70 n = 7*)	13	12 3 years 20% 5 years 20%	n.r.	13 3 years 32% 5 years 20%
Schreiner *et al.*[12]	2018/13 (8/5; median = 56 at Sx)	50.4	21.9 5 years 44%	DP 5, LRF 5	29.7 3 years 46% 5 years 46%

*Timepoint or mean/median specifically mentioned.
CRTx, chemoradiotherapy; DP, distant progression; EFS, event free survival; LF, local failure; LRF, locoregional failure; M/F, male/female; n.r., not reported; OS, overall survival; PFS, progression-free survival; RF, regional failure; Sx, surgery.

Dickhoff et al.
Ther Adv Med Oncol 2018

Salvage surgery

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

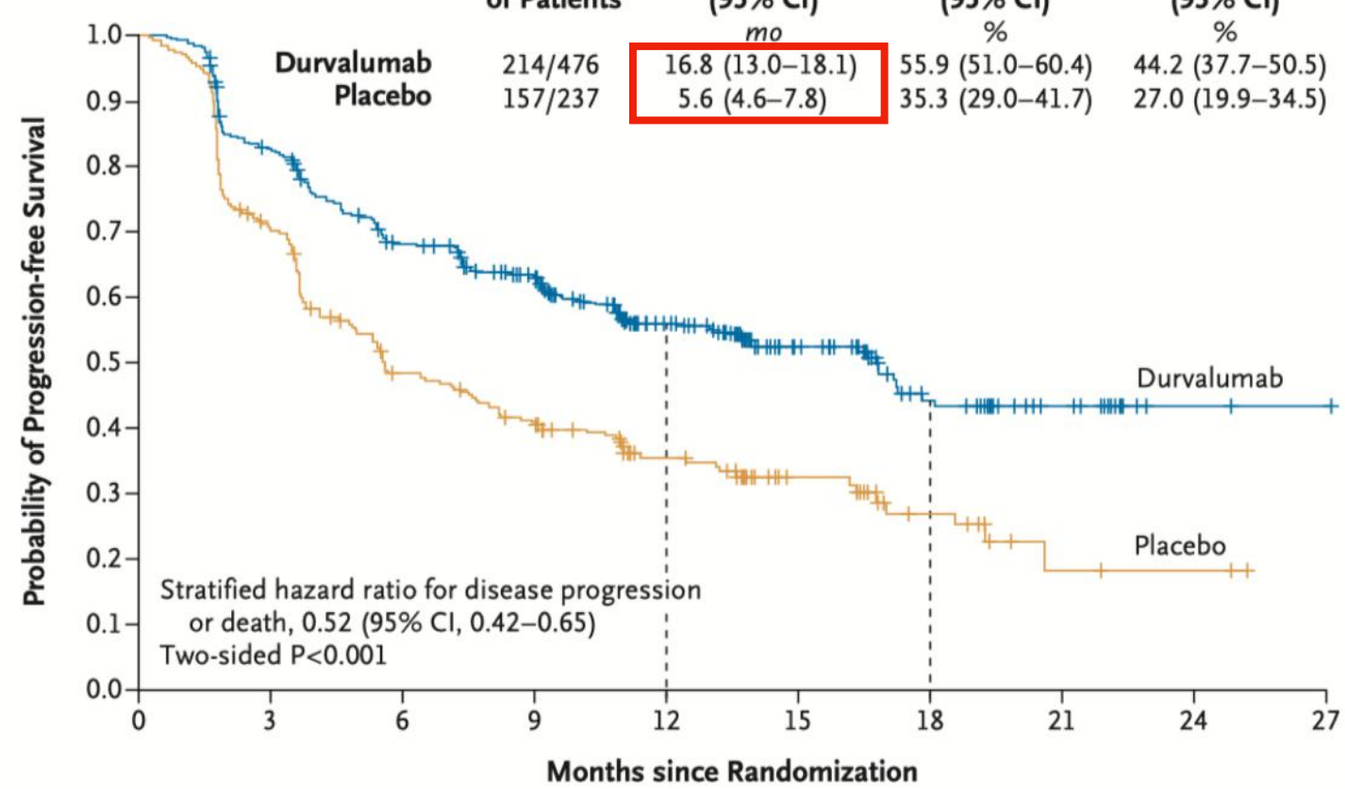
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

