Overview of Lung Cancer Treatment

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Audience Response Question

- Learning about the treatment of lung cancer is:

A: Confusing

B: Frustrating

C: Sleep-inducing

D: Enjoyable

The Story of Lung Cancer

- **The Beginning:** Prevention
  - Smoking cessation (combined pharmacologic and behavioral therapy is most effective)
  - Low dose CT lung cancer screening (age 55-74, ≥ 30 pack-years, cessation < 15 years ago
- **The Middle:** Diagnosis & Treatment
  - Integration of multidisciplinary care provided by various oncologists
  - Monitoring for recurrence
  - Survivorship care
- **The End:** Palliation
  - Early palliative care involvement
  - Effective symptom management
  - Appropriate advance care planning and use of hospice

Treatment Modalities

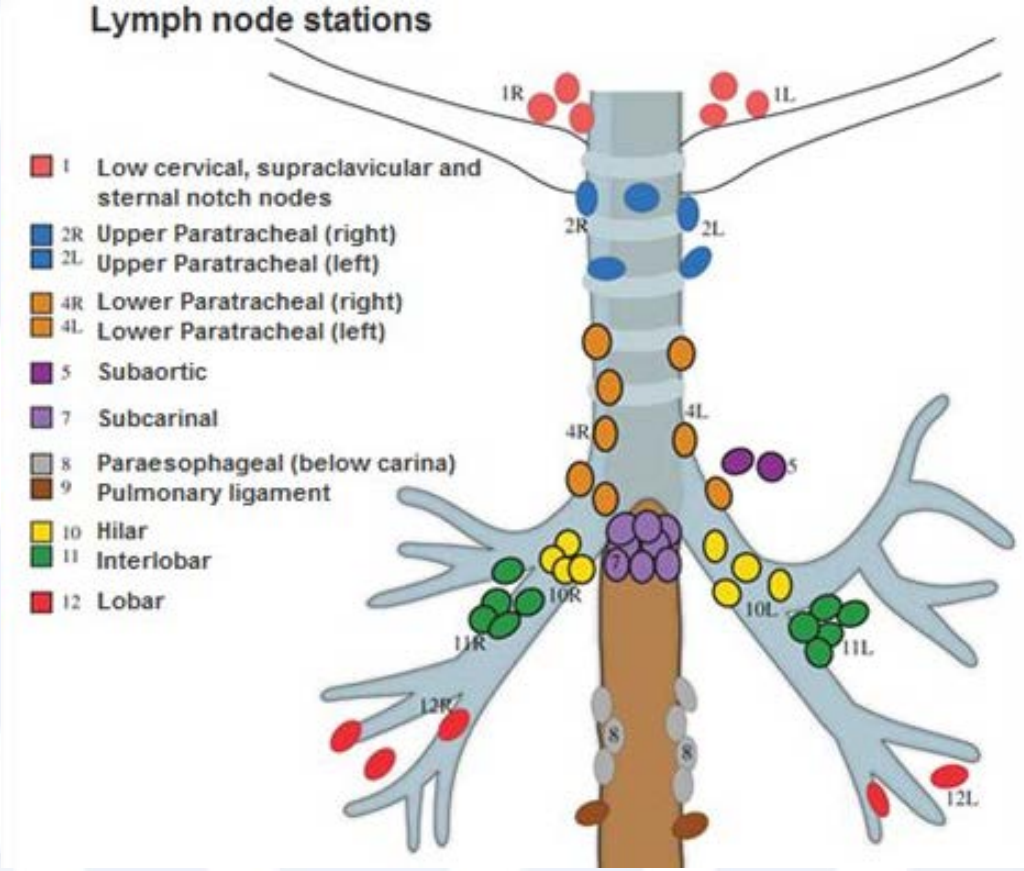
- **The Army:** Surgery
  - Open vs. VATS or robotic-assisted approaches
  - Lobectomy vs. Pneumonectomy vs. Sublobar Resection
- **The Navy:** Systemic Therapy
  - Chemotherapy, Targeted Therapy, Immunotherapy
- **The Air Force:** Radiation
  - External Beam Radiation Therapy
  - Stereotactic Body Radiation Therapy
- **The CIA:** Pathology
  - Tumor morphology, IHC, biomarkers, genomic profiling

AJCC 8th Edition Staging

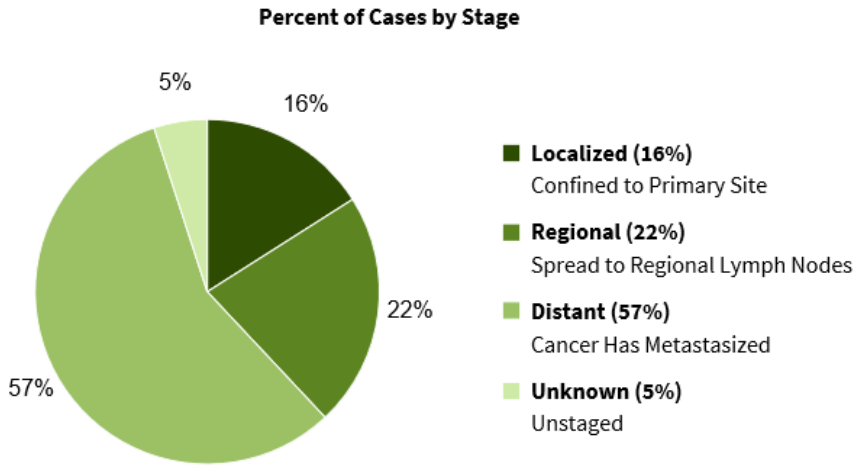
T		Primary Tumor
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2		Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3		Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a ipsilateral lobe different from that of the primary

