Surgical Management of Lung Cancer

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Disclosures

I have no disclosures.

Overview

- TNM Stage
- Mediastinal staging
- Surgical evaluation
- Surgical Resection

Bottom Line

- Surgery is the primary treatment for NSCLC I – IIIA
- Order of treatment depends on stage and many factors
- “Curative” for early stage (IA)
- Locally advanced disease (IB-IIIA) combines multimodal approach
- IIIA – Neoadjuvant Tx then surgery
- Evolving field

Overview of Staging

What is the extent of the disease? (TNM)

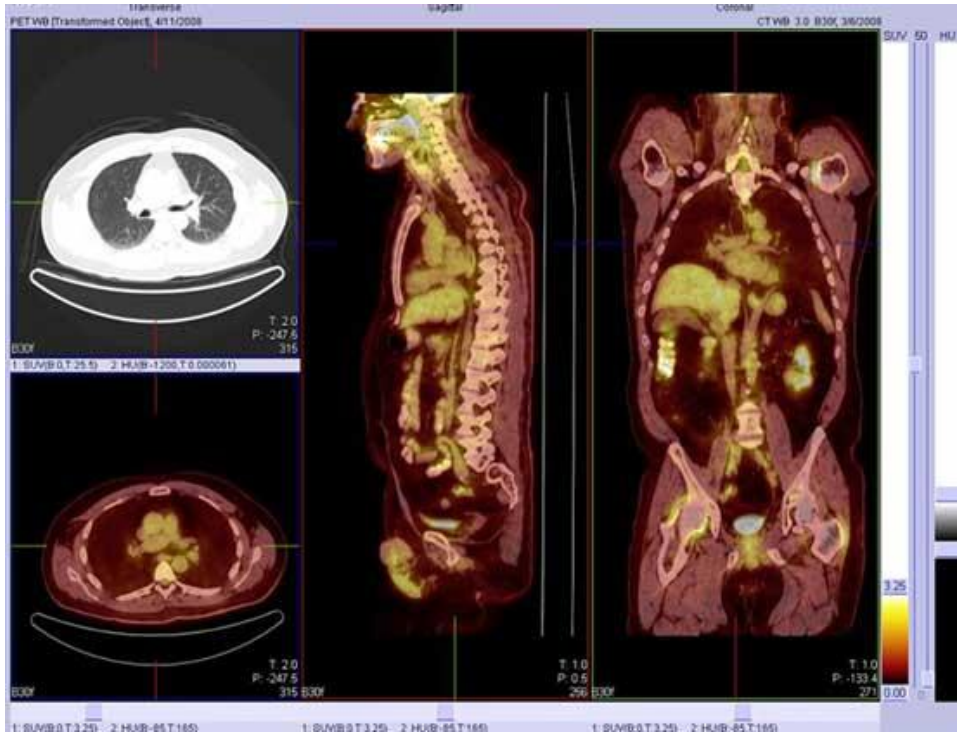
- Limited to lung
- Nodal involvement
- Distant mets

How do I prove it? (Workup)

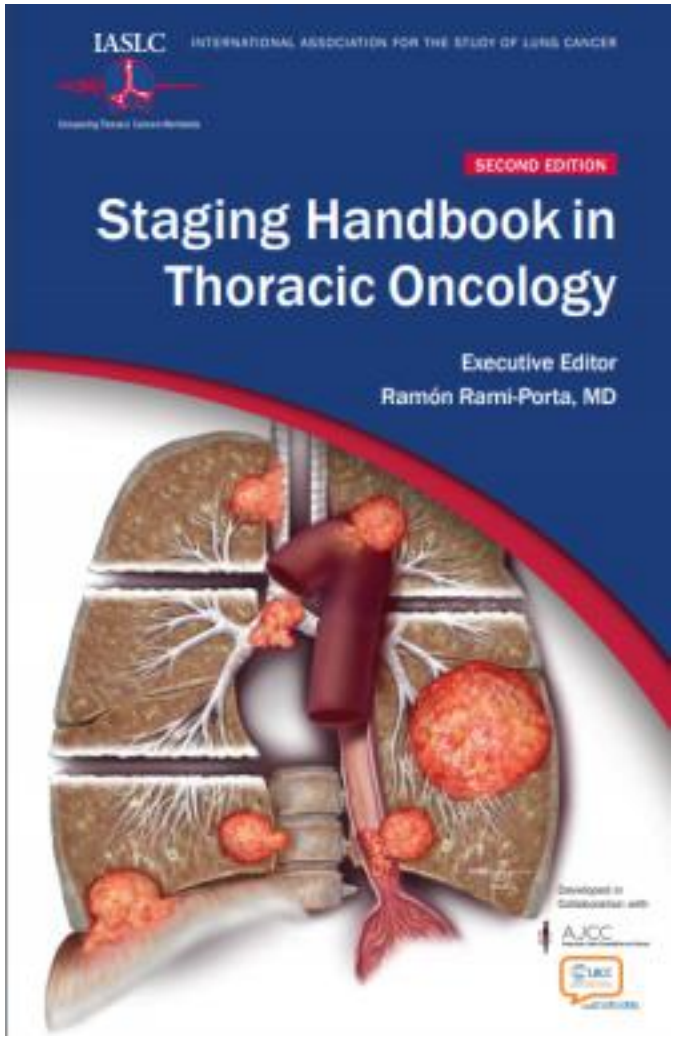
- PET/CT, Brain MRI
- Mediastinal staging
- VATS

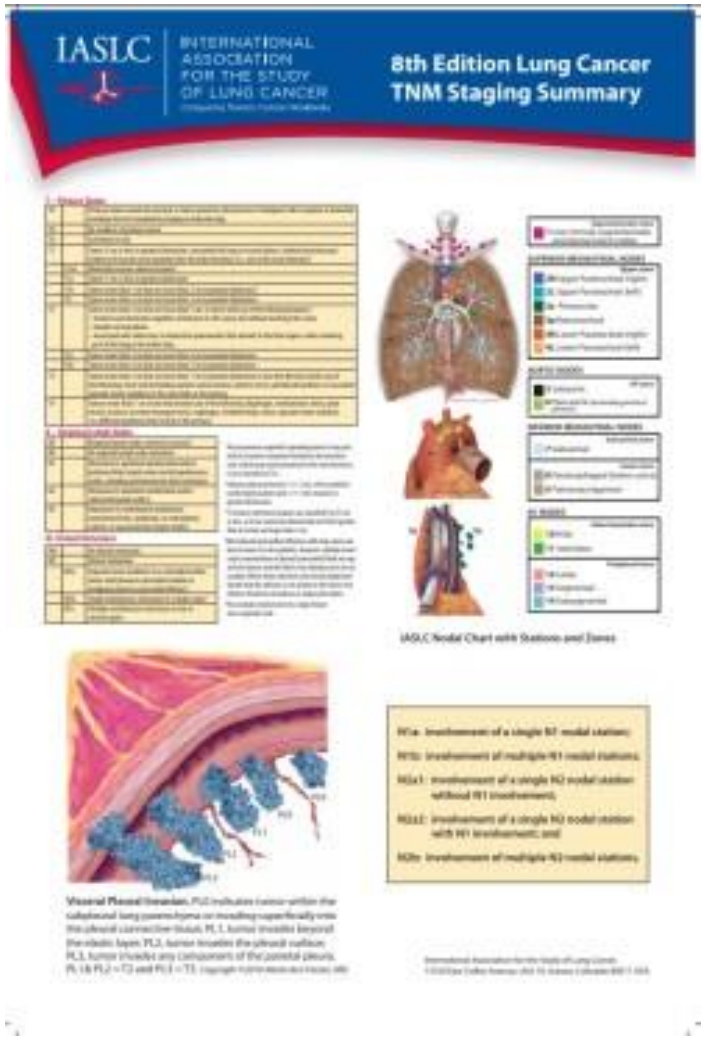
Is the patient a surgical candidate?

- “Eye” test
- PFTs
- Exercise tolerance, 6-min walk



Lung Cancer Stage Classification (8th Ed)





