Lung Cancer
Fresh Approaches

PIERCE COUNTY CANCER SURVIVORSHIP CONFERENCE

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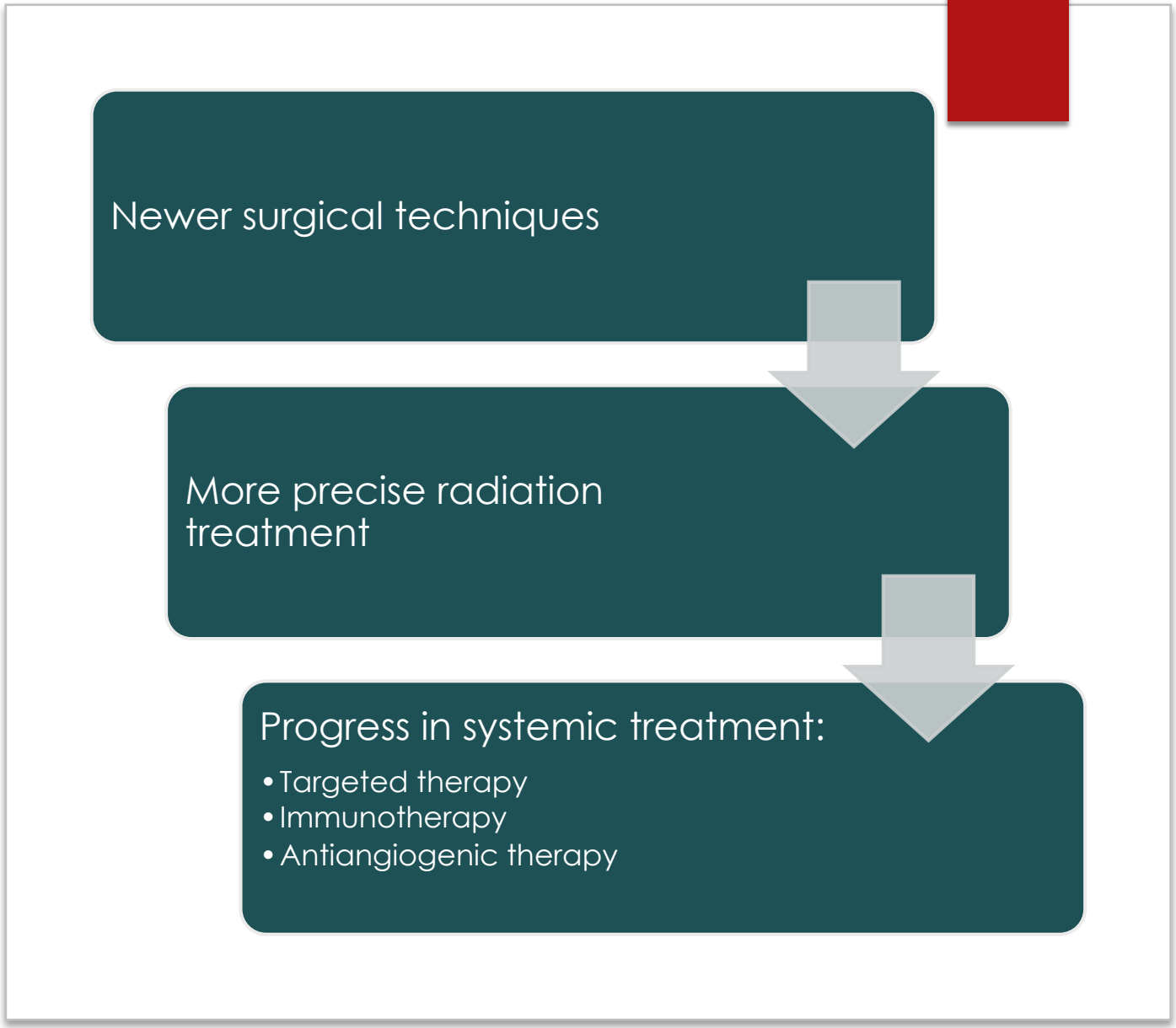
NORTHWEST MEDICAL SPECIALTIES

Surviving Lung Cancer

- Living with, through and beyond lung cancer
- Lung cancer survivorship has become a reality