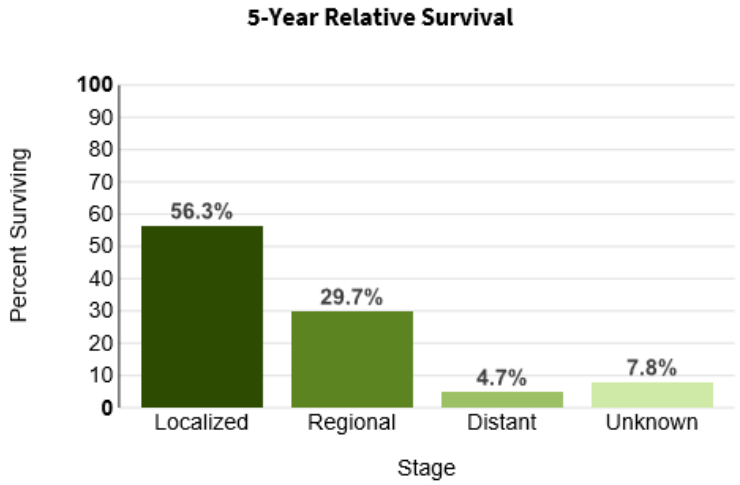
AJCC 8th Edition Staging

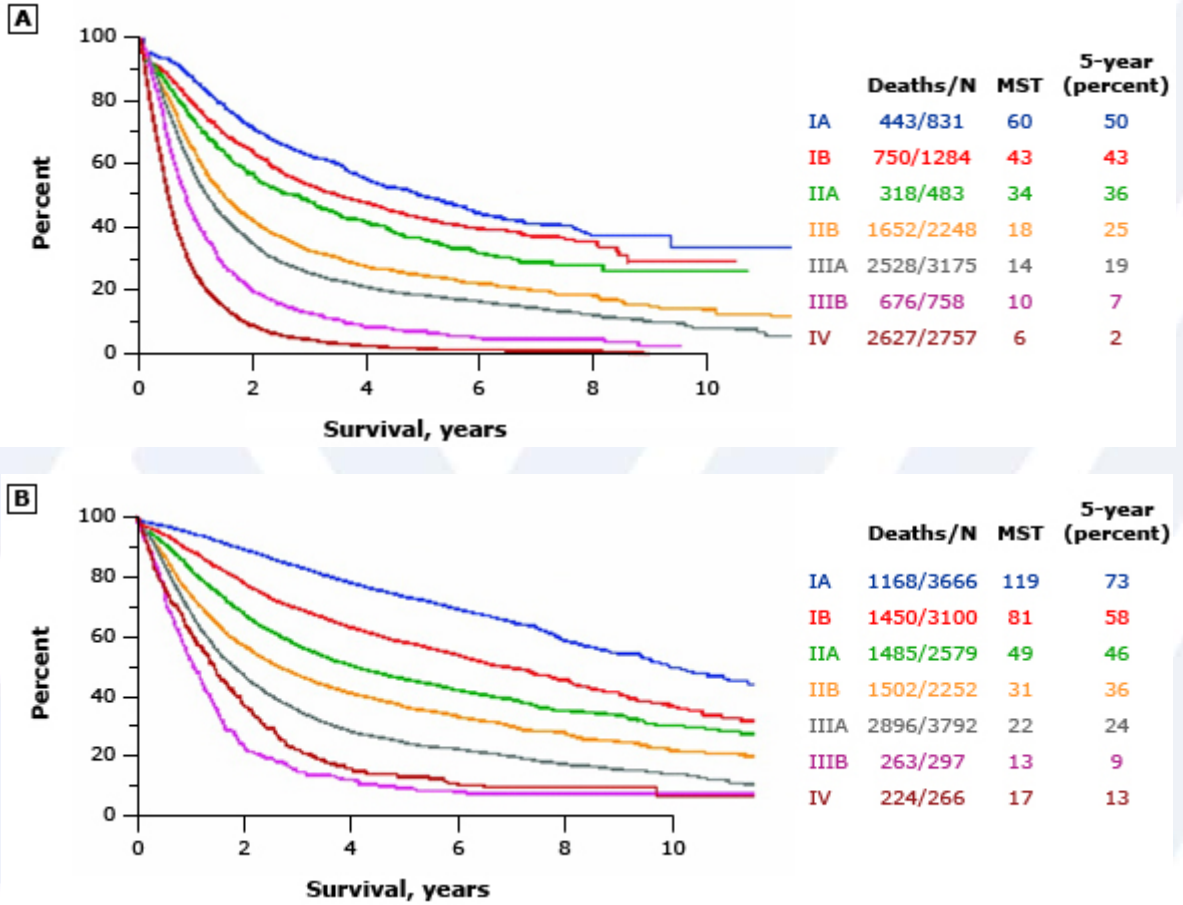
N		**Regional Lymph Nodes**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M		**Distant Metastasis**
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion[a]
	M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
	M1c	Multiple extrathoracic metastases in a single organ or in multiple organs



Lung Cancer Incidence and Prognosis



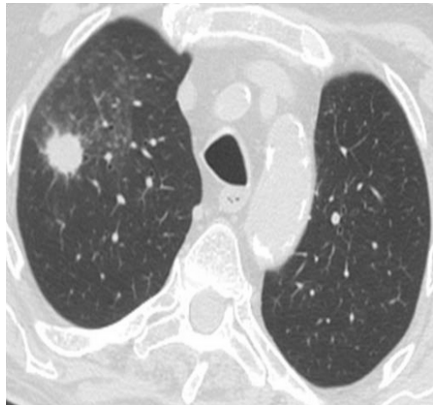


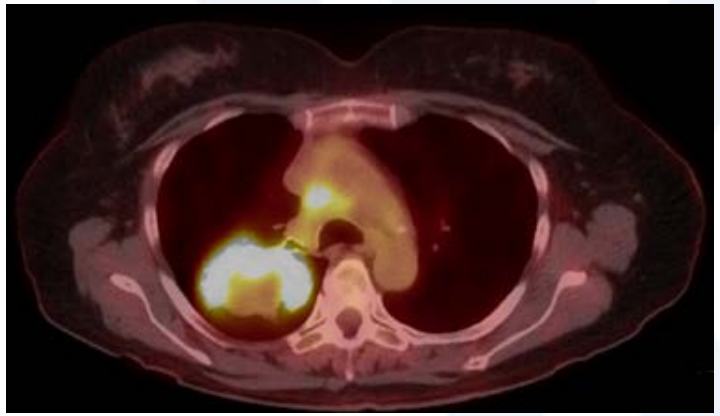


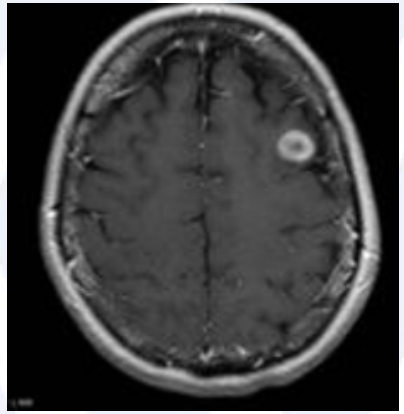
Overall survival, expressed as median survival time (MST) and five-year survival, using the seventh edition of TNM staging system by (A) clinical stage and (B) pathologic stage.