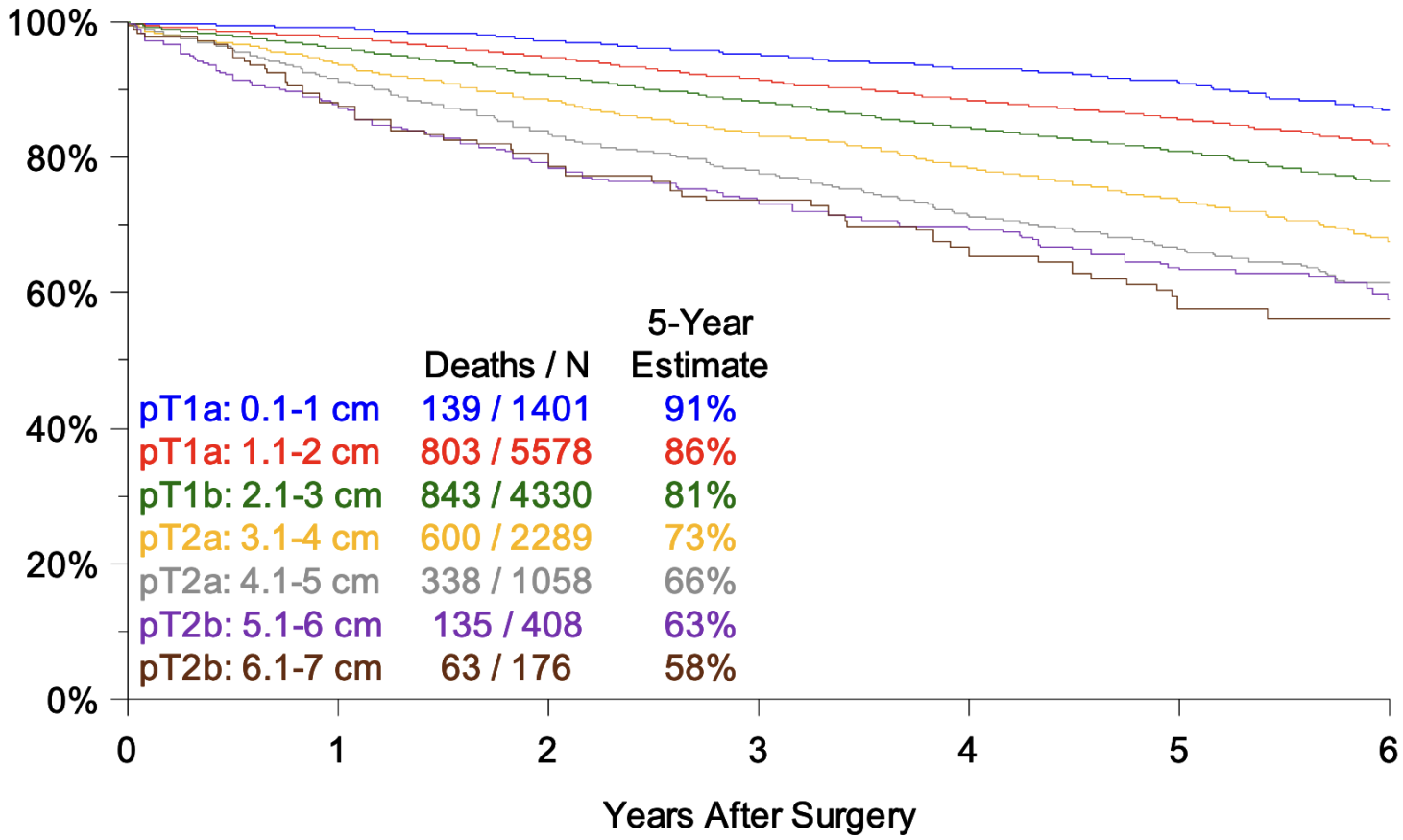
T Stage *(Think 1, 3, 5, 7 cm)*

T (primary tumor)	
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)
T1	Tumor ≤3 cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways*
T1a	Tumor ≤1 cm
T1b	Tumor >1 but ≤2 cm
T1c	Tumor >2 but ≤3 cm
T2	Tumor >3 but ≤5 cm or tumor involving: visceral pleura,† main bronchus (not carina), atelectasis to hilum†
T2a	Tumor >3 but ≤4 cm
T2b	Tumor >4 but ≤5 cm
T3	Tumor >5 but ≤7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor >7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe

Figure. Courtesy of International Association for the Study of Lung Cancer.

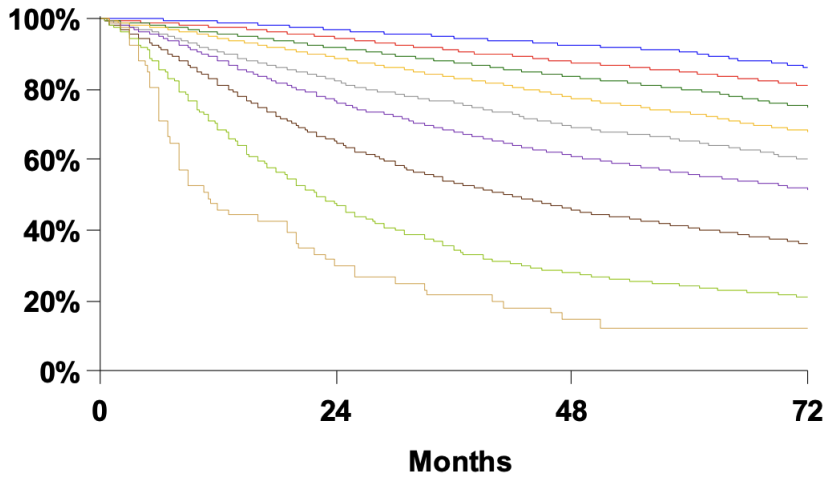
Core IASLC Data in Support of Recommendations for T
Survival of pathologically staged T1-T2 N0 R0 tumors according to size only, at 1-cm intervals.

by Size Only
pT1-2 N0 M0 R0 NSCLC



From: Rami-Porta R, Bolejack V, Crowley J, et al. Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2015;10:990-1003.

Overall Survival by Pathologic Stage (8th Ed)

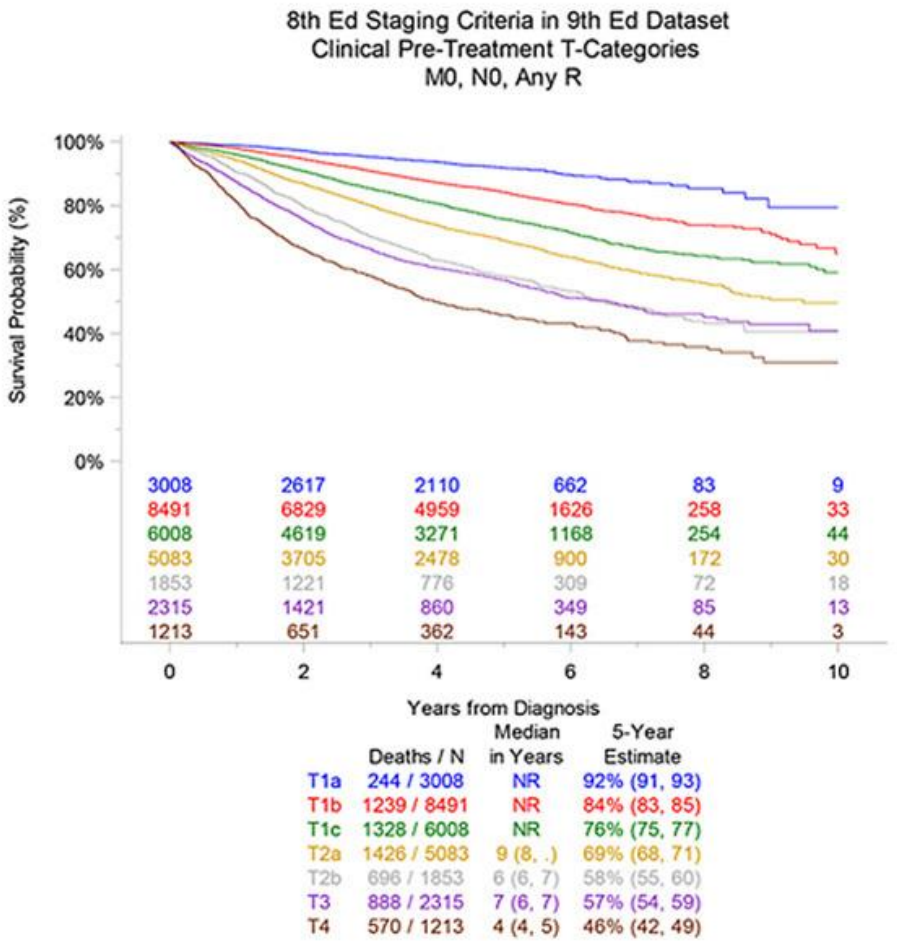


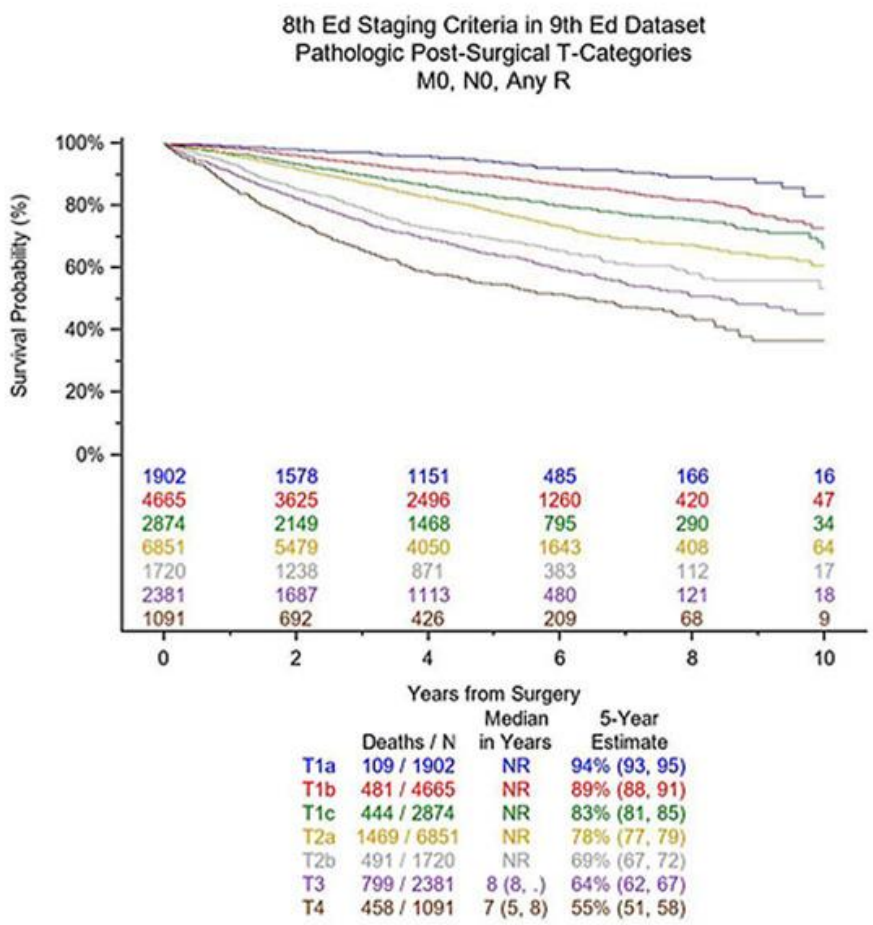
Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

From: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39-51.