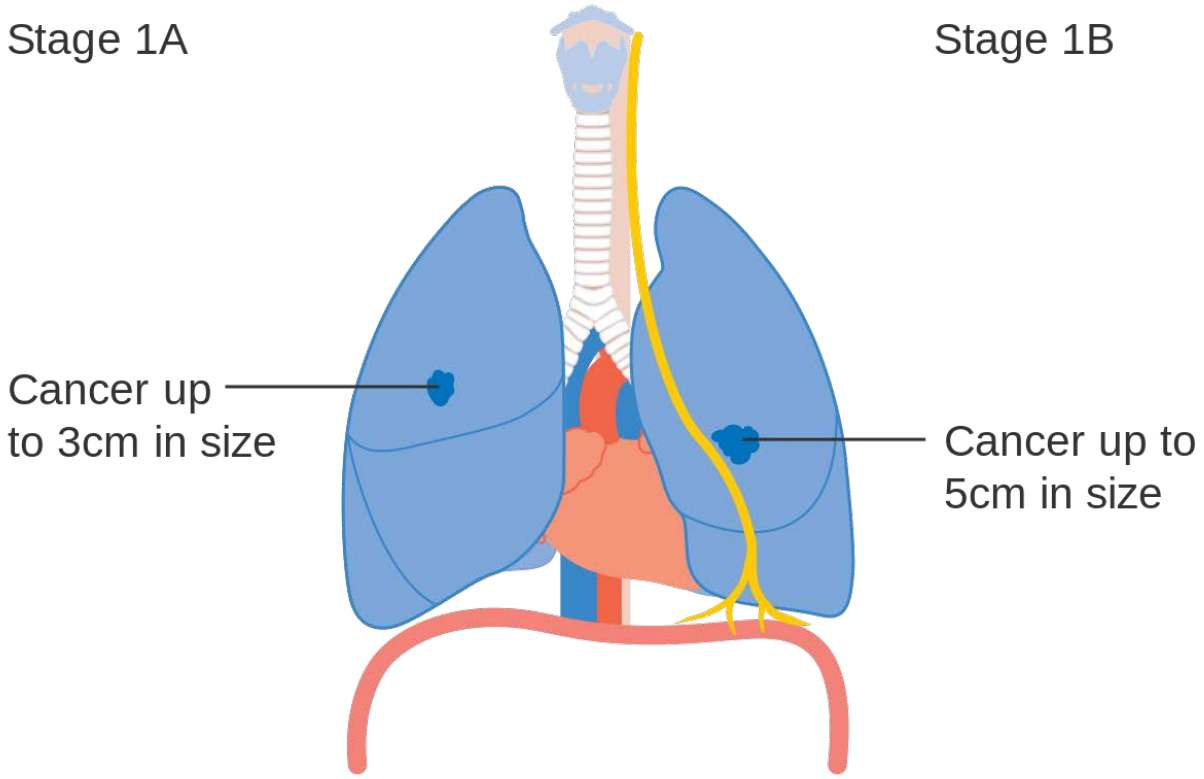
Lung Cancer Treatment has Evolved



Stage and survival at the time of diagnosis

Stage	% of patients	5-year survival
I	10%	> 60%
II	20%	30-50%
IIIA/IIIB	30%	5-30%
IV	40%	<5%

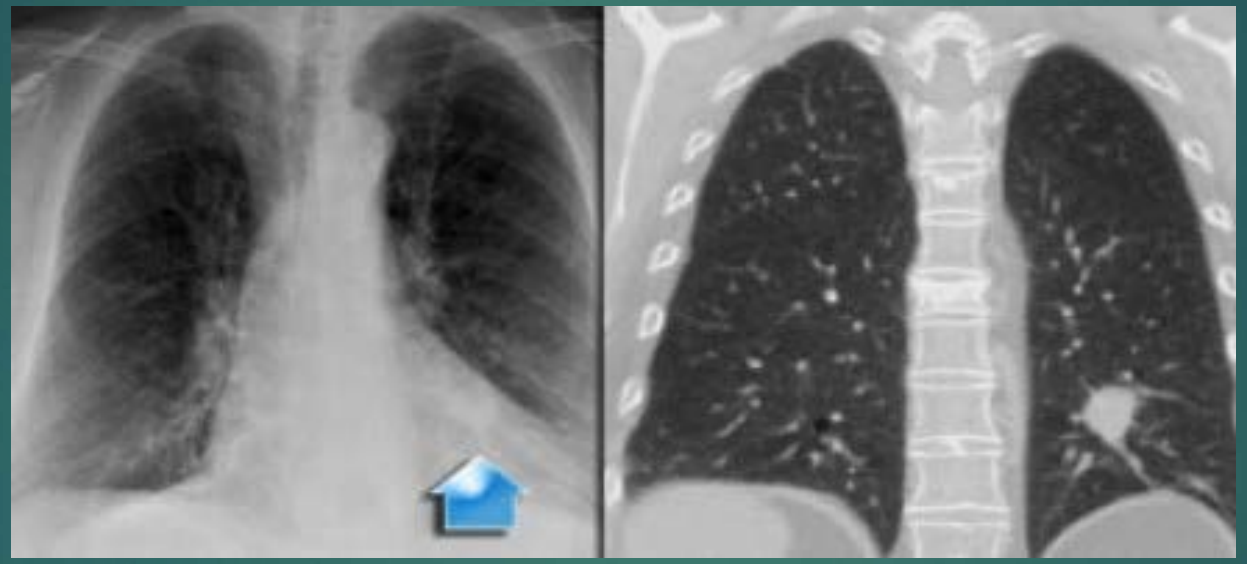
Stage I NSCLC cancer



Stage I NSCLC cancer

CANCER RESEARCH UK / WIKIMEDIA COMMONS

T1 Tumor
Size ≤ 3 cm



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Stage I NSCLC

Tumor size: 0- 4 cm

- Tx, T0, Tis, T1a (<1 cm), T1b (1-2 cm), T1c (2-3 cm), T2a (3-4 cm)
- Lymph nodes are not involved
- No distant metastasis