Diagnostic Modalities Used for Staging

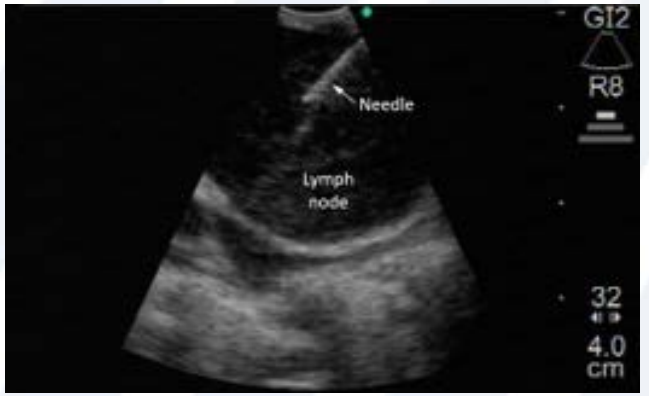
- **Imaging:** CT, PET/CT, MRI brain







- **Obtaining Pathology:** Bronchoscopy, EBUS, Mediastinoscopy, CT-guided biopsy



Stage I-III NSCLC
Treated with Curative Intent

Early Stage Node-Negative NSCLC

- **Surgical resection** is the preferred local treatment (lobectomy is preferred to segmentectomy or wedge resection).
  - Includes sampling of at-risk ipsilateral hilar and mediastional LN
- **SBRT** for patients who are medically inoperable or refuse surgery.
  - Hypofractionated RT for “ultra-central” tumors
  - No data supporting the addition of systemic therapy
- Other suboptimal options: RFA, observation

Basic Principles of Surgical Selection

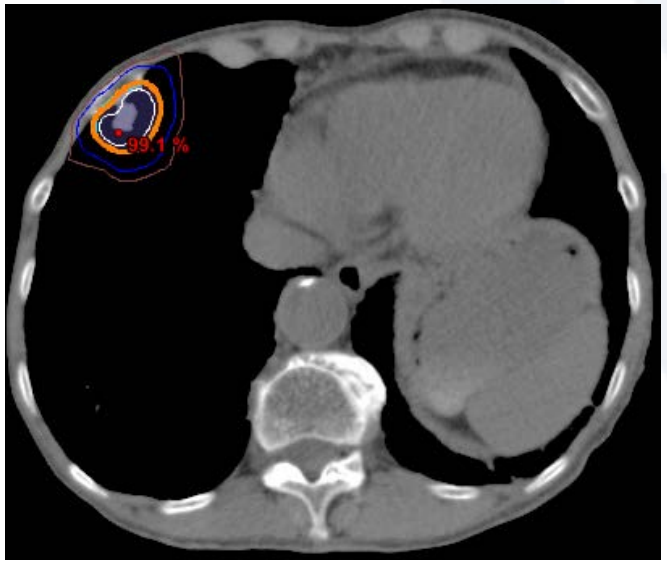
- **The definition of medically inoperable varies substantially between surgeons**
- Surgery should not be denied on the grounds of age alone
- PFTs that suggest a patient should tolerate surgery include:
  - Pre-op FEV_1 >2 L (or ≥80% predicted) if patient needs a pneumonectomy
  - Pre-op FEV_1 >1.5L if patient needs a lobectomy
  - Predicted post-op FEV_1 >800 mL (>40% predicted)
  - DLCO > 50-60%
  - Tumor location in relation to most of emphysema also matters
- Patients with cardiac risk factors should have a preoperative cardiologic evaluation
- Contemporary 30-day mortality rates are 1-3% for lobectomy or sublobar resection and 2-11% for pneumonectomy
  - Active smokers have a mildly increased risk of post-op complications

Outcomes of SBRT for Early Stage NSCLC

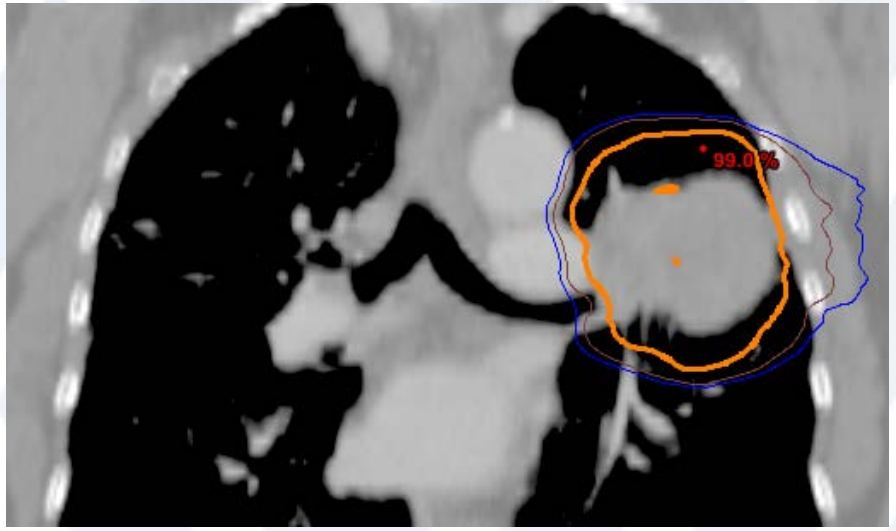
- **RTOG 0236** - Multicenter phase II study of 55 patients with cT1-2N0M0 medically inoperable NSCLC (<5 cm, peripheral only)
  - 5Y-LC **93%**, 5Y-lobar control 80%, 31% distant failure, 5Y-OS 40%
  - Toxicity: Grade 3 in 13%, Grade 4 in 4%, Grade 5 in 0%

- **Dutch Series** – Retrospective study of 676 patients with cT1-2N0M0 NSCLC (some medically operable, risk-adapted dosing for central tumors)
  - 3Y-LC **90%**, 3Y-OS 53% (but 85% among operable patients)
  - Acute Toxicity: fatigue ~30%, chest wall pain ~10%, nausea ~10%, cough/dyspnea 5%
  - Late Toxicity: G3 pneumonitis 3%, rib fracture 2%, chronic pain ~2%

Potential SBRT Toxicity Depends on Tumor Site



- Fatigue
- Rib fracture, neuropathic pain
- Skin Erythema/fibrosis



- Fatigue
- Pneumonitis, atelectasis hemoptysis, fibrosis
- Rib fracture, neuropathic pain

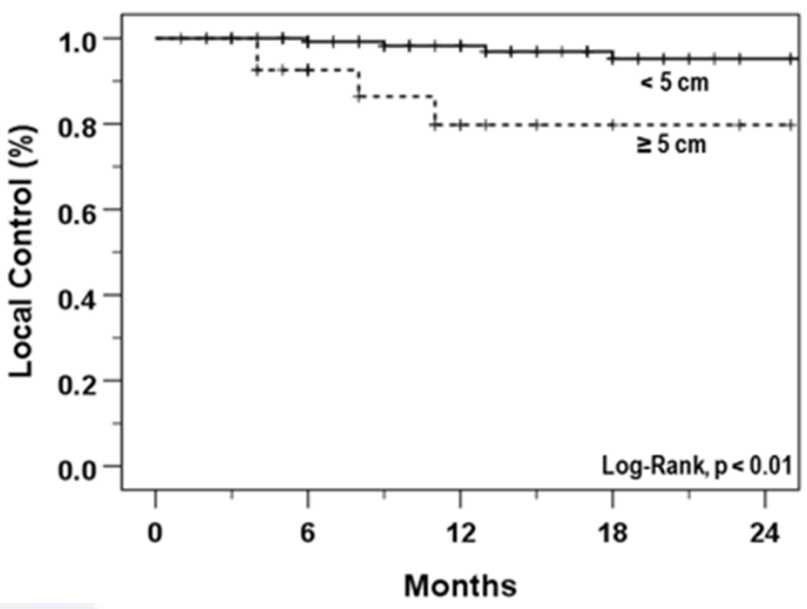
How Does SBRT Compare to Surgery?