The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer

Journal of Thoracic Oncology





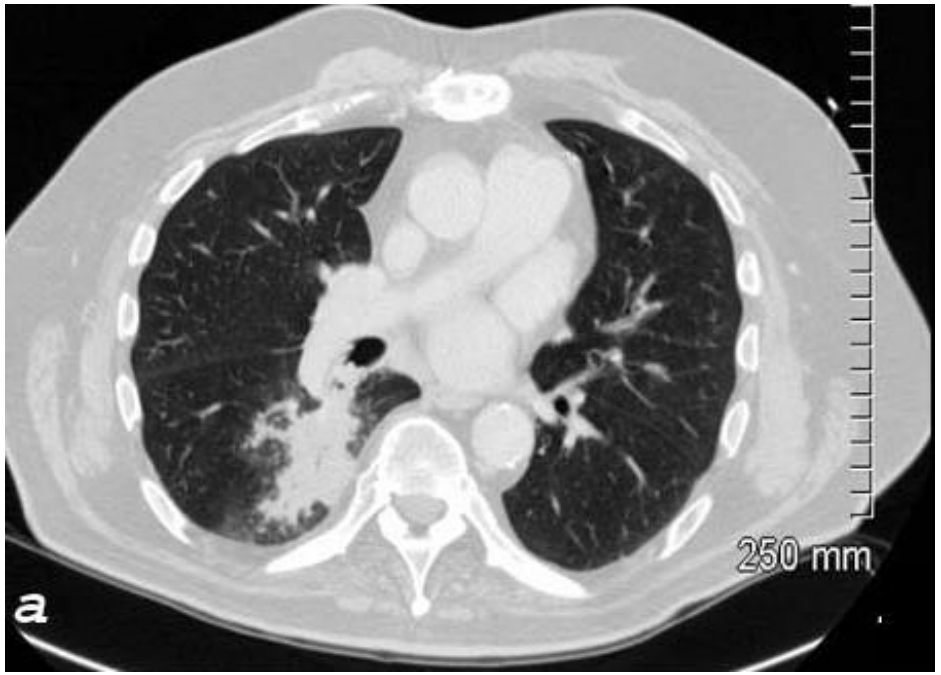
CONCLUSION: The IASLC T-subcommittee proposed not to implement any changes and keep the current 8th edition T-descriptors for the 9th edition.

IASLC

Van Schil P et al. *J Thorac Onc* (2023)

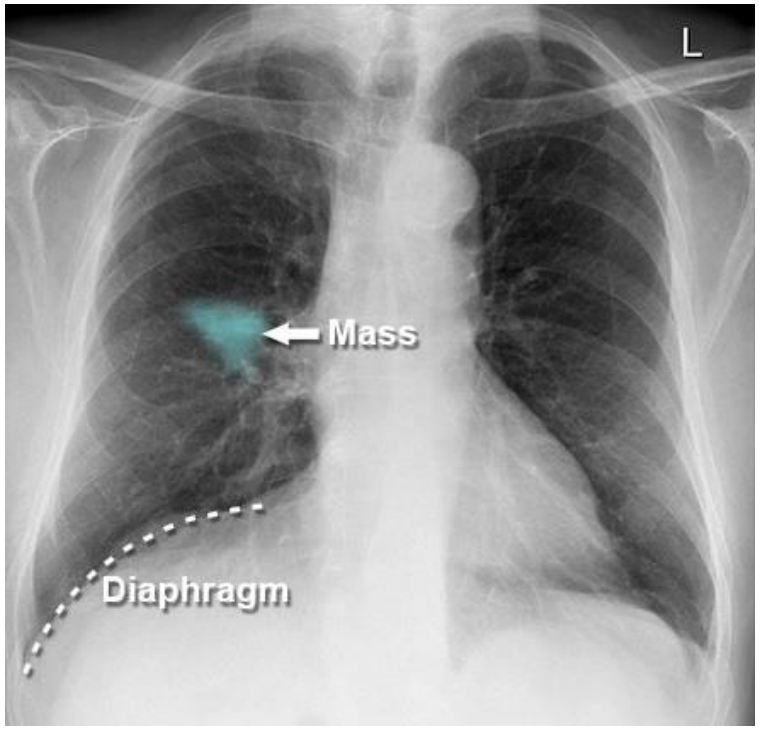
T2 (3 – 5 cm)

- Main bronchus (not carina)
- Visceral pleural invasion (VPI)
- Post-obstructive atelectasis to hilum



T3 (5 – 7 cm)

- Chest wall
- Phrenic nerve (elevated hemidiaphragm)
- Pericardium
- Satellite nodules within <u>SAME</u> lobe



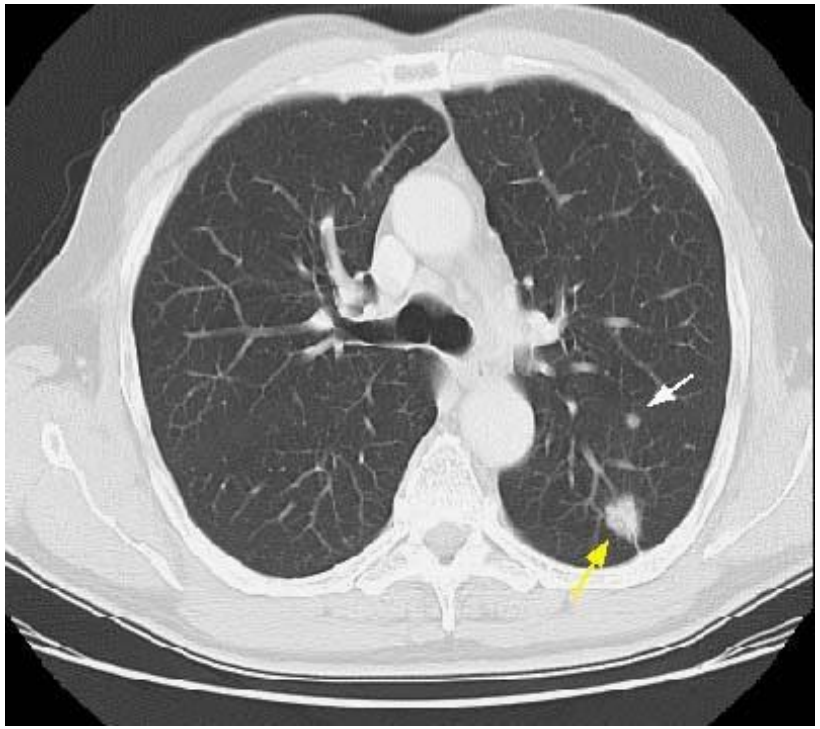


Figure. Courtesy of International Association for the Study of Lung Cancer.

T4 (> 7 cm)

- Mediastinum
- Heart, Great vessels, Trachea, Esophagus, Spine
- Diaphragm
- Separate IPSILATERAL tumor in DIFFERENT lobe