Stage III unresectable* lung cancer

2 or more cycles of platinum based CT
+
Definite concurrent RT (54-66Gy)

Durvalumab **Placebo**

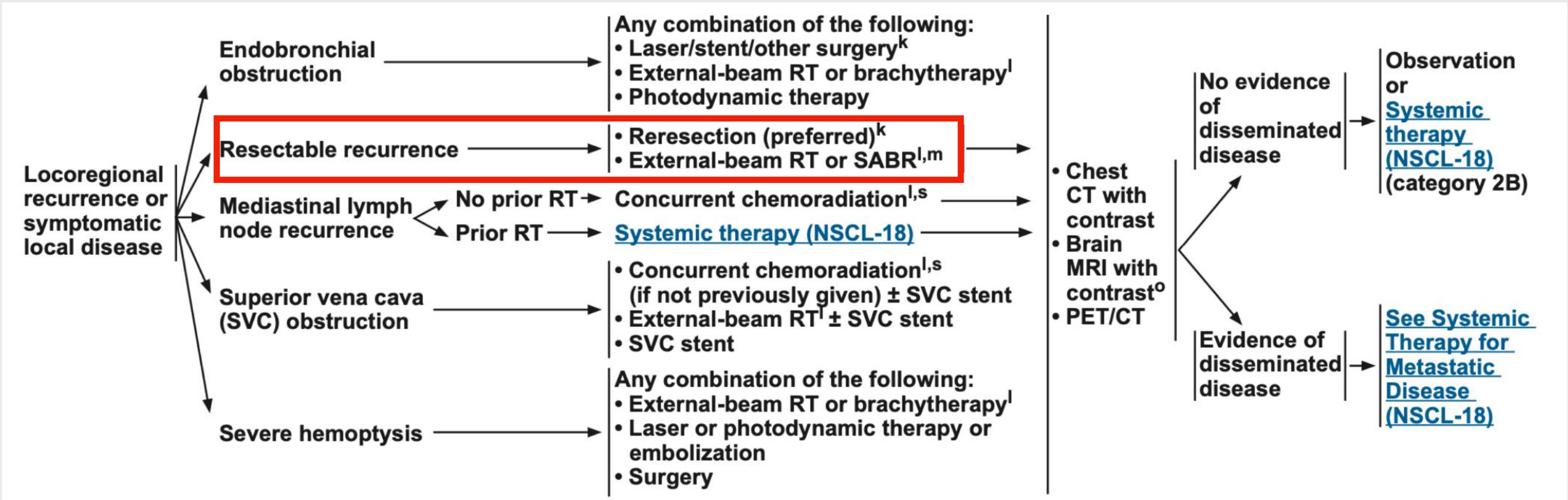
	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-Mo PFS (95% CI)	18-Mo PFS (95% CI)
		mo	%	%
Durvalumab	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
Placebo	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)



No. at Risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Antonia et al.
N Engl J Med 2017

Following Durvalumab



- Before PACIFIC: Salvage surgery following definitive CRT for resectable localized disease
- After PACIFIC: Salvage surgery following definitive CRT and durvalumab for resectable localized disease

So who is the ideal surgical candidate?

- We have no way to know prospectively which patients will benefit from a surgical resection
- For T3 and T4 tumors the ideal candidate is the one for whom we are sure there is no mediastinal disease
- For T3 and T4 tumors R0 resection is an absolute necessity
- Cardiopulmonary reserves
- For N2 disease the better the response to induction treatment the more the benefit of a surgical resection
- Following immunotherapy, localized and resectable disease might benefit from salvage surgery

Many thanks!