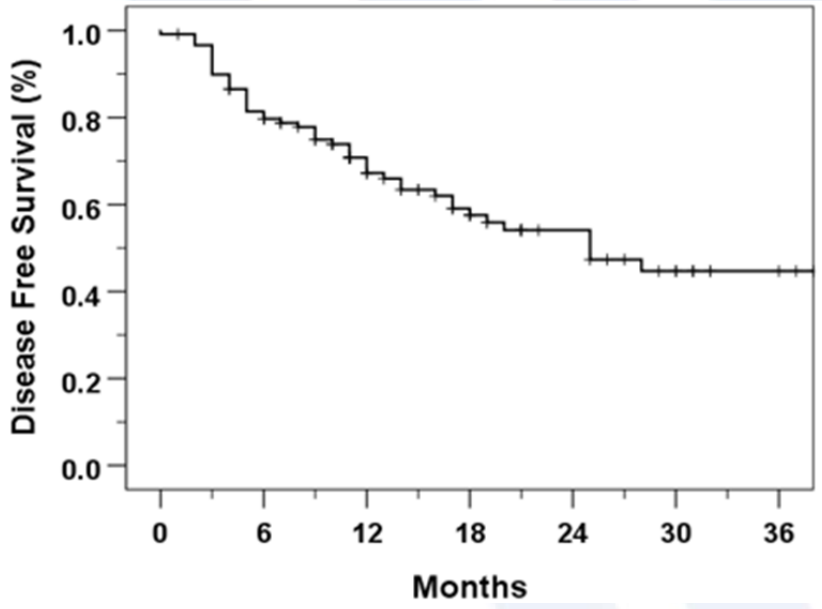
- **No completed randomized trials**
- **Selection bias** when comparing survival numbers from non-randomized cohorts of patients are difficult to compare with surgery
  - Radiation patients are generally medically inoperable, or older with worse PS, and often don't undergo full mediastinal staging

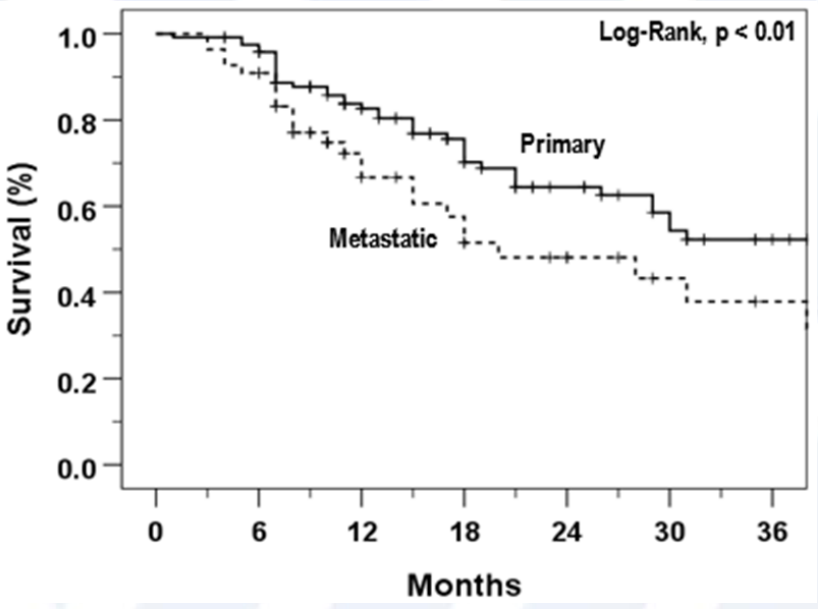
- **Pooled Analysis of STARS and ROSEL Randomized Trials (Chang, Lancet Oncol 2015)**
  - 58 pts, operable T1-2a (<4 cm) N0 M0 NSCLC randomized to lobectomy vs. SBRT
  - Results: SBRT → ↑ **3Y-OS** (79→95%) with no difference in RFS (~83%)
  - Why the difference?
    - Surgery has higher M&M (G3-5 toxicity (48% vs. 10%).
    - Abscopal effect from RT?

The WVU lung SBRT experience

- Retrospective, 144 patients with 100 primary (57.1%) and 75 metastatic (42.9%) lung tumors treated with SBRT from 2012-2018, median follow-up of 15.0 months
  - Results: 1Y and 2Y local control = 95.1% and 92.7%







Sean Parker *et al*, *Practical Radiation Oncology,* 2018

Hilar LN Positive (cN1M0) NSCLC

- **Surgical resection + LND** is the preferred local treatment if patient is medically and surgically operable
  - All patients receive adjuvant chemotherapy.
  - Neoadjuvant therapy may be given if surgically inoperable up-front

- **Conventional 3DCRT or IMRT over 6 weeks with concurrent chemotherapy** for patients who are medically or surgically inoperable or refuse surgery.
  - For frail patients, sequential chemo and RT, or RT alone (+/- altered fractionation) are appropriate options

Mediastinal LN Positive (cN2M0) NSCLC

- Surgical resection is generally NOT recommended as the up-front treatment approach due to the high probability of distant micrometastases.
  - 2 randomized trials showed that surgery had no survival benefit, but well selected patients may benefit after neoadjuvant therapy.

- Treatment options:
  - Definitive chemo-RT
  - Neoadjuvant chemo or chemo-RT → surgery

- Factors favoring incorporation of surgery:
  - Single involved LN station > multiple involved stations
  - Microscopic N2 > clinical N2 (especially if bulky LN >3cm)
  - Successful downstaging of the mediastinum s/p neoadjuvant therapy
  - Avoiding pneumonectomy (especially right pneumonectomy)
  - T3/4 due to size alone > invasion/extension
  - Good PS, younger age, no weight loss, female gender

Special Cases

- N3 disease
  - Chemo-RT
- Superior Sulcus T3-4N0-1
  - Neoadjuvant chemo-RT → surgery

Post-Operative Therapy

- Adjuvant Chemotherapy:
  - pN+
  - pT3-4
  - +/- pT2a/b N0 if high risk features (>4cm tumor, high grade, LVSI, visceral pleural involvement, or pNx
- Adjuvant Radiation:
  - Positive margin not amenable to re-resection
  - pN2
  - +/- pN1 in patient not getting adjuvant chemotherapy

How to Add Chemo to Definitive RT

- Both sequential & concurrent chemo → survival benefit
  - Concurrent chemo → improved local control → improved survival
    - At expense of ↑ in-field toxicity (especially esophagitis)

Trial	Patients, *n*	Med. Survival, *mo*		% Survival, *y*		% Esophagitis (Gr. 3-4)	
		S	C	S	C	S	C
Furuse[15]	314	13.3	16.5	8	16(5)	4	23
RTOG-9410[16]	400	14.6	17.1	12	21(4)	5	26
GLOT[17]	212	13.9	15.6	24	35(2)	3	17
Czech[19]	102	13.2	20.6	15	42(2)	4	28
BROCAT[20]	303	14.0	19.0	—	—	0	26
LAMP[21]	178	13.8	17.4	31	33(2)	3	26

What Type of Chemotherapy is Used?