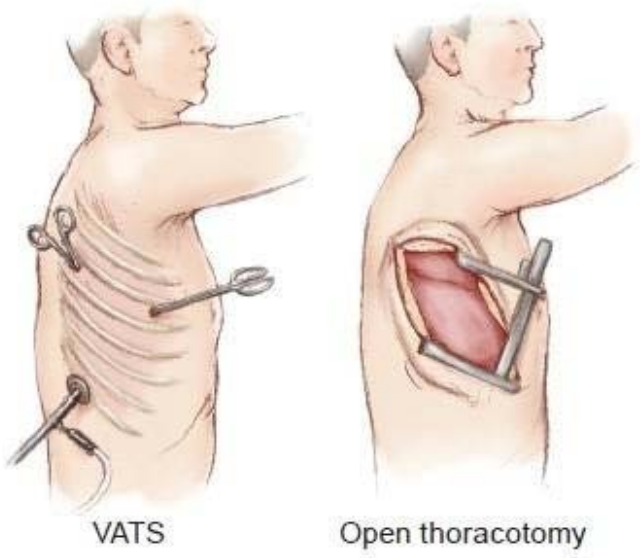
Treatment for Stage I NSCLC is local therapy

- Surgery
- Radiation
- No systemic therapy (no chemotherapy) after local therapy

Minimally Invasive Surgery

- Robotic and video assisted thoracoscopic surgery vs open thoracotomy
  - Incisions are smaller, less tissue damage, less blood loss
    - Less pain
    - Less time in the operating room
    - Less recovery time, less hospital time, less cost
    - Smaller scar
    - Reduced chance for post operative wound complication
  - More accurate staging: 30% upstaged (worse than expected), 12% downstaged (better than expected)*

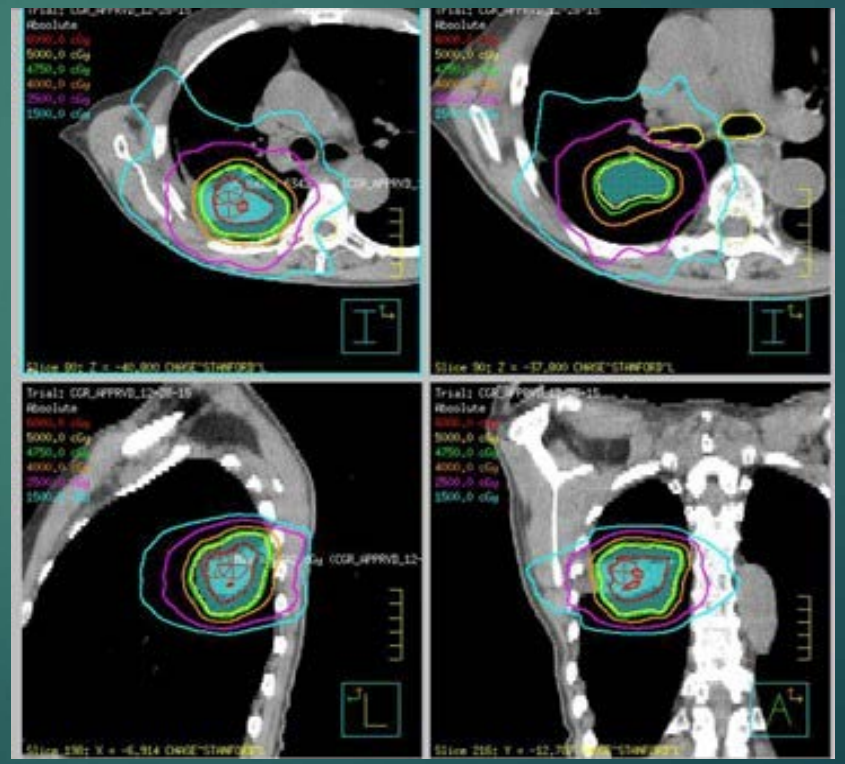
*JTO 8(9), 9/16 Velez-Cubian et al



Stereotactic Body Radiation Therapy

- Medically inoperable early stage NSCLC
- RTOG –0236 Survival rate 55% at 3 years, 97% rate of tumor control
- Metastatic disease: Patients with < 3 metastatic lesions
- Less toxicity
- Less fractions (doses, example 5 treatments instead of 34)
- Complications:
  - inflammation at the treatment site that looks like pneumonia
  - Bronchial injuries if too central
  - Chest wall toxicity: pain, fracture

Stereotactic radiosurgery



Courtesy of: Washington University School of Medicine Department of Radiation oncology
Courtesy of: Dr Hak Choy

Stage II Lung cancer

Stage II NSCLC

Tumor size: 3-5 cm in size or lymph node involvement(N1)

- IIA T2b (4-5 cm)N0
- IIB T1a-T2b (1-5 cm) N1 or T3 (5-7 cm)N0
- Simpler said, a tumor up to 5 cm, and positive N1 lymph node or a large tumor 5-7 cm without N1
- No distant metastasis

Treatment is local(surgery/radiation) and systemic(chemotherapy)