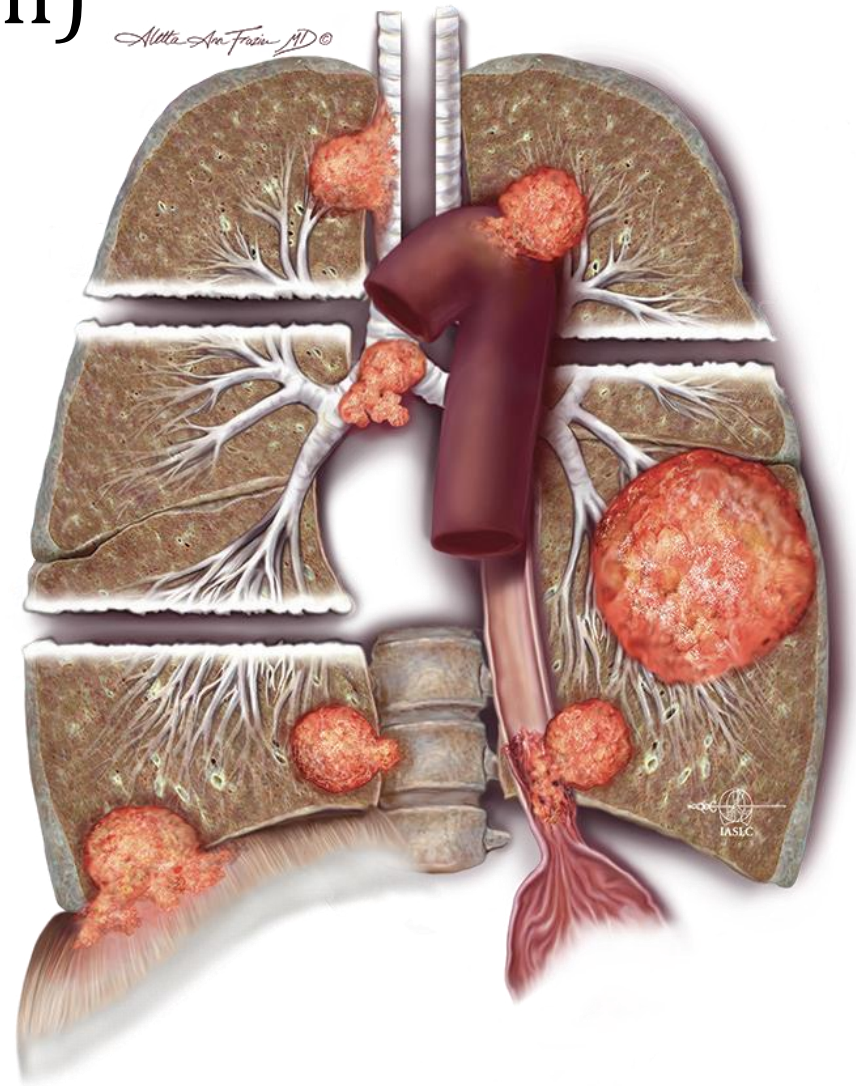
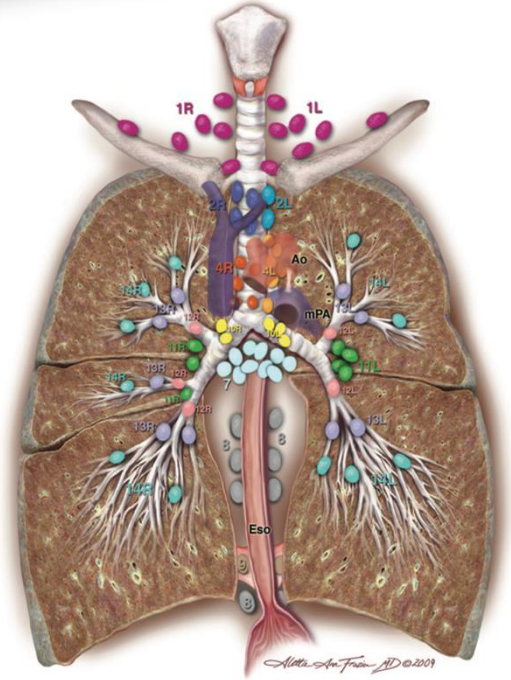
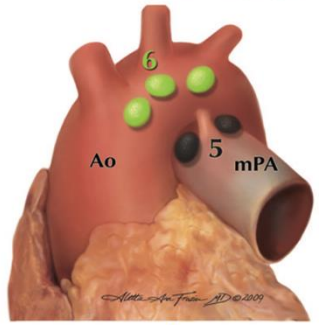
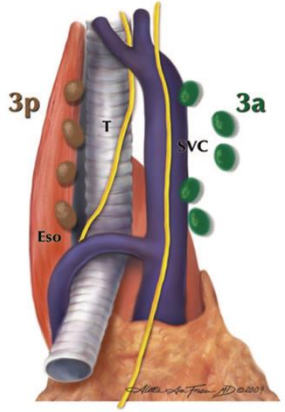


Figure. Courtesy of International Association for the Study of Lung Cancer.







Supraclavicular zone

1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone

- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone

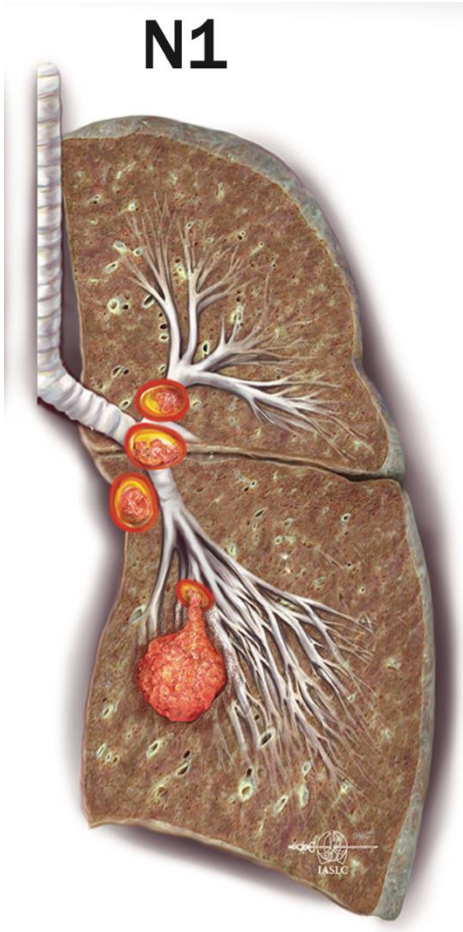
- 10 Hilar
- 11 Interlobar

Peripheral zone

- 12 Lobar
- 13 Segmental
- 14 Subsegmental

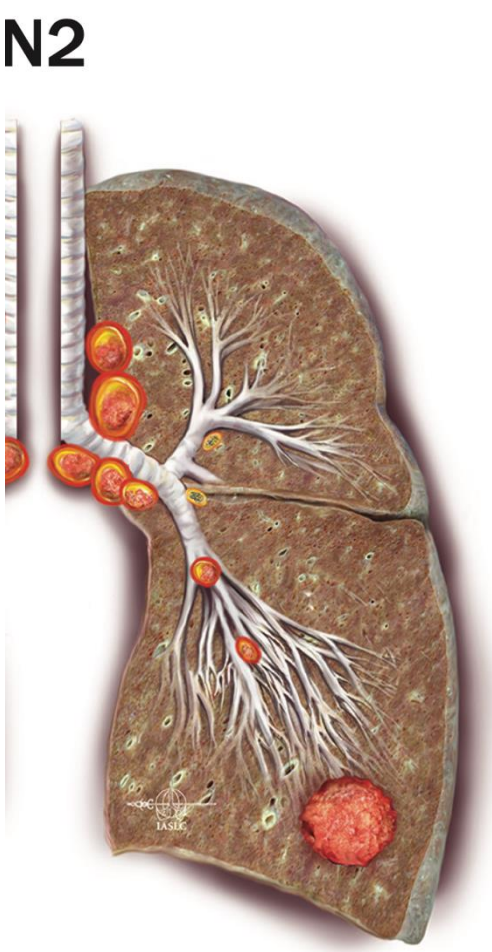
N Stage

N1



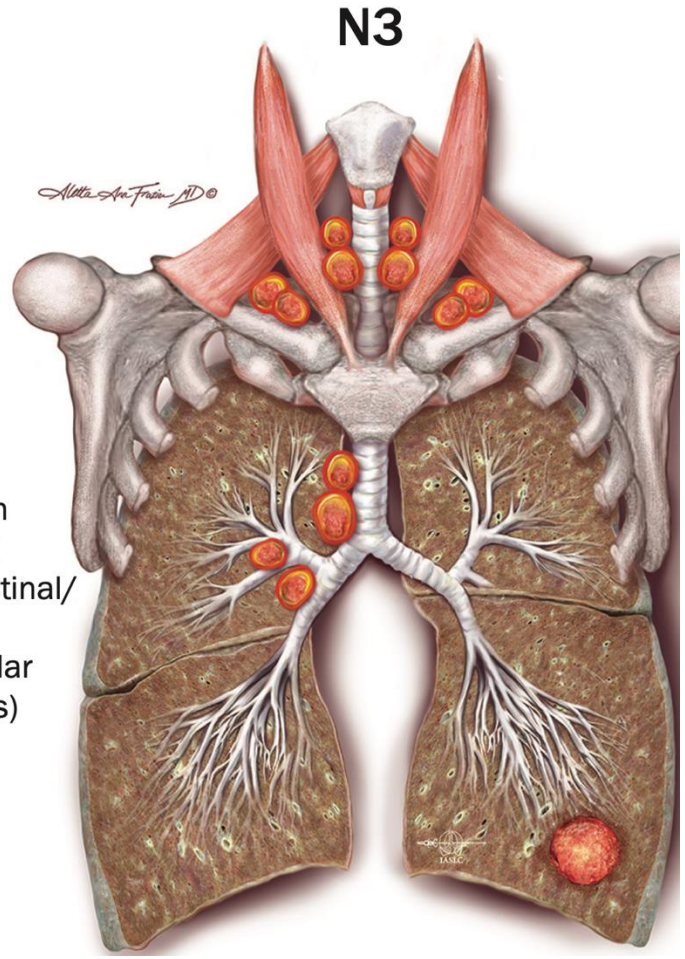
Metastasis in ipsilateral intrapulmonary/ peribronchial/ hilar lymph node(s), including nodal involvement by direct extension

N2



Metastasis in ipsilateral mediastinal and/or subcarina lymph node(s) associated with N1 disease

N3



Metastasis in contralateral hilar/mediastinal/ scalene/ supraclavicular lymph node(s)