- Neoadjuvant/Adjvuant/Sequential:
  - Cisplatin + (vinorelbine, etoposide, gemcitabine, docetaxel, or pemetrexed*)
  - Carboplatin + (paclitaxel, gemcitabine, or pemetrexed*)

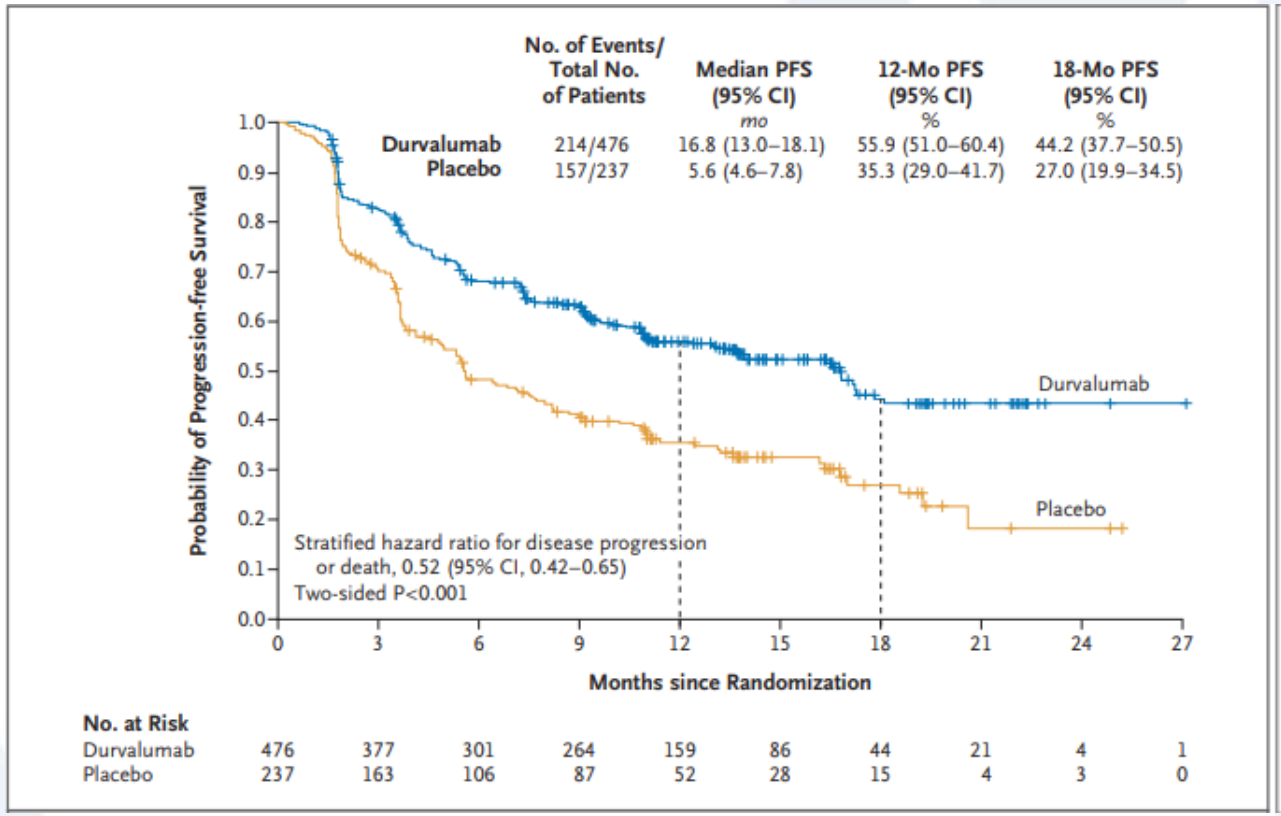
- Concurrent with RT:
  - Cisplatin + (etoposide, vinblastine, or pemetrexed*)
  - **Carboplatin + paclitaxel** (+/- 2 additional cycles)

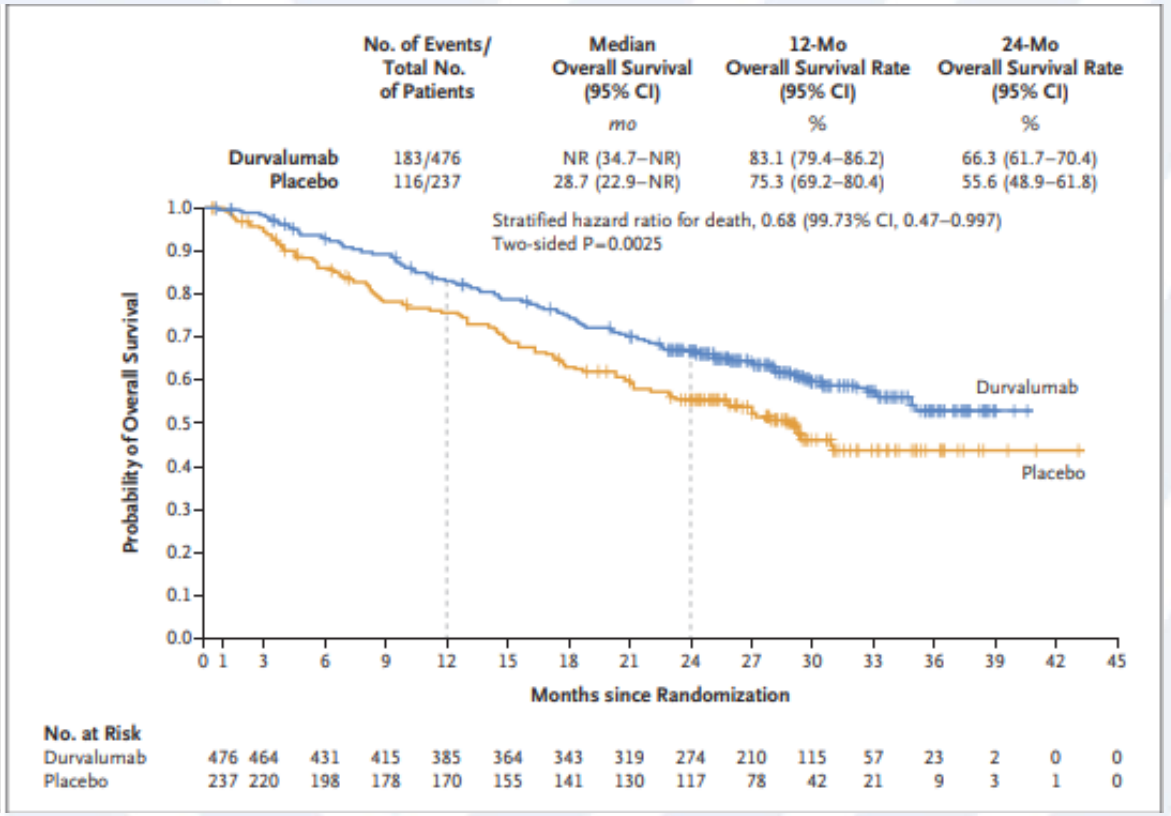
- Consolidation after chemo-RT:
  - Durvalumab q2weeks for up to 12 months