T2 Tumor

3-5 cm or invasive to other structures

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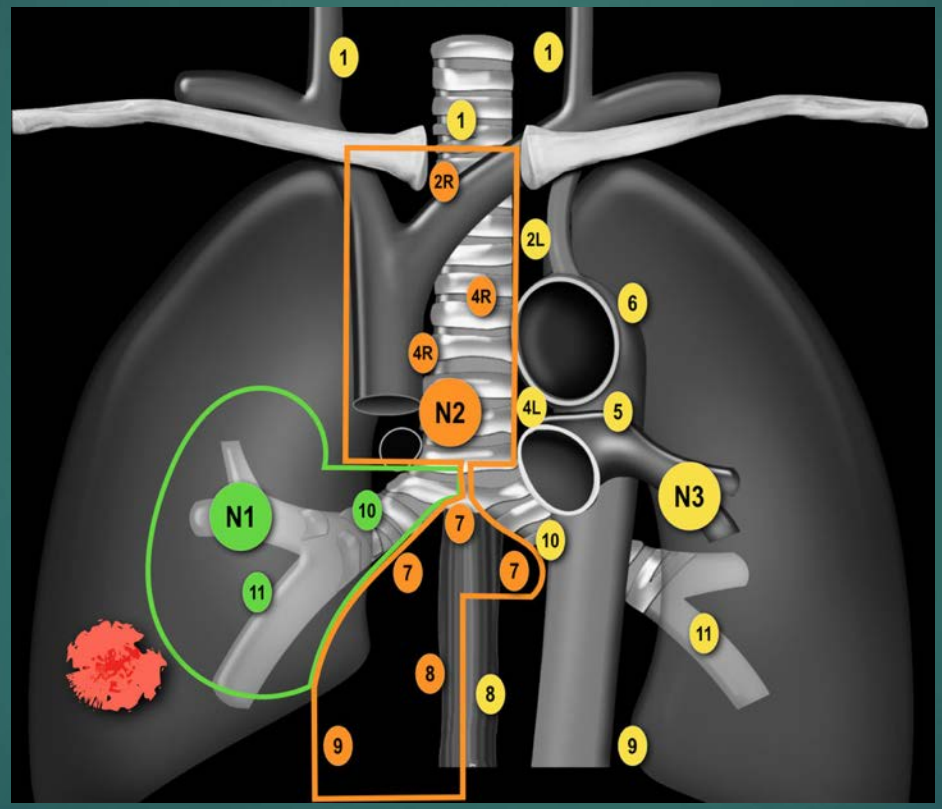
N1 Lymph Nodes



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Chemotherapy after surgery

- Adjuvant (after surgery) chemotherapy for stage I-III lung cancer
- Not recommended for stage IA
- 5-10% improvement in 5 year survival

STUDY	Chemo	# pts	5 yr OS Chemo	Observe	P value
IALT	PE,PN, PV	1867	44%	40%	0.03
JBR.10	PN	482	69%	54%	0.002
ANITA	PNP	840	+8.6%		0.017

- *Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010; 28:35.*
- *Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010; 28:29.*
- *Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006; 7:719.*

Choice of Chemotherapy

- Chemotherapy selection depends upon histology
  - Adenocarcinoma: cisplatin/pemetrexed
  - Squamous cell carcinoma: Cisplatin/navelbine, cisplatin/docetaxel or cisplatin/gemitabine
- Chemotherapy given after surgery
- 4 cycles of treatment

Stage III Lung Cancer

Stage IIIA

- T1a – T2b N2 (1-5 cm tumor)
- T3 N1 (5-7 cm)
- T4 N0-N1 (>7 cm or invading structures)

T3 Tumor

- 5-7 cm
- Separate tumor nodules in the same lobe
- Tumor invading chest wall, pericardium or phrenic nerve

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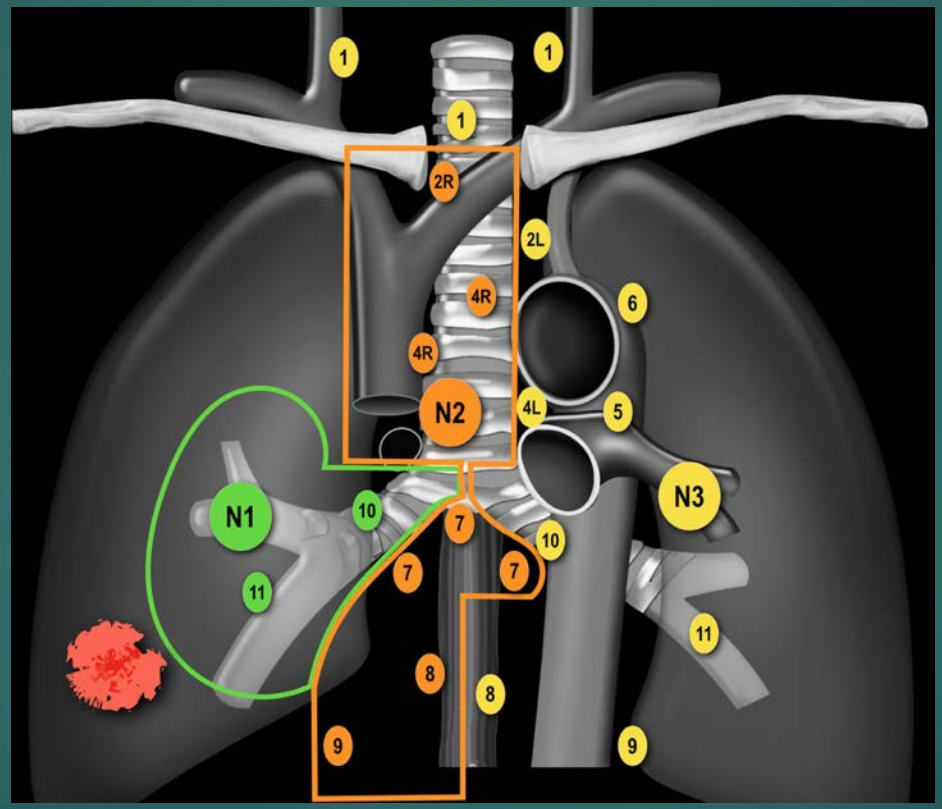
N2 Lymph Nodes