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0

STAGE	T	N	M
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0

Mediastinal Staging – PET/CT

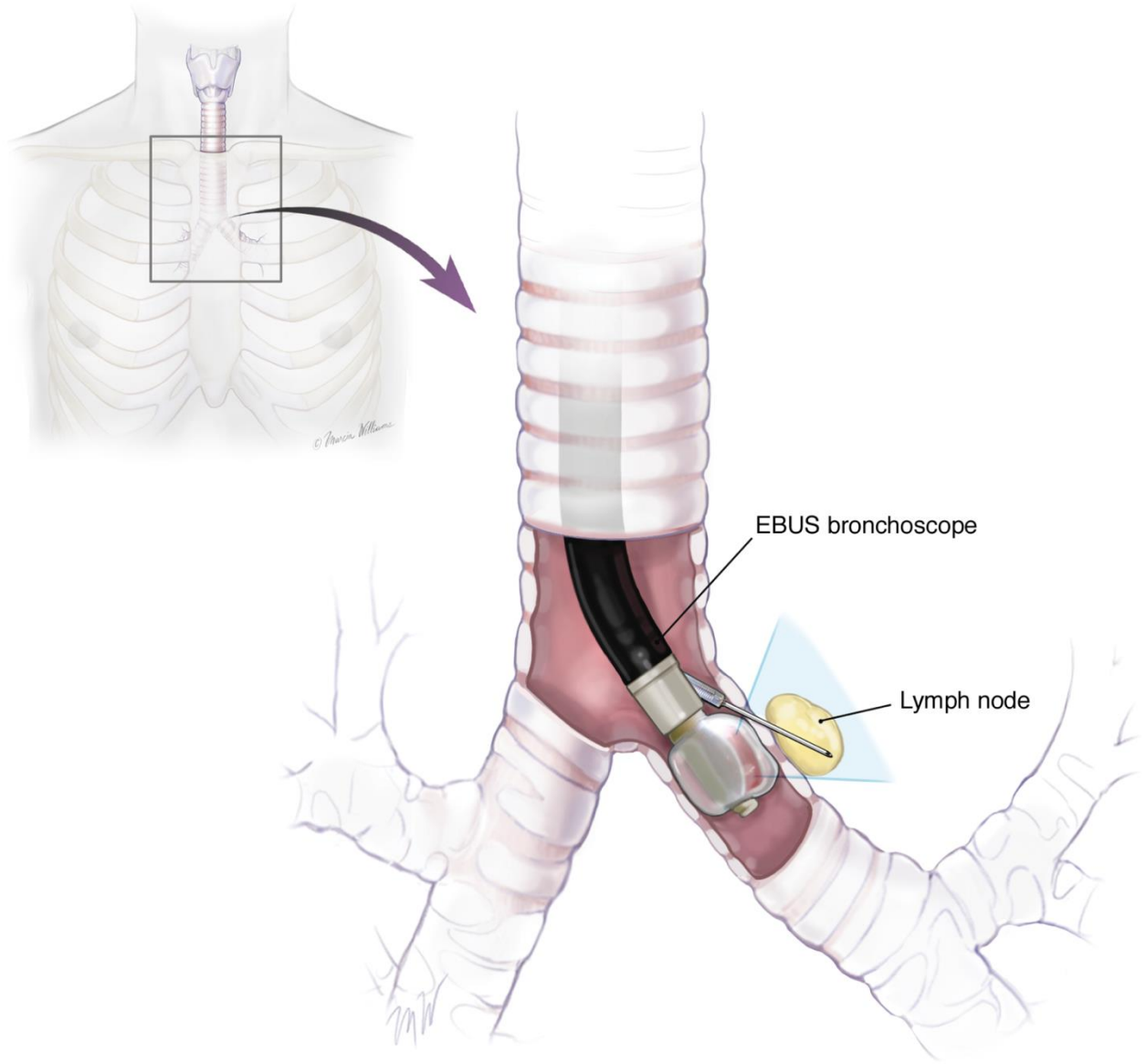
- Accurate for diagnosis of cancer in SPN
  - Sensitivity 96%, specificity 88%, accuracy 94%
- Accurate at excluding distant metastatic disease
  - Except for brain metastases
- Lacks accuracy to replace invasive mediastinal staging for NSCLC
- ACOSOG Z0050 trial:
  - Sens 61%, Spec 84%, NPV 87%, PPV56%
  - Positive PET needs to be verified pathologically
  - Negative PET does not preclude N2 or N3 disease

Mediastinal Staging

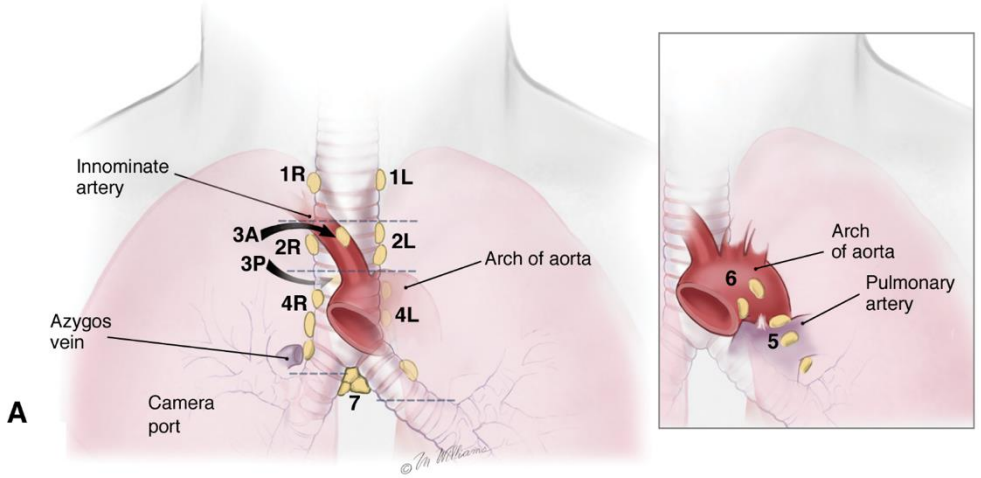
Invasive staging needed for

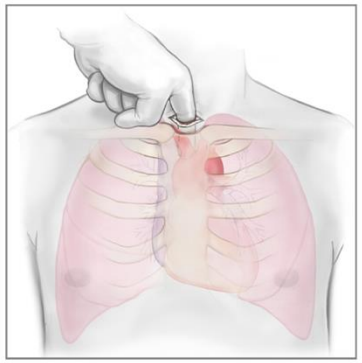
- Tumor size > 2 cm
- Central tumors
- Synchronous primaries, Contralateral lesions
- Aggressive pathology / features
- PET+ nodes
- Prior to pneumonectomy

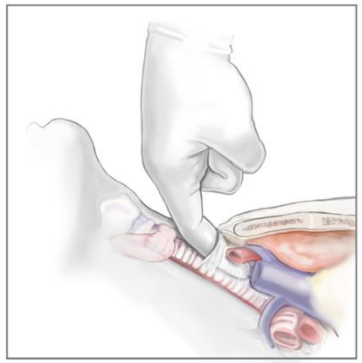
Endobronchial Ultrasound (EBUS)