* for non-squamous histology only

The PACIFIC Trial

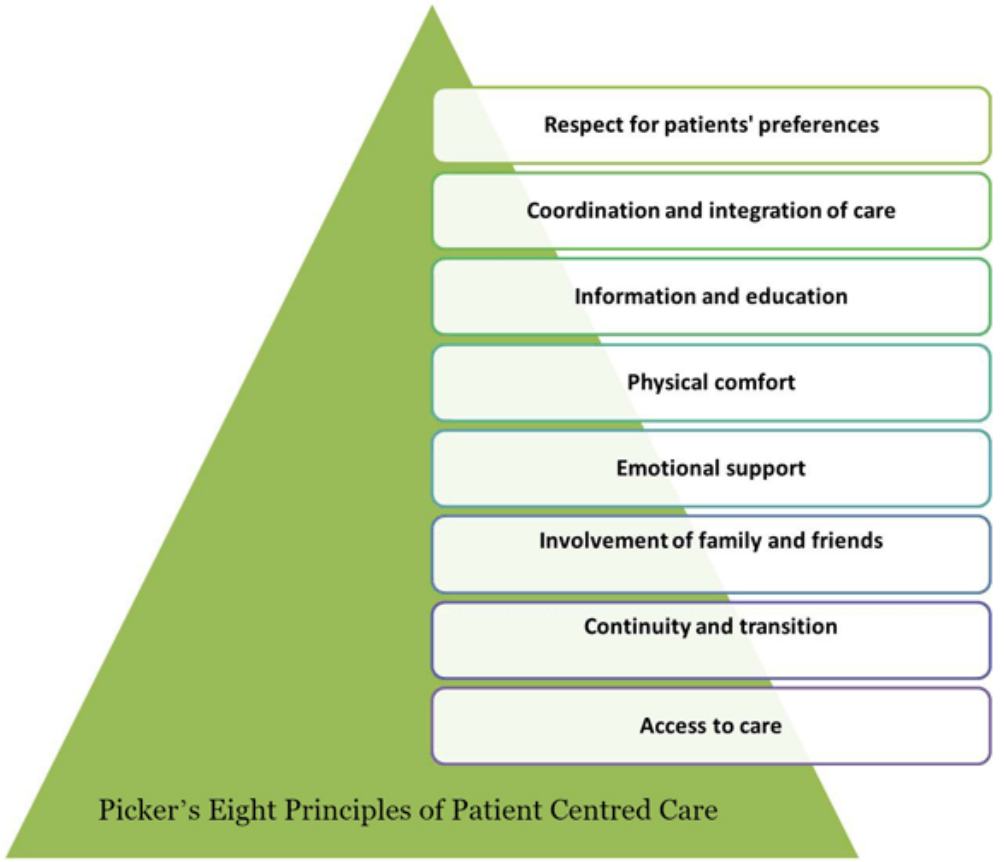
- 713 patients with unresectable Stage III NSCLC with PS 0-1 and no disease progression after chemo-RT randomized 2:1 to +/- consolidation Durvalumab





What Is Patient-Centered Care?

- In patient-centered care, an individual's specific health needs and desired health outcomes are the driving force behind all health care decisions and quality measurements. **Patients are partners with their health care providers,** and providers treat patients not only from a clinical perspective, but also from an emotional, mental, spiritual, social, and financial perspective.



Patient-Centered Care In Oncology

- The optimal “cancer control” approach is not necessarily the optimal patient-centered approach.
- Physicians are often not the best judges of patient-centered outcomes (e.g. PROs).
- There are multiple examples of where well-selected patients can safely undergo radiation therapy instead of surgery and preserve QOL:
  - prostate, larynx, pharynx, anus, bladder, advanced cervix, *advanced NSCLC, early NSCLC*
- Multidisciplinary involvement is the best way to ensure patient-centered care and truly informed consent.

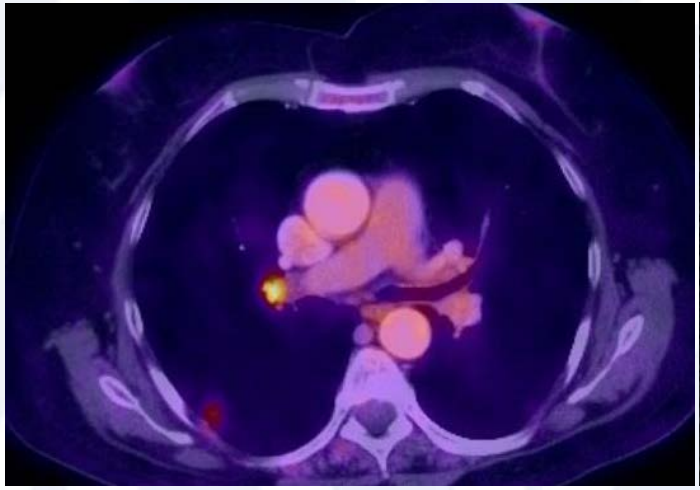
Survivorship Care

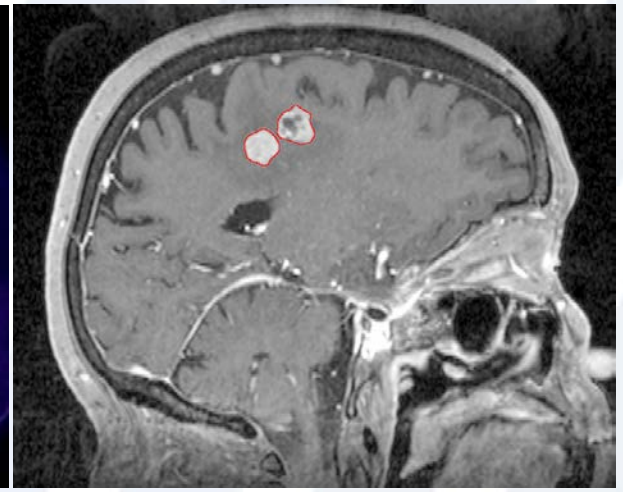
- Surveillance H&P + imaging (CT q3-6mo) for recurrence
- Manage long term side effects of treatment (e.g. fatigue, dyspnea, pain, etc.)
- Other age-appropriate cancer screening
- Immunizations (influenza, zoster, pneumococcal)
- Health promotion (healthy weight and diet, 30 min moderate intensity physical activity most days, limit alcohol, pulmonary rehabilitation)
- Monitor BP, cholesterol, glucose, bone health, dental health, sun protection