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Stage IIIA Treatment

- Concurrent chemoradiotherapy is the standard of care
  - Chemotherapy 4 cycles
  - Radiation 7 week course
- Undetected N2 disease prior to surgery is followed by adjuvant chemotherapy
- Neoadjuvant chemotherapy followed by surgery, select circumstances
  - Single station N2, T< 3m, responded to therapy, lobectomy resection feasible

Stage IIIB and Stage IIIC

Stage IIIB

- T2a – T2b N3
- T3N2
- T4N2

Stage IIIC

- T3N3
- T4N3

T4 Tumor

- ≥7 cm or invasive to major structures
- Separate nodule in a different ipsilateral lobe
- Invades diaphragm, mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, or esophagus

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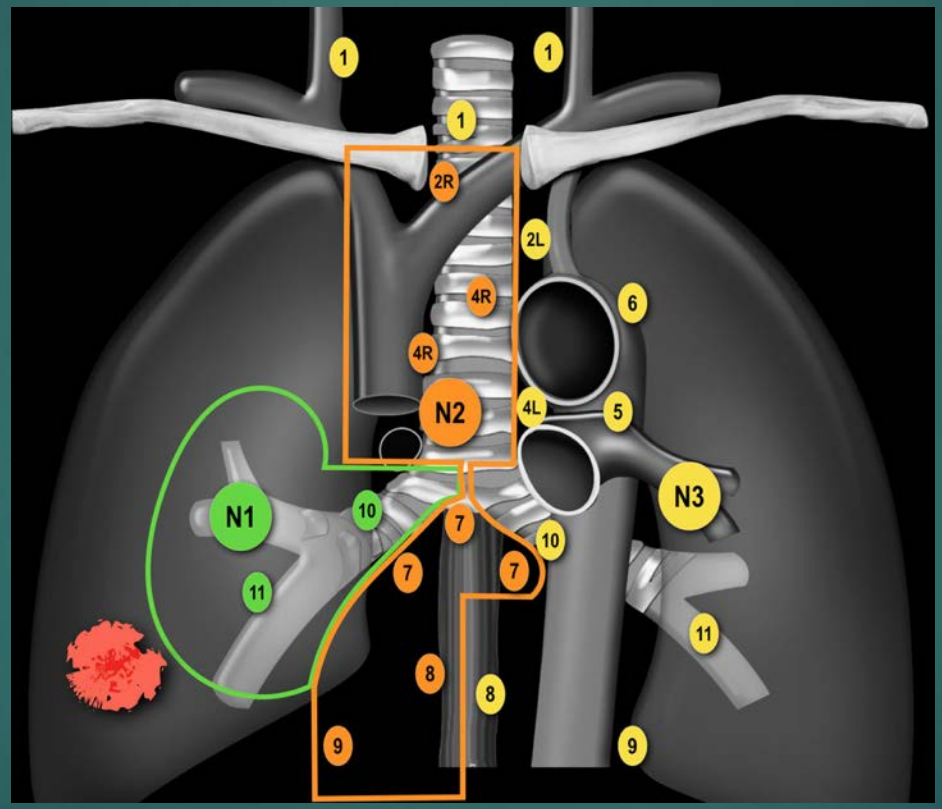
N3 Lymph Nodes



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New Approach in Stage III lung cancer

- Unresectable stage III NSCCA treated with concurrent chemoradiotherapy followed by 12 months of durvalumab
- Historical 5 year OS (overall survival) for stage III lung cancer is 5-30%
- PACIFIC study NEJM 2017, 2018
  - 700 patients randomized to observation vs durvalumab
  - Progression free survival 5.6 months vs 16.8 months
  - 12 month survival rates 75% vs 83%
  - 24 month survival rates 55% vs 66%
  - 3 year survival: 44% w placebo vs 57% with durvalumab

- N Engl J Med. 2018;379(24):2342. Epub 2018 Sep 25
- N Engl J Med. 2017;377(20):1919. Epub 2017 Sep 8

Stage IV Lung Cancer

Survival Benefit for Treatment

- Standard chemotherapy compared to supportive care
  - 2714 patients evaluated in a meta-analysis
  - Standard chemotherapy (4-6 cycles)
  - 29% vs 20% one-year survival

Stage IV NSCCA

Factors influencing therapy

Immunohistochemistry	Nonsquamous Squamous cell carcinoma
Molecular characterization of the tumor	Somatic driver mutations predict sensitivity to specific inhibitors
PDL-1 testing	

Testing prior to treatment

- Determine histology and site of origin
  - Squamous cell carcinoma
    - PDL-1 testing
  - Non- squamous carcinoma
    - PDL-1 testing
    - Molecular testing
      - EGFR/ALK/ROS1/BRAF