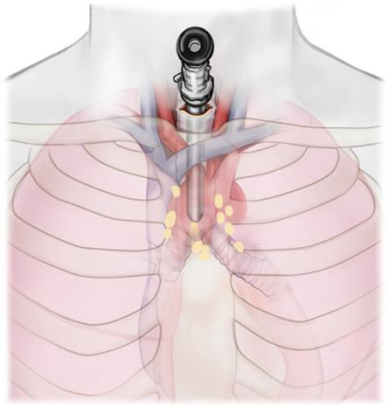


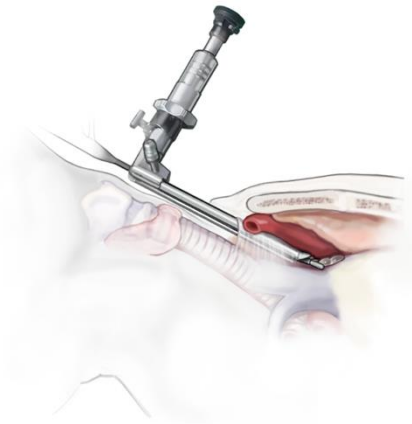
Mediastinoscopy



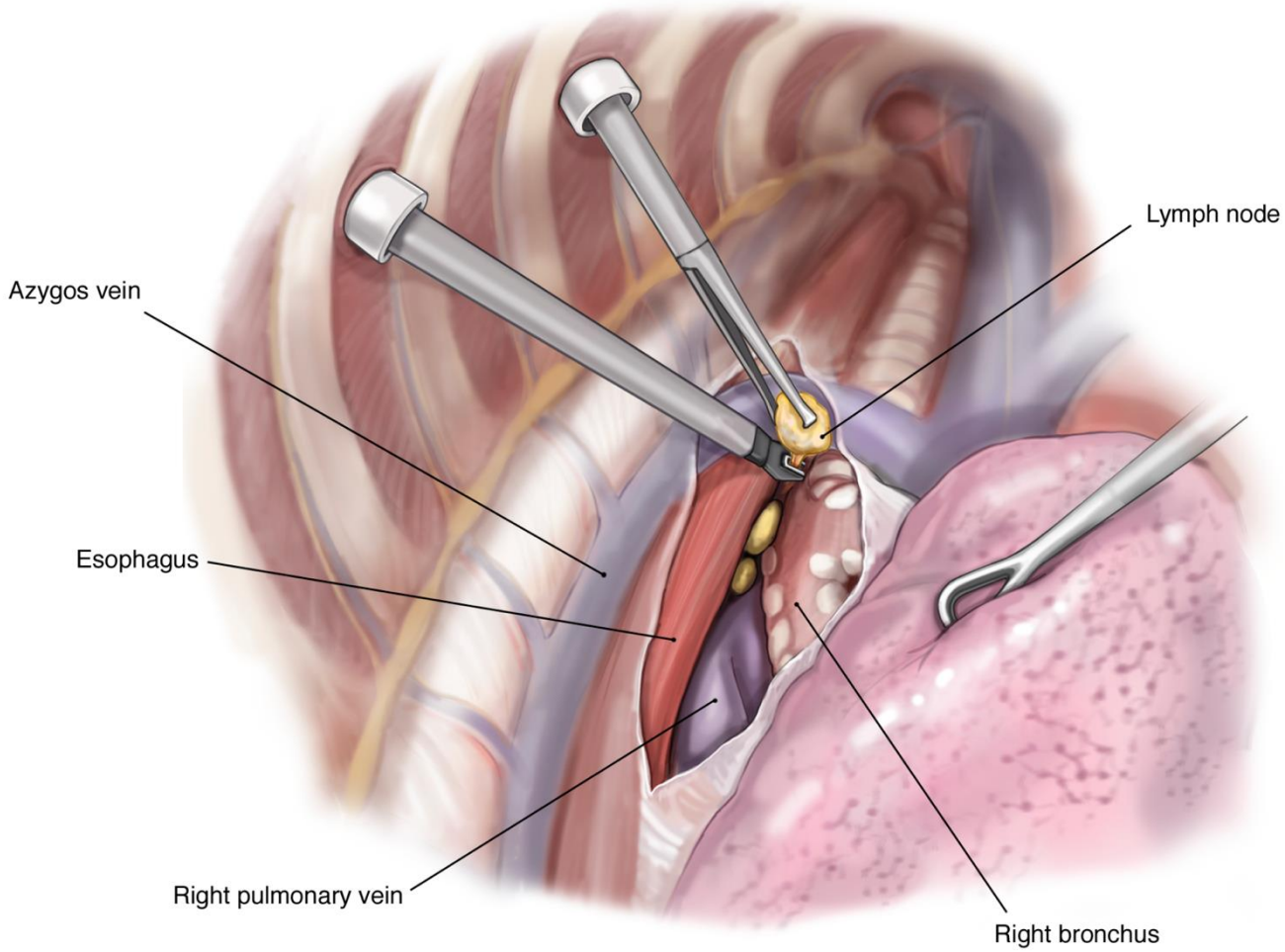








Thoracoscopic Lymph Node Dissection



Simplified Treatment for Lung Cancer (NSCLC)

- Stage I
  - Surgery
- Stage II
  - Surgery

- Adjuvant: > 4 cm
- Increasing evidence for neoadjuvant Tx

- Stage III A/B-N2
  - Neoadjuvant → Surgery → *(+/- Adjuvant)*
- Stage IIIC / IV
  - Definitive chemo/immuno / RT

Determining Operability

- Functional operability
  - (i.e. medical fitness)

- Oncologic operability
  - Cell type
  - Metastatic disease
  - Lymph node invasion, bulky disease, etc

- Resectability

Determining Operability

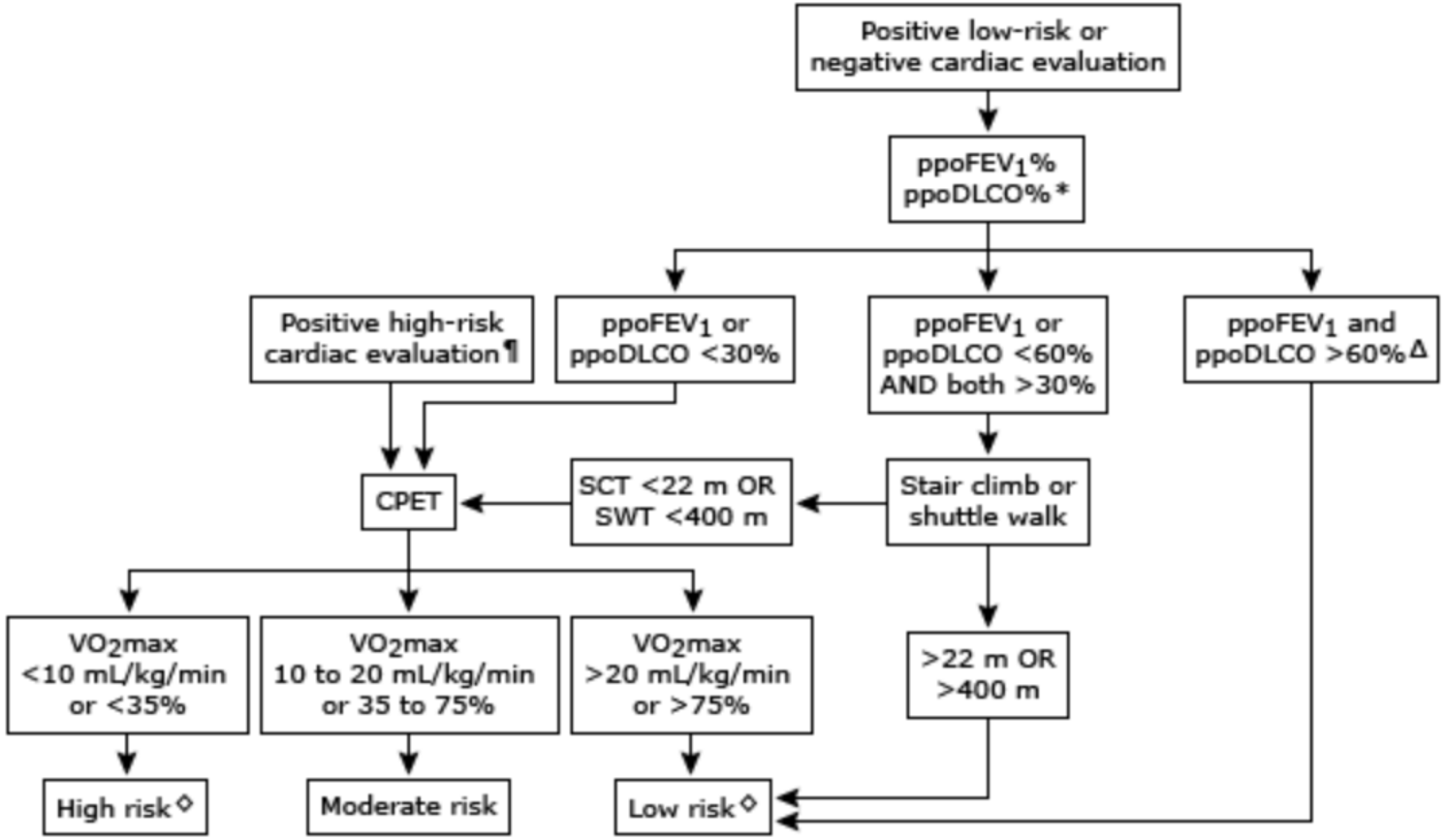
FEV_1

- Correlates well with the degree of respiratory impairment in patients with COPD
- Preoperative FEV_1 (<60 percent predicted) strongest spirometric predictor of postoperative complications.

Diffusing capacity

- Retrospective studies have reported that actual DLCO (as a percent of the predicted value) and predicted postoperative DLCO are the most important predictors of mortality and postoperative complications in patients undergoing resection

Determining Operability

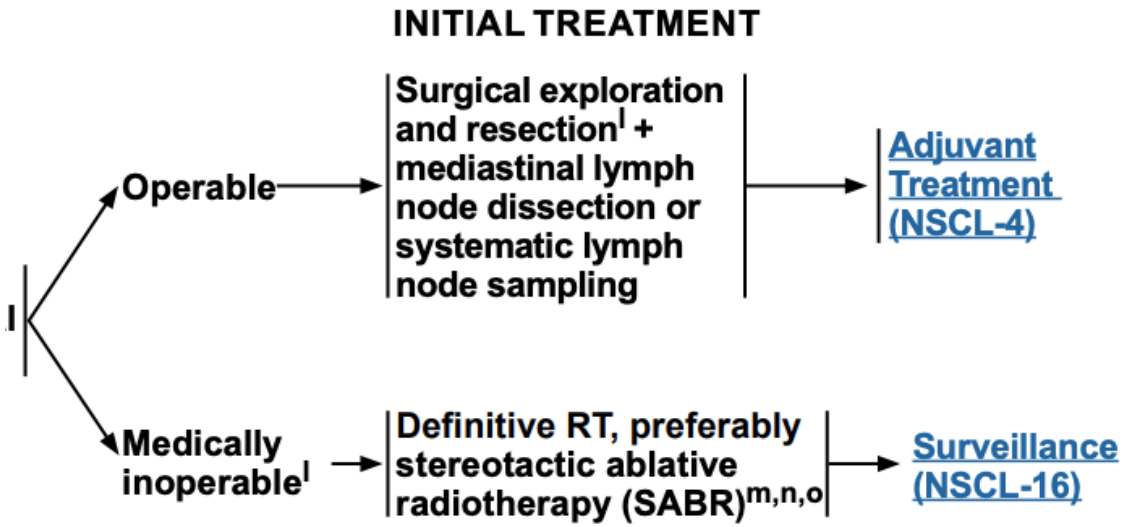


VO2max = **maximum amount of oxygen that a patient can utilize during intense or maximal exercise**. Often considered the best indicator of cardiovascular fitness and aerobic endurance.