Stage IV NSCLC
Treated with Palliative Intent

Case Presentation

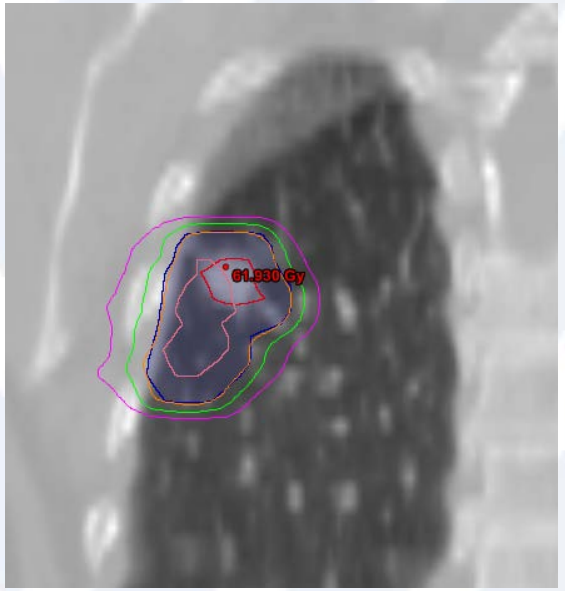
- 64F active smoker p/w difficulty writing and right foot weakness.
- MRI brain showed 2 enhancing lesions
- PET/CT showed a 1.3cm RLL nodule (SUV 2.9) and a 1.1 x 0.9cm right hilar LN (SUV 3.8)
- CT-guided biopsy showed NSCLC





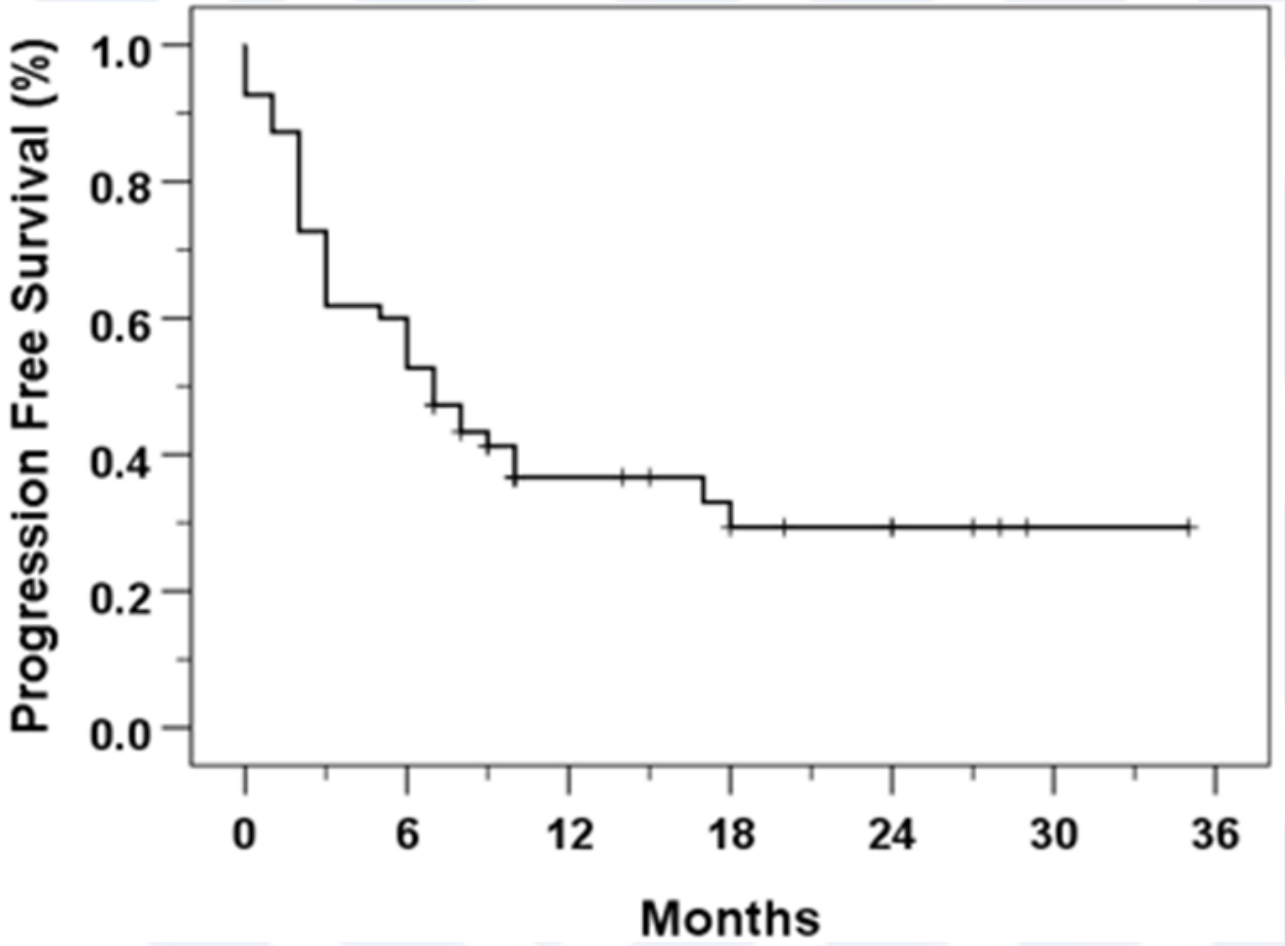
Case Presentation

- Stereotactic Radiosurgery (SRS) to 4 brain metastases using the Gamma Knife
- 2 cycles carboplatin/pemetrexed → SD in lymph node but PD in lung nodule
- SBRT to the RLL nodule
- 5 cycles carboplatin/Nab-Paclitaxel (d/c'ed due to intolerance)
- Follow-up imaging → no evidence of disease in body or brain since then (now 40 months since diagnosis)