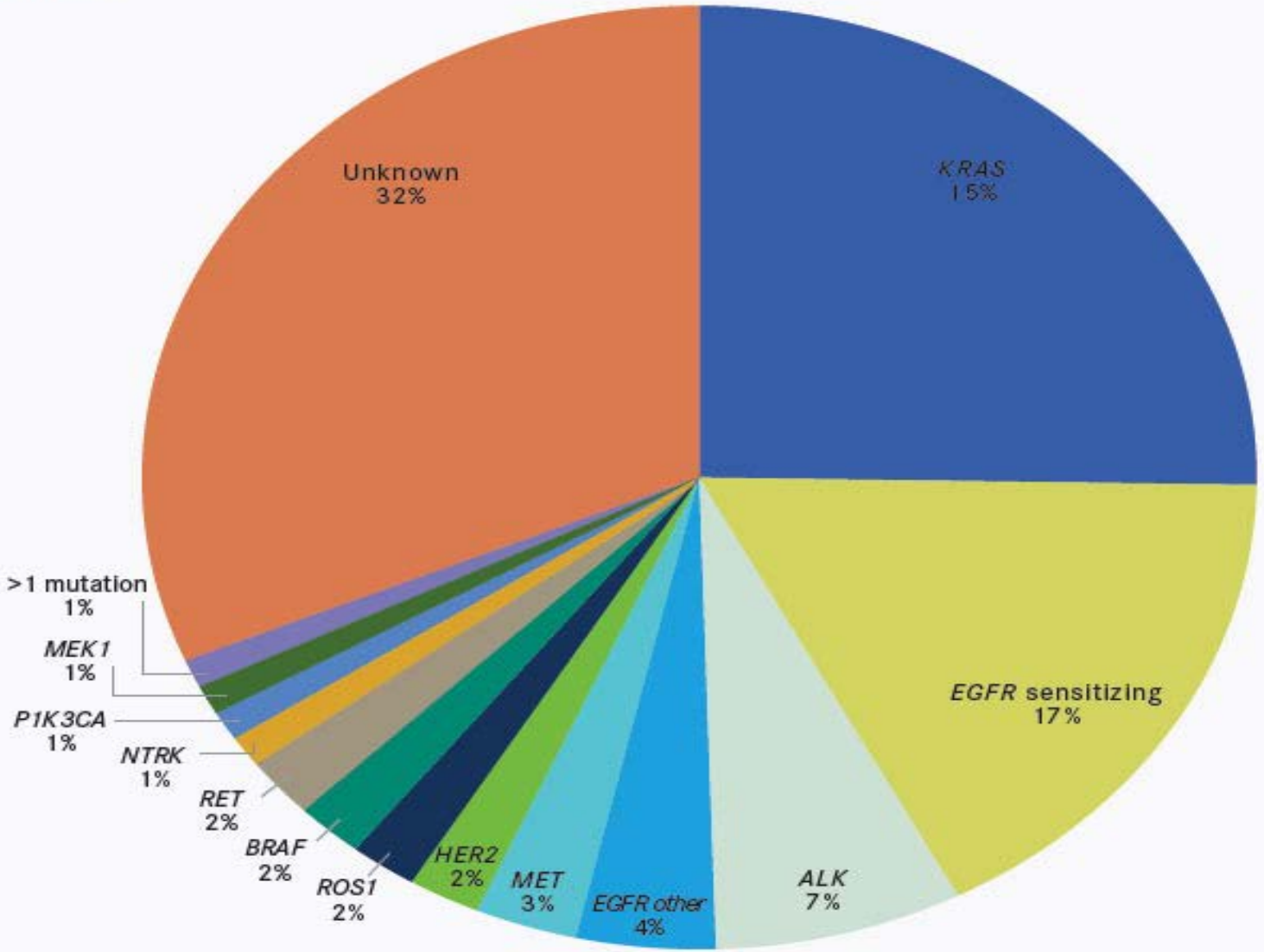
Molecular testing in lung cancer

- Molecular testing is standard of care for metastatic lung cancer
  - Targeting a specific driver mutation
  - Targeted therapy
    - More convenient dosing
    - Milder toxicity
    - Improved survival
    - Improved quality of life

Molecular testing in lung cancer

- Molecular tests
  - Targets with approved targeted therapies
    - EGFR/ALK/ROS1/BRAF/NTKF
  - Targets with off label targeted therapies
    - HER2/MET/RET
- Testing individual genotypes vs NGS Next Generation Sequencing

FIGURE 1. ALTERATIONS OBSERVED IN NON-SMALL CELL LUNG CANCER[1]



Adapted from Shepherd FA. Targeted therapy: the new frontier. Presented at: 2019 American Society of Clinical Oncology Annual Meeting; June 1-4, 2019; Chicago, IL. https://meetinglibrary.asco.org/record/168046/video.

GENOMIC VARIANTS

Somatic - Potentially Actionable — **Variant Allele Fraction**

TP53	p.V217fs Frameshift - LOF	64.2%

Somatic - Biologically Relevant

SMARCA4	p.A903fs Frameshift - LOF	63.4%
MEF2B	Copy number loss	

Germline - Pathogenic / Likely Pathogenic

No pathogenic variants were found in the limited set of genes on which we report.