Determine Operability

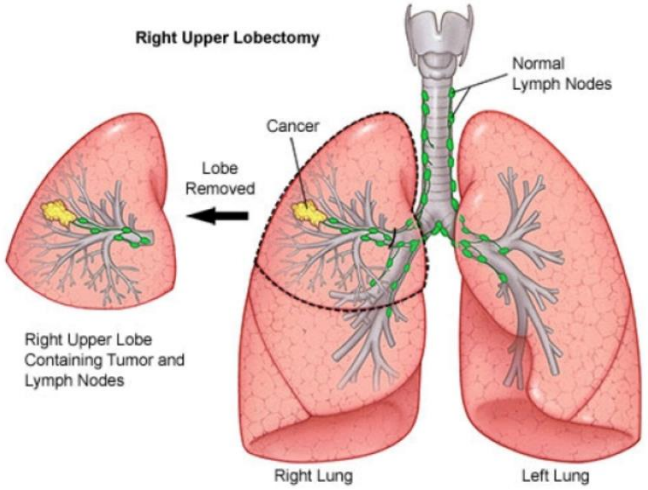
- If FEV 1 and DLCO are both >80% predicted based on age and height, then surgery can follow without expected increased perioperative risk.
- If less than 80%, calculate postoperative predictive FEV1
- PPO FEV_1 = preoperative FEV_1 x (1 – a/b) where "a" is the number of segments to be resected and "b" is the total number of unobstructed segments (total number of segments is 19 [10 on the right and 9 on the left]).
- If ppo FEV1 is 30% or less, than patient is considered high risk.
- If values don't seem to match functional status, can check CPET.
- Stair climbing and walking tests are adjuncts that can inform decision making

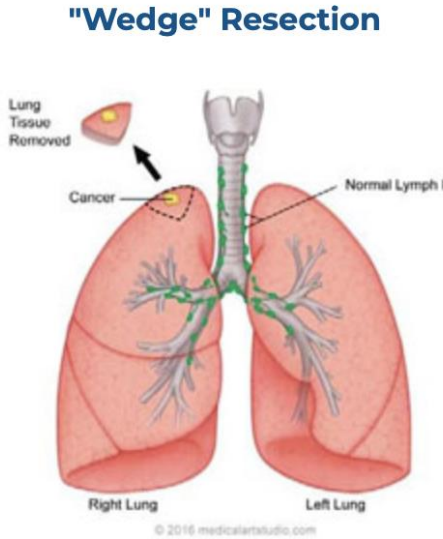
Early Stage Treatment



Which operation to perform for early-stage NSCLC?

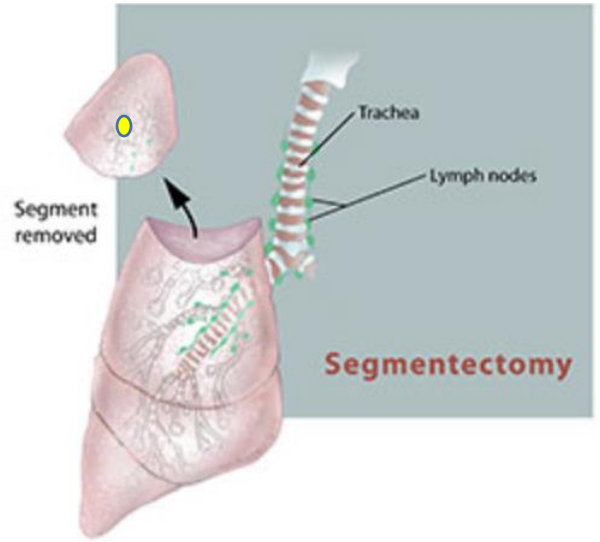
Lobar Bronchus, Artery and Vein Divided





Lung Parenchyma divided only

Individually ligated segmental vein, artery and bronchus



Segmentectomy

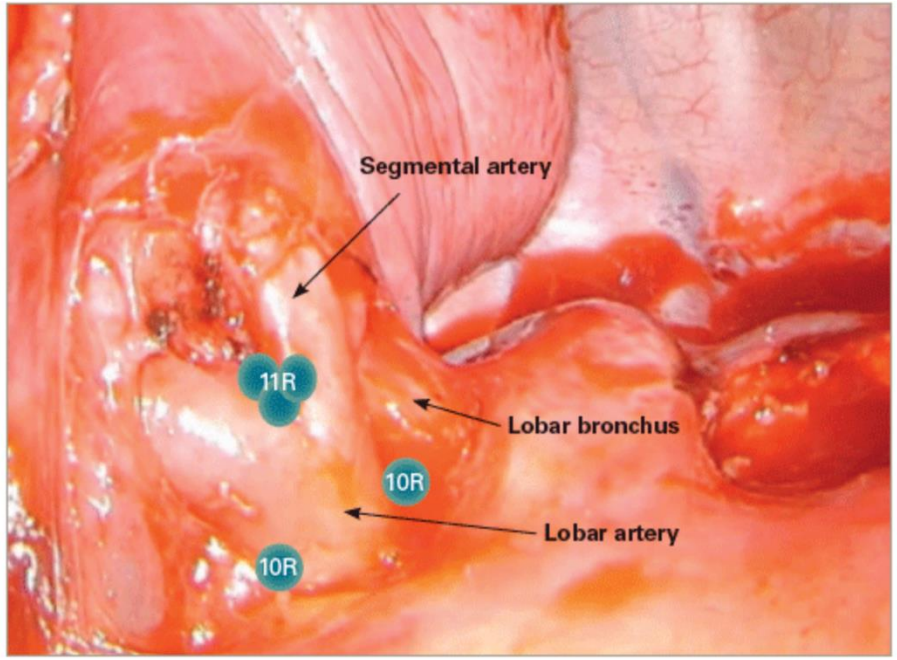


Figure 2. Segmentectomy— Anatomic dissection of segmental structures involves sampling of hilar (10R), interlobar (11R), and lobar (12R, not shown) lymph nodes. If the patient can tolerate it, conversion to lobectomy is performed if intraoperative pathology assessment reveals that these lymph nodes contain cancer.

R = right.

Minimally Invasive Surgery for Early-Stage Lung Cancer: From Innovation to Standard of Care

By Abby White, DO and Scott J. Swanson, MD

November 15, 2016

cancernetwork
Cancer Network
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Randomized Controlled Trials: JCOG

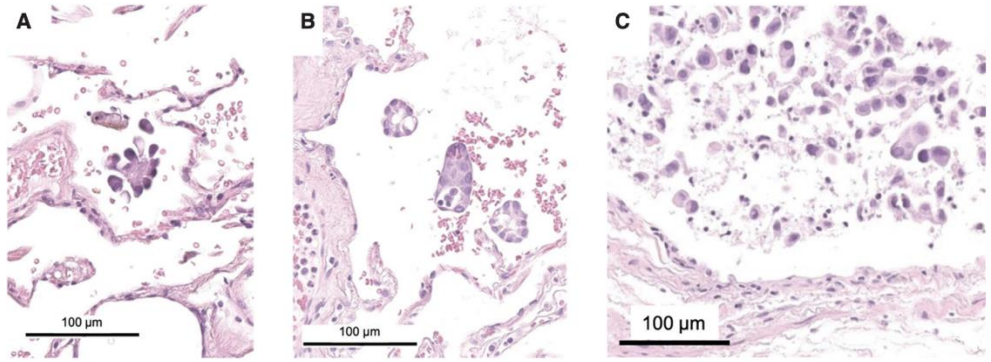
- JCOG 0802 10
  - Phase III Trial to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter ≤2 cm) peripheral NSCLC
  - 1106 patients accrued from 71 institutions.
  - 51% of tumors had a ground glass component
  - Median follow-up of 7 yrs
    - 5y OS 91.1% for lobectomy and 94.3% for segmentectomy ($p < 0.0001$ for noninferiority and $p = 0.008$ for superiority).
    - Improved overall survival was observed consistently across all subgroups
    - DFS was not significantly different between the two groups.
      - More locoregional recurrences occurred in the segmentectomy group (11% vs. 5%, $p = 0.0018$)
    - Segmentectomy patients were more likely to be treated with additional surgery for relapse than those patients who underwent index lobectomy
      - BUT more likely to have ipsilateral or contralateral mediastinal nodal failure than those patients undergoing lobectomy (11% vs. 5%, $p = 0.0018$)
    - Excluded basilar segmentectomy, patients with multiple nodules and inner 2/3 of the lung lesions.

Randomized Controlled Trials: CALGB

- CALGB 140503
  - US-accrued trial between 2007 and 2017
  - Patients with lung nodules ≤2 cm (clinical T1aN0) (excl GGO)
  - Intraoperative mediastinal and hilar lymph nodes were sampled
    - if negative →randomized to sublobar resection or lobectomy, with the type of sublobar resection at the discretion of the surgeon (wedge vs. segmentectomy).
  - 697 patients, 357 undergoing lobectomy, and 340 undergoing sublobar resection.
  - For the primary endpoint of disease-free survival
    - Sublobar resection was noninferior to lobectomy (p = 0.0176, HR: 1.01).
  - Similar 5yr disease-free survival (63.6% vs. 64.4% for sublobar resection and lobectomy, respectively)
  - 5-year overall survival was 80.3% for sublobar resection and 78.9% for lobectomy (p = 0.014 for noninferiority)
  - No difference in cancer related deaths.
  - Recurrence rates were similar between the two groups at 30%
  - The locoregional recurrence rate was higher in the sublobar resection group (10% vs. 13.4% p = 0.2011) but this did not meet statistical significance.

Does histology make a difference?

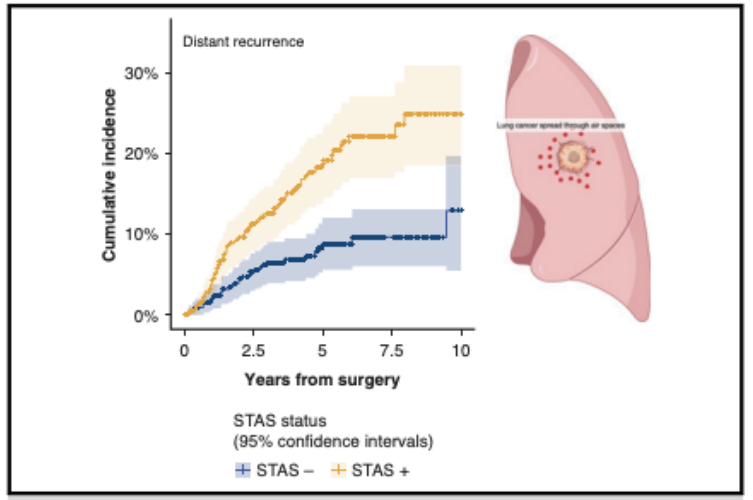
- Carcinoma in-situ
- Minimally invasive adenocarcinoma
- Lepidic-predominant adenocarcinoma
- Spread of Tumor Through Airspaces (STAS)?