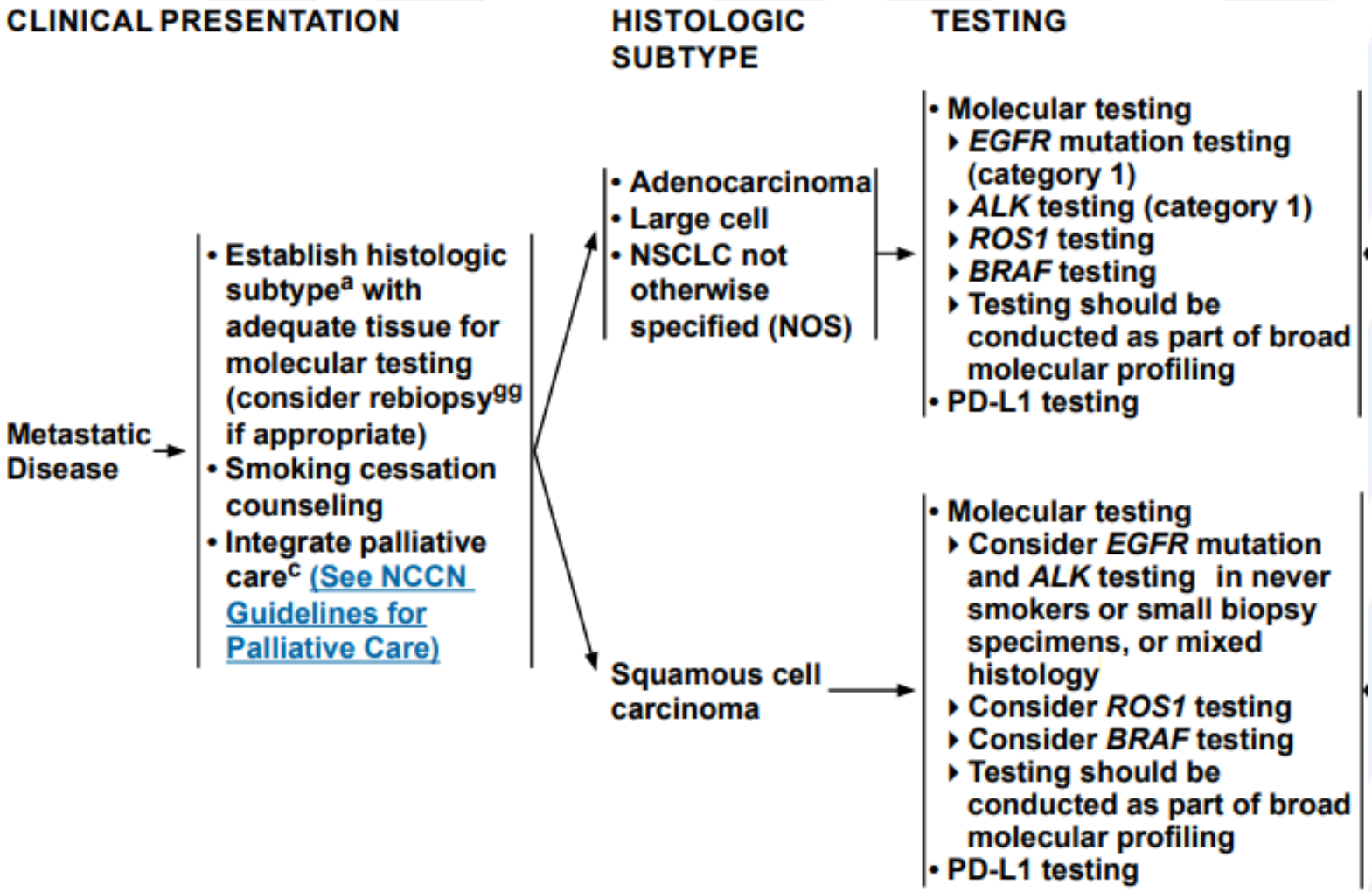


Oligometastatic Disease

- This is not the average patient, but I've had several like her.
- In some cases, adding targeted surgery or radiation therapy to a limited number of oligometastatic or oligoprogressive sites of disease can lead to a more sustained response to systemic therapy.



NCCN Guidelines for Metastatic Disease



Targeted Therapies

- EGFR Mutation:
  - First line: Erlotinib, Afatinib, Gefitinib
  - If progression → rebiopsy for T790M mutation testing
  - Subsequent Therapy: Osimertinib (if T790M+)
- ALK Rearrangement:
  - First line: Crizotinib, Alectinib, Ceritinib
  - Subsequent Therapy: Alectinib, Brigatinib, Ceritinib
- ROS1 Rearrangement:
  - First line: Crizotinib, Ceritinib
- BRAF V600E Mutation:
  - First line: Dabrafenib/trametinib
  - Subsequent Therapy: Dabrafenib/trametinib
- PD-L1 Expression $\geq$ 50% and all of the above negative:
  - First line: Pembrolizumab (+/- concurrent carboplatin/pemetrexed)
  - Subsequent Therapy: Atezolizumab, Nivolumab, Pembrolizumab

Principles of Systemic Therapy for Metastatic Disease

- If patient is PD-L1 positive immunotherapy is often involved in 1st line therapy. Otherwise a number of platinum based chemo regimens are available.

- Platinum-based chemo → prolonged survival, better symptom control, better QOL
  - Response rate ~30%, M-TTP ~5mo, MS ~9mo
  - Cisplatin/Pemetrexed is generally favored for non-squamous histology
  - Single agent maintenance chemo may be used after 4-6 initial cycles

Palliative Radiation For Symptom Relief

- Pain
  - bone metastases
- Neurologic symptoms
  - spinal cord compression
  - brain metastases
- Bleeding
  - endobronchial tumor
- Obstruction
  - SVC, airway, esophagus

Small Cell Lung Cancer

- 15% of all lung cancer, poor prognosis
- AJCC Staging is preferred (same as NSCLC staging)
  - Limited stage is M0 and extensive stage is M1
  - 66% of patients present with Stage IV (extensive stage)

- Cisplatin (or carboplatin) + etoposide for 4-6 cycles is the backbone of treatment regardless of stage.
  - 70-90% response rate
  - Initially chemosensitive, but often develops drug resistance

Limited Stage SCLC

- cT1-2N0 → Lobectomy + LND → Chemotherapy
  - Adjuvant RT if LN+

- All others → Concurrent chemo-RT
  - Early concurrent RT → small ↑ OS compared to late concurrent or sequential RT
  - Poor performance status may mandate delays in starting RT.
  - Optimal dose of RT has not been established,
    - 45/1.5Gy BID is superior to 45mg daily
    - For daily RT, recommend 60-70/2.0Gy

- If CR or PR on reimaging and good PS →
  - Prophylactic cranial irradiation (PCI) is recommended

Extensive Stage SCLC

- Chemotherapy
- Palliative RT to symptomatic sites
  - Sequencing of chemo and palliative RT depends on extent of symptoms.

- If CR or PR on reimaging → consider PCI +/- thoracic RT

Questions?