Pertinent Negatives

No pathogenic single nucleotide variants, indels, or copy number changes found in:

EGFR · KRAS · BRAF · ALK · ROS1 · RET · MET · ERBB2 (HER2)

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

5.8 m/MB 78th percentile

Microsatellite Instability Status

Stable | Equivocal | High

INVESTIGATIONAL THERAPIES

WEE1 Inhibitor	**Adavosertib**	TP53 p.V217fs Loss-of-function Clinical research, Solid Tumors: PMID 27601554

CLINICAL TRIALS

A Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 in Participants With Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors (NCT03261947)	**Phase II** Seattle, WA - 31 mi ✓ **TP53 mutation**
Nintedanib in Molecularly Selected Patients With Advanced Non-Small Cell Lung Cancer (NCT02299141)	**Phase I** Madison, WI - 1615 mi ✓ **TP53 mutation**

EGFR mutation

- EGFR tyrosine kinase inhibitor
- 15% of NSCLC, more frequent in nonsmokers and women
- 13 phase III trials EGFR TKI to chemotherapy prolonged PFS
- Osimertinib is recommended first line for EGFR mutated NSCLC
  - PFS 18 .0 vs 10.2 months (compared to erlotinib or gefitinib)
  - Duration of response 17.2 months vs 8.5 months
  - Overall response rate 80%

ALK mutation

- Anaplastic lymphoma kinase fusion oncogene (ALK)
- Highly sensitive to ALK TKI treatment
  - alectinib, brigatinib, ceritinib, crizotinib
- 5% of NSCLC, more frequent in nonsmokers, younger patients, adenocarcinoma
- Alectinib vs crizotinib PFS: 35 months vs 10.9 months
- Alectinib is recommended first line

ROS1 mutation

- C-ROS-oncogene 1 is a receptor tyrosine kinase
- 1-2% of NSCLC, more frequent in nonsmokers, younger patients, adenocarcinoma
- Sensitive to crizotinib
- Crizotinib therapy after 1 or more prior chemotherapy regimens
  - ORR 72%
  - Median duration of response 17 .6 months
  - Median PFS 15.9 months
- Cabozantinib, entrectinib, repotrectinib are in development

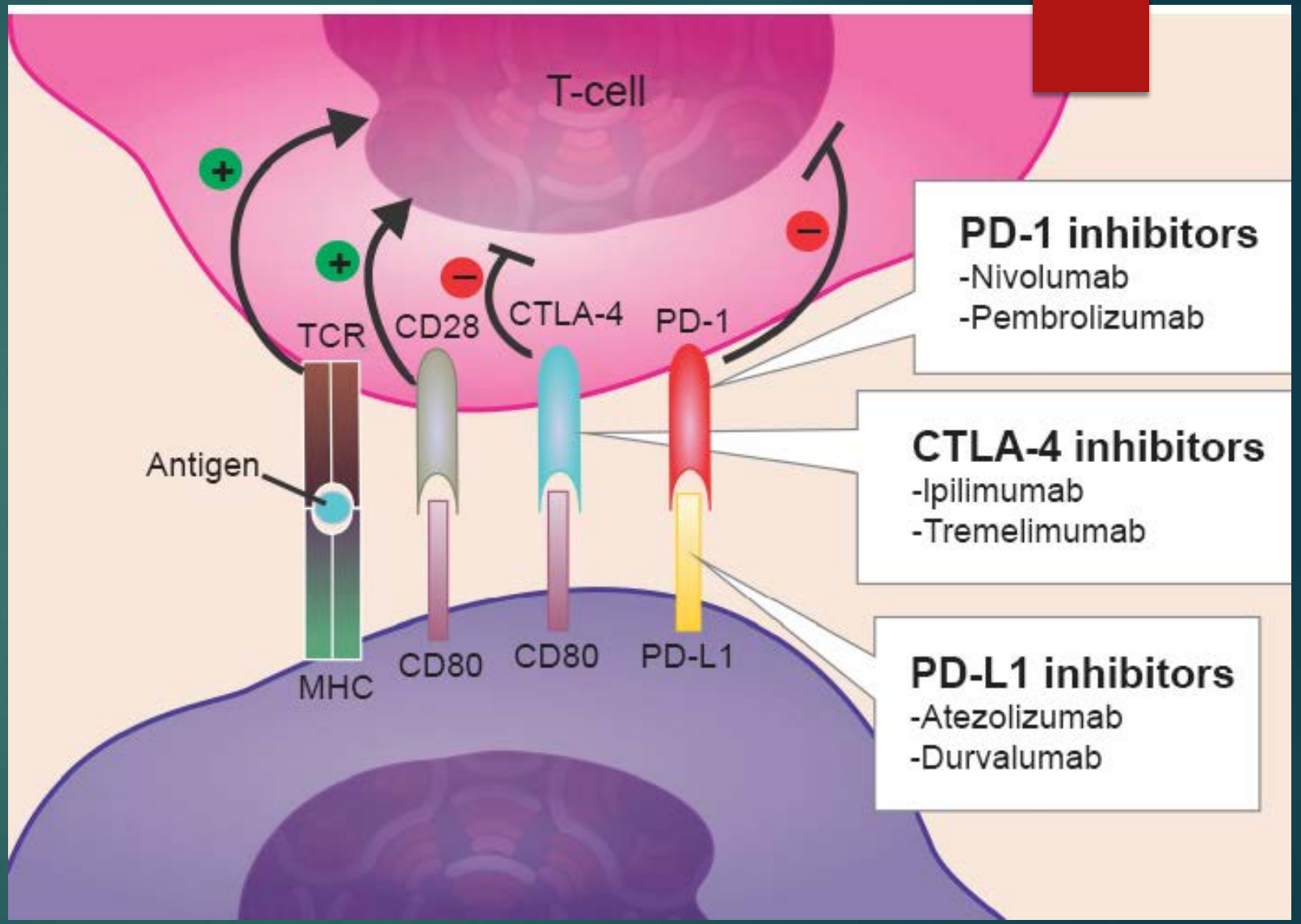
BRAF mutation

- 1-3% of NSCLC, more frequent in smokers
- Second line treatment BRAF + MEK inhibitor
- Dabrafenib + trametinib: ORR 63%, PFS 9.7 months