Khalil HA, Shi W, Mazzola E, Lee DN, Norton-Hughes E, Dolan D, Corman S, White A, Sholl LM, Swanson SJ. Analysis of recurrence in lung adenocarcinoma with spread through air spaces. J Thorac Cardiovasc Surg. 2023 Feb 16:S0022-5223(23)00165-4. doi: 10.1016/j.jtcvs.2023.01.030. PMID: 36935300.

STAS

- Form of invasion in lung adenocarcinoma wherein tumor cells extend beyond the tumor edge but within the air spaces, or lung parenchyma itself
- Incidence of STAS in adenocarcinomas reported between 15-60%
- Marker for increased risk of recurrence with sublobar resection
- Locoregional recurrence or distant recurrence?



STAS is associated with both locoregional and distant recurrence in lung adenocarcinoma. Figure created with http://biorender.com.

Khalil HA, Shi W, Mazzola E, Lee DN, Norton-Hughes E, Dolan D, Corman S, White A, Sholl LM, Swanson SJ. Analysis of recurrence in lung adenocarcinoma with spread through air spaces. J Thorac Cardiovasc Surg. 2023 Feb 16:S0022-5223(23)00165-4. doi: 10.1016/j.jtcvs.2023.01.030. PMID: 36935300.

Nonoperative Candidates

- Stereotactic Body Radiotherapy (SBRT)
- Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR
- Poor accrual to RCTs for comparison

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  - Surgery
- Stage II
  - Surgery
- Stage III A/B-N2
  - Neoadjuvant → Surgery → *(+/- Adjuvant)*
- Stage IIIC / IV
  - Definitive chemo/immuno / RT

Phase III Trials for N2

Study	Registry No.	Stage	No. of Patients	Experimental Arm	Control Arm	Primary Endpoint
KEYNOTE-671	NCT03425643	II, IIIA, IIIB	786	Pembrolizumab + cCT, 4 cycles – pembrolizumab (adj), 13 cycles	Placebo + cCT - Placebo	EFS, OS
CheckMate-816[106]	NCT02998528	IB-IIIA	358	Nivolumab + cCT, 3 cycles or nivolumab + ipilimumab	CT	EFS, pCR
IMpower030	NCT03456063	II-IIIA-IIIB (T3N2)	450	Atezolizumab + cCT, 4 cycles - atezolizumab (adj), 16 cycles	Placebo + cCT - SoC	MPR, EFS
CheckMate-77T	NCT04025879	II-IIIB	452	Nivolumab + cCT, 4 cycles – nivolumab (adj), 1 year	Placebo + cCT - Placebo	EFS
AEGEAN	NCT03800134	II-IIIB	800	Durvalumab + cCT, 4 cycles – durvalumab (adj), 12 cycles	Placebo + cCT - Placebo	MPR, EFS

Abbreviations: adj, adjuvant; cCT, combined chemotherapy; CT, chemotherapy; EFS, event-free survival; MPR, major pathologic response; pCR, pathologic complete response; OS, overall survival, SoC, standard of care.

Phase III Trials for N2

CheckMate 816: Improved EFS (HR=0.68), MPR (37%) and pCR (24%) compared to chemo alone; nivolumab arm without increased toxicity

Keynote 671 (perioperative pembro): Improved EFS (HR=0.59) and MPR 30% and pCR 18%

Aegean: (durvalumab): Improved EFS (HR=0.68); MPR (33%); pCR (17% - 13% difference with control arm)

CheckMate-77T (perioperative nivo): Improved EFS (HR=0.58); MPR (35%) and pCR (25%)

Study	Registry No.	Stage	No. of Patients	Experimental Arm	Control Arm	Primary Endpoint
KEYNOTE-671	NCT03425643	II, IIIA, IIIB	786	Pembrolizumab + cCT, 4 cycles – pembrolizumab (adj), 13 cycles	Placebo + cCT - Placebo	EFS, OS
CheckMate-816[106]	NCT02998528	IB-IIIA	358	Nivolumab + cCT, 3 cycles or nivolumab + ipilimumab	CT	EFS, pCR
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Definition of 'Unresectable' Stage III

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY¶	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE§	POTENTIALLY RESECTABLE*§	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined

¶**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed

§Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Post-induction Imaging and Re-staging

- PET/CT 3-4 weeks post-induction
  - Rule out metastatic disease
  - Assess metabolic response to induction regimen
    - SUVmax of tumor / nodes NOT used as operative decision point
- Mediastinal re-staging is NOT *routinely* performed
  - ↓ EBUS sensitivity (64%)
  - Redo mediastinoscopy performs poorly
  - Persistent N2 disease (if resectable) is not a decision point
- IV contrast CT Chest preferred for operative planning

Post-induction Surgical Resection

- Typically wait 4-6 weeks post-induction for surgery
  - May wait longer to ensure patient is fit for surgery
- Start thoracoscopically on all cases
  - Rule out pleural disease, assess resectability
- Majority of cases are achieved minimally invasive (60-80%)
  - Depends on T size, location, involvement of structures
  - Oncologic principles and safety > > Minimally invasive surgery

Post-induction Surgical Resection

- Bulky nodes are not always cancer
  - "Nodal immune flare" (NIF) – response to IO
  - Typically find immune cell infiltration and granulomas
- Always complete systematic LN dissection
- Post-IO can be more challenging than induction chemo +/- RT
  - NIF, post-treatment inflammation
  - "sticky" or fibrotic tissues, loss of tissue planes
- PORT is not routinely used for completely resected N2 disease

Conclusions

- Accurate staging is critical in guiding treatment
- Surgery remains the gold standard for early-stage lung cancer
  - Sublobar resection is at least equivalent to lobectomy for peripheral T1aN0 cancers when the endpoint is OS
    - Higher risk of locoregional recurrence??
  - Sublobar resection needs to include sampling of appropriate hilar and mediastinal lymph nodes (N1(1) and N2(3)).
  - Histology may be a key confounder and more data is needed
- SBRT is a good second-line option for inoperable early stage patients.

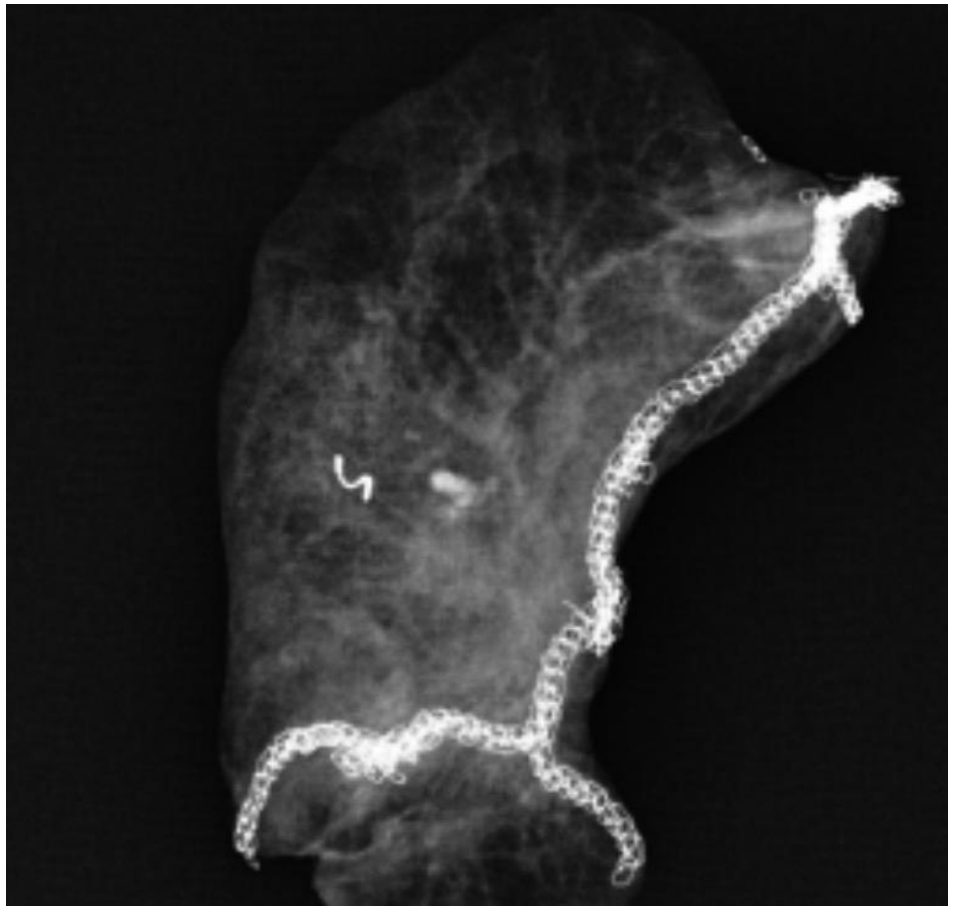
Conclusions

- Neoadjuvant or perioperative chemoIO followed by surgery remains the best available option for Stage III-N2 disease
- Careful selection of patients by evaluation of operability and resectability
- Surgeons should be involved early and throughout treatment
- Current alternative local therapy (ie RT) are poorly studied in patients with resectable NSCLC after chemoIO

From Diagnosis to Resection

Single Anesthesia Event

Single Anesthesia Event



Thank You

BRIGHAM HEALTH

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Mass General Brigham