Immunotherapy in Lung Cancer

Immune checkpoint blockade

- Immune cells can recognize cancer cells as foreign and attack them.
- Cancer cells can evade the immune system
- Checkpoints PD1 and CTLA4 normally serve to protect the normal cells by dampening the immune response to prevent collateral damage to healthy tissue.
- Removal of these blockades make the immune system stronger and fight the cancer



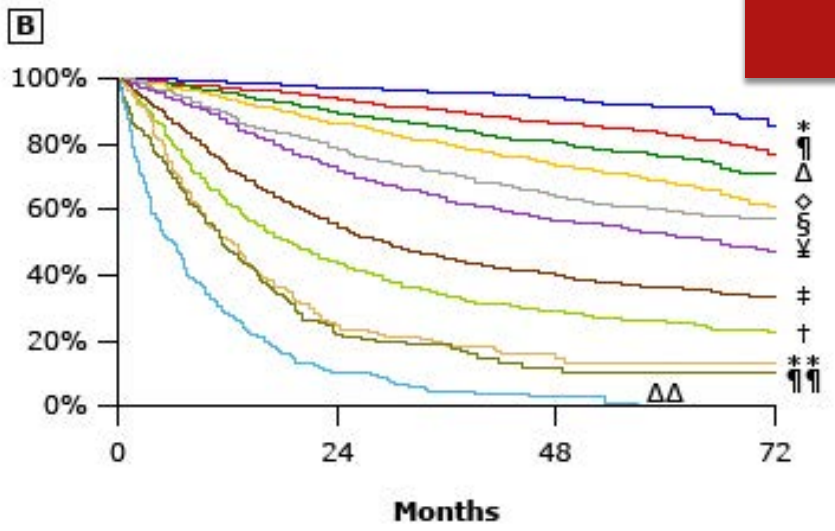
PDL-1 Testing and 1st line Treatment

PD-1 absent or low	• Chemotherapy combined with pembrolizumab is superior to chemotherapy
PDL1 high > 50%	• Pembrolizumab monotherapy • Pembrolizumab and chemotherapy (if rapidly progressive)

Immunotherapy Drugs Approved

- PD-1 inhibitors
  - Nivolumab approved for metastatic disease, after first line therapy
  - Pembrolizumab
    - 1st line in metastatic disease in combination with chemotherapy
    - 1st line in metastatic disease monotherapy in high PDL1 +
- PDL1 inhibitor
  - Atezolizumab
    - 1st line metastatic disease nonsquamous with chemotherapy
    - Previously treated metastatic disease
  - Durvalumab approved for adjuvant therapy after concurrent chemoradiotherapy for unresectable stage III NSCCA

Overall survival by stage



8th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
¶ IA2	505 / 3105	NR	94%	83%
Δ 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%
ΔΔ IVB	328 / 398	6.0	10%	0%

National Lung Cancer Screening Trial

- 53,454 patient, high risk for lung cancer
- Low dose CT scan vs chest x ray
- High risk population
  - Age 55-74
  - 30 + pack years of tobacco use
  - Current smokers or quit within 15 years
- Results: REDUCED MORTALITY 20%
- **LUNG CANCER SCREENING SAVES LIVES**

Criteria for Screening

- Who is eligible
  - Age 55-74
  - At least 30 pack years of tobacco use
  - Current smoker or quit within 15 years
- Annual screening until 15 years elapsed since smoking cessation

Tobacco use: Why quit now

- Smoking increases lung cancer risk 30 fold
- 14 % of patients continue to smoke 5 months after diagnosis
- Smoking intensity at diagnosis is an independent prognostic risk factor
- Chemotherapy less effective
- Higher recurrence risk
- Higher secondary cancer risk (2.3X)
- Mortality 2.9 times higher

Survivor plan after treatment

- Surveillance for recurrence
  - CT scan every 6 months for 2-4 years
  - CT scan annually year 3-5
- Surveillance for second primary lung cancers
- Diet: increased fruits and vegetables reduce risk
- Weight gain is associated with improved survival
- Physical activity improves QOL
- Treatment of sequelae of surgery, radiation, chemotherapy

Summary of Progress

- Minimally invasive surgery
- Stereotactic body radiotherapy
- Adjuvant chemotherapy after surgery, stage II
- Adjuvant immunotherapy after concurrent chemoradiotherapy for stage III
- Immunotherapy and chemotherapy in Stage IV
- Immunotherapy alone in Stage IV for high PDL-1
- Targeted therapy
- Next generation sequencing testing
- Screening has demonstrated beneft

Thank you!